



March 11-16 **2022**  
**WORLD SLEEP**  
*Rome • Italy*



# ABSTRACTS

Aging and Developmental Issues  
Basic Research | Behavior, Cognition and  
Dreaming | Chronobiology/Circadian  
Disorders | Dental | Sleep Health  
Hypersomnia | Insomnia | Memory  
Narcolepsy | Neurological Sleep  
Disorders Affecting Sleep

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Parasomnia | Pediatric  
Pharmacology | Psychiatric Disorders  
Affecting Sleep/Wake | REM Behavior  
Disorders | Restless Legs Syndrome  
Sleep Breathing Disorders  
Technology/Technical  
Women





## 2022 ABSTRACTS

World Sleep Society is pleased to share the abstracts presented at 16th World Sleep congress, which took place in Rome, Italy over March 11–16, 2022. Researchers from around the world gathered in Rome to present the 810 abstracts now published in this supplement, as well as many more symposium, course, and keynote presentations. We thank the World Sleep community for its contributions to the World Sleep 2022 scientific program and the field of sleep medicine.

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## Ageing and Developmental Issues

### AGE ASSOCIATED CHANGES IN SLEEP SPINDLE CHARACTERISTICS IN VIPASANA MEDITATOR: A WHOLE NIGHT POLYSOMNOGRAPHY STUDY

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**Introduction:** With normal aging process, the notable changes in micro-sleep architecture is observed in sleep spindles – a signature of thalamocortical oscillation during sleep. Reduction of sleep spindle density, duration and amplitude, a shift from fast to slow spindles and decrease in the spindle power are the prominent changes that are associated with ageing. There are many reproducible evidences demonstrating the neural plasticity changes brings about strengthening of thalamocortical network by long-term vipassana (mindfulness) meditation practices. We have earlier reported that long-term practice of Vipassana meditation can bring about enhanced N3 and REM sleep stage when compared to age matched non-meditating controls. In this study, we aimed to assess the sleep spindles characteristics during NREMsleep stage N2 to understand the effect of aging in long term vipasana practitioners.

**Materials and Methods:** Whole-night polysomnography was conducted on healthy male (30–60 years, meditators = 49, control=61) subjects. Meditators were practicing regularly Vipassanameditation. Controls were healthy non meditating age matched participants. All the participants underwent two consecutive whole night polysomnographyand sleep was scored offline with Polymansoftware as per ASSM guidelines. YASA spindle detection algorithm was used to identify and analyses the sleep spindle characteristics during N2 sleep stage. Mann–WhitneyUand Spearman's correlation was applied.

**Results:** Whole night polysomnography recordings that demonstrated sleep efficiency index more than 85% were considered for the analysis, thus the analysis was only among good sleepers. Meditators showed significantly reduced N2 (control =185±54.88, meditators =165.55±47.44, p=0.037) and increased REM (control =58.87±25.05, meditators =75.49±39.00, p=0.01) sleep duration when compared to controls. The spindle duration (controls r=-0.43, p=<0/001, meditators, r=-0.29, p=0.04)and number of spindle oscillations(controls r =- 0.45, p=<0/001, meditators r= - 0.29, p=0.05), showed a significant negative correlation with age in both the groups, however, the changes in meditators were significantly less than the controls. Meditators showed a trend towards lower spindle density (control =270.16±128.65, meditators =218.52±98.77, p=0.023). Other sleep spindle characteristics amplitude and spindle frequency were comparable with controls and showed a similar declining trend with ageing.

**Conclusions:** Changes in the sleep spindle characteristics is the foremost physiological changes observed with normal ageing process. We observed similar age related changes in sleep spindle characteristics both in controls and meditators, however, such changes were less in meditators. There are report demonstrating reduced spindle density associated with better cognitive performance in a nap among experienced vipassana meditators which is attributed to efficiency of thalamo-cortical network. In accordance, in the present study, we are reporting from whole night

polysomnography data that the impact of ageing on sleep spindle modulation is less pronounced in long-term Vipassana meditators than controls, which probably could be due to neural plasticity changes.

**Acknowledgements:** Central Council for Research in Yoga Naturopathy and Department of Science and Technology for funding our research projects. Vipassana research institute, Igathpuri, for their support in facilitating meditators to participate in the study.

### ASSOCIATION BETWEEN AGE AND SLEEP QUALITY: FINDINGS FROM A COMMUNITY HEALTH SURVEY

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**Introduction:** This study aimed to investigate the changes in sleep quality with increasing age and the effect of age on the components of the Pittsburgh Sleep Quality Index (PSQI).

**Materials and Methods:** We used data from the Community Health Survey conducted by the Korea Center for Disease Control and Prevention in 2018. A total of 228340 participants in this nationwide survey.

Sleep quality was assessed using the PSQI. Adults aged ≥ 19 years were divided into six age groups and one-way analysis of variance (one-way ANOVA) was used to compare the mean values of PSQI of each group. By comparing the scores for each PSQI component in those aged ≥ 65 years and < 65 years, we aimed to reveal the differences in special components according to age group.

**Results:** In total, 223334 respondents were included in the study. Based on a one-way ANOVA, the PSQI score generally increased with age. Although the average PSQI score of patients in their 40s was lower than that of patients in their 30s, there was no significant difference between the two groups (p = 0.11). When the PSQI component was compared between the population aged over and under 65 years, the population aged ≥ 65 years scored higher in most components. In contrast, daytime dysfunction scored higher in the population aged < 65 years.

**Conclusions:** Sleep quality tends to decrease with increasing age. Several factors, including physiological changes, underlying physical conditions, and psychosocial factors, may contribute to a decrease in sleep quality with age.

**Acknowledgements:** For this study, we used the Korea Community Health Survey data, conducted by the Korea Centers for Disease Control and Prevention.

### ASSOCIATIONS BETWEEN OBSTRUCTIVE SLEEP APNEA, ANTI-INFLAMMATORY INTERLEUKINS, AND CORTICAL B-AMYLOID BURDEN IN COGNITIVELY UNIMPAIRED OLDER ADULTS

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**Introduction:** Alzheimer's disease (AD) is a neurodegenerative disorder with no cure that is thought to be triggered by the accumulation of B-amyloid (AB) plaques. Obstructive sleep apnea (OSA) increases risk for developing AD, and has been associated with longitudinal accumulation of AB pathology. However, the mechanisms for the link between OSA and AB burden remains unknown. One candidate mechanism is inflammation, which is increased by OSA and interacts with AB to facilitate AD pathophysiological progression. Here, we test the hypothesis that OSA severity is associated with anti-inflammatory interleukin (IL) cytokines that are also associated with cortical AB burden.

**Materials and Methods:** Eighteen cognitively unimpaired older adults (Mini Mental State Exam scores  $\geq 27$ ; mean age =  $73.1 \pm 5.3$ ; 10 female) enriched for OSA (mean AHI =  $21.2 \pm 22.7$ ) were evaluated with overnight polysomnography (PSG). Plasma samples were collected both prior to sleep and following sleep. OSA severity was quantified using PSG measures of Apnea-Hypopnea Index (AHI), Respiratory Disturbance Index (RDI), and measures of blood oxygen desaturation (number, duration, and frequency of desaturations  $\geq 4\%$ , desaturation nadir) stratified by non-rapid eye movement (NREM) and REM sleep stages. Concentrations of inflammatory cytokines were determined with Simoa CorPlex Human Cytokine 10-plex Panel 1 assay (CPX) (interferon gamma (IFN $\gamma$ ), IL-1 $\beta$ , IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70, IL-22, and Tumor Necrosis Factor alpha (TNF- $\alpha$ )). Subjects underwent 18F-florbetapir positron emission tomography (PET) amyloid imaging, and cortical standardized uptake value ratios (SUVR) were collected 50–70 minutes post-injection using a cerebellar gray matter reference to estimate AB burden. Pearson's correlations, Kendall's tau-B, and multiple linear regressions were implemented where appropriate to examine associations between OSA severity, inflammation measures, and cortical amyloid.

**Results:** OSA severity during NREM sleep (log NREM sleep RDI) was significantly correlated with reductions in log IL-5 plasma levels ( $r = -0.478$ ,  $p = 0.045$ ), and REM sleep AHI ( $r = -0.677$ ,  $p = 0.002$ ) and RDI ( $r = -0.692$ ,  $p = 0.001$ ) were significantly associated with reductions in anti-inflammatory IL-10 concentrations. These relationships survived adjustment for sex and age in regression models (e.g.,  $R^2 = 0.488$ ,  $p = 0.0216$ , with REM sleep RDI as a predictor for IL-10  $p = 0.006$ ). IL-10 was also significantly associated with PET-measured cortical AB burden (Kendall's tau =  $-0.414$ ,  $p = 0.016$ ).

**Conclusions:** These findings support suppression of anti-inflammatory marker IL-10 as a candidate linking OSA to AB pathophysiology, and inflammation as factor linking OSA to AD risk. That decrements in IL-10 were associated with both OSA severity during REM sleep and AB burden suggests that REM sleep-related apnea may be particularly relevant for AD risk. Future studies should utilize OSA treatment to determine if reducing hypoxemia and sleep fragmentation impacts anti-inflammatory cytokines such as IL-10, reduces longitudinal AB accumulation, and delays AD onset.

**Acknowledgements:** American Academy of Sleep Medicine Foundation SRA-1818, NIA K01 AG068353, R01 AG053555, F31 AG074703

## BEHAVIORAL AND LIFESTYLE CORRELATES OF SLEEP IN AN OLDER ADULT POPULATION: RESULTS FROM THE CANADIAN LONGITUDINAL STUDY ON AGING

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**Introduction:** Poor sleep patterns represent an emerging risk factor for mortality and chronic disease outcomes and tend to be associated with behavioral factors such as diet, smoking and physical activity. While these associations are widely acknowledged in the available evidence, it is important to quantify the direction and magnitude of these associations, in order to inform clinical and public health guidelines and improve prediction of health outcomes. The objective of this study was to explore the

associations between sleep patterns and a range of behavioral and neighborhood correlates.

**Methods:** We used cross-sectional baseline data from the Canadian Longitudinal Study on Aging (CLSA), a survey of 30,097 community-dwelling adults, aged 45–85 years at baseline. Self-reported sleep measures included sleep duration, sleep dissatisfaction (vs satisfied/neutral), and sleep disturbances (difficulty initiating or maintaining sleep). A range of behavioral and neighborhood factors were explored, including tobacco and alcohol use, physical activity, perceived neighborhood safety, nutrition, condition/repair of living environment, and social media usage. The factors of interest were selected based on a review of the existing literature. Univariate logistic regression analyses were used to estimate odds ratios (ORs) for the associations between each individual behavioral/lifestyle factor and a binary outcome of dissatisfied sleep vs neutral/satisfied sleep. Multiple variable logistic regression was performed with all behavioral factors included. Each model was additionally adjusted for individual level sociodemographic variables including age, sex, BMI, education, household income, marital status, and rural/urban location.

**Results:** In the primary unadjusted models, we observed that daily and former smokers had higher odds of dissatisfied sleep than non-smokers (daily smoker OR: 1.28, 95%CI: 1.15 – 1.42; former smoker OR: 1.10, 95% CI: 1.04 – 1.16). Frequent alcohol drinkers had a lower OR of dissatisfied sleep compared to non-drinkers (OR: 0.87, 95%CI 0.79 – 0.94). Higher nutritional risk scores (AB-SCREEN II) were associated with higher odds of sleep dissatisfaction than persons with low nutritional risk (OR: 1.62, 95%CI: 1.53 – 1.71). Living in an area perceived to be unsafe was associated with higher odds of experiencing sleep dissatisfaction than living in a perceived safe area (OR: 1.12; 95%CI: 1.03 – 1.22). Individuals who experienced no issues with home repair had lower odds of sleep dissatisfaction than those with home repair issues (OR: 0.70, 95%CI: 0.66 – 0.74). The OR for the association between physical activity and sleep dissatisfaction in our sample was statistically significant, but the OR was close to one (OR: 1.0, 95%CI: 0.99 – 1.0). Results from the fully adjusted analysis will be available at the conference presentation.

**Conclusion:** These findings improve our understanding of how different behavioral and neighborhood factors may be correlated with sleep and provide additional insight into the complex associations between various behavioral and lifestyle factors and self-rated sleep satisfaction in a population-based sample of middle-aged and older adults in Canada.

## CHANGES IN SLEEP DISORDERS IN OLDER ADULTS PRODUCED BY THE COVID-19 PANDEMIC

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**Introduction:** The COVID-19 pandemic has rocked our society to its core. Ageing is associated with alterations in circadian activity rhythms, a tendency toward internal desynchronization and decreased sensitivity to phase-resetting signals, including light and those induced by sleep medications. Insomnia is the most common sleep disorder in later life and affects approximately 20–50% of older adults >65 years. The objective of this study is to analyze changes in sleep disorders in older patients affected by the COVID-19 pandemic.

**Materials and Methods:** consecutive noninstitutionalized individuals aged  $\geq 65$  years of the sleep unit were recruited, 50 patients before a COVID-19 pandemic (BeCOVID) and 50 patients posterior a COVID-19 pandemic (PostCOVID). Clinical history specific for sleep disorders; scores on sleep-questionnaires: Epworth Sleepiness Scale (ESS)  $\geq 8$  meaning mild, moderate or severe sleepiness; Insomnia Severity Index (ISI)  $\geq 15$ , indicating moderate or severe clinical insomnia; psychological tests Beck depression inventory (BDI-II), being non-depressed or mild with  $\leq 19$  points and moderate or severe with 20–63 points; the state-trait anxiety inventory (STAI) was positive above 50th percentile. Polysomnography parameters were made according to the American Academy of Sleep Medicine (AASM). Diagnosis of sleep disorders was made according to

ICSD3 criteria. Statistical analysis: general descriptive statistics, ANOVA, Wilcoxon signed-rank test and Mann-Whitney were performed using SigmaStat.

**Results:** A total of 44/34% BeCOVID/POSTCOVID women and 56/66% men. Chronic disease 46/88% (hypertension 64/70%; mellitus diabetes 24/22%, dyslipidemia 32/52%; heart disease 10/18%, glaucoma 18/8%), psychiatric disease previous 10/8%. Regarding sleep disorders, a significant increase of chronic insomnia 16/46% ( $P = <0.001$ ). No significant difference in other sleep disorders, obstructive sleep apnea 88/92%, rest leg syndrome 20/24%, periodic leg movement (PLM) disorders 48/32%, REM sleep behaviors disorders 8/8%, Circadian rhythms disorders 2/4%. When comparing polysomnography significant difference were observed in changes of phases number ( $P=0.004$ ), no significant changes in others sleep architecture parameters such as sleep latency, REM sleep latency, efficiency, total sleep time, proportion of sleep stages (N1, N2, N3 y REM), wake after sleep onset, arousals index, PLM index or apnea-hypopnea index (AHI) were observed. Moderate or severe clinical insomnia in 42/54%. Significant increase of anxiety state ( $P = 0.008$ ) and trait ( $P = <0.001$ ) and sleepiness ( $P = 0.008$ ). No significant difference in depression ( $P = 0.125$ ).

**Conclusion:** The COVID-19 pandemic has brought us relevant changes in sleep disorders in older people, as a rise in chronic insomnia and generalized anxiety disorder.

#### CHRONOTYPE ADVANCE AS A PREDICTOR OF SUBSEQUENT COGNITIVE FUNCTION AND BRAIN VOLUME REGRESSION: A 4-YEAR LONGITUDINAL COHORT STUDY

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**Introduction:** Maintaining adequate sleep quantity and quality is vital for many aspects of overall health and neurocognitive function in the elderly. Accumulating evidence suggests that there exists a bidirectional link between circadian rhythm deterioration and neurodegeneration. We aimed to investigate the impact of circadian rhythm disruption on structural and functional brain deteriorations in a late adulthood population.

**Materials and Methods:** We analyzed data from 1874 participants (aged 49–80 years, women 50.3%) in the Korean Genome and Epidemiology Study. Midsleep time on free days corrected for sleep debt on workdays (MSFsc) at baseline was adopted as a marker of chronotype in late adulthood and used to categorize the participants into three groups. "Advancers" were defined as those falling in the bottom third of MSFsc (earlier than 2:15 am), while "delayers" were defined as those falling in the top third (later than 3:30 am). The relationships of chronotype with longitudinal change in cognitive function and gray matter volume (GMV) over four years were investigated.

**Results:** The average MSFsc at baseline was 2:45 am, and the earlier chronotype was linearly associated with lower right entorhinal GMV ( $p = 0.001$ ) in addition to the poor visual memory function test scores ( $p < 0.001$ ). Compared to baseline, follow-up GMVs were all reduced with advancing age regardless of brain lobes. In longitudinal analysis, the earlier chronotype was significantly associated with more faster atrophy in the temporal lobe ( $p = 0.018$ ). Advancers exhibited significantly decreased scores in the digit-symbol coding test and categorical verbal fluency test. Compared to the practice effect in the delayer group, there was no definite change in verbal memory test score in the advancer group.

**Conclusion:** Given the long preclinical period, it is imperative to find a clinically useful indicator for screening high-risk groups in the preclinical stages of neurodegenerative disorders. We suggest that chronotype in midlife measured using a questionnaire can be a practical and valuable indicator for selecting a target group that should be closely monitored for

further neurodegenerative disorder development.

**Acknowledgments:** This study was supported by grants from the Korean Centers for Disease Control and Prevention, Korean Ministry of Health and Welfare (Grant 2011-E71004-00, 2012-E71005-00, 2013-E71005-00, 2014-E71003-00, 2015-P71001-00, 2016-E71003-00, 2017-E71001-00, 2018-E7101-00, 2011-E71004-00, 2012-E71005-00, 2013-E71005-00, 2014-E71003-00, 2015-P71001-00, 2016-E71003-00, 2017-E71001-00, 2018-E7101-00 to C Shin), the Korea Health Technology R & D Project through the Korea Health Industry Development Institute, funded by Korean Ministry of Health & Welfare (HI19C1065 to H J Kim), and the National Research Foundation of Korea through the Ministry of Science, Information and Communication Technologies/Ministry of Education & Future Planning (NRF-2019M3C1B8090803 and 2020R1A2C2013216 to H W Lee).

#### EFFECTS OF INTERACTION BETWEEN SEX AND APOE GENOTYPE ON SLEEP-STAGE SPECIFIC EXPRESSION OF OBSTRUCTIVE SLEEP APNEA AND SLEEP-DEPENDENT MEMORY

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**Introduction:** Alzheimer's disease (AD) is a world-wide healthcare crisis among older adults resulting in cognitive decline and dementia. It is therefore imperative to understand how AD risk factors interact to impact cognition in healthy older adults at risk for AD. Sex and apolipoprotein E (APOE) genotype are among the most impactful risk factors for developing late onset AD. Sleep disturbance, such as the presence of obstructive sleep apnea (OSA) is also impacted by sex and APOE genotype, and is a risk factor for developing AD. However, it remains unclear how these risk factors interact and how they may disrupt episodic memory, a cognitive ability particularly sensitive to AD. Here, we tested the hypothesis that sex and APOE genotype ( $\epsilon 4$  carrier/non-carrier) would interact to impact the expression of OSA events across non-rapid eye movement (NREM) and REM sleep stages and sleep-dependent consolidation of episodic memory.

**Materials and Methods:** Fifty-eight cognitively unimpaired, older adults (mean $\pm$ SD; 61.4 $\pm$ 6.3 years, 38 female, 15 APOE  $\epsilon 4$  carriers) underwent in-laboratory polysomnography during their habitual time. Participants encoded 88 word-pairs in the evening prior to sleep. Encoding was followed by an immediate recall test, and a delayed recall test occurred in the morning following sleep. Memory consolidation was computed by comparing performance accuracy across testing sessions (post-sleep – pre-sleep memory accuracy). Sleep architecture (TST: total sleep time, time and percent spent in each sleep stage N1, N2, N3 and REM sleep) and OSA severity (apnea-hypopnea index, AHI, measured during REM and NREM sleep stages) were quantified. Univariate ANOVA and post hoc testing was implemented to examine interacting effects of sex and APOE genotype on OSA expression and sleep-dependent memory.

**Results:** A significant sex $\times$ APOE genotype interaction predicted sleep-dependent memory consolidation ( $p=0.04$ ). Post hoc analysis revealed a trend among APOE  $\epsilon 4$  carriers, such that sleep-dependent memory consolidation was reduced in men as compared to women ( $p=0.06$ ). Associations between OSA severity and sleep-dependent memory consolidation also differed by sex and APOE genotype. Specifically, among APOE  $\epsilon 4$  non-carriers, AHI during REM sleep was negatively associated with sleep-dependent memory ( $r=-0.44$ ,  $p=0.02$ ) in women but not men ( $r=0.25$ ,  $p=0.39$ ). Further, these two correlation coefficients were significantly different ( $z$ -score=  $-1.98$ ,  $p=.05$ ). Among APOE  $\epsilon 4$  carriers, REM sleep duration was negatively associated with sleep-dependent memory in men ( $r=-0.89$ ,  $p=0.04$ ) but not women ( $r=-0.51$ ,  $p=0.16$ ). However, these two correlations coefficients were not significantly different ( $z$ -score= $-1.05$ ,  $p=0.29$ )

**Conclusions:** These findings indicate that sex and *APOE* genotype interact to impact OSA expression and sleep-dependent episodic memory consolidation, and that the relationship between OSA expression during REM sleep and memory depends on both sex and *APOE* genotype. Taken together, the findings suggest that both sex and *APOE* genotype should be considered when examining relationships between sleep and cognitive impairment in older adults.

#### ***APOE-ε4* GENOTYPE AND SLEEP DISTURBANCE IN INDIVIDUALS WITH AND WITHOUT DEMENTIA**

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**Introduction:** Apolipoprotein E Epsilon 4 (*APOE-ε4*) carrier status is an established risk factor for Alzheimer's Disease (AD) Dementia. It has also been linked with sleep disturbance in healthy older adults, increased insomnia risk and sleep disordered breathing in adults and children. This association may be driven by the effect of *APOE-ε4* on AD pathological change, itself associated with sleep abnormalities. However, here we test the hypothesis that *APOE-ε4* exerts an independent effect on sleep disturbance separate from its effects on AD pathology through evaluation of post-mortem histopathological findings in a cohort with and without cognitive impairment which underwent extensive pre-mortem clinical assessment.

**Materials and Methods:** This retrospective cohort study utilised UK Brain Banks Network data. Eligible subjects were aged over 50 and underwent pre-mortem neuropsychological assessments comprising the Neuropsychiatry Inventory measure of sleep disturbance (NPI-K), neurocognitive testing and functional cognitive status assessment through use of the Clinical Dementia Rating scale within 12 months of post-mortem. Neuropathological status was determined by full pathological evaluation of Thal phase, Braak tangle stage and CERAD scores (measures of Aβ plaque distribution, tangle distribution and neuritic plaque density respectively). Participants with significant intracerebral pathology or pathological features of non-AD dementia were excluded.

Multivariate linear regression was performed with NPIK Global Score consisting of the NPIK frequency score multiplied by severity score as the dependent variable and *APOE-ε4* heterozygosity and homozygosity as independent variables. Covariates included age, gender, *APOE-ε2* status, NPI measures reflecting depression and anxiety and the NIA-AA ABC Score reflecting AD neuropathology. Further models stratified by ABC score and functional cognitive status were also produced.

**Results:** 728 records were identified with 202 participants included in final analysis, mean (SD) age 84.0 (9.2) and MMSE 14.0 (11.8). Mean sleep disturbance scores were highest in those homozygous for *APOE-ε4* (n=11), 4.55 (5.4), intermediate in those heterozygous for *APOE-ε4* (n=95), 2.03 (4.0) and lowest in non *APOE-ε4* carriers (n=96), 1.36 (3.3). Full multivariate regression controlling for pathological status, age, gender, depression, anxiety and CDR-SOB status, revealed *APOE-ε4* homozygosity as independently associated with sleep disturbance (Est 2.53, p=0.034) and *APOE-ε4* heterozygosity similarly independently associated in individuals without significant cognitive impairment (Est 1.21, p=0.048).

**Conclusions:** These findings lend weight to the hypothesis that *APOE-ε4* genotype confers effects on sleep independent from those arising directly from intracerebral AD pathological change. There are a range of plausible mechanisms by which this effect could be exerted, further systematic testing of which would enhance understanding of sleep disturbance pathways and potentially provide treatment targets for this distressing symptom also linked to AD progression.

**Acknowledgements:** David Telling Charitable Trust

#### **INFANT SLEEP AS A MARKER OF NEURODEVELOPMENT**

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**Introduction:** The brain develops rapidly during infancy and early

childhood and sleep plays a crucial role in this development. Sleep patterns, as viewed on the EEG, evolve as a consequence of brain maturation and quantitative features of sleep may represent biomarkers of neurodevelopment. In this study we analysed macrostructural, sleep spindle and quantitative features (qEEG) of the sleep EEGs of infants at 4-months of age to identify features that are associated with neurodevelopment at 18 months.

**Materials and Methods:** Neonates born at term were recruited at Cork University Maternity Hospital, Ireland. EEGs were recorded during a nap at 4-months. Sleep was staged according to AASM criteria and spindles were identified manually. Macrostructural features analysed included: latencies to sleep and to REM, duration of 1st cycle sleep stages. Sleep spindle features analysed included: number, density, mean frequency, Brain Symmetry Index (spindles only), synchrony and spectral power. qEEG features analysed included: range-EEG, spectral power, interhemispherical coherence and Brain Symmetry Index. qEEG results were compartmentalised into sleep stages and frequency ranges. At 18 months of age, the participants had a Griffiths-III neurodevelopmental assessment evaluating the following domains: A – Foundations of Learning, B – Language and communication; C – Eye and Hand Coordination; D – Personal-Social-Emotional and, E – Gross Motor; a general developmental score (GD) was also calculated from the subscales. Relationships between sleep features and neurodevelopmental outcome were assessed using Spearman's correlation coefficient and the Partial Rank correlation coefficient (adjusting for postnatal age of both EEG and Griffiths-III assessments, gestational age, and sex).

**Results:** A recorded sleep at 4 months with accompanying clinically normal EEG and a neurodevelopmental assessment at 18 months was available for 92 infants. The mean (SD) postnatal age was 19.6 (1.3) weeks at the sleep recording and 18.5 (0.4) months at neurodevelopmental assessment. Only infants who had a full first sleep cycle recorded (n=69) were included in sleep macrostructure and qEEG analysis. After adjusting for postnatal age of both EEG and Griffiths-III assessments, gestational age, and sex, sleep macrostructure parameters showed no association with neurodevelopmental outcomes at 18 months. Positive statistically significant correlations were observed between upper and lower range-EEG margins (similar to amplitude-integrated EEG) and, B subscale (r=[0.25-0.26]); positive significant correlations were found between EEG spectral power particularly between low-frequency delta and subscales: B, D, E and GD (r=[0.24-0.33]); interhemispherical coherence in beta and gamma frequencies during N2 sleep was positively correlated with subscale A and gamma with GD (r=[0.27,0.30]) whilst coherence in delta frequencies during REM showed negative correlation with subscale D (r=[-0.39,-0.30]). Sleep spindles synchrony was negatively correlated with subscales C, D, and E and GD (r=[-0.33,-0.24]); spindle duration was also negatively correlated with D and E subscales (r=[-0.32,-0.22]).

**Conclusions:** Several sleep features at 4-months age were associated with neurodevelopmental outcomes at 18-months. EEG analysis may be useful as an early biomarker for abnormal development, allowing early intervention. Further analysis should include similar EEG analyses of neurodiverse patient groups.

**Acknowledgements:** To all participating families and the BabySMART team at the INFANT Research Centre.

#### **INSOMNIA DISORDER PREDICTS SELF-REPORTED COGNITIVE DECLINE IN MIDDLE-AGED AND OLDER ADULTS**

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**Introduction:** Sleep complaints increase with aging and are associated with cognitive impairment in older adults. The presence of self-reported 'subjective' cognitive decline (SCD) (e.g., a complaint of decreased memory) confers an elevated risk of progression to mild cognitive impairment or dementia (~40.7% over 4-years). Such conversion may occur progressively over 10-15 years, depending on numerous factors, including sleep quality. However, no study to date has evaluated the association between insomnia disorder and SCD in older adults. The aim of this study is to examine the longitudinal risk of self-reported cognitive decline in middle-aged and older adults with probable insomnia disorder (PID), insomnia symptoms only (ISO) or no insomnia symptoms (NIS).

**Methods:** A total of 26,363 participants, aged 45 years and older, completed baseline and 3-year follow-up assessments from the Canadian Longitudinal Study on Aging (CLSA), which included self-reported evaluations of sleep and memory. The CLSA is a national, 20-year, prospective cohort study that collects information on the biological, medical, cognitive, psychological, social, lifestyle, and economic aspects of middle-aged and older adults. Participants were categorized as having PID, ISO, or NIS using an eight-question instrument assessing participants' sleep. The questions were selected to reflect standardized DSM-V diagnostic criteria for insomnia disorder. Participants were further grouped based on the progression from baseline to follow-up, either 1) the progression from NIS to ISO vs. NIS to PID, or 2) the worsening (i.e., NIS to ISO, ISO to PID, NIS to PID) vs. improvement (i.e., PID to ISO, ISO to NIS, PID to NIS) of their sleep status. The risk of self-reported memory worsening at follow-up was assessed for each group via the questions: "Do you feel like your memory is becoming worse?" and "Has a doctor ever told you that you have a memory problem?", using logistic regression models, adjusted for lifestyle and clinical factors.

**Results:** Participants who had NIS and developed PID at follow-up (NIS to PID) showed greater risk (OR 1.95; 95% CI 1.49 – 2.55;  $P < 0.0001$ ) of self-reported memory worsening compared to those who developed ISO (OR 1.24; 95% CI 1.14 – 1.35;  $P < 0.0001$ ) or remained NIS, after adjusting for lifestyle and medical outcomes. Participants whose sleep worsened from baseline to follow-up displayed greater risk (OR 1.28; 95% CI 1.18 – 1.39;  $P < 0.0001$ ) of self-reported memory worsening at follow-up compared to those who improved their sleep or remained without insomnia symptoms, after adjusting for lifestyle and medical variables. There were no significant associations between the development of PID or worsening sleep and objective cognitive performance on neuropsychological tests across the entire sample, however a significant negative association was observed in men only ( $P < 0.01$ ).

**Conclusion:** These findings demonstrate an increased risk of subjective memory decline in middle-aged and older adults with insomnia disorder, compared to adults with insomnia symptoms alone or without any sleep complaints. Subjective memory complaints are often a precursor to mild cognitive impairment (MCI) and dementia, and our findings suggest that insomnia disorder contributes to the early stages of cognitive decline.

#### MAP2K5 DEFICIENT MICE MANIFEST PHENOTYPES AND PATHOLOGICAL CHANGES OF DOPAMINE DEFICIENCY IN THE CENTRAL NERVOUS SYSTEM

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**Introduction:** MAP2K5, a member of MAPK family, is associated with central nervous system disorders. However, neural functional of Map2k5 from animal models were not well examined so far.

**Materials and Methods:** Here, we established a Map2k5 targeted knockout mouse model to investigate the behavior phenotypes and its underlying molecular mechanism.

**Results:** Our results showed that female Map2k5 mutant mice manifested decreased circadian-dependent ambulatory locomotion, coordination and

fatigue. Male Map2k5 mutant mice displayed impairment in open field exploration and prepulse inhibition of acoustic startle response when compared to wild type controls. Furthermore, Map2k5 mutant mice showed a decreased dopaminergic cells survival and tyrosine hydroxylase levels in nigrostriatal pathway, indicating a crucial role of MAP2K5 in regulating dopamine system in the central nervous system.

**Conclusions:** In conclusion, this is the first study demonstrating that Map2k5 mutant mice displayed phenotypes by disturbing the dopamine system in the central nervous system, implicating Map2k5 mutant mouse as a promising model for many dopamine related disorders.

**Acknowledgements:** We thank Minghan Tong (Shanghai Institute of Biochemistry and Cell Biology, Chinese Academy of Sciences) for technical assistance and manuscript modifications. We thank GemPharmmatech Co., Ltd. for technical assistance and cooperation.

#### MRI MEASUREMENT OF BRAIN IRON CONTENT IN OBSTRUCTIVE SLEEP APNEA: THE HYPNOLAUS STUDY

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**Introduction:** There is cumulating evidence for the association between obstructive sleep apnea (OSA) and cognitive decline. Given the role of brain iron dyshomeostasis in neurodegenerative diseases, we sought to investigate the impact of OSA on brain tissue iron. Building on the statistical power of large-scale data from a community-dwelling population, we test for an association between objective polysomnographic features of OSA and magnetic resonance imaging (MRI)-derived brain iron content.

**Materials and Methods:** We studied participants of the CoLausPsyCoLaus cohort who underwent polysomnography (HypnoLaus) and brain MRI (BrainLaus). We used MRI metrics of the effective transverse relaxation rate ( $R2^*$ ) to infer brain tissue iron content in 34 regions of interest. The sample was categorized into four groups according to the apnea-hypopnea index (AHI): no OSA (AHI < 5/h), mild OSA (AHI 5.0-14.9/h), moderate OSA (AHI 15.0-29.9/h), and severe OSA (AHI  $\geq 30$ /h). First, we tested for differences in  $R2^*$  between OSA groups using analysis of covariance (ANCOVA). Second, linear regression models estimated the associations between  $R2^*$  and sleep parameters. All models were adjusted for age, sex, time interval between polysomnography and MRI, cardiovascular risk factors (body mass index, diabetes, dyslipidemia, hypertension, and smoking), continuous positive airway pressure therapy, and chronic obstructive pulmonary disease. To account for multiple testing, we set the level of statistical significance at a p-value < 0.005.

**Results:** The final sample included 773 participants (mean age  $55.9 \pm 10.3$  years, age range 40-84 years, 50.5% females). The number of participants with mild, moderate, and severe OSA was 286 (37.0%), 164 (21.2%), and 82 (10.6%), respectively. Participants with severe OSA had higher  $R2^*$  in the middle temporal gyrus ( $F_{3,760} = 4.35$ ,  $p < 0.001$ ), angular gyrus ( $F_{3,760} = 4.65$ ,  $p = 0.003$ ), and supramarginal gyrus ( $F_{3,760} = 4.35$ ,  $p = 0.004$ ) compared to the other groups, consistent with higher iron levels. AHI and all hypoxemia measures (oxygen desaturation index, sleep time with oxygen saturation < 90%, and hypoxic load) were independently associated with  $R2^*$  in individual cortical areas of the temporal, parietal, and occipital lobes. Total sleep time, sleep stages (N1, N2, N3, and REM sleep), sleep efficiency, wake after sleep onset, and arousal index showed no association with  $R2^*$  across the brain.

**Conclusions:** This study provided evidence of increased brain iron content in obstructive sleep apnea, which appeared to be primarily related to hypoxemic mechanisms. The observed increase in iron content could reflect undergoing neuropathological processes. Further studies are needed to examine the relationship between brain iron content and cognitive decline in OSA.

**Acknowledgements:** Swiss National Science Foundation, University of Lausanne, GlaxoSmithKline, Leenaards Foundation, Lancardis Foundation, Swiss Lung Association, Roger De Spoelberch Foundation, and Partridge Foundation.

## OBSTRUCTIVE SLEEP APNEA AND COGNITIVE DECLINE IN THE ELDERLY: THE HYPNOLAUS STUDY

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**Introduction:** Obstructive sleep apnea (OSA) has been associated with cognitive impairment in middle age. However, the link between OSA and cognitive decline is still controversial in the elderly population. We tested the hypothesis about an association between OSA features and cognitive decline in the community-dwelling elderly population.

**Materials and Methods:** We studied non-demented participants aged  $\geq 65$  years from the CoLausPsyCoLaus cohort who underwent polysomnography and cognitive assessment at baseline, followed by a second cognitive assessment 5.2-year apart. OSA was defined as an apnea-hypopnea index (AHI)  $\geq 15$ /h. The neuropsychological test battery included Mini-mental state examination (MMSE), Free and cued selective reminding test (FCSRT), Stroop test, verbal fluency test, DO-40 naming test, CERAD constructional praxis test, and clinical dementia rating (CDR). The primary outcome was the cognitive change over the follow-up ( $\Delta \text{score} = \text{score}_{\text{follow-up}} - \text{score}_{\text{baseline}}$ ). The secondary outcome was the presence of a significant cognitive decline defined as a worsening  $> 1.0$  SD above the mean change. Robust regression estimated associations between cognitive changes and OSA parameters. Logistic regression estimated associations between incidence of cognitive decline and OSA parameters. The moderator effect of age, sex, and apolipoprotein E4 (ApoE4) was also examined. Analyses were adjusted for age, sex, education, ApoE4, cardiovascular risk factors, alcohol, Epworth sleepiness scale, depression, psychotropic drugs, continuous airway positive pressure (CPAP) therapy, chronic obstructive pulmonary disease, and baseline cognitive score. The significance threshold was set at a  $p < 0.01$ .

**Results:** The final sample included 340 participants (mean age  $71.0 \pm 4.1$  years, 58.0% females). In the whole sample, there was no significant association between OSA status and cognition. However, mean oxygen saturation (meanSpO<sub>2</sub>; standardized  $\beta = 0.23$ ,  $p < 0.001$ ) and sleep time with SpO<sub>2</sub>  $< 90\%$  (T90;  $\beta = -0.19$ ,  $p < 0.001$ ) were associated with  $\Delta$ FCSRT delayed free recall. MeanSpO<sub>2</sub> (OR for +1% = 0.70,  $p < 0.007$ ) and T90 (OR for +1% = 1.04,  $p < 0.001$ ) were also associated with decline in FCSRT delayed free recall. After investigation of moderator effects, OSA was associated with  $\Delta$ Stroop test 1 and 2 in participants aged  $\geq 74$  years ( $\beta = 0.86$ ,  $p = 0.007$ ;  $\beta = 1.02$ ,  $p = 0.005$ ), T90 was associated with  $\Delta$ FCSRT delayed total recall in men ( $\beta = -0.25$ ,  $p = 0.009$ ), and T90 was associated with FCSRT delayed free recall in ApoE4 non-carriers ( $\beta = -0.30$ ,  $p < 0.001$ ). In addition, T90 was associated with decline in FCSRT delayed free recall in men (OR = 3.34,  $p = 0.002$ ), meanSpO<sub>2</sub> was associated with decline in CDR in men (OR = 0.40,  $p = 0.008$ ), and meanSpO<sub>2</sub> and T90 were associated with decline in FCSRT delayed free recall in ApoE4 non-carriers (OR = 0.40,  $p = 0.001$ ; OR = 2.26,  $p < 0.001$ ).

**Conclusions:** The presence of OSA was associated with worsening of the Stroop test 1 and 2 (processing speed) only in older participants ( $\geq 74$  years old). Markers of nocturnal hypoxemia (low meanSpO<sub>2</sub> and T90) were associated with worsening of the FCSRT (memory) and CDR in the whole sample, men and/or ApoE4 non-carriers.

**Acknowledgments:** Swiss National Science Foundation, University of Lausanne, GlaxoSmithKline, Leenaards Foundation, Lancardis Foundation, Swiss Lung Association.

## PREDICTIVE VALUE OF THE EPWORTH SLEEPINESS SCALE, THE PITTSBURGH SLEEP QUALITY INDEX AND THE BERLIN QUESTIONNAIRE IN ADULT AND ELDERLY PATIENTS WITH OBSTRUCTIVE SLEEP APNEA SYNDROME: A RETROSPECTIVE OBSERVATIONAL STUDY.

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**Introduction:** Obstructive sleep apnea syndrome is a disease caused by a complete or partial obstruction of the upper airways which occurs during sleep and which gives rise, respectively, to phenomena of apnea or hypoapnea. Although epidemiological studies have shown a high prevalence of the disorder, obstructive sleep apnea syndrome remains under-diagnosed. Various screening questionnaires have been developed, with the aim of identifying as many patients as possible at risk with low-cost procedures. Considering the high costs, the limited availability at a territorial level and the long waiting lists of polysomnography, the gold standard in the diagnosis of OSAS, this would have the advantage of directing existing resources towards a population selected on the basis of tests (in addition to and guidelines), reducing the number of negative tests as much as possible.

**The aim of the study:** To evaluate the predictive value of the Epworth Sleepiness Scale (ESS), the Pittsburgh Sleep Quality Index (PSQI) and the Berlin Questionnaire (BQ) in adult ( $< 65$ ) and elderly ( $> 65$ ) patients with Obstructive Sleep Apnea (OSAS), comparing the results of the individual tests with the AHI values detected by polygraphy.

**Materials and methods:** The data were collected on a sample of 1160 patients who came to visit the clinic from 2012 to 2019. Paper medical records were used from which the following data were extrapolated: age; sex; results from the ESS, the PSQI and the BQ; polygraphy report (AHI, ODI). Only 961 people out of the total sample analyzed were eligible because they met the minimum requirements for the study, the remaining 199 were excluded. Exclusion criteria: lack of informed consent, absence of tests, absence of AHI and ODI parameters.

**Results:** In patients under 65, setting the AHI cut-off to 5, the Epworth Sleepiness Scale (ESS) was found to be the most sensitive (61.49%) and the most specific (73.53%).

In patients over 65, always setting the AHI cut-off to 5, the Pittsburgh Sleep Quality Index (PSQI) was found to be the most sensitive (68.37%) while as regards specificity it was found to be similar (75%) in the ESS and PSQI. Finally, the Berlin questionnaire (BQ) was found to be the least sensitive (60.61% - 59.69%) and the least specific (61.76% - 58.33%) in both groups. False negatives detected in screening tests decrease as the OSA grade increases and, in parallel, the number of true positives increases as the AHI index increases.

**Discussion and Conclusions:** In the under 65s the Epworth Sleepiness Scale (ESS) is the most sensitive (61.49%) and most specific (73.53%) test, while in the over 65s the Pittsburgh Sleep Quality Index (PSQI) is the most sensitive (68.37%) and the most specific (75%) together with the ESS, which showed a similar specificity. Given the sensitivity and specificity values detected, none of the three tests were found to be accurate enough to be used alone.

However, by using all three tests in the screening phase, we are able to do a good stratification of patients with high and low OSA risk.

## SELF-REPORTED SLEEP DISTURBANCES ATTRIBUTED TO LIGHT, TEMPERATURE, AND NOISE DECLINE LINEARLY WITH AGE: A BIG-DATA ANALYSIS OF 92,702 USERS

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**Introduction:** Age related changes to sleep and sleep quality are well-characterized. Older adults experience less deep and consolidated sleep, with more frequent awakenings. It remains unclear to what extend potential sleep disturbing factors impact sleep across age in the general population. The purpose of the present data analysis was to examine the relations between age, gender, and self-reported awakenings attributed to sleep disruptors in general and to specific ambient sleep disruptive factors (light, temperature, and noise).

**Materials and Methods:** The data set contained the responses of 92,702 individuals to the questionnaires included in the SleepScore mobile application (SleepScore Labs, Carlsbad, US), collected between 2017-10-11 and 2021-07-29. Age, gender, and sleep disruptive factors were included in the data set. We utilized logistic regression models to analyze how the likelihood of reporting these disruptors was related to age and gender. Disruptors entered into the models included: 1) the occurrence of any

disruptor; 2) the occurrence of any ambient disruptor; 3–5) the occurrence of light, temperature and noise as disruptive factors. P values of  $< 0.000001$  are reported.

**Results:** Overall, females were more likely to attribute at least one sleep disruptive factor to regular awakenings ( $\beta: 0.85$ ). This likelihood was also higher in older age ( $\beta: 0.03$ ). In contrast with the occurrence of any sleep disruptor, the likelihood of reporting ambient sleep disruptive factors (light, temperature, and noise) declined with age ( $\beta: -0.02$ ) yet remained higher for women ( $\beta: 0.50$ ). When running the models for each ambient sleep disruptive factor separately, a similar association was observed for noise ( $\beta$ : sex: 0.46,  $\beta$ : age: -0.02), light ( $\beta$ : sex: 0.43,  $\beta$ : age: -0.02), and temperature. ( $\beta$ : sex: 0.44,  $\beta$ : age: -0.02).

**Conclusions:** Generally, the elderly complain more often of sleep disturbances, and an increased sensitivity to sleep disruptive factors might contribute to this rise in age-related sleep issues. This data analysis confirmed an increase in reported sleep disturbing factors with age. Interestingly, we observed a reduction in the occurrence of ambient sleep disruptors including light, temperature, and noise. This decline with age may be attributed to the decreased sensitivity of the human senses due to aging coupled with the emergence of other physiological, psychological, social, or health-related factors that may negatively impact sleep and sleep comfort. Based on these results, improvement strategies that focus on optimizing the sleeping environment may be more effective in younger populations. Future work should address the impact of other sleep disruptors beyond ambient sleep disruptive factors and examine objective sleep parameters and sleep disturbances.

#### SLEEP ARCHITECTURE AND HIPPOCAMPAL SUBFIELDS IN HEALTHY OLDER ADULTS

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**Introduction:** Scalp electroencephalogram recordings of spindles and slow-waves during N3 offers an indirect route to studying intracranial events, such as hippocampal-thalamic-cortical interactions, and their roles in memory and cognition. We investigated whether sizes of different hippocampal subfields as measured by MRI, are associated with sleep stage durations or spindle densities in N3.

**Materials and Methods:** 30 healthy elderly (65–79 years, 19 females) underwent T1 and T2 structural MRI scans, with parameters optimised for whole hippocampal imaging and subfield segmentation, and a full night of polysomnography. Hippocampal subfields CA1, CA2, CA3, dentate gyrus (DG) and adjacent temporal lobe regions (subiculum and entorhinal cortex, EC) were segmented using an automated procedure. PSG was staged manually. An automated filtering and thresholding algorithm was used to identify sleep spindle events during N3.

**Results:** N3 duration in minutes was negatively correlated with CA2 ( $r = -0.44$ ,  $p = 0.014$ ), DG ( $r = 0.063$ ,  $p < 0.001$ ) and EC volumes ( $r = -0.42$ ,  $p = 0.020$ ). No other relationships were found between the subfields (CA1–3, EC and subiculum) and sleep stage durations (N2, N3, REM). We ran a multiple stepwise linear regression model to predict |N3 duration, with body weight and CA2, DG, and EC volumes. The end equation  $F(1, 28) = 6.81$ ,  $p = 0.014$ ,  $R^2 = 0.17$  included CA2 volume, but not body weight, EC, or DG. Average slow wave sleep duration reduced by 2.8 minutes with each  $\text{mm}^3$  decrease in CA2 volume.

EEG data quality for two participants did not allow spindle detection (n spindle analyses = 28). We found that N3 spindle density (n spindles per minute) was positively correlated with volumes of CA2 ( $r = 0.52$ ,  $p = 0.004$ ) and subiculum ( $r = 0.46$ ,  $p = 0.014$ ). A stepwise linear regression was performed as above but to predict spindle density from subfield

volumetrics. The end equation included ( $F(1, 26) = 9.8$ ,  $p = 0.004$ ,  $R^2 = 0.25$ ) CA2 volume only. Spindle density increased by 0.17 spindles per minute with each  $\text{mm}^3$  increased in CA2 volume. Aforementioned findings were significant at  $\alpha = 0.05$  level following false discovery rate adjustment. It is possible intercorrelations between subfield volumes affected the end results of the linear regression models.

**Conclusions:** Larger subiculum and CA2 volumes are associated with increased spindle density, but only larger CA2 volume predicts shorter N3 duration. This may point to distinct roles of CA2 and subiculum in generating sleep spindles. Subiculum is the major output region of the hippocampus and functional hippocampal-cortical connectivity increases in humans during non-REM sleep. The role of CA2 is less clear. In animals, CA2 activity is associated with hippocampal ripples and memory replay during wake and sleep. These findings shed light on potentially dissociable roles of individual subfields in sleep and memory.

**Acknowledgements:** BRACE Bristol, The Wellcome Trust and the David Telling Charitable Trust for funding this study

#### SLEEP ARCHITECTURE DEVELOPMENT IN BLIND AND SIGHTED CHILDREN

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**Introduction:** The sleeping brain has been investigated during most of the twentieth century. However, its underlying mechanisms remain mostly unclear, such as plastic changes in the absence of vision. It is still unclear whether visual deprivation affects sleep only through circadian desynchronization or through a reorganization of sleep-related structures and how this possible reorganization evolves with age. The presence of circadian disorders in blind children is rare in clinical practice, differently from adults, but the development of sleep architecture in this population is a poorly investigated issue. Starting to explore the differences between blind and sighted children, we investigated their nap macro- and microstructure.

**Materials and Methods:** The population comprises 45 blind/severely visually impaired and 58 sighted children aged 6 months to 6 years subdivided into two age-bins [0–3] and [3–6] years. Naps were recorded using 21 electrodes video-EEG and extracerebral polygraphy, including breath, heart rate, and electromyography. All traces were analyzed to evaluate macro-structure, e.g., sleep statistics, spectrograms (focusing on sigma [11–16] Hz and delta [0–4.75] Hz bands), and sleep micro-structure (considering sleep spindles and slow-waves).

**Results:** About sleep macrostructure, the percentage of N3 on total sleep time (TST) was higher in sighted children considering that the TST is similar in the two groups. REM sleep was higher in young blind than sighted children. However, delta activity showed only a reduction with age in N1 and N2 stages. Sigma activity was stronger in sighted children during NREM2 and increased with age in the N3 sleep stage. About sleep microstructure, fast spindles were denser in young sighted than in blind peers, and only in the sighted children decreased with age. Fast spindles were denser than slow spindles. In all age-bins for the sighted children, while only in the old age-bin for the blind group. Group, frequency band, and age-bin differences were also found in spindle duration and amplitude. N2 slow-waves, related to K-complexes, showed a main effect of group and age-bin in amplitude and morphologic features (downslope and upslope) but not in density. N3 slow waves showed an age-bin main effect in amplitude and a group main effect in morphology.

**Conclusions:** These results show notable differences in the development of sleep architecture between blind and sighted children, probably related to sleep stability and cognitive skills and involving different maturation and synaptic pruning processes.

**Acknowledgements:** This research was partially supported by the European Research Council (PI Monica Gori; Grant agreement No. 948349).

### SLEEP BODY POSITION CORRELATES WITH COGNITIVE PERFORMANCE IN MIDDLE AGE OBSTRUCTIVE SLEEP APNEA SUBJECTS.

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**Introduction:** The association between sleep disturbances, mainly obstructive sleep apnea (OSA), cognition and neurodegeneration may be bidirectional. Sleep disturbances may alternatively cause or result from neurodegenerative processes in the brain. The characterization of sleep with cognitive performance is essential in understanding the potential neurobiological mechanisms that underlie the connection between sleep disruption and neurodegenerative manifestations and progression.

**Objective:** We explore the inter-relationships between body position during sleep, that can affect cerebral glymphatic system transport and cognitive status.

**Methods:** All consecutive subjects greater than 18-years old attending our Sleep laboratory between June 1, 2021 to January 31, 2022 were included. We excluded patients with unreadable or incomplete polysomnographic studies. All cases were evaluated according to AASM guidelines together with a rigid clinical protocol including demographic data, clinical history, anthropometric measures, previous diagnosis of OSA, snoring, sleep quality measures, and reporting of different sleep body position (supine, prone, right, and left side) together with a screening cognitive evaluation assessed by the Self-Administered Gerocognitive Exam (SAGE) to detect early signs of cognitive impairment. SAGE score was used as continuous and categorical variable [18–22, normal cognition; 15–17, mild cognitive impairment (MILD); below 14, dementia]. We used a generalized linear model to measure the degree of association between duration of sleep spent in a different body position and SAGE scoring, controlling for confounding variables [age, body mass index, apnea-hypopnea index (AHI), oxygen desaturation index (ODI) as measures of OSA severity].

**Results:** Of 157 consecutive cases, 152 subjects (91 men; mean age±SD: 66.5±13.0 years) were included. Seventeen (11.2%) subjects were normal, 47 (30.9%) have mild, 47 (30.9%) moderate, and 41 (27.0%) of them had severe OSA. We did not find any correlation between anthropometric and demographic variables, OSA severity and sleep quality with SAGE scoring (all  $p>0.05$ ). SAGE scores were only correlated with minutes spent in right lateral ( $r=0.270$ ,  $p=0.001$ ) but not in prone ( $r=0.127$ ;  $p=0.118$ ) or left lateral sleep posture ( $r=0.015$ ;  $p=0.856$ ) and inversely correlated with time in supine sleep one ( $r=-0.233$ ;  $p=0.004$ ). After adjusting for confounding variables in the GLM model, SAGE scoring remained significantly correlated only with time in supine sleep posture ( $F=4.131$   $p=0.018$ ) while all other sleep positions were not more significant. Subjects with normal cognition usually spent significantly less time (hh:mm) in supine position when compared with dementia patients (-01:02±00:23;  $p=0.023$ ) and with MILD patients (-01:11±00:36;  $p=0.050$ ). Other sleep positions apparently did not show any significant effect on SAGE scoring punctuations (all  $p>0.05$ ).

**Conclusion:** Our preliminary observations suggest that taking supine position for longer time during sleep is negatively correlated with cognitive performance in middle aged subjects. This effect was independent by OSA severity, sleep quality, demographic data, clinical history, and anthropometric measures. Our findings warrant further investigation, particularly in light of the recent evidence suggesting that sleep body position may have an active role in the brain's ability to optimize the clearance of metabolic leftovers and interstitial solutes.

### SLEEP FRAGMENTATION, ASTROCYTE ACTIVATION, AND COGNITIVE IMPAIRMENT IN OLDER ADULTS

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**Introduction:** Alzheimer's Disease (AD) and other dementias are a growing public health concern. Emerging evidence suggests that sleep disruption may contribute to the risk of dementia. In model organisms, sleep disruption can lead to astrocyte activation and impaired cognition. However, the extent to which sleep fragmentation is associated with astrocyte activation in older humans is uncertain.

**Objective:** To test the hypothesis that sleep fragmentation is associated with astrocyte activation and downstream cognitive impairment

**Materials and Methods:** We used human single nucleus RNA-seq data to identify marker genes for human activated astrocytes. Then we quantified the expression of these genes from bulk RNA-seq of post-mortem dorso-lateral prefrontal cortex blocks from 1080 community dwelling adults in the Rush Memory and Aging Project- a community-based cohort study of the chronic conditions of aging. Antemortem cognitive function was measured with a battery of 19 neuropsychological tests. In 408 individuals, antemortem sleep fragmentation was quantified from antemortem actigraphy recordings.

**Results:** Individuals with greater antemortem sleep fragmentation had higher composite expression gene characteristic of activated astrocytes (estimate=+0.141 standard units of expression per 1 standard unit of sleep fragmentation, SE=0.050,  $P=0.0053$ ), independent of demographic covariates and co-morbid neurodegenerative neuropathologies. Furthermore, greater expression of genes characteristic of activated astrocytes was associated with worse composite cognition proximate to death (estimate=-0.083 standard units of cognition per 1 standard unit expression, SE=0.035,  $P=0.018$ ), independent of dementia-associated neuropathologies.

**Conclusions:** Astrocyte activation may be a clinically important brain correlate of sleep fragmentation in older adults with and without Alzheimer's disease; further work is needed to determine if interventions targeting sleep fragmentation may prevent adverse impacts on astrocyte biology and cognition.

**Acknowledgements:** We acknowledge the participants in the ROS and MAP cohorts and their families.

### SLEEP MODERATES THE ASSOCIATION BETWEEN STRESS AT WORK AND INCIDENT DEMENTIA: STUDY FROM THE SURVEY OF HEALTH, AGEING AND RETIREMENT IN EUROPE

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**Introduction:** Both psychosocial stress at work and sleep disturbances may predispose impaired cognitive function and dementia in later life. However, whether sleep plays a moderating role for the link between stress at work and subsequent dementia has yet to be investigated.

**Materials and Methods:** Data from the Survey of Health, Ageing and Retirement in Europe were used for the study. A cohort of 7799 dementia-free individuals (aged 71.1±0.2 years) were followed up for a median of 4.1 years for incident dementia. Job demand and control were estimated using questions derived from the Karasek's Job Content Questionnaire. Sleep disturbance was ascertained by a question in the EURO-Depression scale. Cox proportional hazard models adjusted for age, sex, education, cognitive test score, and other potential covariates were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) of dementia in relation to different job strain levels.

**Results:** An interaction between job demand and sleep disturbance regarding the risk of dementia was detected. Data suggested a protective role of high-level job demand for dementia in individuals with sleep disturbance (HR [95%CI]: 0.69 [0.47, 1.00]) compared with low job demand. A four-category job strain model based on the combination of job demand and job control levels suggested that among individuals with sleep disturbance, passive job (low demand, low control) was associated with a higher risk of dementia (1.54 [1.01, 2.34]), compared to active job (high demand, high control).

**Conclusions:** The link between work related stress and risk of dementia is limited to individuals suffering sleep disturbance.

**Acknowledgements:** We thank Dr. Axel Börsch-Supan and other team members of the Survey of Health, Ageing and Retirement in Europe

(SHARE) for their great contribution to the design, data collection, and management of the project. This research was supported by the Swedish Research Council (grant number 2018-02998) and the Swedish Research Council for Health, Working Life and Welfare (grant numbers 2019-01120 and 2020-00313).

### SOCIODEMOGRAPHIC, PSYCHOLOGICAL, AND BEHAVIOURAL PREDICTORS OF SLEEP CHANGES IN OLDER ADULTS DURING THE COVID-19 PANDEMIC: A LONGITUDINAL STUDY

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**Introduction:** To mitigate the spread of COVID-19, strict lockdown measures were implemented in March of 2020. Although these measures have been shown to disrupt sleep in older adults beyond the effects of typical ageing, the long-term effects of the pandemic on sleep in this population are unclear. The objective of this study is to identify sociodemographic, psychological, and behavioural factors that predict sleep changes throughout the pandemic in older adults.

**Materials and Methods:** The longitudinal study included 645 older adults (73.10% female;  $M_{age} = 78.69$ ;  $SD = 5.67$ ) who completed self-report questionnaires at four timepoints: April 2020 (T1), July 2020 (T2), Fall 2020 (T3), and March 2021 (T4). Sociodemographic factors were age, gender, education, income, and living situation. Psychological factors that were assessed were loneliness (UCLA Loneliness Scale), psychological distress (Kessler Psychological Distress Scale), and perceived threat of the pandemic (questionnaire created by our team). Behavioural factors that were measured included physical activity (International Physical Activity Questionnaire) and sleep-related behaviours (retrospective sleep diaries), such as sleep duration, time in bed, and social rhythm within the prior two weeks of administration. The Insomnia Severity Index (ISI) was used to evaluate the severity of insomnia symptoms. Using the total ISI scores at each timepoint, group-based trajectory modelling was conducted to identify sleep trajectories. Subsequently, multinomial logistic regression was performed to find the aforementioned factors at T1 that predicted these trajectories.

**Results:** Three groups with distinct sleep trajectories were identified: high ISI ( $n = 76$ ), intermediate ISI ( $n = 163$ ), and low ISI ( $n = 406$ ). The high ISI group reported having greater psychological distress ( $OR = 3.88$ , 95% CI: 2.42, 6.24), increased variability in time out of bed in the morning ( $OR = 1.59$ , 95% CI: 1.13, 2.23), more time in bed ( $OR = 2.73$ , 95% CI: 1.68, 4.45), and shorter sleep duration ( $OR = 0.09$ , 95% CI: 0.05, 0.17) at T1 than the low ISI group. The intermediate ISI group reported having more psychological distress ( $OR = 2.01$ , 95% CI: 1.47, 2.75), more time in bed ( $OR = 2.14$ , 95% CI: 1.47, 3.11), and shorter sleep duration ( $OR = 0.26$ , 95% CI: 0.17, 0.39) at T1 than the low ISI group. Those in the high ISI group were more likely to be male ( $OR = 0.25$ , 95% CI: 0.09, 0.68) and reported having greater psychological distress ( $OR = 1.93$ , 95% CI: 1.25, 2.98), increased variability in time out of bed ( $OR = 1.71$ , 95% CI: 1.19, 2.45), and shorter sleep duration ( $OR = 0.36$ , 95% CI: 0.21, 0.60) at T1 than the intermediate ISI group.

**Conclusions:** Being male as well as having elevated psychological distress and poorer sleep at the start of the pandemic were risk factors for sleep disturbances over time in older adults. Interventions aimed at reducing psychological distress and sleep disturbances should be implemented.

**Acknowledgements:** This study was supported by the Centre de recherche de l'Institut universitaire de gériatrie de Montréal and by the Quebec

Network for Research on Aging, a thematic network supported by the Fonds de Recherche du Québec - Santé.

### SUBJECTIVE SLEEP QUALITY IS THE STRONGEST PREDICTOR OF MENTAL AND PHYSICAL HEALTH INDEPENDENT OF CHRONOTYPE, SLEEP DURATION, APOE-ε4 CARRIERSHIP, AGE, SEX, ALCOHOL CONSUMPTION, AND RETIREMENT STATUS IN HEALTHY OLDER ADULTS

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**Introduction:** Sleep and circadian rhythm disturbances are risk factors for mental and physical health problems. Carriership of the apolipoprotein E (APOE) gene variant, APOE-ε4, has been associated with objective sleep disturbances; mixed evidence suggests APOE-ε4 may also be implicated in worsened mental and physical health outcomes. This study aims to extend previous findings by examining how self-reported sleep quality, sleep duration, and chronotype independently associate with mental and physical health in healthy older adults, while controlling for APOE-ε4 carriership and other demographic characteristics.

**Materials and methods:** In total 166 participants (117 female) between 42 and 90 years old ( $M = 64.69$ ,  $SD = 9.42$ ) were recruited as part of the screening phase for a sleep-circadian and cognition experiment. Sleep quality was assessed using the Insomnia Severity Index (ISI), Pittsburgh Sleep Quality Index (PSQI) global score, and PSQI subjective sleep quality item. Chronotype was assessed via the Morningness-Eveningness Questionnaire (MEQ) and the Munich Chronotype Questionnaire (MCTQ). Sleep duration was assessed using the PSQI and the General Medical Questionnaire (GMQ). Mental health and physical health were measured using the Short Form Health Survey (SF-36). Data was collected on APOE-ε polymorphism using genotyping; participants were coded as APOE-ε4 carriers or APOE-ε4 non-carriers.

**Results:** A series of linear regression models assessed the independent associations of self-reported sleep quality, sleep duration, and chronotype with mental health and physical health. Secondary models controlled for age, sex, APOE-ε4 carriership, alcohol consumption, and retirement status. Poor sleep quality was the strongest independent predictor of lower mental health across all measures and models; ISI ( $Beta = -.410$ ,  $p < .001$ ), PSQI global score ( $Beta = -.260$ ,  $p = .006$ ), and PSQI subjective sleep quality ( $Beta = -.254$ ,  $p = .003$ ). The regression models were then run separately for men and women. Lower sleep quality was found to be the strongest predictor of worse mental health, particularly in men ( $Beta = -.951$ ,  $p < .001$ ), compared with women ( $Beta = -.325$ ,  $p = .001$ ). Lower sleep quality was also associated with lower physical health, but only in women ( $Beta = -.285$ ,  $p = .006$ ). Limited meaningful associations were found for chronotype and sleep duration. APOE-ε4 carriership was not found to predict mental or physical health and did not adjust the results of the studied associations in any of the models.

**Conclusions:** This study found that sleep quality was the strongest independent predictor of mental health in older adults, especially in men. Similarly, lower sleep quality was independently associated with poorer physical health; however this was only found in women. Sleep quality should therefore be considered alongside the assessment and treatment of physical and mental health problems in older adults, independent of APOE-ε4 status and demographic characteristics.

**Acknowledgements:** This research was supported by funding from the Wellcome Trust to Dr Lazar (207799/Z/17/Z).

### THE AGES OF SLEEP ONSET: SPATIO-TEMPORAL EEG PATTERNS IN PREADOLESCENTS, YOUNG AND OLDER ADULTS

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**Introduction:** Sleep and wakefulness are no more considered mutually exclusive states. In the last decades, several findings pointed out the local and use-dependent nature of sleep features, demonstrating that electrophysiological patterns of both sleep and wakefulness can co-occur simultaneously, in different cortical areas. By definition, Sleep Onset (SO) is an instable state of transition between wakefulness and sleep, and its spatiotemporal dynamics have been exhaustively described in healthy adulthood. The human sleep electroencephalographic (EEG) topography is characterized by strong age-related changes. However, the specific local EEG features of SO during preadolescence and healthy aging have been not extensively described.

**Materials and Methods:** We aimed to investigate regional and temporal electrophysiological patterns of SO in a group of 23 preadolescents (9–14 years, Exp. 1) and in a group of 36 older participants (59–81 years, Exp. 2). Specifically, the pre- vs- post-SO changes in the topography of the 1 Hz bins' EEG power and the time course of the EEG frequency bands during the wake-sleep transition were assessed in both experimental groups. Furthermore, we compared delta activity and delta/beta ratio during the SO between these two groups (Exp. 1: preadolescent, Exp. 2: elderly) and a group of 40 healthy young adults (18–29 years).

**Results:** In Exp. 1 preadolescents exhibited: a) a generalized post-SO increase in the low frequencies (0.5–6 Hz), especially in the lowest bins (0.5–2 Hz) with a central predominance; b) activity in the 12–13 and 14–15 Hz increased over frontal or central areas, respectively; c) the slowest bins in the beta band showed a slight central increase post-SO. Compared to young adults, delta/beta ratio in preadolescents was higher in posterior areas in both pre- and post-SO and lower in frontal areas in the post-SO. This finding was paralleled by higher delta power in posterior (pre-SO) and centro-posterior areas (post-SO) and lower delta activity in frontal areas (post-SO) in preadolescents.

Exp. 2 showed that elderly had: a) a generalized post-SO power increase in the slowest frequencies; b) a specific pattern of post-SO changes of the alpha frequency; c) a slight post-SO increase of the sigma activity, whereas its highest bins exhibited a frontotemporal decrease. Older adults showed a global decline of the delta power and delta/beta ratio in both pre- and post-SO intervals compared to young adults.

**Conclusions:** In preadolescents the predominance of the delta activity in more posterior areas compared to young adults and the observation of a not completely mature spindles should be ascribed to development-related maturational processes, pointing to higher homeostatic need from the more mature areas, rather than to different SO dynamics. The reduced delta activity and delta/beta ratio observed in elderly likely depict lightened homeostatic pressure at SO. Taken together, findings parallel the SO process in adults, with a notable difference concerning homeostatic process. In fact, most differences point to crucial developmental changes in homeostatic regulation that play a role in determining age-related wake-sleep transition features.

**Acknowledgements:** Dr Ludovica Annarumma is funded by grants from the Italian Ministry of Health, grant number RF-2018-12365682.

## THE IMPACT OF OBSTRUCTIVE SLEEP APNEA AND ITS TREATMENT IN CELLULAR AND MOLECULAR AGING

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**Introduction:** Obstructive Sleep Apnea (OSA) is one of the most common sleep disorders worldwide. There is sizable evidence showing the association of OSA with aging by inducing cellular and molecular aging mechanisms (Gaspar, et al. 2017, 2021). Understanding OSA putative negative effect on aging progression might contribute to understand new strategies to develop new OSA diagnosis and treatment but also to counteract aging.

**Aim:** To investigate whether OSA patients show peripheral aging-related cellular and molecular impairments and the impact of OSA treatment.

**Materials and Methods:** Twenty-six adult male patients (56±10 years) diagnosed with severe OSA were monitored from the moment of diagnosis with polysomnography (PSG), and up to 4 months and 24 months of treatment with continuous pressure positive mask (CPAP) and 13 men of the same age group (49±8 years). Several hallmarks of cellular and molecular aging were evaluated in Peripheral Blood Mononuclear Cells (PBMC). This study was approved by the ethical committee of the Faculty of Medicine of the University of Coimbra and by Coimbra Hospital and University Centre, Portugal.

**Results:** OSA patients' blood samples show increased mRNA levels of genomic instability players, in comparison with 24 months of treatment (p<0.05). In addition, telomeres of OSA patients showed to be shorter in comparison to healthy controls (p<0.01), an alteration that accentuates with the treatment (t<sub>4M</sub>: p<0.01; t<sub>24M</sub>: p<0.001). Regarding proteostasis impairments, mRNA levels of autophagy receptors in OSA patients are upregulated in relation to age-matched controls (p<0.01).

**Conclusions:** These results suggest that OSA might induce impairments in hallmarks of aging and CPAP treatment might partially re-establish some alterations. Hence, OSA early diagnosis and specific treatment may constitute a new strategy to delay ageing.

**Acknowledgements:** This work was financed by the European Regional Development Fund (ERDF), through the Centro 2020 Regional Operational Programme, under the project CENTRO-01-0145-FEDER-000012 (HealthyAging 2020); through Operational Programme for Competitiveness and Internationalisation (COMPETE 2020) and Portuguese national funds via Fundação para a Ciência e a Tecnologia (FCT), under the projects POCI-01-0145-FEDER-029002 (noOSAnoAGEING, PTDC/MEC-MCI/29002/2017), UIDB/04539/2020 and UIDP/04539/2020; and by the European Social Fund through POCH - Human Capital Operational Programme and Portuguese national funds via FCT under PD/BD/135497/2018, 2020.04499.BD and 2021.05334.BD.

The authors have no conflicts of interest to declare.

## THE LINK BETWEEN SLEEP AND GAIT AMONG COMMUNITY DWELLING ADULTS

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**Introduction:** Alarming recent findings indicate that older adults with poor sleep quality have as much as a 4.5-fold higher risk of falls. The potential comorbidity between reduced sleep quality and balance problems has led to growing interest in the study of the relationships between them. Gait and sleep are two basic, modifiable functions that decline throughout the aging process and are associated with deterioration in health and functional outcomes. Although seemingly distinct, both functions share common cognitive, psychological and physiological mechanisms; however, the associations between sleep and gait among community adults with no sleep or balance complaints are poorly understood. The present study aims to explore the associations between sleep indices and gait performance among community dwelling adults.

**Materials and Methods:** This cross-sectional investigation is based on the “Kibbutzim” longitudinal study. One hundred and three community-dwelling adults (mean age 64±13 years), with no sleep or gait complaints participated. Sleep was evaluated objectively by 7-days of actigraphy (ActiGraph, LLC) and by self-report. Measures included bedtime (BT), sleep duration (SD), sleep efficiency (SE), and wake after sleep onset (WASO). Gait parameters (speed, variability) were measured using the Dual-Task Paradigm, in which gait is assessed twice during a one-minute walk by a mobility lab (APDM Wearable Technologies, Inc.), once with (dual task – DT) and once without (single task – ST) an added cognitive load.

**Results:** Based on actigraphy, increasing age was significantly associated with earlier BT (p=0.007), lower SE (p=0.1) and increased WASO (p=0.1). Consistent with the literature, sex differences were found for objective (actigraphy, p=0.002) and subjective (p<0.001) SD, with women sleeping significantly longer than men. No sex differences were found for BT, SE or WASO. A significant main effect was found for SD on gait speed. When comparing gait speed by actigraphy-based SD tertiles (short / intermediate / long), gait speed was significantly slower under the DT condition in long

compared to short and intermediate sleep duration ( $p=0.018$ ). No associations were found for stride length. These findings are consistent with studies demonstrating negative health outcomes for long vs. short and intermediate sleepers.

**Conclusions:** This study demonstrates early pre-clinical manifestations of comorbidity between sleep and gait, both of which significantly affect daily functioning in older adults. The Dual-Task Paradigm is a sensitive tool that can easily be used for early diagnosis of comorbid gait-sleep deterioration. Such investigations may pave the way to a better understanding of the mechanisms underlying their comorbidity and lay the groundwork for interventions.

**Acknowledgements:** Basic Research

#### ALTERED SLEEP BEHAVIOR IN A GENETIC MOUSE MODEL OF ALZHEIMER'S DISEASE FOLLOWING ANESTHETIC EXPOSURE

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**Introduction:** Due to demographic changes, the number of senior patients undergoing surgery and suffering from Alzheimer's disease (AD) is expected to expand. It has been hypothesized that anesthetics may deteriorate or even trigger the development of AD. Upon administration of anesthetics, AD patients may experience sleep disturbances, exacerbated initial postoperative emergence delirium or even postoperative delirium (POD), which may concomitantly lead to worsening of cognitive impairments. Recent research suggests that certain volatile anesthetics such as sevoflurane may not only cause short-term cognitive dysfunction but may even exacerbate AD-related long-term cognitive decline. Concurrently, accumulating evidence indicates a linkage of sleep disorders with AD not only as a symptom, but also as a potential facilitator of the disease. With this study, we aimed to examine face validity and constructive validity of the AD ArcA $\beta$  mouse model by inspecting whether anesthetic exposure has an altered detriment on sleep architecture. Additionally, we investigated potential predictive EEG-biomarkers deriving from the basal sleep/wake behavior for estimating the extent of anesthetic detriment following its exposure.

**Materials and methods:** We used 14 ArcA $\beta$  mice (7 transgenic with AD pathology and 7 wildtype) with an age of 8-11 months. Chronic electroencephalogram (EEG) and electromyogram (EMG) recordings were performed to assess sleep/wake behavior. Following baseline recordings, experimental administration of sevoflurane was performed (0.2%vol every 2 min up to 3%vol max.) until EEG burst suppression was achieved (10s inter-burst interval). Sevoflurane concentration was then reverted to 0%vol in 0.2%vol steps, followed by another set of EEG/EMG recordings.

**Results:** Age-independent baseline EEG recordings showed significant differences in spectral features, most importantly decreased delta power in transgenic mice during NREMS compared to wildtype littermates with a relative increase in remaining power spectra. Administration of experimental anesthesia in wildtype mice, regardless of age, did not result in any profound alterations in sleep architecture. On the other hand, transgenic mice showed increased transitions from NREMS to wakefulness, accompanied by a decrease in delta power during NREMS compared to wildtype littermates, independent of the age group.

**Conclusions:** Our results, supporting face validity and constructive validity, suggest that anesthetic administration results in an age-independent disruption of sleep-wake behavior in ArcA $\beta$  mice. Further, wildtype mice appeared to regain basal sleep/wake behavior, whereas transgenic mice showed a reduction in sleep quality and an alteration of sleep architecture after anesthesia. Spectral EEG-biomarkers, as found in our study, could potentially play a role in predicting cognitive decline after anesthesia. Our future experiments will focus on impaired sleep quality in ArcA $\beta$  mice after anesthetic exposure as a potential trigger for cognitive impairments due to anesthetics.

#### AN EEG STUDY ON SLEEP HOMEOSTASIS IN A SONGBIRD SPECIES, THE EUROPEAN STARLING (*STURNUS VULGARIS*): REM SLEEP, WHY BOTHER?

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**Introduction:** Sleep is considered to be of crucial importance for optimal performance and health. However, most of what we know about sleep is based on a handful of mammalian species under laboratory conditions. Perhaps much can be learned from comparative studies in other species. Birds are interesting in that respect because they exhibit two sleep states that are similar to mammalian rapid eye movement (REM) and non-REM (NREM) sleep. We therefore did a series of electro-encephalogram (EEG) studies in European starlings (*Sturnus vulgaris*) for a detailed assessment of sleep architecture and sleep homeostasis under laboratory and semi-natural conditions.

**Materials and Methods:** We implanted 12 European starlings with epidural EEG electrodes and applied miniature dataloggers to record their sleep-wake behavior. In the first experiment under controlled indoor conditions, we measured baseline sleep and sleep homeostatic responses to 4 and 8-hour sleep deprivations. In the second experiment, we measured sleep under seminatural outdoor conditions across the seasons.

**Results:** The birds showed a homeostatic NREM sleep response reflected in elevated EEG spectral power across a broad frequency range and increased daytime napping. Starlings had hardly any REM sleep (1.6% of total sleep time) and no REM sleep rebound after sleep deprivation.

Under seminatural outdoor conditions, the birds showed extreme variation in the amount of NREM sleep across the seasons with 5 hours more sleep in winter than in summer (12.5 h and 7.5 h respectively,  $p < 0.001$ ). The daily sleep variation was best explained by photoperiod ( $p < 0.001$ ) and was also negatively affected by moonlight ( $p < 0.001$ ). During long photoperiod, starlings showed an increased sleep pressure that was reflected in the slope of the decay of EEG spectral power during the nights ( $p = 0.008$ ), resulting in an increase in daytime naps. Also, under seminatural conditions starlings only displayed negligible amounts of REM sleep.

**Conclusions:** This study confirms homeostatic regulation of NREM sleep in songbirds. Yet, it also demonstrates high flexibility and strong photoperiodic regulation of NREM sleep under natural conditions. Finally, this study does not support an important role for REM sleep.

**Acknowledgements:**

This study was supported by an Adaptive Life Program scholarship from the Groningen Institute for Evolutionary Life Sciences and an Ubbo Emmius scholarship provided by the Faculty of Science and Engineering at the University of Groningen. N.C.R. was supported by the Max Planck Society.

#### A NEW METHOD FOR PRECISE OSCILLATORY PHASE TARGETING AFFECTS SLOW WAVES AND SLEEP SPINDLES ON THE SHORT AND LONGER TERM

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**Introduction:** Several studies have shown manipulation of slow oscillations and sigma power through sensory stimulation during sleep. Most of the evidence, however, regards effects immediately following stimulation rather than longer-term effects. Moreover, effects on discrete spindles have as yet not been assessed. Here we use a modeling-based approach to predict upcoming oscillatory activity in the EEG and phase-lock subtle acoustic stimuli to the start of the SO positive deflection.

**Materials and Methods:** Here we use a modeling-based approach to predict upcoming oscillatory activity in the EEG and precisely phase-lock subtle acoustic stimuli to the start of the SO positive deflection. We assess effects the effects of stimulation on discrete slow oscillations and spindles on the short (seconds) and longer () term. We relate our findings to

observations at the level of spectral measures and evoked potentials.

**Results:** Our observations show that slow wave measures were consistently increased, as apparent in measures of discrete SO's, SO and delta power and deflections in the ERP. On the other hand, fast spindle measures showed a short-term grouping (local increase) during a stimulus-induced Slow wave positive deflection around 1 second after stimulation, but were globally decreased, both on the short and long term. This was apparent in measures of discrete fast spindles and PSD across longer periods of sleep.

**Conclusions:** Acoustic stimuli precisely phase locked to the SO onset increase SO's and delta power globally, therewith deepening sleep. Fast sleep spindles are globally depressed. This appears to be due in part to interruption of ongoing spindles by the stimulus, and may furthermore reflect a depressing influence of slow oscillations (sleep depth) on fast spindle dynamics.

**Acknowledgements:** We thank the European Space Agency (ESA) for their support and collaboration on this study.

#### AUDITORY STIMULATION ALIGNED TO THE ASCENDING PHASE OF THETA OSCILLATIONS DURING REM SLEEP

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**Introduction:** Closed-loop auditory stimulation (CLAS) approaches have been gaining popularity and have been used extensively to investigate brain oscillations during non-REM sleep. Here, for the first time, we present a new method based on sine wave fitting approach to model and predict EEG oscillatory dynamics and to track and phase-target theta oscillations (4–8 Hz) during human REM sleep.

**Materials and Methods:** Twenty-four subjects (19 female, 5 male; M = 20.46 years, SD = 2.06) were recorded overnight with polysomnography. During periods of REM sleep, an advanced oscillatory phase prediction algorithm was deployed to target auditory stimuli at the start of the positive deflection (0°) of ongoing theta oscillations.

**Results:** Results showed that the up-wave of REM sleep theta waves was precisely targeted (336 ± 58 degrees), evoking significantly boosted theta and beta activity shortly after stimulus onset.

**Conclusions:** The present study concludes that sine wave fitting can be reliably applied to precisely detect phase of theta activity during human REM sleep theta activity. This study contributes to a technical advance, introducing a non-invasive method to influence theta wave activity in the brain during REM sleep. In this way, paving the way to reliably interact with arbitrarily chosen phases of theta waves, possibly bringing light to research questions that would benefit of direct interference on theta oscillations, to further explore its link to human cognition

**Acknowledgements:** We wish to thank Timo van Hattem for their help with this project

#### BED-SHARING IN THE FIRST 6 MONTHS: ASSOCIATIONS WITH INFANT-MOTHER ATTACHMENT, INFANT ATTENTION, MATERNAL BONDING, AND SENSITIVITY AT 18 MONTHS

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**Introduction:** The objective of this study was to investigate whether bed-sharing during the first 6 months of life is associated with infant's attachment and behavioral outcomes and mother's bonding and sensitive parenting at 18 months of age.

**Materials and Methods:** The sample with complete longitudinal data comprised 178 infants and their caretakers. Bed-sharing was assessed with maternal report at term, 3, 6, and 18 months. Infant attachment was measured at 18 months using the strange situation procedure. Infant behavioral outcomes (i.e., poor attention/hyperactivity and task persistence) were assessed with 2 observational measures at 18 months. Maternal sensitivity was observed at 3 and 18 months, and mothers reported on bonding to their infant at term, 3, and 18 months.

**Results:** Bed-sharing was common at term (41.2%), which decreased at 3

months (22.6%) followed by a slight increase at 6 (27.5%) and 18 months of age (31.3%). No associations between bed-sharing during the first 6 months and infant-mother attachment and infant behavioral outcomes at 18 months were found. Similarly, there were no associations between bed-sharing during the first 6 months and maternal bonding and sensitivity at consequent assessment points (i.e., 3 and 18 months).

**Conclusions:** Bed-sharing during the first 6 months is not associated with positive or negative outcomes about infant-mother attachment, infant behavior, maternal bonding, or sensitive parenting.

**Acknowledgements:** The authors would like to thank the researchers who assisted in recruitment and data collection: Tina Gutbrod, Libi Rust, and Karine Edme. The authors would also like to thank the participating hospitals (Addenbrookes Hospital, Cambridge; Luton and Dunstable Hospital, Luton; and Queen Elizabeth II Hospital, Welwyn Garden City) and the parents and their children.

#### BOOSTING VOCABULARY LEARNING DURING SLEEP VIA A PORTABLE CLOSED-LOOP TARGETED MEMORY REACTIVATION SYSTEM IN A HOME SETTING: A PILOT STUDY

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**Introduction:** Sleep plays a critical role in the process of memory consolidation. Targeted memory reactivation (TMR) is a well-established methodology to manipulate memory processing overnight, typically employed in a laboratory setting. Sensory cues are used to non-invasively reactivate associated memory traces during the deepest sleep stage (N3), thus promoting memory consolidation. Considering the comprehensive literature supporting the high efficacy of the TMR approach, the next step consists of translating this paradigm to daily life. We developed a portable closed-loop TMR (CL-TMR) system that automatically delivers sound stimuli during N3, relying on the ongoing electroencephalographic (EEG) activity recording of a commercial wearable EEG headband. We applied CL-TMR to enhance vocabulary learning by presenting verbal stimuli during sleep in a home setting.

**Materials and Methods:** A total of 12 healthy young Italian native speakers (mean age ± standard deviation, 24.50 years ± 2.32) participated in the pilot study. In the evening, subjects performed a vocabulary learning task requiring the acquisition of the Italian translation of pseudo-words (T1). During the subsequent night, half of the pseudo-words were aurally presented (*cued*) during the ascending phase of the slow oscillations (SOs) through the CL-TMR system. Half of them consisted of pseudo-words that participants translated correctly at T1, while the other half were pseudo-words whose translation was not learned. EEG signals were recorded with the *Dreem Headband* (Rythm SAS, Paris, France). Stimulations were triggered by the SO detection algorithm of the headband. Vocabulary memory performance was re-evaluated in the morning post-stimulation (T2). We compared the T1-T2 differences between *cued* and *uncued* correctly translated pseudo-words. At the electrophysiological level, we evaluated event-related potentials (ERPs) and event-related spectral perturbations in the 5–18 Hz range for *cued* pseudo-words. We compared cortical responses leading to a successful recall of the Italian translation with those associated with a not-remembered translation in the morning.

**Results:** Re-exposure to pseudo-words during sleep improved later memory for the Italian translation of the *cued* words (mean ± standard deviation, +13.20% ± 20.75) compared with *uncued* words (−5.26% ± 22.31;  $p=0.04$ ). EEG analysis showed that successful reactivation during sleep was associated with higher frontal positivity and negativity in ERPs. Time-frequency analysis revealed an increase in the spindle band in the 1000–2000 msec time window after the stimulation onset ( $p<0.05$ ) as the correlate of the reactivation of memory traces correctly recalled in the morning.

**Conclusion:** This pilot study showed the effectiveness of our CL-TMR system in boosting vocabulary learning during sleep in an ecological home setting. The successful cueing was characterized by increased spindle activity after stimulus presentation, confirming the importance of specific oscillatory dynamics in supporting the TMR effect. The application of a

portable CL-TMR system could pave the way to the application of the TMR paradigm in everyday life, promoting the well-known electrophysiological rhythms involved in the sleep-dependent memory consolidation process.

### BRAIN RESPIRATORY PULSATILITY OF FAST FMRI STABILIZES DURING NREM STAGE 2 SLEEP

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**Introduction:** Studies suggest that respiratory pulsatility is one phenomenon that drives the cerebrospinal fluid (CSF) flow<sup>1,2</sup>, that is known to contribute in metabolic waste clearance during slow wave sleep<sup>3,4</sup>. Important physiological change in NREM sleep is, that ventilation becomes more regular than during awake<sup>5</sup>. It is not known whether this regularity of the respiratory pulsatility can be seen in the brain during different sleep stages.

**Materials and Methods:** 23 healthy subjects (27.0 ± 4.9 years, 12 females) were scanned with fast functional magnetic resonance imaging (fMRI) called magnetic-resonance-encephalography (MREG, repetition time 100 ms) during awake in the afternoon and during sleep in the evening (10 subjects) or in the morning after sleep deprivation (13 subjects). EEG and end-tidal carbon dioxide (EtCO<sub>2</sub>) signals were measured in synchrony with MREG. Our trained EEG specialists made sleep scoring for the data based on standard AASM criteria. Physiological EtCO<sub>2</sub> signals were used to specify individual respiratory frequency range (varying between 0.08–0.49 Hz) for each subject, so that minimum and maximum values met the starting noise level. After standard preprocessing steps with FSL program, MREG data were bandpass filtered to individual respiratory frequency range. Then, spectral entropy, the measure of complexity or stability of the signal, was calculated for filtered MREG data. Awake data was compared with NREM stage 1 (21 subjects) and separately to NREM stage 2 (14 subjects) sleep data using two-sample paired T-test with FSL randomize (with Threshold-Free Cluster Enhancement and family-wise error).

**Results:** We found that spectral entropy decreased during NREM stage 2 sleep and, that no difference was found between awake and NREM stage 1 sleep. Decrease of spectral entropy in stage 2 sleep was brain wide ( $p < 0.05$ ) and the regions with smallest  $p$ -values were found in ventromedial prefrontal cortex and visual cortex ( $p < 0.015$ ).

**Conclusions:** Our results show that whole brain respiratory pulsatility stabilizes in NREM stage 2 sleep, which is in line with respiratory physiology<sup>5</sup>. Prefrontal cortex has been suggested to initiate slow waves with decreased blood flow<sup>6</sup>, and visual cortex is known to produce increased very low frequency fluctuations in low vigilance levels and sleep<sup>7,8</sup>. These both could be further studied in relation to respiratory pulsations. We suggest that brain respiratory pulsatility change towards more regular pattern may contribute to CSF flow in NREM stage 2 sleep.

**Acknowledgements:** We would like to thank all subjects for their participation in the study, and for staff members who were working in the study. We are thankful for devices and data provided by Oura. We wish to acknowledge Jussi Kantola for data management and reconstruction of MREG data, the CSC–IT Center for Science Ltd., Finland for generous computational resources. This work was supported by Uniogs/MRC Oulu DP-grant(HH), TERTTU-säätiö(HH,VKo), JAES-Foundation(VKi), Academy of Finland and TERVA grant 314497(VKi), Academy of Finland Grant 275342(VKi), The SalWe Research Program for Mind and Body (Tekes—the Finnish Funding Agency for Technology and Innovation, Grant No.1104/10)(VKi), The Finnish Medical Foundation(VKi), Finnish Neurological Foundation(VKi), KEVO grants from Oulu University hospital(VKi), Finnish Brain Foundation sr(VKi).

### CHARACTERIZATION OF ELECTROENCEPHALOGRAPHIC AND ELECTROMYOGRAPHIC AROUSALS DURING SLEEP

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**Introduction:** Though there are some studies dealing with the details of spontaneous arousal, they are mainly about micro-arousals (MAs) happening with K-complex during N2 phase of NREM sleep. The spontaneous arousals (with EEG and EMG signals) that happen throughout night have not been characterized in detail. It is also important to compare the final arousal that occurs in the morning with spontaneous arousals that take place during sleep. There are no studies on the sequence of appearance of physiological signals like EEG and EMG during spontaneous arousals and final arousal in the morning. The study of the time delay in the appearance of these two physiological signals may help in the better understanding of sleep-wake (SW) regulation. Spectral analysis of EEG power band and EMG activity, computed as the root mean square (RMS), will improve the quality of the findings

**Materials and Methods:** The research was approved by the Institutional Ethics Committee (No. IECPG/119/1/2019). Adult healthy non-smoker male participants (n=15), in the age group of 18 to 35 years with a normal SW cycle were included in the study. All the participants filled sleep diaries for a week followed by overnight Polysomnography as per standard AASM criteria

**Results:** Spontaneous arousals, with associated EEG and EMG changes, occurred almost uniformly throughout non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep. EEG changes preceded EMG changes during a majority of the spontaneous arousals. While waking up finally in the morning, which mostly happened during the REM sleep, increased EMG activity preceded the EEG in the majority of the events. There was a delay of more than a second in between EEG and EMG changes, in both spontaneous arousals and early morning awakenings. There was a significant increase in the delta power and in all the frequency bands during spontaneous arousals, compared to the pre-arousal values. Though similar changes in EEG happened during the early morning awakenings also, there were significant differences in beta and sigma EEG powers and computed root mean square EMG during the early morning awakenings

**Conclusions:** The differences in the characteristic features of EEG and EMG changes during spontaneous arousal and early morning arousal indicated the probable role of these changes in facilitating the continuance of sleep in the former, and waking up from sleep in the case of the latter

**Acknowledgements:**

### DETECTING OFF PERIODS IN MULTIUNIT ACTIVITY SIGNALS

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**Introduction:** OFF periods are times of neuronal silence associated with slow waves during NREM sleep, thus providing a link between fine-grain neuronal dynamics and whole brain EEG activity. Although there is general consensus on the concept of an OFF period, definitions and therefore methods of detecting OFF periods vary. Using a combination of clustering and thresholding informed by the behaviour of the data itself, we designed a pipeline for detecting OFF periods in multiunit activity signals (MUA) with the same dynamics as previously described but without the need for arbitrary thresholding.

**Materials and Methods:** Seven C57BL/6 mice were implanted with a laminar probe for recording local field potential (LFP) and multiunit activity (MUA) in motor cortex. Screws were implanted in the cranium and nuchal muscle to record electroencephalograms (EEG) and electromyograms (EMG) respectively. Mice were recorded over a 48 hour period; a baseline day (BL) with no intervention and a sleep deprivation day (SD) in which mice were prevented from sleeping from ZT0–ZT6. Four second epochs were scored as wake, NREM or REM based on electrophysiology. OFF periods were detected in a 3 stage pipeline. First, negative zero-crossings in a decimated variant of the MUA were detected. Second, we fit Gaussian Mixture Models (GMM) to a 2D dataset of NREM MUA signals smoothed at two different window lengths. Third, the intersection of negative zero-crossings and points clustered to the lowest amplitude

GMM component was calculated to find the final population of OFF periods.

**Results:** The majority of OFF periods were detected in NREM sleep (88.59%, CI=84.18 - 92.97) and REM sleep (6.87%, CI=3.46 - 10.29) with a small proportion detected in wake (1.15%, CI=0.39 - 1.91). Mean OFF period length across all animals and states was 114ms. The average LFP profile of all detected OFF periods shows a strong positive deflection that peaks ~45ms after OFF period initiation. There was a positive correlation between OFF period LFP amplitude and OFF period length with the regression of these variables significant (linear model,  $R^2=0.85$ ,  $t=9.46$ ,  $p<0.001$ ). There was a significant fixed effect of prior experience on OFF period occupancy (linear mixed model,  $t=7.36$ ,  $p<0.001$ ), frequency (linear mixed model,  $t=7.39$ ,  $p<0.001$ ) and length (linear mixed model,  $t=13.42$ ,  $p<0.001$ ) during the second half of the dark phase (ZT6 - T12) with all three metrics higher for the sleep deprivation treatment. The temporal coincidence of OFF periods increased as laminar probe channel distance decreased.

**Conclusions:** OFF periods detected by our pipeline show similar properties to those previously described. OFF periods occur predominantly in NREM sleep and are associated with slow-wave like LFP profiles that increase in amplitude as a function of OFF period length. OFF periods show strong homeostatic dynamics, increasing in frequency, length and overall occupancy time after sleep deprivation. Finally, OFF periods are shown to be both a global and a local phenomenon across layers of motor cortex.

**Acknowledgements:** EPSRC, NPIF

#### DISRUPTION OF SLEEP ARCHITECTURE AND RETICULAR THALAMIC (RT) NEURONAL FIRING ACTIVITY IN NEUROPATHIC PAIN

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**Introduction:** Neuropathic pain (NP) is an important public health problem with no effective treatments. It has been demonstrated that chronic pain condition produces changes in sleep pattern in about 80% of the patients (Finan et al., 2013). Indeed, poor sleep occurred in patients with a widely variety of pain disorders including musculoskeletal (Yu-Lin Wu et al 2017), post-herpetic trigeminal neuropathy (Roth et al. 2010), post-surgery neuropathic pain, HIV, multiple sclerosis, trigeminal neuralgia, cancer, trauma/accident and diabetes (Wafik Said Bahnasy et al, 2018). To date, the brain mechanisms linking pain and insomnia are yet to be clarified. In this work, we thus examined the effect of NP in the L5-L6 ligature rat model in sleep architecture and in the electrical activity of the neurons of the reticular thalamus (RT), which is an area related to both pain and sleep.

**Material and Methods:** We induced NP in Wistar rats. 14 days later, rats were evaluated for allodynia using von-Frey filament. Animals with NP were then separated in 2 groups: one group was implanted with six stainless-steel wire electrodes in the skull for the EEG/EMG 24h recording, while the second group underwent in vivo electrophysiological recordings in the reticular thalamus (RT) (for details in methods see Ochoa-Sanchez et al., 2011). Sham operated animals were used as a control for both groups.

**Results:** EEG/EMG analysis showed that NP animals displayed a reduced time in non-rapid eyes movement (NREM) sleep (-20%,  $t_{(14)}=3.94$ ,  $p<0.001$ ) and an increase in wakefulness (+19.13%,  $t_{(14)}=3.47$ ,  $p<0.05$ ). In addition, NP animals displayed a fragmented sleep architecture ( $t_{(14)}=4.3$ ,  $p<0.0001$ ) represented by transient EEG arousals. No changes in the latency to NREM sleep ( $t_{(14)}=4.3$ ,  $p=0.15$ ) were detected. Baseline firing rate as well as burst-firing activity of RT neurons in NP animals were significantly higher than in control rats (firing rate: +344 %,  $t_{(10,3)}=3.12$ ,  $p<0.01$ ; burst-firing activity: +843.1%,  $t_{(8,6)}=3.86$ ,  $p<0.004$ ).

**Conclusions:** These findings indicate that NP is associated with significant changes in the sleep-wake cycle, particularly a reduced duration of NREM sleep, and in the activity of the RT neurons.

**Acknowledgments:** This work was supported by the Ministry of Economy, Science and Innovation (MESI) of Québec and the Merit scholarship program for foreign post-doc students, PBEEE, Faculty of Medicine, McGill.

#### EFFECT OF HIV INFECTION ON SLEEP AND CHRONOTYPE IN AN AGEING RURAL SOUTH AFRICAN COHORT

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**Introduction:** Sleep disturbances are a well-established consequence of HIV infection. The pathophysiology of these disturbances have yet to be experimentally defined, but theories suggest that HIV infection may both impact the homeostatic and circadian systems of sleep-wake regulation. Studies to date have primarily explored sleep quality using the Pittsburgh Sleep Quality Index (PSQI), with limited objective data available to probe specific sleep characteristics in people living with HIV (PLWH). Those that have employed objective measures have utilised PSG, which describes aspects of sleep architecture, but does not allow for longer term monitoring of sleep habits in the home environment unlike actigraphy. Crucially, much of the research on HIV and sleep has been conducted in industrialised societies with greater access to HIV education and health-care. Therefore, the aims of this study are to utilise actigraphy to explore sleep parameters in PLWH, and assess whether HIV infection impacts chronotype in a rural dwelling South African population.

**Materials and Methods:** Participants (N = 688; aged 45-100y, mean 66.4 ± 12.07y; 426 women, 166 HIV+) from the Agincourt Socio-demographic and Health Surveillance System (Mpumalanga, South Africa) were selected randomly for inclusion in this study. Participants were required to complete the Munich Chronotype Questionnaire (MCTQ), and a subset of these participants (N = 172; aged 45-93y, mean 67.06 ± 11.6y; 99 women, 31 HIV+) wore an accelerometer for a minimum of 5 nights of actigraphy (ActiTrust, Condor Instruments). MCTQ data were processed in Rstudio using the 'mctq' package. ANOVA and subsequent multiple linear regressions were performed in RStudio to determine the relationship between HIV status and both actigraphy and MCTQ parameters, controlled for age and sex.

**Results:** Actigraphy analyses showed no significant relationship between HIV status and measures of sleep efficiency. However, there was a significant relationship between HIV status and total sleep time, with HIV+ individuals sleeping significantly less ( $F_{(3,168)} = 2.69$ ;  $P=0.482$ ). Analysis of the MCTQ showed that the effects of HIV infection were most prominent on working days, with HIV+ individuals going to bed earlier ( $F_{(3,599)} = 15.17$ ;  $P<0.001$ ) and spending more time in bed ( $F_{(3,599)} = 18.79$ ;  $P<0.001$ ). This effect was most pronounced in HIV+ men, and was not observed on free days. Analyses also revealed that HIV status had an interesting interaction with age on MCTQ derived chronotype ( $P=0.002$ ). In HIV+ individuals, chronotype was significantly later before the age of 60, but shifted earlier with age, whereas the opposite relationship was observed in HIV- individuals ( $F_{(4,264)} = 3.24$ ;  $P=0.012$ ).

**Conclusions:** Together, these data suggest that PLWH are more fatigued by work than HIV- individuals, and their earlier bedtimes may reflect an effort to combat. However, the reduced actigraphically derived total sleep time suggests that sleep needs may not be met, resulting in a cycle of sleep restriction and fatigue. Moreover, HIV may impact phase of the internal biological clock producing a shift in chronotype. Analysis of circadian phase markers will complement these data.

**Acknowledgements:** Supported by Academy of Medical Sciences

#### EFFECTS OF AUDITORY SLEEP MODULATION APPROACHES ON SLOW WAVES AND AUTONOMIC RECOVERY FUNCTIONS

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**Introduction:** Non-rapid eye movement (NREM) sleep is considered an important period of rest for the brain. However, the brain is not fully uncoupled from the body during sleep and the cardiovascular system is mainly under control of the autonomic nervous system (ANS). The large amplitude, low-frequency slow waves, the hallmark oscillations of NREM sleep, are positively correlated with the recovery promoting branch of the ANS, the parasympathetic nervous system (PNS). Therefore, slow waves may be a driver for promoting cardiovascular recovery. Yet, it is currently not known whether slow waves are functionally involved in cardiovascular restorative functions.

**Materials and Methods:** 23 healthy male participants (age 19–59) underwent one night of polysomnographic recordings using high-density EEG and simultaneous ECG recordings to obtain heart rate variability (HRV) measurements such as the root mean square of successive differences between two heart beats (RMSSD). We applied various auditory stimulation conditions (e.g., 1 Hz rhythmic stimulation (IS1), targeting the up or down phase of slow waves, binaural-beats, sham-control) in a windowed 10 s ON followed by 10 s OFF approach, within a single sleep period to modulate sleep slow waves.

**Results:** We found a significant slow wave activity (SWA) enhancement for all stimulation conditions (electrode Fz,  $p < 0.001$ ) using a linear mixed model approach. Up-phase targeting ( $p = 0.008$ ), down-phase targeting ( $p = 0.031$ ) and binaural-beats ( $p < 0.001$ ), caused significant increases in the RMSSD, a HRV measurement indicating PNS activity, whereas the effect of IS1 ( $p = 0.0504$ ) remained on trend-level. The increased PNS activity is reflected by a prolongation of the longest interval between two heart beats (RRI) within a stimulation window (all  $p < 0.05$ ) indicating a temporal slowing of the heart rate. Furthermore, we applied a repeated measures correlation that showed a significant positive correlation between the change of SWA within the first five seconds of the stimulation ON window and the change of RMSSD ( $r_{\text{rm}} = 0.24$ ,  $p = 0.03$ ) and the longest RR ( $r_{\text{rm}} = 0.42$ ,  $p < 0.001$ ) for all stimulation conditions.

**Conclusions:** Overall, our findings indicate that auditory slow wave modulation increases SWA and subsequently, may evoke a temporally coupled increase in PNS activity causing a temporal slowing of the heart rate. Furthermore, the extent of the increase in PNS activity is positively correlated with the increase in SWA. Thus, these findings suggests that cardiovascular recovery conditions exists when slow waves are prevailing.

**Acknowledgements:** This work was conducted as part of the SleepLoop Flagship of Hochschulmedizin Zürich and funded by the Swiss National Science Foundation (PZ00P3\_179795 to CL).

#### EFFECTS OF CLOZAPINE-N-OXIDE AND COMPOUND 21 ON SLEEP IN LABORATORY MICE

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**Introduction:** Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) are chemogenetic tools to activate or inhibit a targeted cell population. However, recent reports suggest that the prototypical DREADD agonist, Clozapine-N-Oxide (CNO), can affect brain activity and animal behaviour, putatively through conversion to clozapine. Despite the common use of DREADDs in neuroscience and sleep research, the potential effects of CNO upon sleep have never been systematically tested.

**Materials and Methods:** We assessed sleep in 16 male C57BL/6 mice after intraperitoneal injections of commonly used doses of CNO and Compound 21 (Cmpd-21), a DREADD agonist which cannot convert to clozapine. Mice

were housed under a 12/12 h light/dark cycle, chronically recorded with electroencephalography (EEG) and electromyography (EMG), and injected at light onset. All mice received saline and 5 mg/kg CNO in a counter-balanced design. Some animals also received 10 mg/kg CNO ( $n = 14$ ), 1 mg/kg CNO ( $n = 12$ ), and 3 mg/kg Cmpd-21 ( $n = 7$ ). Conditions were separated by a rest interval of at least 72 hours.

**Results:** Compared to saline, CNO suppressed rapid eye-movement (REM) sleep over the entire six hour observation period ( $F_{1,788,22.05} = 7.382$ ,  $p = 0.005$ ). Changes in sleep architecture consisted of reduced sleep onset latency and increased REM latency, particularly in the 1 mg/kg condition, as well as an increased duration and reduced number of non-REM (NREM) episodes for the 5 mg/kg and 10 mg/kg CNO conditions in line with a report by Varin et al. 2018. We also found an increased duration and reduced number of REM episodes for 10 mg/kg CNO. EEG NREM power spectra showed a significant power increase between 0.5–1.25 Hz and decrease above 6 Hz in the 5 mg/kg CNO condition. In addition, CNO reduced the frequency of brief awakenings (4–16s wakefulness,  $F_{1,968,23.62} = 10.38$ ,  $p < 0.001$ ) during the first two hours after injection. Interestingly, Cmpd-21 also suppressed REM sleep, increased the duration and reduced the number of NREM episodes, and reduced the frequency of brief awakenings.

**Conclusions:** Our preliminary results indicate that CNO and Cmpd-21 affect sleep. The pattern is similar to sleep after clozapine injections in rats (Sorge et al., 2004). However, the effects of Cmpd-21 suggest that even without clozapine back-metabolism, DREADD agonists can exert behavioural effects. This might be due to off-target binding at endogenous receptors (Jendryka et al., 2019). Our results require replication with alternative CNO and Cmpd-21 products and in an optimised experimental design. However, they indicate that chemogenetic experiments should include a DREADD-free control group and highlight the need for novel DREADD agonists and chemogenetic tools.

**Acknowledgements:** The authors declare no conflict of interest.

#### EFFECTS OF SLEEP DEPRIVATION IN THE PROCESS OF TAU PROTEIN DEPHOSPHORYLATION FOLLOWING SYNTHETIC TORPOR IN THE RAT

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**Introduction:** One of the main hallmarks of tauopathies is the hyperphosphorylation of neuronal Tau protein. Interestingly, the accumulation of hyperphosphorylated Tau (PPTau) also characterizes “synthetic torpor” (ST), a torpor-like condition that can be pharmacologically induced in rats (Cerri et al., 2013). However, after few hours of the recovery from ST, PPTau levels reverse to control (Luppi et al., 2019). Since during the first hours of the recovery from ST rats show a strong sleep-pressure, aim of the present study has been to investigate the role of sleep in the dephosphorylation of PPTau following ST.

**Materials and Methods:** Twelve Sprague-Dawley male rats (250–350g), adapted to an ambient temperature ( $T_a$ ) of  $24 \pm 0.5^\circ \text{C}$  and to a 12h:12h Light-Dark cycle, were implanted under general anesthesia with a microcannula in the Raphe Pallidus (RP). After one-week of recovery, ST was induced for 6 hours according to the protocol described by Cerri et al. (2013), by the repeated injection (one injection/h) in the RP of the GABA-A agonist muscimol (100 nL - 1 mM). Soon after their return to normothermia, animals were either sleep deprived by gentle handling for 3 ( $n = 3$ ) or 6 ( $n = 3$ ) hours (R3SD and R6SD, respectively) or allowed to sleep (normal sleep, NS) for 3 ( $n = 3$ ) or 6 ( $n = 3$ ) hours (R3NS and R6NS, respectively). Soon after animals' euthanasia, fresh sample of parietal cortex (P-Cx) were collected in order to evaluate by Western Blot the levels of the following proteins and enzymes: AT8 (p[Ser202/Thr205]-Tau, phosphorylated Tau form), Tau-1 (unphosphorylated Tau form), p[Thr205]-Tau (a neuroprotective form of phosphorylated Tau; Ittner et al., 2016); p[Ser9]-GSK3 $\beta$  (the inhibited form of the main kinase targeting Tau); PP2A (the main phosphatase targeting Tau) and p[Ser473]-Akt2 (active anti-apoptotic factor and GSK3 $\beta$  inhibitor). Moreover, the plasma levels of melatonin were determined by ELISA.

**Results:** Overall, AT8 levels were reduced in the SD groups compared to the NS ones ( $p < 0.05$ ), while Tau-1 levels were not significantly affected. A clear trend towards higher p[Thr205]-Tau levels was also observed after SD. The decrease in PPTau induced by SD was accompanied by an increase in both p[Ser9]-GSK3 $\beta$  and p[Ser473]-Akt2 levels, although statistical significance was reached only for the latter ( $p < 0.05$ ). Also, PP2A levels were lower in R3SD vs. R3NS ( $p < 0.05$ ). Finally, melatonin levels were higher in R3SD vs. R3 ( $p < 0.05$ ).

**Conclusions:** The present results indicate that SD soon after ST enhances PPTau dephosphorylation, coherently with the observed concomitant increase of p[Ser9]-GSK3 $\beta$  and p[Ser473]-Akt2. This molecular pattern is known as being neuroprotective, and may be mediated by melatonin that can activate Akt2 and, consequently, inhibit GSK3 $\beta$  by acting on the PI3K/Akt2/mTOR antiapoptotic pathway (Risso et al., 2015). These findings open interestingly translational perspectives in the use of sleep deprivation in patients suffering from hypothermia-induced brain PPTau formation due to general anesthesia (Whittington et al., 2013).

**Acknowledgements:** The authors wish to thank Fondazione Carisbo that supported this work.

### ELITE ATHLETES PILOT STUDY OLYMPIC GAMES RIO 2016

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**Introduction:** The data suggest that shifting the time with late-night race simulation tends to desynchronize circadian rhythms, compromising the physiological and psychological state of athletes. The results indicated that there are effects on HRV (cardiac variability), SQ (quality) and TMD (mood disorders).

**Materials and Methods:** Three male swimmers (age  $21 \pm 1$ ), qualified in the sprint races for the 2016 Olympic Games in Rio. Monitored over the course of a week of night training sessions with the same time schedule as the Olympic semi-finals and finals. Athletes were monitored during sleep for quality assessments (SQ), where the ratio of total time in bed was calculated using actigraphy (SenseWear, BodyMedia USA). The athletes were monitored in the two days before the start of the protocol (T0) and in the following days, respectively after 1, 3, 5 days (T1, T2, T3). Resting Heart Rate (HRR) and Cardiac Variability (HRV) were evaluated upon awakening (Minicardium, Hosand - Italy). All athletes responded to an "Evening/Morning" questionnaire in relation to the chronotype profile. The assessment of mood disorder using the "Total Mood Disturbance" (TMD) was conducted before and after the week of night training. Nutrition has been specially adjusted to contribute to the maintenance of sleep quality. For each variable (mean and DS) a time-factor univariate ANOVA (T0-T1-T2-Y3) was performed to compare the significant effects between the individual sessions. At the same time, a t-test was performed to verify any differences in the TMD (at the beginning and at the end of the protocol). The significance level was set at  $p < 0.05$  using SPSS 15.0 Software.

**Results:** The data suggest that shifting the time with late-night race simulation tends to desynchronize circadian rhythms, compromising the physiological and psychological state of athletes. The main results indicated that there are effects on HRV (cardiac variability), SQ (quality) and TMD (mood disorders). The sleep detected is below the required physiological limit and higher than the alert levels of partial deprivation, starting from the second day of the protocol. Similar results were reported with a study that predicted partial sleep deprivation for four days for 2.5h, with a mood alteration, increased depression, tension, confusion, fatigue, rashes, decrease in strength.

**Conclusions:** Increased sleep disorders, increased fatigue and tiredness, as well as alterations of the nervous system are present in 82% of athletes before competitions and seem to be assimilated to a state of overreaching in the short term even in swimmers. The time shift was shown to have a significant effect on the observed psychological and physiological variables, indicating potential effects on athletes' behaviour as early as day two. Therefore, to limit the effects of an induced change in circadian rhythms, proper education of the athlete seems to be particularly effective.

**Acknowledgements:** Migliaccio, GM., Di Nino A., Avaldi F., Bazzu A., Mullen G., Padulo J., Sport Science Lab (London, UK), CONI Italian Olympic Committee (Sardinia, Italy), A.D.N. Swim Project (Italy), Nutrition Area AC Milan (Milan, Italy), Energy Standard Swimming Club (Ukraine), Swimming Science (USA), 7: eCampus University (Italy), Faculty of Kinesiology, University of Split (Croatia)

### ARC GENOTYPE MODULATES SLOW WAVE SLEEP AND EEG SPECTRAL POWER FOLLOWING TOTAL SLEEP DEPRIVATION

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**Introduction:** The activity-regulated cytoskeleton associated protein (ARC) gene is an immediate early gene that is involved in synaptic plasticity. Evidence from a rodent model suggests that Arc may also be involved in sleep homeostasis. In humans, sleep homeostasis is manifested by a marked increase in slow wave sleep (SWS) following acute total sleep deprivation. There are large, trait individual differences in the magnitude of this SWS rebound effect, with concomitant changes in EEG spectral power. However, little is known about the molecular mechanisms regulating the sleep homeostat and the expression of individual differences therein. We sought to determine whether a single nucleotide polymorphism (SNP) of the ARC gene is associated with individual differences in SWS rebound and EEG spectral power.

**Materials and Methods:** 50 healthy normal sleepers ( $27.3 \pm 4.9$  years; 28 females) participated in one of two in-laboratory studies. Each participant had a 10-hour baseline sleep opportunity (22:00–08:00), 38 hours of consecutive wakefulness, then a 10-hour recovery sleep opportunity (22:00–08:00). Sleep periods were recorded polysomnographically and scored visually according to standardized criteria. Genomic DNA was assayed for the ARC c.\*742+58C>T non-coding SNP, rs35900184. The genotype effect on time spent in SWS was assessed using mixed-effects ANOVA with fixed effects for ARC genotype, night, and their interactions. Log-transformed spectral power over 0.2 Hz frequency bins in each of four frequency bands – delta (0.8–4.0 Hz), theta (4.2–8.0 Hz), alpha (8.2–12.0 Hz), and beta (12.2–16.0 Hz) – was analyzed by band using a mixed-effects ANOVA with fixed effects for ARC genotype, night, frequency bin, and their interactions. All analyses included study and age as covariates and a random effect over subjects on the intercept.

**Results:** The genotype distribution in this sample was 33 C/C homozygotes, 11 C/T heterozygotes, and 6 T/T homozygotes. There was a significant ARC x night interaction on SWS rebound ( $F_{2,47} = 4.84$ ,  $p = 0.012$ ). C/C homozygotes exhibited  $60.4 \pm 3.0$  minutes more SWS, whereas C/T heterozygotes exhibited only  $46.0 \pm 5.2$  minutes and T/T homozygotes only  $42.4 \pm 7.1$  minutes more SWS during recovery sleep compared to baseline. There was also a significant ARC x night interaction on theta ( $F_{2,1833} = 5.94$ ,  $p = 0.003$ ) and alpha ( $F_{2,1833} = 8.58$ ,  $p < 0.001$ ) power. C/C homozygotes had 18.9% more theta power and 8.7% more alpha power, whereas C/T heterozygotes had 17.9% more theta and 7.6% more alpha power and T/T homozygotes had 20.0% more theta power and 15.1% more alpha power during recovery sleep compared to baseline sleep.

**Conclusions:** Our results show that ARC genotype is associated with individual differences in SWS and in NREM EEG spectrum responses to sleep deprivation. ARC appears to mediate these physiological responses to sleep loss through two seemingly distinct dynamics, with homozygosity for the T allele being associated with a blunted SWS response and an amplified increase in spectral power in the theta and alpha bands. The functional implications of these ARC effects remain to be determined.

**Acknowledgements:** Research supported by ONR grant N00014-13-1-0302, NIH grant R21CA167691, and USAMRDC grant W81XWH-18-1-0100.

## EXAMINING THE IMPACT OF EXPOSURE TO NATURAL & BUILT ENVIRONMENTS ON CHILDREN'S SLEEP DURATION

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**Introduction:** Inadequate sleep among school-aged children is a critical public health issue which has been linked to a variety of physical health problems. Lack of quality sleep can also negatively impact cognitive functioning and social behaviours. A growing body of research suggests that exposure to natural environments can have positive benefits for children's physical health, emotional well-being, and cognitive development. The purpose of this study is to examine the impacts of children's daily exposure to different environments (natural and built) on their sleep duration.

**Materials and Methods:** Data was collected for 614 children (aged 9–14 years) drawn from 22 elementary schools throughout London, Ontario. Participants completed the two-week STEAM (Spatial Temporal Environmental Activity Monitoring) protocol which involved completion of a survey, daily activity diary, and tracking the time they spent in different environments with a portable GPS for two weeks. Hierarchical multiple linear regressions were used to explore the relationship between children's sleep duration and exposure to neighbourhood level environmental features.

**Results:** In addition to a number of important individual level variables, analysis revealed that the amount of time spent in public parks and green spaces during the day had a positive impact on children's sleep duration. Implications for policy will be discussed.

**Conclusions:** This research fills gaps in our understanding of how natural and built environments may influence children's sleep. Implications for future research and policy will be discussed.

**Acknowledgements:** Thanks to research staff of the Human Environments Analysis Lab at Western University. This research was supported through grants from the Children's Health Research Institute, Canadian Institutes of Health Research and the Heart and Stroke Foundation of Canada.

## FAVORIRE L'APPRENDIMENTO DI VOCABOLI DURANTE IL SONNO ATTRAVERSO UN SISTEMA DI CLOSED-LOOP TARGETED MEMORY REACTIVATION IN SETTING DOMESTICO: UNO STUDIO PILOTA

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**Introduzione:** Il sonno svolge un ruolo cruciale nel consolidamento delle memorie. La *Targeted Memory Reactivation* (TMR) è una tecnica in grado di manipolare il processamento notturno delle memorie, tipicamente utilizzata in *setting* laboratoriale. Stimoli sensoriali presenti nel contesto di apprendimento vengono usati per riattivare in maniera non invasiva tracce mnestiche durante il sonno profondo (N3). Considerando la vasta letteratura scientifica che supporta l'efficacia della TMR nel favorire il consolidamento delle memorie, il passo successivo consiste nella traslazione di questo paradigma alla vita di tutti i giorni. Pertanto, abbiamo sviluppato un sistema portatile per la presentazione automatica di stimoli uditivi durante la fase N3 (*closed-loop* TMR, CL-TMR) che si basa sulla registrazione dell'attività EEG di una *headband* EEG commerciale. Tale sistema è stato utilizzato per favorire il consolidamento di memorie dichiarative attraverso la presentazione di suoni durante il sonno in un *setting* domestico.

**Metodologia:** Dodici studenti universitari, (età media  $\pm$  deviazione standard, 24,50 anni  $\pm$  2,32) hanno partecipato allo studio pilota. Nel tardo pomeriggio, i partecipanti hanno svolto un compito di apprendimento di vocaboli che richiedeva l'acquisizione della traduzione italiana di pseudo-parole (e.g., "tacipaca"), seguito da una sessione di test (T1). Durante la notte, metà delle pseudo-parole è stata ripresentata acusticamente durante la fase ascendente delle oscillazioni lente attraverso il sistema di CL-TMR. Metà dei suoni consisteva nelle pseudo-parole tradotte

correttamente nella sessione T1, mentre l'altra metà era composta da quelle pseudo-parole la cui traduzione non era stata appresa. I segnali EEG sono stati acquisiti utilizzando la *Dreem Headband* (Rythm SAS, Paris, France), il cui algoritmo di detezione delle oscillazioni lente è stato utilizzato per innescare la presentazione dei suoni. La rievocazione mnestica è stata misurata al mattino seguente (T2). È stata valutata la differenza tra T1 e T2 delle pseudo-parole tradotte correttamente, confrontando la *performance* per le pseudo-parole presentate durante la notte con quelle non presentate. A livello elettrofisiologico, sono stati valutati i potenziali evento-correlati (ERP) e la perturbazione spettrale evento-correlata alle stimolazioni nel range 5-18 Hz. Sono state confrontate le risposte corticali associate a una corretta traduzione al mattino con quelle associate a una mancata/errata traduzione.

**Risultati:** La riepocizzazione alle pseudo-parole durante il sonno migliorava la memoria per le rispettive traduzioni italiane (media  $\pm$  deviazione standard,  $+13.20\% \pm 20.75$ ) rispetto a quelle non presentate ( $-5.26\% \pm 22.31$ ;  $p=0.04$ ). Le effettive riattivazioni erano associate a una maggiore positività e negatività frontale degli ERP. L'analisi tempo-frequenza ha evidenziato un incremento nella banda *spindle* a 1000–2000 msec dall'inizio della stimolazione ( $p<0.05$ ) come correlato della riattivazione delle tracce mnestiche correttamente rievocate al mattino.

**Conclusioni:** Questo studio pilota dimostra la validità del sistema di CL-TMR nel favorire l'apprendimento di memorie durante il sonno in un *setting* domestico. Una stimolazione efficace determina un successivo aumento di attività *spindle*, confermando l'implicazione di specifiche dinamiche oscillatorie nell'effetto della TMR. L'utilizzo di un sistema portatile di CL-TMR potrebbe aprire la strada all'applicazione del paradigma di TMR alla vita quotidiana, promuovendo quei ritmi elettrofisiologici coinvolti nel consolidamento sonno-dipendente delle memorie.

## FREQUENCY OF OBSTRUCTIVE SLEEP APNEA SYNDROME IN AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE PATIENTS

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**Introduction:** Autosomal dominant polycystic kidney disease (ADPKD), the most common inherited renal cystic disease, is characterized by progressive cyst growth in the kidney and other organs. Cyst expansion leads to focal areas of renal ischemia. Increased activity of the renin-angiotensin system (RAS) secondary to ischemia seems to play an important role in the rise in blood pressure. On the other hand, obstructive sleep apnea (OSA) which is most seen sleep-disordered breathing, is characterized by apneas, hypopneas related to repeated upper airway obstruction during sleep, leading to intermittent hypoxaemia and sleep fragmentation (5). Hypoxia stimulates RAS activation. This activation leads to local inflammation in the carotid body which plays a pathogenic role in sleep apnea. Moreover, this activation leads to increase in blood pressure. In this study, we investigated the frequency of obstructive sleep apnea syndrome (OSAS) in ADPKD patients either with chronic kidney failure (CKF) or not. We also compared frequency of OSAS between ADPKD patients and a control group with normal kidney function and normal blood pressure. We also aimed to see effect of RAS blockage on obstructive sleep apnea.

**Materials and Methods:** We recruited 51 ADPKD patients for the study. Additionally, presence of sleep apnea syndrome symptoms, other comorbidities including hypertension, use of ACE-I or ARB were asked to all participants. Finally, 43 patients were enrolled into polysomnography (PSG) study. In-laboratory full night PSG which is gold-standard diagnostic test for OSA was performed to all participants. Patients with apnea hypopnea index (AHI) score higher than 5 were accepted as having OSAS. Patients with eGFR values below 60 ml/min were accepted as CKF patients. We matched the patients and controls with normal kidney function and normal blood pressure.

**Results:** 26 patients had OSAS in the study group. Regarding **severity of OSAS among 26 patients, 16 patients had mild OSAS, 7 patients had moderate OSAS and 3 patients had severe OSAS.** Frequency of OSAS in patients with eGFR levels below 60 ml/min were significantly higher than individuals with eGFR levels above 60 ml/min (14/17 (82,3%); 12/23 (52,1%), respectively,  $p=0,048$ ). In terms of presence of OSAS, there was no significant difference between ADPKD and control groups ( $p=0,367$ ). Subgroup

analysis of study group was conducted and subgroups were compared with control groups after adjusting age, gender and BMI. Regarding presence of OSAS, there was no significant difference between e-GFR>60 ml/min ADPKD patients and control group ( $p=0,759$ ). However, there was significant difference between e-GFR<60 ml/min ADPKD patients and control group ( $p=0,018$ ). Regarding effect of RAS blockage on frequency of OSAS in hypertensive ADPKD patients, there was no significant difference in terms of OSAS between patients using ACE-I/ARB compare to patients not using RAS blockers (18/27(66,6%), 3/5(60%), respectively;  $p=0,77$ )

**Conclusions:** It is well known that ESRD (e-GFR<15 ml/min) is associated with sleep disorders. In our study, we showed that ADPKD patients with CKF(e-GFR 15-60 ml/min) had higher rate of OSAS compare to non-CKF patients and healthy control group. As conclusion, uremia progression of rather than RAS activation seems to play a role for OSAS in ADPKD patients.

**Acknowledgements:** We thank Dr. Sinan Trabulus.

## HEARTBEAT-RELATED RESPONSES OF FRONTAL CORTICAL NEURONS IN THE SLEEP-WAKE CYCLE IN CATS

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**Introduction:** The visceral theory of sleep (Pigarev, 2013) assumes that the cerebral cortex switch to the analysis of interoceptive information coming from visceral organs during sleep. This was first confirmed in gastrointestinal tract researches, when cortical responses related to its activity were actually detected in visual cortical areas during sleep. Moreover, we found some sleep-related responses for cardiac activity on iEEG and local field potentials (LFPs), which appeared in normal sleep in frontal and insular cortical region. This study aimed to explore heartbeat-related activation of single neurons in frontal cortex regions during sleep-wake cycle.

**Materials and Methods:** In two adult cats, LFP and neuronal firing were recorded with transcranial intracerebral bipolar microelectrodes from frontal cortex. Electrodes' placement was selected according to pre-existing assumptions about the possible whereabouts of cortical areas related to heart activity. ECG was recorded with two electrodes located in the stomach and on the cats head. We recorded iEEG, breath rhythm and eye movements as well, to identify the sleep phases. Our analysis included 2-5 hours records, with periods of wake, normal NREM and REM sleep. The processing and statistical analysis were made with Spike2 CED, including special self-made scripts.

**Results:** In 20 records, we marked out over 120 single neurons. Heartbeat-related responses as changes of neuronal firing were found in 32,4%, in frontal cortex of both hemispheres. This connection between neuronal firing and cardiac activity appeared during slow-wave sleep but was not observed in wakefulness.

**Conclusions:** Now we see that information related to cardiac activity reaches cerebral cortex during sleep indeed. Our results confirm that cerebral cortex becomes visceral-analyzing during sleep, and this special brain-heart axis develops information in sleep in order to restore the somatic functionality of all the body organ systems.

**Acknowledgements:** This study was supported by RFBR grant No 16-04-00413.

## HUMAN SERUM PROTEIN CHANGES AFTER 6 H OF SLEEP DEPRIVATION INVESTIGATED WITH NEWER PROTEOMIC METHODS

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**Introduction:** Sleep-wake associated studies using omic-methodology are increasing (O'Callaghan et al. 2019). Studying effects of partial sleep deprivation (SD) at night using proteomics- and systems biological approach has been sparse (Mauvoisin, 2019 and Noya et al. 2019). Earlier finding revealed changes in 34 proteins in human blood serum after 6 hour

of sleep deprivation at night (Bjørkum et al. 2021). The aim of this study was to further identify differentially expressed proteins in human blood serum after loss of 6 h sleep at night using newer proteomic methods and exploring systems biological databases.

**Materials and Methods:** In a within subject-design-study a control night were the participants (n=6 females) slept from 10:00 pm to 07:00 am and the following night sleep deprivation (SD) was performed from 10.00 pm to 04:00 am. Sleep/wake data can be found in Bjørkum et al. 2021. Venous blood was sampled at 4:00 am. Proteins from blood serum was heat denatured at 95°C for 5min, prior to reduction (DiThioThreitol) and alkylation (Iodoacetamide). Denatured proteins were digested overnight (16h) at 37°C and desalted using Oasis (waters) spin columns. Desalted proteins were lyophilized and dissolved in HEPES buffer (pH 8.5). TMT-labels were added to each sample (16plex, ThermoFisher), and desalted and lyophilized prior to high-pH fraction using an offline HPLC (Waters, HPLC). The samples were run a Orbitrap Exploris massspectrometer (ThermoFisher) coupled to an Ultimate 3000 HPLC. Raw-files were search against the Swissprot database using Proteome Discoverer 2.5. Further analysis of the data was performed in Perseus. Gene ontology analysis were performed using Gene Set Enrichment Analysis, Omim, Webgestalt.

**Results:** We identified 590 proteins, 63 proteins were differentially expressed, 25 upregulated and 38 downregulated. The 63 proteins took part in 229 biological processes and 31 molecular functions.

The differentially expressed proteins after 6 hours of sleep deprivation at night could be linked to affected biological processes such as e.g., immune-, coagulation- and metabolic related cellular processes. Also, proteins associated with pathological conditions such as cardiovascular- and dementia related diseases and various types of cancer were affected.

Earlier published omic-studies after lack of sleep indicate cellular stress reflected in a distinctly changed serum proteome by identifying specific protein markers to reveal distinctly affected biological processes, molecular functions, cellular pathways, DNA damage and repair and disease related proteins after sleep deprivation (see refs. In Bjørkum et al. 2021). Impaired immune system and diseases associated with sleep deprivation have been reported (Bjørkum et al. 2021, Ma et al, 2018; O'Callaghan et al. 2019, Pellegrino et al., 2012 and Pinotti et al., 2010).

**Conclusions:** Acute sleep deprivation as little as 6h at night, at least in females, affects several differential expressed proteins taking part in several distinct biological processes- and molecular function categories. Also, the differentially expressed proteins are related to pathological associated conditions like impaired coagulation, oxidative stress, inflammation and immune suppression, neurodegenerative related disorders, and cancer. This is in line with earlier studies from our group (Bjørkum et al. 2021).

**Acknowledgements:** Beate Kluge, Tiril Knutsen, Kristina Lærdal, Siri Bildøy

## HYPOCRETIN RELEASE AND PLASTICITY OF HYPOCRETINERGIC RECEPTORS IN A PHARMACOLOGICAL MODEL WITH NARCOLEPSY-LIKE FEATURES INDUCED BY SUVOREXANT IN RATS

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**Introduction:** The hypocretinergic (Hrct) system is a neuromodulatory network involved in many physiological processes among which is the control of the sleep-wake cycle. This system comprises two excitatory hypothalamic neuropeptides -Hrct1 and Hrct2 (or orexins A/B)- and two G-protein-coupled receptors -HrctR1 and HrctR2- widely distributed throughout the central nervous system. Malfunction of this system is related to narcolepsy. Low or undetectable levels of Hrct1 in cerebrospinal fluid (CSF) constitutes a diagnostic criterion for Narcolepsy Type I. In the present study we have used Suvorexant, a dual Hrct receptor antagonist, to obtain a pharmacological experimental model with Narcolepsy-like features in rats by blocking the two Hrct receptors. In this model we have explored CSF Hrct1 levels and HrctR1 and HrctR2 expression within the hypothalamus.

**Materials and Methods:** In three groups of 8 rats daily i.p. injections of Suvorexant (10 or 30 mg/kg doses) or vehicle (DMSO) were done in the

dark period for 7 days. Body weight was monitored throughout the treatment. After treatments, CSF Hcrt1 concentration was determined by competitive enzyme immunoassay (EK-003-30, Phoenix Pharmaceuticals Inc). HcrtR1 and HcrtR2 levels within the hypothalamus were analyzed by western blotting (HcrtR1 antibody - ab68718; HcrtR2 antibody - ab183072). Paired t-tests, ANOVAs for repeated measures and independent samples, and post-hoc Fisher PLSD test were used for statistical comparisons.

**Results:** Systemic blockade of the hypocretinergic transmission with the high dose of Suvorexant produced a statistical significant increase in body weight by the end of the treatment. In control conditions hypothalamic HcrtR1 expression was significantly higher than that of HcrtR2. The high dose of Suvorexant also produced statistical significant changes in both, Hcrt1 levels in CSF and HcrtR1 expression in the hypothalamus, while, not significant changes occurred with the low dose. That is, daily i.p. administration of 30mg/kg of Suvorexant produced a significant decrease in Hcrt1 concentration in CSF together with a significant overexpression of HcrtR1 in the hypothalamus with respect to the control group. HcrtR2 hypothalamic levels did not change significantly.

**Conclusions:** The pharmacological model with narcolepsy-like features induced by chronic administration of high doses of suvorexant showed a significant increase in body weight and a significant decrease in CSF Hcrt1 levels as observed in narcoleptic type1 patients. These effects were accompanied by a compensatory overexpression of HcrtR1 in the hypothalamus while HcrtR2 expression remained almost unchanged. Altogether, they indicate an autoregulatory role of HcrtR1 within the hypothalamus for the synthesis and/or release of hypocretins.

**Acknowledgements:** This study was supported by F119058 FEDER grant

#### INVESTIGATING THE RELATIONSHIP BETWEEN SLEEP AND FASTING-INDUCED TORPOR IN THE LABORATORY MOUSE

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**Introduction:** Torpor is a controlled state of hypometabolism that many species utilise to conserve energy. It is thought that there is a relationship between torpor and sleep. For example, torpor is entered via non-rapid eye movement sleep (NREMS), and a rebound in slow wave activity (SWA, EEG power density between 0.5–4 Hz) is observed in sleep immediately following arousal from torpor in Djungarian hamsters. Laboratory mice are known to readily enter bouts of torpor when undergoing food restriction protocols, which are commonly used in sleep and circadian studies, and behavioural neuroscience. However, the relationship between euthermic sleep and torpor in laboratory mice has not been well characterised, as such torpor induction may be confounding data generated in these fields when food restriction (FR) is used. The aim of this study was to further investigate how torpor and euthermic sleep processes interact.

**Materials and Methods:** Chronic EEG/EMG implants were performed in adult male C57Bl/6J mice (n=4). Mice subsequently underwent a 6-hour sleep deprivation (ZT 21-3) under ad libitum feeding conditions. Following a recovery period, mice were fed once daily and maintained at ~85% of their free feeding weight to induce torpor. Peripheral body temperature (T<sub>skin</sub>) was continuously monitored using non-invasive thermal imaging cameras, to detect hypothermia bouts associated with torpor. Torpor bouts were operationally defined as a T<sub>skin</sub> of >2 standard deviations below baseline for at least 1 hour. Once the animals were reliably entering torpor, another 6-hour sleep deprivation was conducted, followed by feeding. As a control, mice were also fed following a ~6-hour torpor bout occurring between ZT 21-3. Vigilance states were scored offline by visual inspection of EEG/EMG signals in 4s epochs.

**Results:** On days where no manipulations were performed, mice spent a greater percentage of time in NREMS during FR compared to during ad libitum (56% vs 38%, P<0.05). In the 6 hours following sleep deprivation, mice spent significantly less time in NREMS when food restricted compared to when fed ad lib (52.1 ± 2.5% vs 62.9 ± 4.9%; p=0.04). Mice fed after a torpor bout also spent less time in NREMS compared to post-sleep

deprivation in ad libitum conditions (48.6 ± 3.8% vs 62.9 ± 4.9%; p<0.05). In the 24 hours following sleep deprivation/torpor, mice spent more time in NREMS (Ad lib: 42.6 ± 5.1%; FR: 50.8 ± 2.1%; Torpor: 53.1 ± 2.9%), but less time in REMS (Ad lib: 7.0 ± 1.4%; FR: 6.0 ± 1.3%; Torpor: 6.2 ± 1.3%), when undergoing food restriction although these differences were not significant (P>0.05). In all conditions, initial sleep after sleep deprivation or torpor was characterised by increased levels of SWA. However, peak SWA in the FR and post-torpor condition was delayed and lower than during ad libitum conditions (Ad lib peak: 153 ± 1.3%; FR peak: 118 ± 2.1%; Torpor peak: 98 ± 4.6%).

**Conclusions:** Our preliminary results support the notion that daily sleep architecture is altered in association with fasting-induced torpor in mice, but provide limited evidence for that fasting-induced torpor is a sleep-depriving state.

**Acknowledgements:** NC3Rs (NC/S001689/1)

#### MACHINE LEARNING APPROACH FOR DETECTION OF INTRACRANIAL INTERICTAL DISCHARGES IN THE MEDIAL TEMPORAL LOBE DURING SLEEP

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**Introduction:** Interictal epileptiform discharges (IEDs) are brief paroxysmal electrographic events observed between spontaneous recurrent seizures in epilepsy patients. IEDs (i) have a duration of 70–200 ms (for a sharp wave) or 20–70 ms (for a spike), (ii) entail an abrupt change in polarity, (iii) have a restricted physiological spatial field, and (iv) are most prevalent in non-rapid eye movement (NREM) sleep. IEDs occurring in the medial temporal lobe (MTL) during sleep may impair memory by affecting hippocampal-cortical coupling, and their reliable detection has clinical value in epilepsy and other neurological conditions. Here we set out to develop and validate automatic detection of IEDs with a machine learning approach in intracranial EEG (iEEG) and in scalp EEG.

**Methods:** Six drug-resistant mesial temporal lobe epilepsy (MTLE) patients underwent clinical pre-surgical evaluation and were implanted with intracranial depth electrodes in the MTL. Overnight iEEG recorded with Blackrock system, referenced to a central scalp electrode sampled at 2KHz and bandpass-filtered between 0.1-500Hz. Sleep was scored using established guidelines of the American Academy of Sleep Medicine. We focused on three channels per hemisphere: the anterior hippocampus referenced to Cz, the anterior hippocampus referenced to adjacent electrode (5mm more laterally), and the amygdala referenced to Cz. Pre-processing included segmentation of the signal to 250ms intervals and extraction of signal features for the current and the previous interval, such as spectral power in specific frequency bands and statistical features such as variance and skewness. Then, we split intervals randomly into train (75%) and test (25%) subsets and trained two algorithms- Random forest and LightGBM. The first task aimed at detecting IEDs in iEEG. To this end, we used a dataset that contained 337 IEDs in NREM sleep (overall: 30 minutes, n=6) tagged by an expert neurologist. The second task aimed at detecting IEDs in a limited number of scalp EEG (Fz, Cz, Pz) and EOG electrodes. To this end, we used the results from the first model on the entire overnight dataset. This dataset contained 3466 IEDs (overall: 40 hours, n=6) as tagged by the random forest classifier. For each task and algorithm, we assessed the test results using standard metrics of precision (number of positive class predictions that indeed belong to the positive class) and recall (also known as sensitivity; number of positive class predictions out of all positive examples in the dataset).

**Results:** Results of the first task (automatic detection in intracranial data) were assessed by comparing model outputs to manual annotation by expert neurologists. We obtained with random forest classifier: precision=92% and recall=66%, and with LightGBM classifier: precision=88% and recall=74%. Results of the second task (automatic detection in scalp

EEG/EOG electrodes) were assessed by comparing model outputs to the automatic intracranial results. We obtained with random forest classifier: precision=77% and recall=2%, and with lightGBM: precision=67% and recall=3%.

**Conclusion:** The presence of a small (<5%) subset of IEDs in the MTL can be automatically detected with acceptable (>75%) precision non-invasively. We are now exploring the extent to which our models can generalize across individuals.

**Acknowledgment:** Supported by the European Research Council (ERC-2019-CoG 864353).

### MORNING PERCEPTION OF SLEEP, STRESS AND MOOD, AND ITS RELATIONSHIP WITH OVERNIGHT PHYSIOLOGICAL SLEEP PROCESSES IN ADOLESCENTS

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**Introduction:** Adolescence is characterized by profound biopsychosocial maturation, including changes in sleep physiology and behavior. Insomnia frequently emerges in adolescence, toward a greater prevalence in older girls. Although the objective-subjective sleep discrepancy is among the principal factors considered in insomnia diagnosis, the extent to which the profound developmental sleep changes occurring in adolescence are reflected in changes in subjective sleep perception is still unknown. In this study we aimed to investigate age- and sex-dependent differences in morning sleep perception, mood (e.g., sadness, stress, irritability), and readiness (e.g., concentration, fatigue, readiness), and explore the physiological correlates (polysomnographic (PSG) and electroencephalographic (EEG) sleep measures, and indices of sleep cardiac autonomic function) of morning perception of sleep, mood and readiness, in adolescents.

**Materials and Methods:** The sample consisted of 137 healthy adolescents (Age Range: 12–21 years; Mean Age: 15.5±2.3 y; 61 girls; Body Mass Index: 21.9 ±4.8 kg×m<sup>-2</sup>; 105 Caucasian), who were participating in the baseline sleep study of the National Consortium on Alcohol and Neurodevelopment in Adolescence (NCANDA) at SRI International (N = 109) and the University of Pittsburgh (N = 28). Participants underwent a laboratory-based PSG evaluation and rated their sleep quality, mood, and readiness the following morning. PSG, EEG, and autonomic indices were included in models to determine predictors of morning sleep perception, mood and state of readiness. Analyses were performed using Lasso predictor selection and linear regression with robust variance estimates.

**Results:** There was a significant effect of age for perceptions of sleep, with older adolescents reporting a deeper and less restless sleep than younger adolescents (p<0.05), however, they also reported more awakenings than younger adolescents (p<0.05). There were no sex differences in perceptions of sleep, however, older boys had greater discrepancy between the subjective and objective assessments of time spent awake at night (i.e., underestimation of PSG wakefulness), compared to younger boys and younger and older girls (p<0.05). Overall, PSG, EEG, and autonomic (heart rate and vagal-associated heart rate variability) measures explained between 3% and 29% of variance in morning sleep perception, mood, and readiness indices. Equally for both sexes, PSG measures (sleep timing, duration, and continuity) were the strongest predictors of morning self-reported measures, however, quantitative sleep EEG delta activity and autonomic measures also contributed to predicting sleep depth and restlessness, alertness, fatigue, sensation of being exhausted, and irritability (p<0.05).

**Conclusions:** For both boys and girls, the subjective experience of sleep is a complex and multi-component phenomenon, in which distinct physiological sleep processes only partially contributing to the morning perception of sleep and related measures of mood and readiness.

**Acknowledgements:**

### NEURONS IN PREFRONTAL CORTEX RESPOND TO SLEEP DEPRIVATION BY INITIATING SLEEP PREPARATORY BEHAVIOUR AND NREM SLEEP

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**Introduction:** Animals undertake specific behaviours before sleep, yet little is known about whether these innate behaviours, such as nest building, are actually an intrinsic part of the sleep-inducing circuitry. The prefrontal cortex (PFC) contributes to executive functions and planning and is particularly sensitive to sleep deprivation. We examined the role of a subset of mouse PFC somatostatin/GABAergic (SOM/GABA) neurons which we found become activated during sleep deprivation.

**Materials and Methods:** We used cfos-based activity tagging to selectively capture SOM/GABA neurons in the mouse PFC cells that became active with sleep deprivation. To dissect the behavioural functions of these SOM/GABA cells, tagged mice were then challenged both chemogenetically and optogenetically. Projection specificities of the cells were tested by immunohistochemistry and electrophysiology.

**Results:** We found that mouse PFC SOM/GABA neurons, which become activated during sleep deprivation, induce sleep preparatory behaviour (nest building) when directly re-activated. Furthermore, if their activation is prolonged, these tagged neurons induce sustained global NREM sleep. We also found that these sleep-deprivation tagged PFC SOM/GABA neurons have long-range projections to the lateral preoptic (LPO) and lateral hypothalamus (LH) and these projections govern induction of nesting and NREM sleep respectively.

**Conclusions:** Our findings provide a circuit link for how the PFC responds to sleep deprivation by coordinating sleep preparatory behaviour and subsequent sleep. In the case of the PFC, with its role in executive function and planning, a direct connection to hypothalamic centres to initiate sleep preparation, and to help reinforce global sleep, could be a survival advantage to ensure the animal is in a safe place prior to sleeping.

**Acknowledgements:** This work was supported by the Wellcome Trust, the UK Dementia Research Institute at Imperial College, an MRC UK DRI studentship, an Imperial College Schrodinger Scholarship, an Imperial College/China Scholarship scheme, and EPSRC studentship, EPSRC Centre for Doctoral Training in Neurotechnology for Life and Health.

### OBESITY-HYPOVENTILATION SYNDROME PREVALENCE IN PATIENTS WITH METABOLIC SYNDROME: INTERMEDIATE ANALYSIS ESTIMATES OBESITY-RELATED SLEEP HYPOVENTILATION PREVALENCE AT 6%

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**Introduction:** Obesity-hypoventilation syndrome (OHS) is defined by the combination of obesity (Body-Mass Index (BMI) ≥30kg.m<sup>-2</sup>), sleep-disordered breathing, and awake daytime hypercapnia (awake resting PaCO<sub>2</sub> > 45 mm Hg at sea level), after excluding other causes for hypoventilation. Worldwide OHS prevalence is estimated to be 10-20% in obese patients with obstructive sleep apnea (OSA) and 0.4% in the general adult population but is still unknown in France. Although frequently associated with OSA, it is a distinct clinical entity. The European Pneumology Society stages OHS severity from 0 (no OHS), 1-2 (obesity-related sleep hypoventilation measured by nocturnal capnography) to 3-4 (daytime hypercapnia). Under-diagnosed, OHS is most often discovered during an acute respiratory failure, which increases health-related costs and risk of hospitalization and death. It is thus critical to determine the prevalence of

early stages OHS (1-2) thanks to the use of capnography, and the clinical and environmental predictive factors within this obese population.

**Materials and Methods:** In this prospective multi-centric observational study, inclusion criteria were adults patients with obesity without past or current non-invasive ventilation or continuous positive pressure treatment and no recent hospitalization. In this intermediate analysis, OHS prevalence and staging, BMI and associated factors (gender, age, mean peripheral saturation, night-time desaturation < 90% (min and % of total sleep time), arterial blood gases values, SF-36 quality of life measurement, Ricci & Gagnon physical activity assessment, Epworth) were examined from the first 100 patients (67% women).

**Results:** In these patients, the prevalence of early stage OHS was 6% that is not routinely assessed. Stage 0 were 68% and stage 3-4 17%. Early stage OHS was associated with elevated level and duration of night-time hypercapnia (PtCO<sub>2</sub> = 51.62mmHg ± 6.88,  $P < 0.001$ ; Time PtCO<sub>2</sub> > 50 mmHg = 144min ± 166,  $P < 0.001$ ), hypoxemia (PaO<sub>2</sub> = 82.55mmHg ± 14.32,  $P = 0.015$ ), lower pH (7.4 ± 0.03,  $P = 0.0086$ ) and elevated bicarbonate (HCO<sub>3</sub><sup>-</sup> = 26.05mmol/L ± 0.92,  $P < 0.001$ ). No difference on BMI, apnea-hypopnea index, physical activity or Epworth score was found among groups.

**Conclusions:** These results suggest that the use of capnography recording allowed to determine the existence of early stage OHS which may be of clinical relevance and independent from BMI.

**Acknowledgements:**

#### ONE-NIGHT TOTAL SLEEP DEPRIVATION DID NOT ALTER THE EFFECTS OF PAVLOVIAN CUES ON INSTRUMENTAL RESPONSES FOR HIGHLY PALATABLE FOOD REWARDS

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**Introduction:** Inadequate sleep is a risk factor for obesity. Prior studies suggest that sleep-deprived individuals may consume more calorie-dense food. The mechanisms underlying such change is unclear. The present study aimed to evaluate if sleep deprivation altered the effects of cues on one's instrumental responses for highly palatable food rewards using the Pavlovian-Instrumental Transfer (PIT) paradigm. The PIT paradigm allowed for the evaluation of specific transfer effects, i.e., increased instrumental responding for a food reward in the presence of a conditioned cue associated with that specific food reward, and general transfer effects, i.e., increased instrumental responding for a food reward in the presence of a conditioned cue associated with other food rewards. It was hypothesized that one-night total sleep deprivation would elevate specific and general transfer effects.

**Materials and Methods:** A within-individual randomized crossover design was used. A sample of 96 healthy adults (mean age = 25.41 years, SD = 8.01, range = 18-51; BMI = 21.41, SD = 3.52, range = 16.61-40.16) were randomized to undergo either one-night total sleep deprivation (TSD) or the normal sleep control (NSD) condition first, followed by a 3-day washout period and the other condition. The PIT paradigm consisted of an instrumental training phase, a Pavlovian conditioning phase, and a testing phase. In the instrumental training phase, participants acquired the associations between pressing two keys on the keyboard (M and N) and two respective food rewards (i.e., instrumental conditioning). Then, in the Pavlovian conditioning phase, they were presented with five neutral graphical pattern cues pairing with the two food rewards used in instrumental conditioning, two other food rewards not previously presented, and a "no food reward" control respectively. In the PIT testing phase, they were told to press either M or N as many times as they can to get the food they wanted, in the presence and in the absence of the five Pavlovian cues. Participants completed the PIT training phases between 20:00 and 22:00 prior to sleep manipulation and the PIT testing phase between 0800 and 10:00 in the following day for both TSD and NSD conditions to control for circadian influences.

**Results:** Repeated-measure ANOVA showed that there was a main effect of satiation, indicating that instrumental responses decreased after satiation. Significant specific transfer effects were observed regardless of sleep conditions or satiation but not for the general transfer effect, indicating that the presence of cues associated with the key increased instrumental responses on that key. However, there was not a main effect of sleep on the

specific transfer effects nor general transfer effects.

**Conclusions:** This finding did not support the hypothesis. Sleep deprivation did not alter the effect of Pavlovian cues on instrumental responses for highly palatable food rewards. It is possible that one-night TSD might not be sufficient to induce changes in habitual control of behavior. Future research directions will be discussed.

**Acknowledgements:** This study was supported by the HKU Seed Fund for Basic Research #201904159003

#### PERSONALIZED EEG/fNIRS: A PROMISING TOOL TO STUDY WHOLE-NIGHT SLEEP IN HEALTHY AND PATHOLOGICAL CONDITIONS

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**Introduction:** Sleep is a crucial period during which neuronal and hemodynamic activities interact to support healthy brain functions. Simultaneous Electro-Encephalography and functional Magnetic Resonance Imaging (EEG-fMRI) remain the reference to study the hemodynamic responses associated with neuronal activity (Dang-Vu et al., 2010; Gotman et al., 2011). However, fMRI, only sensitive to fluctuations in deoxygenated hemoglobin, is limited by the difficulty to perform long-duration recordings. To overcome this issue, functional Near-Infrared Spectroscopy (fNIRS), a wearable technique sensitive to both cortical hemodynamic fluctuations of oxyhemoglobin (HbO) and deoxyhemoglobin (HbR), has been considered as an emerging technique for sleep monitoring (Ren et al., 2020). However, most fNIRS sleep studies relied only on a few optical sensors on the forehead, therefore not allowing accurate localization of the sleep-specific hemodynamic fluctuations. Although, it is well known that there are strong interactions between sleep and epilepsy with an increase of epileptic activity during non-rapid eye movement sleep (Frauscher et al., 2019, Lambert et al., 2018), the influence of sleep stage on the hemodynamic response to epileptic discharges remain unknown. In this preliminary work, we are proposing personalized EEG/fNIRS whole night monitoring as a promising tool to study sleep, where personalized fNIRS maximizes signal sensitivity to targeted cortical regions and allows an accurate localization of the hemodynamic responses (Cai et al., 2021).

**Materials and Method:** We performed whole-night personalized EEG-fNIRS monitoring on 4 healthy (20-35 years old) subjects and 3 focal epilepsy patients (21-42 years old). EEG electrodes were glued in the 10-20 layout using clinical adhesive (collodion) along with EOGs, EMG, and ECG. For the healthy subjects, we installed 54 fNIRS channels covering bilateral auditory cortices. For the epileptic patients, we installed 52 fNIRS channels targeting the epileptogenic focus and its homologous contralateral region (Pellegriano et al., 2016, Machado et al., 2018). The focus was estimated using EEG and Magnetoencephalography source localization of epileptic discharges. Using EEG, sleep stages and epileptiform discharges (bursts of spikes, spike, and waves and seizures) were marked and scored by sleep and epilepsy experts. We used a multi-taper approach to estimate HbO/HbR oscillatory characteristics during each sleep stage (Scheeringa et al., 2011).

**Results:** Average total bedtime was 7hours 11minutes (SD: 55minutes). Sleep efficiency was above 90% for all healthy subjects and was ranging from 70 to 80% in epilepsy patients. We found a gradual decrease of HbO oscillations power from awake to N3 followed by an increase in REM within endothelial (0.005-0.02Hz), neurogenic (0.02- 0.04Hz), and myogenic (0.04-0.15Hz) frequency bands in both healthy and epileptic subjects, in agreement with the existing literature (Näsi et al., 2011). In the epilepsy patients, we observed an HbO decrease and a HbR increase at the time of interictal epileptiform discharges (IEDs) and seizures. In one patient, fNIRS response to the IEDs differed between N2 and N3, suggesting a

possible modulation of the hemodynamic response to IEDs by the respective sleep stage.

**Conclusion:** Our preliminary results suggest that personalized EEG-fNIRS monitoring is a promising approach to assess the cortical hemodynamic fluctuations during sleep in healthy and epilepsy conditions.

#### PRELIMINARY VALIDATION OF IN-EAR EEG AGAINST PSG SYSTEM FOR SLEEP STAGING

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**Introduction:** Conventional sleep staging methods based on electrophysiological signals involve time-consuming setup procedures and maintenance of devices. Conventional recording devices are bulky and expensive making long-term electroencephalography (EEG) monitoring impractical except for controlled clinical environments. The mobile IDUN GUARDIAN system offers a lightweight 2-channel in-ear EEG system, optimised for wearer's comfort and long-term use. One intriguing application is daytime sleep monitoring of patients suffering from narcolepsy, which is characterised by severe drowsiness or sudden periods of sleep. The GUARDIAN may facilitate the narcolepsy patient journey by identifying sleep onset and narcolepsy attacks throughout the day and potentially offer to support treatment decisions regarding medications and lifestyle. Here, we present preliminary findings for the validation of the GUARDIAN for sleep marker detection in comparison to gold-standard polysomnography (PSG).

**Materials and Methods:** In order to compare the GUARDIAN to a gold-standard sleep staging device, we recorded 1 h daytime naps of a total of 10 datasets from 8 healthy participants (2 females; age range: 23–37). Sleep staging was based on the AASM (Version 2.6; Berry et al., 2020) criteria. The recordings were divided into 30 s periods, which were scored as wakefulness (W), non-REM 1 (N1), non-REM 2 (N2), deep non-REM 3 (N3), or REM sleep (R). PSG data (SOMNOscreen plus, Randersacker, Germany), involving 5 EEG channels (F3, F4, C3, C4, O1; referenced to contralateral mastoid), 2 EMG channels placed on the chin, 2 EOG channels placed around the eyes, and ECG channels (Lead II placement) on the torso. The GUARDIAN was connected directly to the PSG amplifier and referenced to contralateral mastoid in order to ensure time-synchronisation and identical preprocessing of all channels.

**Results:** Visual comparison between in-ear and scalp-EEG channels reveal a clear correlation in regards to neural activity differentiating sleep stages. Such sleep markers include alpha and beta activity during W, alpha-to-theta shift during sleep onset (W-N1), sleep spindles and K complexes during N2, slow wave activity in N3, and short bursts of arousal during different sleep stages. In addition, the GUARDIAN revealed - similar to frontal scalp-EEG electrodes - onset of slow rhythmic eye movements, characteristic for the transition between wakefulness and sleep in some participants. Sleep scoring was first performed on PSG channels (F3, C3, O1, EMG, EOG, and ECG), and in a second step, data of the in-ear EEG channel were scored. Pearson's correlation coefficients between scorings of PSG and the GUARDIAN revealed moderate to high correlations across all datasets (average:  $r = 0.78$ ).

**Conclusions:** The IDUN in-ear EEG solution is able to accurately detect sleep markers, while ensuring wearer's comfort, enabling long-term mobile use. The monitoring of narcolepsy patients with in-ear EEG is a possible application. By measuring sleepiness as well as onset and duration of narcoleptic attacks during the day in an unobtrusive and comfortable way, while only minimally interfering with everyday life activities, in-ear EEG-based biomarkers could be used for symptom monitoring and as surrogate endpoints in future clinical trials.

#### PSYCHEDELIC COMPOUND 5-MEO-DMT INDUCES AN ALTERED WAKE STATE IN MICE

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**Introduction:** The traditional view that the serotonergic system plays an important role in subcortical control of global sleep-wake states is supported by observations that administration of serotonergic psychedelics suppresses rapid eye movement (REM) sleep and results in increased sleep fragmentation. However, the possibility that potentiating the serotonergic system through psychedelics results in an occurrence of altered states of vigilance has received less attention. We hypothesise that the serotonergic system plays a role in controlling the quality rather than the quantity of specific sleep-wake states, as reflected in the EEG. The aim of this study is to characterise the effects of a short-lasting psychedelic compound, 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT), on brain activity and sleep-wake states in laboratory mice.

**Materials and Methods:** 10 adult male C57BL6 mice were implanted with frontal and occipital EEG screws and nuchal muscle EMG wires. The animals were kept under a 12 – 12 hour light-dark cycle and recorded continuously for 8 days. In a crossover design, each animal received an IP injection of 5-MeO-DMT (5 mg/kg, in a solution at a concentration of 1 mg/mL) and vehicle solution at light onset, with 2 days between injections. Vigilance states were manually scored in 4s epochs using SleepSign, and EEG spectra were analysed with Matlab. So far, only a subset of these animals has been analysed ( $n = 4$ ), thus the values presented below are preliminary.

**Results:** We found that in the first hour following the injection of 5-MeO-DMT, wake was increased in three out of four animals, by on average 15.17 min (-3.2 min – 32 min) and the first episode of REM sleep was delayed by on average 45.6 min (63 min – 131.4 min). During the initial wakefulness (0 – 20 min after injection) in all the animals, EEG theta-frequency activity (6 – 9 Hz) was markedly suppressed by 42.18 % (-0.06 % – -70.34 %), while EEG slow wave activity (0.5 – 4 Hz) was increased by 23.43 % (10.16 % – 41.91 %). These changes returned to baseline levels within 60 minutes, and no further changes in the total amount of vigilance states were observed beyond this point.

**Conclusions:** Our data support the notion that the effects of 5-MeO-DMT are short-lasting, as the changes in vigilance states and the EEG were primarily apparent within 1 hour from the injection. Importantly, this compound did not merely change the amount and distribution of vigilance states but had an observed effect on state-specific brain activity patterns. Reduced theta-activity and increased slow wave activity during waking after administration of 5-MeO-DMT reflect an occurrence of qualitatively different, “hybrid” or “dissociated” state, having features of both waking and sleep.

**Acknowledgements:** This project was supported by a BBSRC Scholarship. The Compound was provided by Beckley Psytech.

#### RESTNET-AROUSALS: A END-TO-END DEEP LEARNING APPROACH TO AROUSAL DETECTION

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**Introduction:** Arousals are defined as abrupt shifts of electroencephalography (EEG) frequency that last at least 3 seconds, preceded with at least 10 seconds of stable sleep. The identification of arousals is important for the evaluation of sleep continuity and diagnosis of sleep disorders. Arousals are difficult for human experts to score and the low inter scorer agreement makes this a particularly challenging task for artificial intelligence (AI) models to learn. However, a well designed AI model might be helpful in improving scoring consistency, leading to more consistent clinical results.

Here we present an end-to-end deep learning approach to robustly identify arousals from standard polysomnogram recordings (PSG) and from Self Applied Somnography (SAS) studies. The SAS setup allows patients to self-administer frontal EEG and EOG leads in a home sleep study, which reduces cost and is more convenient for the patients.

**Materials and Methods:** The RestNet-Arousals model structure was inspired by ResNet convolutional neural network architecture, which has been highly successful in image recognition tasks. The model has the characteristic residual blocks with an added Temporal component to increase the temporal receptive field of the model.

The model makes predictions from the raw EEG, EOG and EMG signals, in

an end-to-end fashion to avoid manual feature extraction. This allows for short prediction times and allows the model to learn more complex relations as the size of the training data increases. The model output is a temporal sequence of arousal probabilities, which are then used to generate discrete arousal events in a post-processing step. Furthermore, the output probabilities are calibrated to correct for the poor calibration of modern neural networks.

The model was trained and tested on over 1800 and 900 manually scored PSG and SAS sleep studies, respectively. The PSG data came from a population of patients referred to a sleep clinic by a medical doctor, but the SAS data from various research datasets.

**Results:** The ResTNet-Arousals model was validated on two previously unseen datasets. The first included traditional PSG sleep studies (N = 160, epochs = 119,774) and the other SAS sleep studies (N = 88, epochs = 70,349). On PSG data, the ResTNet-Arousal model achieved a positive percentage agreement (PPA) 68.82% (95%CI 63.87 - 69.67%) and a negative percentage agreement (NPA) 90.06% (95%CI 88.57 - 91.41%). The model had similar results when validated on data from SAS sleep studies, with a PPA of 68.10% (95%CI 65.52 - 70.64%), and an NPA of 94.48% (95%CI 93.33 - 95.46%).

**Conclusions:** The ResTNet-Arousal model shows good performance both for PSG and SAS sleep studies. Furthermore, a systematic comparison of manually scored arousals from different sleep clinics and the model predictions showed a systematic difference between the sleep clinics in the propensity to score arousal events; a manifestation of the low inter scorer agreement when scoring arousals.

### SAMELISANT (SUVN-G3031), A HISTAMINE H3 RECEPTOR INVERSE AGONIST IN ANIMAL MODELS OF SLEEP DISORDERS

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**Introduction:** Samelissant (SUVN-G3031) is a potent and selective H3 receptor (H3R) inverse agonist with hKi of 8.7 nM. It is selective against 70 other targets which includes GPCRs, ion channels, transporters, enzymes, peptides, steroids, second messengers, growth factors and prostaglandins. Samelissant exhibited desired pharmacokinetic properties and favorable brain penetration in preclinical species. Samelissant blocked R- $\alpha$ -methyl-histamine induced dipsogenia in rats and increased *tele*-methylhistamine levels in brain and cerebrospinal fluid as well, which confirm its binding towards H3R.

Samelissant is currently being evaluated in a Phase-2 proof-of-concept study as monotherapy for the treatment of excessive daytime sleepiness (EDS) in patients with narcolepsy with and without cataplexy (Clinical-Trials.gov Identifier: NCT04072380). In the current research work, samelissant was evaluated for neurotransmitter modulation and sleep wake profile in orexin knockout mice, a reliable animal model for narcolepsy.

**Materials and Methods:** In brain microdialysis, samelissant was evaluated for its effects on modulation of neurotransmitters like dopamine, histamine and norepinephrine in prefrontal cortex. In male orexin knockout mice, electroencephalography (EEG), electromyography and activity were monitored using telemetric device. Effects of Samelissant on sleep/ wake were evaluated during active period of animals. Animals were allowed recovery period of 3 weeks after surgery.

**Results:** Samelissant significantly increased histamine, dopamine and norepinephrine levels in the prefrontal cortex. Samelissant did not change dopamine levels in the striatal and accumbal brain regions. These results suggest that samelissant may not have propensity to induce abuse liability. Samelissant produced significant increase in wakefulness with concomitant decrease in non-rapid eye movement sleep in orexin knockout mice. It also significantly decreased number of cataplectic episodes in orexin knockout mice.

**Conclusions:** The results from non-clinical studies presented here provide a strong evidence for the potential utility of samelissant for the treatment of EDS and cataplexy in patients with narcolepsy.

**Acknowledgements:** None

### SELECTIVE THERMAL STIMULATION TO MANIPULATE THE CIRCADIAN COMPONENT OF SLEEP REGULATION

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**Introduction:** Borbély's two-process model of sleep regulation entails circadian rhythm Process C and homeostatic sleep pressure Process S. We developed a novel thermal sleep system composed of selective thermal stimulation (STS), i.e., mild heating (39°C) of the skin over the cervical spine to manipulate blood flow to the dense network of arteriovenous anastomoses (AVAs) of the glabrous skin, e.g., hands and feet, plus a dual-temperature zone mattress with a warmer (33°C) peripheral zone to improve vasodilation of AVAs on the hands and feet and a cooler central (27°C) zone to enhance heat transfer by conduction from the central body core to the environment. We hypothesized this novel thermal sleep system, which increases heat transfer by redistributing blood flow from the body core to the glabrous skin, increases the distal-proximal-gradient temperature (DPG) and reduces core body temperature (CBT), elements of Process C, resulting in shortened sleep onset latency (SOL) and improved sleep quality.

**Materials and Methods:** After acclimating to the study environment and conditions through an afternoon nap, 11 healthy normal sleeper males, 23.6±3.9 [mean±SD] years of age, were randomly subjected to two non-consecutive nocturnal sleep sessions –a treatment night with the thermal sleep system activated and a control night with it deactivated. Participants were challenged to go to bed (lights-out) two hours earlier than usual. Data collection commenced 45 min before lights-out to establish baseline values of the study variables. On the treatment night, the dual-temperature zone mattress was activated during the entire sleep period, while the STS pillow was activated only during the first 30 min.

**Results:** There was no significant difference between the control and treatment nights in the baseline values of glabrous skin blood flow (GSBF), DPG, and CBT. During the first 30 min after lights-out on the treatment night, when both the STS pillow and dual-temperature zone mattress were activated, GSBF ( $\Delta=49.77\pm19.13$  PU,  $P=0.013$ , Cohen's  $d=0.85$ ) and DPG ( $\Delta=2.05\pm0.62^\circ\text{C}$ ,  $P=0.005$ , Cohen's  $d=1.10$ ) were significantly higher and CBT ( $\Delta=-0.15\pm0.07^\circ\text{C}$ ,  $P=0.029$ , Cohen's  $d=0.58$ ) was significantly reduced compared to the control night. Moreover, the SOL was significantly shorter ( $\Delta=-48.6\pm23.4$  min,  $P=0.032$ , Cohen's  $d=0.83$ ), and participants rated their subjective sleep quality statistically significantly better ( $P<0.001$ ) on the treatment night than on the control night.

**Conclusions:** This proof-of-concept study supports the proposed hypotheses that the dual-temperature zone mattress, which maintains high blood flow in the glabrous skin (via the warm peripheral zone) and increases conductive heat transfer from the body core to the environment (via the cooler central zone), in combination with STS resulting in increased GSBF and DPG and decreased CBT, with beneficial effects being shortening of the SOL through re-enforcement of Process C plus improvement of sleep quality that is consistent with diminution of the sleep pressure of Process S.

**Acknowledgements:** This research was sponsored in part by the Robert and Prudie Leibrock Professorship in Engineering at UT Austin. UT Austin owns patent rights to intellectual property relating to the technologies described in this article.

### SLEEP AND SHOUTS: THE INTRINSICALLY AVERSIVE NATURE OF ROUGH SOUNDS IS PRESERVED DURING NREM SLEEP

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**Introduction:** Screams are powerful vocalizations that are intrinsically aversive in humans. These vocalizations are characterized by a high roughness, an acoustic dimension which is potentially at the root of the aversiveness of screams. Current knowledge posits that this simple acoustic feature serves to alert conspecifics about the presence of a danger. It induces the urge to act, while generating strong and negative emotions. Here, we hypothesized that roughness should still be processed as an alarm signal in states of reduced responsiveness. We investigated this question by playing recorded screams to sleeping participants.

**Materials and Methods:** We acquired electroencephalography (EEG) data in 12 participants during wakefulness and during a full night of sleep while we played screams (with various levels of roughness) at a low intensity to the participants. We also presented pitch- and intensity-matched control vocalizations without roughness. We then compared the evoked brain responses to the two types of vocalizations by analyzing the event-related potentials and time-frequency decomposed responses.

**Results:** At wakefulness and during NREM sleep, we found that screams at a low intensity generated brain responses that are better time-locked, hence more consistent in time, than control vocalizations. In addition, screams evoked more sleep spindles. Finally, a regression with the roughness and pitch of vocalizations revealed that spindle generation was linked to sound roughness but not pitch.

**Conclusions:** Our results suggest that the response to screams is more reliable than to controlled vocalization across both wakefulness and sleep, thus consistent with screams representing powerful and pervasive alarm signals in humans. In addition, the link between acoustic roughness and spindle generation supports a link between stimulus emotional relevance and spindle generation during sleep, a relation that is receiving increasing attention in the literature. This study shows that, beyond loudness, acoustic roughness, which is produced by numerous human activities (e.g., snoring, traffic noise, construction work), should be measured and strongly avoided in the proximity of sleeping environments.

**Acknowledgements:** This work was supported by the National Center of Competence in Research (NCCR) Affective Sciences (financed by the Swiss National Science Foundation, 51NF40-104897; and hosted by the University of Geneva), the Private Foundation of the University Hospital of Geneva (grant number: CONFIRM RC1-23) and by grants from the Swiss National Science Foundation (320030-159862 to S.S.; Ambizione - PZ00P3-148112 to J.D.B.).

## SLEEP AND THE MENSTRUAL CYCLE: A REVIEW OF 48,720 CYCLES

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**Introduction:** The Oura Ring is a wearable health platform that enables users to track their sleep, heart rate, activity, menstrual cycles, and more. Here, we assess changes across the reproductive lifespan through sleep physiology and sleep behaviors in an Oura dataset containing 1.3 million nights of sleep summary data. This dataset contains 48,720 complete menstrual cycles from 7877 unique Oura ring users.

**Materials and Methods:** Metrics explored include daily summaries of physiology while asleep, i.e., body temperature, respiratory rate, heart rate, and heart-rate variability (HRV), and also sleep behaviors, i.e., sleep duration, midpoint, and the number of awakenings. Metrics were compared statistically via a mixed ANOVA with a two-level within-participant factor of menstrual cycle phase (luteal or follicular) and six-level between-participant factor containing age groups between 18 and 47. To demarcate the menstrual cycle phases, period onset and ovulation were either labeled by the user in the Oura app or automatically detected via the user's continuously measured body temperature.

**Results:** As expected, body temperature robustly increased in the luteal phase relative to the follicular phase as shown by a large main effect ( $\eta p^2 > .9$ ). Respiratory rate and heart rate were also reliably higher during the

luteal phase (both with large effect sizes, i.e.  $\eta p^2 > .7$ ). Neither respiratory rate nor heart rate showed main effects of age, but heart rate did show a moderate interaction with age across the menstrual cycle, suggesting that as users age their heart rate during sleep is more stable across the menstrual cycle phases. HRV consistently decreased in the luteal phase relative to the follicular phase as shown by a large main effect of menstrual cycle phase ( $\eta p^2 > .4$ ). HRV also showed monotonic decreases with age from an average of 60 ms at age 18 to 40 ms by age 47. HRV had a small but significant interaction between age and menstrual cycle phase, such that HRV in younger users had a stronger association with the phase of their menstrual cycle. Users approaching menopausal ages also exhibited more perturbed sleep, as seen in shorter sleep durations ( $\mu = 12$  minutes), earlier bedtimes ( $\mu = 41$  minutes), and increased awakenings ( $\mu = 5\%$ ).

**Conclusions:** Overall, the Oura Ring reliably captures changes in physiology during sleep across the menstrual cycle and demonstrates how these patterns change across the reproductive lifespan. The interactions of HR and HRV between the menstrual cycle and age are consistent with what would be expected with decreasing progesterone levels as users approach menopause. These findings suggest that HR and HRV may be particularly suitable candidates to help detect early signs of menopause or fertility issues. To our knowledge, this is the largest dataset of its kind and thus these results can guide sleep-based algorithms in accounting for the menstrual cycle and aging across the reproductive lifespan. For future applications, this work provides the foundation to detect abnormal menstrual cycles, monitor sleep interventions outcomes in menopausal women, build custom workouts for female athletes, detect early signs of declining fertility, and more.

## SLEEP EEG SPECTRAL EXPONENTS AND MAXIMAL PEAK FREQUENCIES IN CONSECUTIVE NREM PERIODS: POSSIBLE MARKERS FOR SLEEP REGULATION

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**Introduction:** According to Borbély (1982) a homeostatic and a circadian process define the main aspects of sleep regulation. Although slow wave activity of the sleep EEG is a widely accepted marker of sleep homeostasis, high frequency activity is also changing throughout the night (in the opposite direction). Thus, the ratio of lower to higher frequencies in the EEG power spectrum seems to be a more accurate indicator of sleep homeostasis. In addition, sleep spindle frequency could be a suitable marker of the circadian process since it was shown to follow a U-shaped overnight dynamic and its dampening in aged subjects.

Given the linear association between the logarithm of frequency and logarithm of amplitude the Fourier spectrum can be described by an approximation of the parameters of the following function:  $P(f) = C f^{\alpha} P_{\text{peak}}(f)$ , where P is power as a function of frequency, C is the constant,  $\alpha$  is the spectral exponent which shows the ratio of different frequencies in the signal, and  $P_{\text{peak}}$  is the peak power at frequency f. We hypothesized that (i)  $P_{\text{peak}}(f)$  values of the sleep spindle range (9-18 Hz) are higher in the last and first sleep cycles than in the middle parts of night sleep records, (ii) spindle deceleration in the middle of the night is modulated by age, while (iii)  $\alpha$  is decreasing linearly across the night as the sleep pressure decays (spectral slope flattening).

**Materials and Methods:** Artefact-free NREM sleep periods of successive cycles in the Budapest-Munich database of sleep records (N = 251 healthy subjects, 122 females, age range: 4–69 years) were analysed by FFT routine and power spectrum obtained for selected EEG derivations. Furthermore, the log-log power was fitted with a linear, and a peak detection was applied in the 9-18 Hz (broad sleep spindle) range at derivations O2, O1, P4, P3, C4, C3, F4, F3, Fp2, Fp1. Statistical analysis was based on general linear models.

**Results:** The NREM sleep EEG spectral exponents ( $\alpha$ ) increased in consecutive sleep cycles (absolute values decreased), and this effect was significant at all derivations. The maximum peak frequency was significantly modulated by age at all derivations and by cycle at O2, P4, P3, C4, F4, F3, Fp1. There was a cycle x age group interaction at derivations O2 and F3.

A tendency for the U-shaped dynamic throughout the sleep cycles was seen at all derivations.

**Conclusions:** Our results show that the spectral exponent is a potent marker of the homeostatic process of sleep regulation which supports earlier findings about the associations between this exponent and sleep depth. Furthermore, the maximum spectral peak frequencies could reflect the circadian modulation of sleep. The latter index could be a useful measure in future studies, potentially substituting complicated protocols like melatonin or core body temperature measurements, with assumed applicability in retrospective investigations. Finally, the spectral exponent can serve as a link between sleep regulation and consciousness.

## SLEEPING IT OFF? ARE HOSPITALS TOO NOISY TO ALLOW RECOVERY?

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**Introduction:** Increased overnight noise levels are known to stimulate the release of multiple stress hormones and negatively impact upon objective and subjective sleep quality. Increasing levels of noise impairs physical and psychological recovery, and has been shown to slow wound healing, increase post-operative complication rates, delay recovery, and lengthen hospital admissions. Noise levels are therefore an important factor to consider in hospital care and an important component of recovery. The purpose of this study is to document the actual noise levels experienced by patients on hospital wards overnight, document the sources of this noise and propose some solutions.

**Materials and Methods:** Firstly, five-minute recordings were made during four separate hours throughout the night on two wards - one paediatric and one adult. In both cases, recordings were made inside a six-bedded bay. Secondly, researchers described and categorised the sources of noise.

**Results:** The World Health Organisation (WHO) has recommended that average overnight noise levels in hospitals should not exceed 35 dB. The average recorded on the paediatric and elderly ward was 42.27 dB and 43.91 dB respectively, with peak noise levels of 93.65 dB and 97.01 dB respectively. In every five-minute recording, there was at least one sound louder than 67 dB. Researchers also noted the causes of noise and tallied the number of times they occurred. The sources were categorised as avoidable (or significantly modifiable) vs non-avoidable, constant vs impact, and within the hospital bay vs outside. These descriptions were not matched to the objective data. Examples of constant noises were generally unavoidable and included air-conditioning machines and oxygen delivery devices, though clearly avoidable sources such as a radio were also noted. Impact noises were subjectively thought to be more disruptive, common examples included staff talking, doors closing, patients moving, machine alarms inside the bay, telephones ringing and staff alert systems (e.g. bleeps).

**Conclusions:** The average noise level was significantly greater than the WHO recommendations. Every five-minute recording contained peak sounds of significance. Such noise levels have been linked to poor sleep, increased stress hormone release, delayed wound healing, and an increased recovery times. Staff members also experience higher levels of stress when working in noisy environments. Many avoidable causes of these sounds are identified, several of which could be easily improved by existing solutions (e.g. quietened or vibrating staff alarms overnight, machine alarms directly contacting the appropriate staff member rather than alarming everyone closeby, quiet-closing doors etc). There are also some overnight noises which are likely to be unavoidable overnight and other measures such as the use of ear plugs is likely to be necessary in addition. Addressing the issue of overnight noise is important for hospital wards and is likely to improve patient outcomes, as well as lowering stress levels of staff.

**Acknowledgements:** Dr Miles Buller (Co-Researcher), Dr George Ellison (Lead Supervisor), Dr Sarah Isherwood (Deputy Supervisor).

## THE CIRCADIAN EXPRESSIONS OF METABOLISM GENES IN HUMAN ADIPOCYTES: THE IMPACT OF MELATONIN

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**Introduction:** Numerous key parameters of the metabolism homeostasis display circadian rhythms in their expression and activity. In adipose tissue, this is the case for clock genes, but also for adipokine genes, glucose transporters, and transcription factors. The condition of obesity is associated with a dysregulation of these same factors. In this context, the main circadian hormone and powerful antioxidant melatonin is also modified, and melatonin supplementation is presented as a strategy to limit metabolic damage in people with obesity. In the present work, we investigate if melatonin impacts the circadian expression of clock genes and metabolic genes of human adipocytes.

**Materials and Methods:** The experiments were performed on Primary Human White Preadipocytes isolated from adult subcutaneous adipose tissue. After twenty-four hours in a differentiation medium, supplemented or not with melatonin, mRNAs were extracted at four different times of the day and reverse transcribed. Quantitative PCRs were then performed for the genes Aryl hydrocarbon receptor nuclear translocator-like protein 1 (Bmal1), Cryptochrome (Cry), Period2 (Per2), Peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ), CCAAT/enhancer-binding protein alpha (C/EBP $\alpha$ ), Lipoprotein lipase (LPL), adipocyte protein2 (aP2), Angiotensin (AGT), Melatonin receptor 2 (MT2), Adiponectin (GBP-28) and Plasminogen activator inhibitor-1 (PAI-1). The  $\beta$ -actin gene was used as a reference. For statistical analysis and modeling, R was used, with the packages Cosinor, ggplot2 and dplyr.

**Results:** The circadian expression of the genes are modeled using a cosinor curve. The amplitude of circadian expression was twice as high for all genes compared to the control, but only significantly so for four genes: Cry (control = 15.78  $\Delta$ CT; melatonin = 51.11  $\Delta$ CT; p = 0.002), GBP-28 (control = 35.28  $\Delta$ CT; melatonin = 64.05  $\Delta$ CT; p < 0.001), LPL (control = 38.65  $\Delta$ CT; melatonin = 72.54  $\Delta$ CT; p < 0.001) and Per 2 (control = 34.68  $\Delta$ CT; melatonin = 56.67  $\Delta$ CT; p = 0.005). No clear effect of melatonin treatment was observed on acrophase and mesor of circadian expression of the tested genes.

**Conclusions:** The present results suggest that melatonin acts on the clock genes and on metabolic genes by intensifying the amplitude of the circadian expression. Further investigation is needed to characterize the role of melatonin in adipocytes physiology. If confirmed, this amplification of circadian gene expression could mediate the protective role of melatonin on the metabolic damage in obesity.

**Acknowledgements:** To the laboratories of La Rochelle and Valencia for collaborating and hosting this project, especially to all who made it possible in spite of the sanitary context. Thank you to the World Sleep Congress 2022 for the opportunity to share this work.

## THE INFLUENCE OF LIGHT EXPOSURE AND PHYSICAL ACTIVITY IN THE TIMING AND DURATION OF SLEEP: INSIGHTS FROM A TWO-SHIFT NATURAL MODEL OF DANCE STUDENTS

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**Introduction:** Impaired sleep timing, duration, and quality have major consequences on health, as well as on mental and physical performance. It is recognized that sleep patterns are determined by social, environmental, and behavioral factors. Our first aim was to characterize how shifts shape the different sleep determinants. Our second goal was to provide evidence using this complex natural experiment about the influence of the amount and timing of light exposure and physical activity on sleep patterns.

**Materials and Methods:** In the present study, we continuously recorded the activity and light exposure of 31 dance students attending two extreme training shifts (morning: 08:30 to 12:30, night: 20:00 to 24:00), for 16 days using wrist devices. We estimated daily, morning, and night minutes of moderate to vigorous physical activity (MVPA) and mean light intensities. Besides, we estimated daily sleep patterns (onset, end and duration), and registered if an alarm clock was set to wake-up. Linear models were employed to study type-of-day (training vs free) and shift (morning vs night) differences in minutes of MVPA, light exposure and alarm usage.

Besides, linear models were also employed to study the influence of type-of-day, training shift, alarms, log<sub>10</sub> of light exposure and minutes of MVPA, on the sleep patterns.

**Results:** Higher morning or evening light exposure and minutes of MVPA were found in sync with training shift and training days, with significant interactions (all  $p < 0.001$ ). Alarm usage was also prevalent in the morning shift and in training days, with a significant interaction ( $p < 0.001$ ). Sleep onset delays were associated with attending the night shift ( $b = 1.1 \pm 0.3$ h,  $p < 0.001$ ), free days ( $b = 1.9 \pm 0.2$ h,  $p < 0.001$ ), night light exposure (standardized  $b = 0.2 \pm 0.1$ h,  $p = 0.007$ ), and night MVPA (standardized  $b = 0.3 \pm 0.1$ h,  $p < 0.001$ ), whereas standardized morning light exposure was associated with  $0.3 \pm 0.1$ h onset advance ( $p < 0.001$ ). Sleep end delays were associated with attending the night shift ( $b = 1.2 \pm 0.4$ h,  $p = 0.003$ ), free days ( $b = 1.1 \pm 0.1$ h,  $p < 0.001$ ), and night light exposure (standardized  $b = 0.2 \pm 0.1$ h,  $p = 0.003$ ). Using alarms advanced the sleep end in  $1.8 \pm 0.1$ h ( $p < 0.001$ ). Sleep duration reductions were associated with free days ( $b = -0.7 \pm 0.2$ h,  $p < 0.001$ ), alarms ( $b = -1.7 \pm 0.2$ h,  $p < 0.001$ ), and night MVPA (standardized  $b = -0.2 \pm 0.1$ h,  $p = 0.003$ ), whereas  $0.7 \pm 0.2$ h increase in duration was associated with standardized morning light exposure ( $p = 0.043$ ).

**Conclusions:** School shifts are a good model for studying the influence of social, environmental and behavioral factors on sleep in young people. Although social influences are stronger in sleep pattern regulation, behavioral interventions can aid in sleep health directly or through regulating exposure to environmental factors such as light.

**Acknowledgements:** We are very grateful to the participants, PEDECIBA, CSIC-UdelaR, and END-SODRE.

#### THE INTEGRATION OF SKIN AND CORE BODY TEMPERATURE IN THE EXPRESSION OF REM SLEEP AND THE ROLE OF THE HYPOTHALAMUS

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Rapid eye movement (REM) sleep is characterized by suppression of thermoregulatory defence and is preferentially expressed over non-REM (NREM) sleep during thermoneutral ambient temperature ( $T_a$ ) warming. The lateral hypothalamus (LH) integrates diverse inputs related to temperature, energy balance and circadian time to modulate sleep-wake expression. Although hypocretin (Hcr) neurons promote wakefulness, melanin-concentrating hormone (MCH) neurons increase REM sleep during thermoneutral  $T_a$  warming. However, how the LH controls NREM-REM sleep cycling or what types of temperature information are integrated to modulate REM sleep remain unknown. We hypothesize that skin (TSkin) and core body (TCore) temperature information are integrated in the hypothalamus where the MCH and Hcr systems drive REM sleep and wakefulness, respectively. During thermoneutral warm  $T_a$  pulsing presented during the inactive (light) phase, we show that wild type (WT) mice significantly increased total REM sleep duration and bout number with reduced inter-REM intervals. However, MCH receptor1 knock-out (MCHR1KO) mice showed no effect in vigilance state, and Hcr-KO mice showed increased wakefulness and decreased REM sleep without alterations in inter-REM intervals. All groups demonstrated an intact homeostatic regulation of REM sleep. These data suggest that both the MCH and Hcr systems are required for the dynamic modulation of REM sleep as a function of  $T_a$ , but that neither system is necessary for REM sleep homeostasis. We then further investigated brain temperature (TBrain), TCore and TSkin parameters in a subgroup of mice to investigate which parameters may be integrated within the LH to modulate REM sleep. WT and MCHR1KO mice showed clear ultradian TCore cycling during the inactive sleep phase where REM sleep was preferentially nested during TCore nadirs. Hcr-KO mice, in contrast, showed disrupted ultradian TCore cycling. Moreover, WT mice dynamically increased REM sleep expression across a wider distribution of the TCore cycle as a function of integrated TCore-TSkin, whereas MCHR1KO mice failed to modulate REM sleep timing or duration within TCore cycles. These findings suggest that WT mice integrate TSkin and TCore for dynamic REM sleep expression where the MCH system plays a critical role, whereas an intact Hcr system impacts sleep-wake transitions and the structure of the ultradian rhythm.

#### THE TOPOGRAPHY OF THALAMIC STROKE HAS AN IMPACT ON ASSOCIATED SLOW WAVE SLEEP AND COGNITIVE CHANGES

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**Background and Aim:** The thalamus plays an important role in controlling sleep-wake and memory functions. However, the contribution of discrete thalamic regions to these functions remains unclear. Here we postulate that sleep and cognitive changes in patients with isolated thalamic stroke may depend upon the extent of the underlying lesion.

**Patients and methods:** We included 15 patients with acute isolated (>80% of the total lesion size) thalamic stroke: 8 patients with anteromedial thalamic stroke and 7 patients with lateral thalamic stroke. We assessed stroke characteristics and within the first 5 days post-stroke, nocturnal sleep with high-density electroencephalography (HD-EEG) and respiratory polygraphy. In the evening before the HD-EEG study, subjective sleepiness (Epworth Sleepiness Scale (ESS)), language (Bernese Word Finding Test), neglect (Bells test), verbal memory (Digit span test forward and backward, Hopkins Verbal Learning Test) and visual memory (Corsi block tapping test) were assessed.

**Results:** There were no differences in age, sex, stroke severity (National Stroke Severity Scale Score at admission and modified Rankin Scale Score at discharge) and cardiovascular risk-related comorbidities between patients with anteromedial and lateral thalamic stroke. Total sleep time ( $355.14 \pm 90.63$  minutes and  $306.42 \pm 91.48$  minutes,  $p = 0.383$ ) and sleep efficiency ( $69.65 \pm 14.40$  % versus  $66.05 \pm 17.00$  %,  $p = 0.620$ ) were also similar. However, patients with anteromedial thalamic stroke had shorter duration of NREM3 sleep (% of total sleep time:  $15.31 \pm 7.54$  % versus  $28.42 \pm 7.60$  %,  $p = 0.011$ ) and a higher ESS score ( $7.29 \pm 2.69$  points versus  $4.00 \pm 2.00$  points,  $p = 0.037$ ). ESS score showed a negative correlation with the duration of NREM3 sleep (Spearman correlation:  $r = -0.90$ ,  $p < 0.01$ ) which remained significant after controlling for topography of the thalamic lesion (partial Spearman correlation:  $r = -0.65$ ,  $p = 0.02$ ).

Patients with anteromedial, but not those with lateral, thalamic stroke exhibited confabulations in the HVLt (total number of confabulations:  $2.62 \pm 3.02$  confabulations,  $p = 0.020$ ). The total number of confabulations in HVLt did not correlate with ESS score or with the duration of NREM3 sleep. There were no other cognitive differences between the two groups.

**Conclusion:** These findings support previous human and experimental observations suggesting a role of the anteromedial thalamus in the regulation of slow-wave sleep and cognition. Further analyses are planned to assess the potential correlation between slow-wave sleep changes, excessive daytime sleepiness and cognitive dysfunction in patients with thalamic stroke.

#### TO SLEEP, PERCHANCE TO BREATHE: INVESTIGATING THE IMPACT OF OBSTRUCTIVE SLEEP APNEA ON SLEEP NEUROPHYSIOLOGY AND SLEEP-DEPENDENT MEMORY ACROSS BRAIN STATES IN OLDER ADULTS

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**Introduction:** Obstructive sleep apnea (OSA) symptomatology in older adults is associated with multifarious health risks, including disruption of

sleep architecture and impairment of cognitive functions. Less is known, however, of how OSA severity impacts the local expression of neural oscillations during sleep relevant for cognition. Here, we demonstrate frequency-specific, deleterious impacts of OSA severity on spectral power in memory-relevant oscillatory frequencies within both non-rapid eye movement (NREM) and REM sleep, using high-density electroencephalography (hdEEG) to delineate findings with enhanced spatio-spectral specificity.

**Methods:** 57 cognitively unimpaired older adults ( $61.25 \pm 6.24$  years, 38 female) underwent overnight polysomnography with 256-channel hdEEG. EEG data were cleaned, segmented into concatenated NREM and REM epochs, and spectrally analyzed using the multitaper method. OSA-related measures, i.e., apnea-hypopnea index (AHI), respiratory disturbance index (RDI), and oxygen desaturation index (ODI) were obtained for REM and NREM sleep and were log-transformed to normality. Memory function was assessed using proportion of overnight change in recall performance on a sleep-dependent word paired-associates task (WPT, cube-root transformed to normality). Pearson's correlations with threshold-free cluster enhancement (TFCE, 5000 permutations) were run to identify topographical associations between OSA severity and absolute EEG spectral power. After averaging across spatially segregated clusters of significant associations, multiple regressions adjusting for age and sex were leveraged to model underlying OSA-local sleep relationships. To elucidate the functional significance of these associations, cluster averages of spectral power significantly predicted by OSA-related metrics were then used to predict WPT memory performance in regression models adjusting for sex and age.

**Results:** Within NREM epochs, TFCE-significant negative topographical correlations were seen between  $\log(\text{ODI})_{\text{NREM}}$  and slow sigma power (SSP, 11–13 Hz; global associations),  $\log(\text{ODI})_{\text{NREM}}$  and fast sigma power (FSP, 13–16 Hz; frontal and central-parietal clusters),  $\log(\text{AHI})_{\text{NREM}}$  and SSP (central-parietal cluster),  $\log(\text{RDI})_{\text{NREM}}$  and theta power (4.5–7.5 Hz; frontal and parietal clusters),  $\log(\text{RDI})_{\text{NREM}}$  and alpha power (7.5–11 Hz; frontal and central-parietal clusters), and between  $\log(\text{RDI})_{\text{NREM}}$  and SSP (central cluster). Analyzing REM epochs revealed clusters of TFCE-significant negative associations between  $\log(\text{RDI})_{\text{REM}}$  and theta power (frontal cluster),  $\log(\text{RDI})_{\text{REM}}$  and gamma (28–40 Hz; parietal-occipital cluster), and  $\log(\text{RDI})_{\text{REM}}$  and high gamma (40–55 Hz; frontal and parietal clusters). Subsequent regression models using segregated cluster averages demonstrated significant influences of  $\log(\text{RDI})_{\text{NREM}}$  on central SSP ( $B = -0.162$ ,  $p = 0.033$ ), of  $\log(\text{ODI})_{\text{NREM}}$  on global SSP ( $B = -0.188$ ,  $p = 0.026$ ), frontal FSP ( $B = -0.081$ ,  $p = 0.034$ ), and central-parietal FSP ( $B = -0.132$ ,  $p = 0.029$ ), and of  $\log(\text{RDI})_{\text{REM}}$  on parietal gamma power ( $B = -0.016$ ,  $p = 0.018$ ), frontal high gamma power ( $B = -0.015$ ,  $p = 0.002$ ), and parietal high gamma power ( $B = -0.011$ ,  $p = 0.002$ ). Finally, WPT performance was significantly predicted by cluster averages of central FSP ( $B = 0.288$ ,  $p = 0.011$ ), frontal FSP ( $B = 0.385$ ,  $p = 0.033$ ), global SSP ( $B = 0.216$ ,  $p = 0.007$ ), central-parietal SSP ( $B = 0.230$ ,  $p = 0.008$ ), and parietal gamma power ( $B = 1.639$ ,  $p = 0.048$ ), with parietal high gamma power ( $B = 2.853$ ,  $p = 0.064$ ) exhibiting similar trends.

**Conclusions:** We demonstrate widespread, significant impacts of OSA severity on frontal and central-parietal expression of NREM and REM sleep, with deficits in NREM sigma activity and REM gamma activity disrupting sleep-dependent memory. Further research may examine if OSA treatment could reverse cognitive impairment in older adults with OSA, through its impact on local oscillatory activity.

**Funding:** R56AG052698, P50AG033514, F31 AG048732, K01 AG068353.

## TOTAL SLEEP DEPRIVATION LEADS TO CHANGES IN NEUROMUSCULAR JUNCTION OF SOLEUS MUSCLE IN MALE WISTAR RATS

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**Introduction:** Brain is the biggest beneficiary of sleep. Skeletal muscle atonia is a prominent feature of rapid eye movement (REM) sleep. Neuromuscular junction (NMJ) exhibits high morphological and functional plasticity (Arnold et al., 2014). Functional importance of skeletal muscle

atonia is not known. Sleep deprivation may influence NMJ morphology at presynaptic and postsynaptic terminals levels. In the present study, we have looked into the ultrastructural changes in the rat soleus muscle NMJ after sleep, sleep deprivation and recovery sleep.

**Materials and Methods:** Total 18 rats were divided into three groups. Group I rats had normal sleep wake cycle, Group II rats were subjected to 24 h sleep deprivation (SD) by running wheel method and Group III rats had 24h recovery sleep. At the end of the study, soleus muscle was collected for electron microscopic and neurochemical study. Morphometry was performed by modifying protocol mentioned in Spendiff et al., 2020 and neurotransmitter was measured by ELISA. The study was conducted as per the guidelines of the Institutional Animal Ethics Committee (960/IAEC/16).

**Results:** Electron microscopic observation revealed a significant increase in mitochondrial density in 24h SD ( $p < 0.01$ ) as compared to control in presynaptic terminal. Further, in post synapse we found similar increase in SD ( $p < 0.0002$ ). Within group comparison of intact versus altered mitochondria exhibited a significant increase in the diameter of altered mitochondria in all the experimental groups ( $p \leq 0.0001$ ). Moreover, within group comparison of area of intact versus altered mitochondria showed significant increase in area of altered mitochondria only in Control ( $p = 0.01$ ) and 24h SD ( $p = 0.02$ ). These aforementioned parameters did not show any significant change in recovery sleep. When we looked into the synaptic vesicle density we found significant increase in 24h SD as compared to control ( $p = 0.002$ ), but not in recovery sleep at presynaptic terminal. However, no significant difference was found in vesicle distribution within the active zone of presynaptic nerve terminal and post-synaptic muscle membrane of 24hr SD, control and recovery sleep groups. Interestingly, the number of junctional folds per synapse profile was significantly increased in the 24h SD group as compared to control, ( $p = 0.002$ ). Also, there was a significant difference between 24hr SD and recovery group ( $p = 0.002$ ). Concentration of acetylcholine in 24 h sleep deprivation was decreased ( $p = 0.02$ ). In addition, but acetylcholine esterase activity was significantly increased ( $p = 0.02$ ). The acetylcholine esterase activity did not come back to control level even after 24 of recovery sleep. Pearson correlation between acetylcholine and vesicular density showed a negative correlation ( $r = 0.07$ ,  $p < 0.05$ ) in 24h sleep deprivation. These findings suggest that there are significant changes in neuromuscular junction of soleus muscle after 24hr sleep deprivation.

**Conclusions:** The results of the present study show that 24 h SD produces significant changes in neuromuscular junction morphology of soleus muscle. The changes were not observed after recovery sleep. We conclude that sleep plays a key role in NMJ homeostasis.

**Acknowledgements:** This study was supported by the All India Institute of Medical Sciences, and Indian Council of Medical Research New Delhi, India.

## Behavior, Cognition and Dreaming

### AN EXPLORATION OF EARLY SLEEP DEVELOPMENT IN PRESCHOOL CHILDREN WITH AND WITHOUT A FAMILIAL HISTORY OF ADHD

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**Introduction:** Children with poor sleep are reported to show more problems with attention and do less well in school. Poor sleep is widely reported for children and adults with attention deficit hyperactivity disorder (ADHD), however the link between how this relation develops is relatively unknown. In our study, we investigated sleep and attention in infants and young children with and without a familial history of ADHD. By exploring the early development of sleep and attention we hope to gain a better understanding of how early sleep can impact brain and behaviour development.

**Materials and Methods:** We used both questionnaire and lab based methods to address our study aims. In Study 1, questionnaires on temperament markers of attention control and sleep quality and quantity were completed by parents of children under 6 years with ( $n = 72$ ) and without ( $n = 139$ ) a familial history of ADHD. In Study 2, actigraphs were worn by a subgroup of infants aged 10–20 months with and without a familial history of ADHD, to measure sleep-wake activity, and eye-tracking

measures were utilised to record early markers of visual attention and inhibitory control.

**Results:** In Study 1, parents of the high-risk infant/toddler group report 2.48 night time awakenings in comparison to 1.38 for the low-risk group ( $p=.004$ ) and reported that their children spent .56 hours awake in comparison to .24 hours in the low-risk group ( $p=.046$ ). No group differences for sleep were observed for preschool-aged children, except for more reports of bedtime anxiety (3 to 6 years). Poorer sleep quality predicted higher temperament levels of negative affectivity across the whole group ( $.376, p<.001$ ), and poorer family function predicted lower temperamental levels of effortful control ( $-.290, p=.002$ ). Results in Study 2 suggest that more daytime sleep and a lower proportion of light sleep at night can predict better visual attention in infants, with the former being a more robust marker. Family functioning scores and familial history of ADHD were not related to visual attention on the eye-tracking task, however the familial ADHD group had slower response times.

**Conclusions:** Study 1 highlights for researchers the importance of future research focus on early sleep and family function factors in the context of ADHD risk. Study 2 explores potential relations between infants' sleep behaviour, family factors (family function and familial ADHD), and early attention development and is the first to utilise objective measures of sleep and attention to investigate the link between sleep and concurrent attention in infants. This project is an early step towards learning more about how attention develops in young children. As ADHD is a heterogeneous disorder, gaining a better understanding of how different genetic and environmental factors influence the development of ADHD symptoms is imperative to guide the development of future treatments and interventions.

**Acknowledgements:** This study was funded by The Waterloo Foundation under Grant 1854-3027. Thank you to all the families who participated in this research and to ADHD Ireland for their support.

#### ASSOCIATION BETWEEN REM SLEEP, DREAMING AND STRESS LEVELS IN PATIENTS WITH SOCIAL ANXIETY DISORDER

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**Introduction:** Social anxiety disorder (SAD) is an anxiety disorder characterized by a significant amount of fear when confronted to social situations causing considerable distress in daily life. Based on previous research showing that rapid eye movement (REM) sleep and dreaming are related to the consolidation of extinction memory and to emotional depotentiation in healthy participants, we hypothesized that REM sleep and/or dreaming may have beneficial effects on the stress levels of these patients when exposed to a social situation. Here, we used exposure therapy and targeted memory reactivation (TMR), a technique used to modify memory formation through application of cues during sleep.

**Materials and Methods:** 48 patients (32 women and 16 men, mean age of  $24.41 \pm 4.91$ ) first had a habituation night with polysomnography. The following day, they underwent two sessions of virtual reality (VR) exposure therapy with four phases (baseline, preparation, talk, positive feedback). During the positive feedback phase, a sound was administered in the TMR group only ( $N=24$ ), but not in the control group ( $N=24$ ). During a second night of polysomnography, participants of both groups received the same sound during REM sleep. The next morning, all patients had a third session of VR exposure therapy. During the following week, all participants slept at home with a wearable headband device which identified sleep stages and delivered the sound several times during REM sleep. At the end of the week, participants came for a fourth session of VR exposure therapy. Anxiety level was assessed using measures of sympathetic (electrodermal activity, EDA) and parasympathetic (heart rate variability, HRV – higher HRV indicates lower stress level) activity, and subjective measures (subjective units of distress, SUDS), during the preparation phase at four time points: before (T1a) and after (T1b) the first session of VR exposure therapy, after sleep with auditory stimulation (T2), and after one week of auditory stimulation at home (T3). Participants also filled in a dream diary for one week before the first polysomnography and one week after.

**Results:** There was a positive correlation between REM duration and HRV

levels at T3 ( $p=.047$ ) for the TMR group, but not for the control group. This correlation was found only for REM sleep and not for other sleep stages. Similarly, the auditory stimulation number correlated with HRV at T3 ( $p=.034$ ) in the TMR group. We also observed that the more fear was present in the dreams of patients of the TMR group during the second week compared to the first one, the more these patients were anxious as assessed by SUDS ( $p=.0046$ ) and EDA ( $p=.0155$ ) measures at T3.

**Conclusions:** Our results support the hypothesis that REM sleep has a positive role in the reduction of stress in clinical populations (i.e., SAD patients), but only after a TMR manipulation. Experiencing fear in dreams was not associated with a decrease of stress during wakefulness in these patients, reflecting a potential failure of the fear extinction function of dreaming in anxious patients.

**Acknowledgements:** This study was supported by the University of Geneva and University Hospitals of Geneva.

#### CHANGES IN ALERTNESS OVER CONSECUTIVE WORKDAYS FOR INTERNAL MEDICINE INTERNS: A SECONDARY ANALYSIS OF THE ICOMPARE TRIAL

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**Introduction:** High quality sleep of sufficient duration is essential for optimal daytime functioning. First year medical residents (interns) are expected to maintain a high level of alertness at all times in order to make critical clinical decisions and maintain patient safety. However, interns regularly fail to achieve sufficient sleep which could impair neuro-behavioral function and alertness. While medical interns' sleep is recognized as habitually insufficient, few studies have investigated the impact of consecutive work days on sleep and alertness. The purpose of this study was to examine changes in alertness over consecutive workdays following a day off for internal medicine interns.

**Materials and Methods:** This is a secondary report of a randomized non-inferiority trial of 12 internal-medicine residency programs assigned to either standard duty-hour (80h workweek/16h shifts) or flexible (80h workweek/no shift-length limit) policies. Interns were followed for 2 weeks during inpatient rotations. Each morning, interns selected the type of shift worked (day-off, days, nights, beginning/ending extended overnights, or other) that day, and then completed the Brief Psychomotor Vigilance Test [PVT-B]. Sleep duration was measured using wrist actigraphy and sleep diaries. Sleep duration was defined as the total number of hours slept each 24h day. For this analysis, interns were included if they had  $\geq 1$  day off followed by at least 3 workdays, and had no identified PVT-B results indicating non-adherence. To examine the longitudinal effect of consecutive workdays on alertness (number of PVT-B lapses), a generalized linear mixed model with Poisson distribution and random subject intercept with random slope for time was used to determine the rate of PVT-B lapses for up to 4 work days following a day off. Covariates included type of shift worked, sleep duration, and policy followed, with sleep and shift type interaction. To account for the change in slope after the second workday, a linear spline with a knot at day 2 was added.

**Results:** A total of 328 interns were included (mean age  $27.8 \pm 2.2$  years, 49% males). Mean  $\pm$ SD number of PVT-B lapses were  $3.4 \pm 4.5$ ,  $4.2 \pm 5.6$ ,  $5.3 \pm 6.6$ ,  $4.8 \pm 5.8$ , and  $4.7 \pm 6.0$ , and mean  $\pm$ SD sleep duration was  $9.0 \pm 1.9$ ,  $6.9 \pm 1.3$ ,  $6.5 \pm 2.1$ ,  $6.6 \pm 1.8$ , and  $6.9 \pm 1.7$  hours for a day off and workdays 1-4 respectively. Rate of lapses increased by 1.1 lapse/day from a day off to the second workday ( $p=0.004$ ; 95%CI: 1.03-1.18), and then significantly decreased from days 2 through 4 at a rate of 0.89 lapses/day ( $p<0.0001$ ; 95%CI: 0.85-0.92). Pattern of change in the rate of lapses were similar to changes in sleep duration, where, from baseline, every 1 hour longer sleep duration was associated with 0.91 fewer PVT-B lapses ( $p<0.0001$ ; 95%CI: 0.88-0.94).

**Conclusions:** Both sleep and subsequent alertness were negatively impacted when returning to work following a day off for interns in this study. After two workdays, sleep duration appeared to increase again, with observed improvements in alertness.

**Acknowledgements:** Funded by the NHLBI of the National Institutes of Health and American Council for Graduate Medical Education. M.C. is supported by NIH/NINR (K99 NR019862).

### CHRONOREXIA AND ORTHOSOMNIA: TOWARDS THE DEVELOPMENT OF SCALES TO MEASURE UNHEALTHY OBSESSIONS WITH SLEEP

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**Introduction:** In 2015 Van den Bulck warned that commercially available wearable sleep monitors might lead to an unhealthy obsession with healthy sleep and referred to it as "Chronorexia". In 2017 Glazer Baron et al. documented cases of patients who presented with such an obsession, which they referred to as "Orthosomnia". Both terms were inspired by earlier work on anorexia and orthorexia. This paper argues that there are two concepts that can be linked to those two terms and will use **Orthosomnia** to refer to an obsession with healthy sleep and **Chronorexia** for the belief that *one does (and should) not need a lot of sleep*. Two measurement scales are presented for examining these concepts in questionnaire form.

**Materials and Methods:** 500 adults 18 and older took part in an online survey. Chronorexia and Orthosomnia were assessed with a battery of 22 questions for each concept. The questionnaire included the FAS, CIRENS, PSQI, pre-sleep arousal, Shuteye Latency, social jetlag, and the Big 5 personality traits.

**Results:** Chronbach's Alpha was high for the Chronorexia (alpha=93.8) and the Orthosomnia (alpha=92.9) scale, and both showed normal distributions. Both scales, while orthogonal, correlate with lower levels of self-control, higher levels of fatigue, and higher levels of negative arousal. Neither was strongly related to chronotype. There were notable differences in subscales. Orthosomnia correlated with a much higher reporting of not being able to sleep in under 30 minutes, of waking up during the night, and of using sleep medication, while Chronorexia correlated with lower self-rated sleep quality.

**Conclusions:** Both concepts showed good internal and external validity. They were orthogonal, so they clearly refer to different phenomena. Surprisingly, perhaps, both concepts had similar relationships with several negative sleep outcomes, supporting the idea that both, indeed, are unhealthy beliefs about sleep. While further research is needed, the extent to which either belief predicts outcomes in a clinical setting, or seeking medical attention is an interesting avenue for examining the predictive use of these scales.

### DETECTING CLINICALLY SIGNIFICANT DEPRESSIVE BURDEN IN SLEEP CLINICS THROUGH PHYSIOLOGICAL PARAMETERS: PRELIMINARY DATA AS TO SLEEP STAGES AND HEART RATE

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**Introduction:** Due to the powerful link between sleep and mood regulation, sleep architecture imbalance may lead to an emergence of depressive symptoms. Moreover, the presence of a depressive condition frequently involves subjective and objective sleep disturbance.

In addition to sleep disorders, mood states have been associated with cardiovascular functioning and regulation modifications, revealing an increased heart rate (HR) and a diminished heart rate variability during low mood states, stronger under conditions of sleep.

In this brief report, we present preliminary data from our ongoing clinical study, designed to develop medically graded software device based on a machine learning algorithm used to aid in identifying a clinically significant burden of depressive symptoms (CDB) in individuals referred to sleep clinics (SCs) for polysomnography (PSG) assessment.

These preliminary analyses aimed to compare sleep stages and HR between subjects with and without CDB (+CDB, -CDB respectively) to identify those physiological parameters able to discriminate between the two

groups.

**Materials and Methods:** Cross-sectional, observational, single-arm, multi-center study conducted in 2 SCs in the United States.

**Inclusion criteria:** 1) age  $\geq 18$  and  $\leq 75$  years, 2) informed consent, 3) ability to read and understand the instructions for the study, 4) willingness to undergo a *full night PSG study*. **Exclusion criteria:** subject 1) has a pacemaker, 2) suspected or known current alcohol/drug abuse.

CBD was defined through the Patient Health Questionnaire 9 (PHQ9, 9 items) at the cut-point score of  $\geq 10$ .

For descriptives, continuous and categorical variables were compared between the two groups by T-Test and Chi-square tests, respectively. Multivariate analysis of variance was applied to HR and sleep stages, with age, number of psychotropic medications, and current cardiac diseases as covariates. The significance level was 0.05.

**Results:** 128 subjects (83 -CDB and 45 +CDB) referred to two SCs in the United States were consecutively recruited and analyzed.

The two groups did not differ in the distribution of gender, BMI, diagnosed sleep-wake disorders, and physical activity on regular basis. They significantly differ in age (-CDB >+CDB), current psychotropic medications and number of clinician-diagnosed current anxiety, major depressive and bipolar disorders (+CDB>-CDB), current cardiac diseases (-CDB >+CDB).

Compared to subjects -CDB, subjects +CDB showed statistically significant: higher HR in deep (N3) and REM sleep stages, higher number of cortical arousals in N3, and increased time spent in N3 and REM, associated with an early onset of REM.

**Conclusions:** Despite the small sample size, we found preliminary indications suggesting an unbalanced autonomic control on cardiac function during sleep in +CDB subjects, reflecting increased sympathetic activity in +CDB subjects. Moreover, +CDB patients present an alteration of sleep architecture, as reported consistently in the literature.

On these bases, optimizing the use of PSG data routinely collected in sleep clinics may be of great importance to identify a CDB in this setting, minimizing the chances of misdiagnosis, and foster appropriate and individualized therapeutic strategy.

**Acknowledgment:** Psychometric and sleep data collection was sponsored by Medibio LTD. We thank all participants and personnel involved in the clinical study.

### DISTRESSING NIGHTMARES AND BAD DREAMS DURING THE COVID-19 PANDEMIC ARE ASSOCIATED WITH DEPRESSIVE SYMPTOMS, SOMATIC SYMPTOMS, AND DELUSIONAL IDEATION

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**Introduction.** Distress associated with bad dreams and nightmares is a commonly used measure to assess psychological impact of dysphoric or intensified dreaming. It has previously been associated with negative mental health outcomes, including depression, anxiety, and suicidality. Recent theories of nightmare-formation propose an interaction between environmental stressors and individual psychological/physical reactivity as factors in the etiology of nightmares and bad dreams. Numerous studies have documented a marked increase in frequency of bad dreams and nightmares during the pandemic, but little is known about factors associated with this trend. Sub-clinical delusional ideation is increasingly of interest, since it represents forms of distorted or intensified cognition in non-clinical populations and is likely reactive to a variety of stressors. Somatic symptoms (SS) are another marker of stress, which is expressed through unusual or increased non-specific bodily symptomatology. The objectives of the present study were to investigate the relationship between nightmare/bad dream distress and different markers of psychological distress during the COVID-19 pandemic: depressive symptoms, delusional ideation, and somatic symptoms.

**Materials and Methods** 1516 participants (Canada=634, Mexico=378, USA=315, UK=54, other countries=135; female=976, male=477, other/no answer=63; average age=34.8, s.d.=12.9, range=16-83) completed an online questionnaire between June 17, 2020 and March 24, 2021.

Nightmare/bad dream distress was assessed using a 5-point Likert-type scale. Depressive and delusional symptoms were assessed using the Community Assessment of Psychic Experiences (CAPE) questionnaire. This instrument quantifies three aspects associated with the psychotic continuum: depressive, positive (delusional) and negative (anhedonia and others) symptoms. Somatic symptoms were assessed using the Somatic Symptom Scale-8 (SSS-8).

**Results.** A forward stepwise linear regression analysis revealed that nightmare/bad dream distress was associated with depressive symptoms CAPE score, somatic symptoms and positive/delusional symptoms CAPE score ( $F(3,1509)=67.87, p<.001, R^2_{adj}=.117$ ).

**Conclusions.** Nightmare and bad dreams distress during the COVID-19 pandemic was most strongly associated with the depressive dimension of CAPE, followed by somatic symptoms and by delusional ideation. The relationship between nightmares and depressive symptoms was expected and is well-documented. However, this is the first study to date showing a relationship between delusional ideation and nightmare/bad dream distress outside of a clinical context, suggesting a potentially generalizable mechanism by which cognitive and perceptual distortions associated with mild levels of delusional thinking may contribute to a more global levels of psychological distress, which, in turn, may express itself in bad dreams and nightmares. This association can become even more prevalent in the context of a high stress situation such as a global pandemic. Lastly, a strong association between somatic symptoms and nightmare/bad dream distress lends further support to embodied theories of dream formation, highlighting the contribution of bodily experiences to dream emotions. This work provides further evidence for an interaction between psychological, environmental, and physiological stress reactivity in the development of dysphoric dreams.

**Acknowledgements** ES was supported by the Postdoctoral Fellowships from the Fonds de Recherche du Québec en Société et Culture and from the National Science and Engineering Research Council of Canada.

#### DO LARKS AND OWLS FEEL BETTER AT THEIR OPTIMAL TIMES OF DAY? AN EXPLORATORY STUDY IN PRIMARY SCHOOL CHILDREN

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**Introduction:** In circadian rhythms research, synchrony effects regarding mood diurnal fluctuations (i.e., better mood at optimal, worse mood at suboptimal times of day) have been previously studied in adolescents and adults, with only a handful of studies finding evidence of chronotype X time-of-day effects. At the same time, evidence regarding synchrony effects in children emotional states is lacking. This study investigated the interactive/synchrony effect of chronotype and time-of-day on school-aged children's emotional states daily fluctuations, in a naturalistic setting.

**Materials and Methods:** From an initial pool of 298 participants from the 3<sup>rd</sup> and 4<sup>th</sup> grades, aged from 7 to 11 years old, 134 Morning-type (M-type) and Evening-type (E-type) children were selected for subsequent statistical analysis (n=52 M-types; n=82 E-types; 53% girls, 47% boys,  $M=8.84$  years-old,  $SD=.60$ ). Parents/guardians filled the Children's Chronotype Questionnaire (CCTQ) to assess children's chronotype. In order to control sleep patterns, and psychopathological symptoms, parents/guardians also filled the Child Sleep-Waking Questionnaire (CSWQ) and the Strengths and Difficulties Questionnaire (SDQ). Students completed momentary emotional state measures [i.e., Faces Scale (FS), the State scale of the State-Trait Anxiety Inventory for Children (STAIC), and the Positive and Negative Affect Scale for Children (EAPNC)] on the first (9 a.m.) and last lesson (4 p.m.) of the school day, either on the same or in consecutive weekdays,

counterbalanced to avoid carry over effects. These interrelated measures were used to determine a composite measure of overall momentary emotional state.

**Results:** The results showed a statistically significant small to moderate interactive effect between chronotype and time-of-day on overall emotional state [ $F(1,127) = 4.83, p = .03, \eta^2 = .05$ ]. If tested at their optimal time-of-day, M- and E-type children reported a better overall momentary emotional state (i.e., morning for M-types, afternoon for E-types) when compared to a suboptimal time-of-day (i.e., morning for E-types, afternoon for M-types). Main effects of chronotype and time-of-day were both non-significant. No significant associations were found between the composite measure of overall momentary emotional state, sleep patterns and psychopathological symptoms.

**Conclusions:** The present study have explored the influence of chronotype and time-of-day in primary school children's diurnal emotional experience in a real-life setting, and have identified the presence of a synchrony effect in M- and E-type school-aged children's overall emotional experience. Given the potential relevance of emotional states in subjective well-being, these emotional state fluctuations might differently impact M- and E-type children's daily functioning while engaging in school activities. Future research employing more assessment points and larger samples is needed.

**Acknowledgements:** This work was funded under the larger research project True Times - Morningness-eveningness and time-of-day effects on cognitive performances and emotional states: New lessons from children and adolescents (PTDC/PSI-ESP/32581/2017; CENTRO-01-0145-FEDER-032581), funded by Portugal 2020, Centro 2020, FEDER (UE), and FCT.

#### DREAM EMOTION RECOGNITION THROUGH EEG NONLINEAR ANALYSIS

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**Introduction:** Dreams are exciting unknown experiences which happen every night and are full of emotional content. Emotion recognition during dreaming plays a crucial role in the diagnosis and treatment of psychological disorders such as post-trauma-stress-disorder (PTSD), depression, anxiety, etc. Dream content analysis is challenging since one should deal with long biological signal recordings and also subjective dream reports. This could be one of the most important reasons why researchers have not focused on this topic to a large extent which has consequently resulted in our knowledge about dreaming being limited.

**Materials and Methods:** In this study, a novel method is proposed to process high-density EEG signals in dreaming. Since the brain is assumed as a nonlinear non-stationary complex biological system, nonlinear methods should be utilized to extract reliable information. In the present study, we suggested a new approach to dream emotion recognition using complex networks. Our proposed complex network is reconstructed with regard to EEG phase space which reflects EEG dynamics appropriately and has been used in several previous studies. We used the graph theory and statistical features to quantitatively describe our proposed EEG complex network. Extracted features are selected using statistical analysis and the most significant ones are fed to our classification models where well-known classifiers have been employed. EEG signals during dreaming are classified into four emotional states according to the continuous model of emotions or in other words the arousal-valence plane of emotions.

**Results:** The classification performance (on average) was 82.69% (with a standard deviation of 3.57%). The most significant channels and brain regions in each emotional state are determined as frontal, occipital, and central lobes. Not only did our proposed complex network classify EEG signals into four emotional classes efficiently, but also it was able to describe different dynamics in other complex signals.

**Conclusions:** We managed to associate EEG dynamics with emotions in dreams. To the best of our knowledge, no study has employed computational neuroscientific methods to classify dream emotions. Our results suggest that the proposed method is quite effective and can be used in

future studies to deeply study brain dynamics in dreaming. Although the results were comparable even to those methods focusing on emotion recognition in awakening, our suggested method has some disadvantages which should be resolved in future studies. This method is time-consuming and needs faster computers to process long recordings of EEG signals. Dream reports are subjective and we can work on other ways to ask questions and record dream reports. Nonlinear analysis can be more deeply studied in future studies as EEG signals in dream content analysis are long, complex, and non-stationary signals. This study has motivated us to dedicate our future studies to dream emotion recognition.

**Acknowledgments:** The authors are thankful to Tehran University of Medical Sciences. We thank Dr. Zahra Ale Mohammad for her collaboration in this study. We thank the Occupational Sleep Research Center of Tehran University of Medical Sciences for their great support.

### DREAMS ENGAGING DREAMERS IN PHYSICAL ACTIVITY ARE ACCOMPANIED WITH MORE POSITIVE EMOTIONS AND BETTER MORNING MOOD

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**Introduction:** Research suggests that continuity exists between waking events and dreams. It has been found that beyond continuity, there is a tendency for dream emotions to be more negative than waking emotions. Additionally, dream emotions can influence morning mood, particularly when the dreams are negative, such as nightmares. However, Kuiken et al. 1993 proposed that some dreams can be impactful and influence mood and behavior in a positive or negative fashion. This proposition needs to be studied further, especially as it relates to the influence of positive dreams on mood regulation. In particular, research on athletes suggests that more time spent in physical activity during waking is associated with having more physical activity dreams; however, the emotional valence of these dreams and implications on morning mood remain unknown. Thus we aimed to extend this by examining whether dreams in which dreamers engage in physical activity are associated with more positive than negative dream emotions, which in turn, is followed by more positive morning mood, compared to other types of dreams that do not incorporate physical activity.

**Materials and Methods:** The data was drawn from the Normative Study of the dreams of Canadians, which comprised male and female participants across four age groups (12–17, 18–24, 25–37, 41–64). Participants completed a dream diary questionnaire, which included questions on positive and negative emotions before sleep and upon waking, recalled emotions in their dreams, and dream reports to log the content of their dreams. Text mining analysis, in addition to a thematic analysis by an independent judge, were conducted to identify dreams in which the dreamer was engaging in physical activity. Forty-one dreams met the inclusion criteria and were compared to a control of forty-one randomly drawn dreams that did not include the dreamer engaging in physical activity.

**Results:** A 2 (dream type: physical activity or non-physical activity dream) by 3 (emotions over time: pre-sleep, dream, post-sleep) repeated measures ANOVA revealed a significant main effect of time,  $p < .001$ ,  $\eta_p^2 = .152$ ; dream type,  $p = .003$ ,  $\eta_p^2 = .107$ ; and an interaction between dream type and time,  $p = .025$ ,  $\eta_p^2 = .051$ . Simple effects analyses demonstrated that those who dreamt about engaging in physical activity had more positive dream emotions ( $p < .001$ ,  $\eta_p^2 = .127$ ) and more positive morning mood compared to those who did not ( $p = .045$ ,  $\eta_p^2 = .049$ ). There were no differences in pre-sleep emotions ( $p = .41$ ,  $\eta_p^2 = .009$ ) between the groups.

**Conclusions:** These preliminary results support the notion that dreams in which the dreamer is engaged in physical activity positively impacts morning mood, although causality would need to be established by experimentally manipulating dream content. Further analysis is needed to determine whether the subjects who exhibited physical activity in their dream equally experience positive dreams and morning mood when their dreams do not include physical activity.

**Acknowledgements:** Support from the Social Sciences and Humanities Research Council of Canada

### EFFICACY OF A THEORY-BASED COGNITIVE BEHAVIORAL TECHNIQUE APP-BASED INTERVENTION FOR PATIENTS WITH INSOMNIA: RANDOMIZED CONTROLLED TRIAL

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**Introduction:** Sleep hygiene is important for maintaining good sleep and reducing insomnia.

This study examined the long-term efficacy of a theory-based app (including cognitive behavioral therapy [CBT], theory of planned behavior [TPB], health action process approach [HAPA], and control theory [CT]) on sleep hygiene among insomnia patients.

**Materials and Methods:** The study was a 2-arm single-blind parallel-group randomized controlled trial (RCT). Insomnia patients were randomly assigned to a treatment group that used an app for 6 weeks (ie, CBT for insomnia [CBT-I],  $n=156$ ) or a control group that received only patient education (PE,  $n=156$ ) through the app. Outcomes were assessed at baseline and 1 month, 3 months, and 6 months postintervention. Primary outcomes were sleep hygiene, insomnia, and sleep quality. Secondary outcomes included attitudes toward sleep hygiene behavior, perceived behavioral control, behavioral intention, action and coping planning, self-monitoring, behavioral automaticity, and anxiety and depression. Linear mixed models were used to evaluate the magnitude of changes in outcomes between the two groups and across time.

**Results:** Sleep hygiene was improved in the CBT-I group compared with the PE group ( $P=.02$  at 1 month,  $P=.04$  at 3 months, and  $P=.02$  at 6 months) as were sleep quality and severity of insomnia. Mediation analyses suggested that perceived behavioral control on sleep hygiene as specified by TPB along with self-regulatory processes from HAPA and CT mediated the effect of the intervention on outcomes.

**Conclusions:** Health care providers might consider using a CBT-I app to improve sleep among insomnia patients.

**Acknowledgements:** Partial financial support for the project by the Research Vice Chancellor of Qazvin University of Medical Sciences is appreciated.

### EXAMINING PREMORBID COGNITIVE ABILITIES TO PREDICT TASK-SPECIFIC, INTER-INDIVIDUAL DIFFERENCES IN RESILIENCE TO TOTAL SLEEP DEPRIVATION

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**Introduction:** Resilience to cognitive impairment from total sleep deprivation (TSD) is task-specific, such that impairment on one task does not generally predict impairment on other tasks. This task-specificity may be, at least in part, a reflection of premorbid differences in cognitive abilities and the cognitive requirements of the tasks. We compared the extent to which premorbid differences in fluid intelligence (Gf) predict resilience to TSD for task performance involving speed of processing, known to be strongly related to Gf, versus cognitive flexibility, which is less strongly related to Gf.

**Materials and Methods:** Published data from a 4-day/3-night, in-laboratory study ( $N=47$  healthy adults, ages 22–40; 26 men) were reexamined based on individual differences in Gf. After a baseline sleep opportunity, subjects were randomized to 38h TSD or well-rested control (WRC), which was followed by recovery sleep. Sleep opportunities were 10h (22:00–08:00). After baseline sleep (session 1) and 24h later (session 2), subjects completed two criterial tasks: the stimulus onset asynchrony semantic matching task (SM), which measures speed of access to word meanings and speed of decision processes, and the go/no-go reversal learning task (NGR), which measures cognitive flexibility. We originally found TSD affected only speed of decision processes on the SM (Honn et al., 2018) and particularly impaired discriminability in the two post-reversal test blocks on the NGR (Satterfield et al., 2018); these measures served as dependent variables. At baseline, subjects completed the Shipley Institute

of Living Scale, which measures Gf; the abstraction score was used to categorize premorbid Gf as relatively high ( $\geq 34$ ; WRC  $n=14$ , TSD  $n=14$ ) or low ( $< 34$ ; WRC  $n=9$ , TSD  $n=10$ ). Task performance was analyzed using mixed-effects ANOVAs with fixed effects of session, condition, and Gf-group and their interactions, and a random effect over subjects on the intercept; the GNGr analysis also included fixed effects of post-reversal test block and its interactions.

**Results:** TSD degraded session 2 performance on the SM, as evidenced by a condition by session interaction ( $p < 0.001$ ). We also observed an effect of Gf-group ( $p < 0.001$ ). The expected benefit of Gf to speed of processing on the SM was observed regardless of session or condition.

TSD also degraded session 2 performance on the GNGr, whereas subjects in the WRC showed performance improvement in session 2 (condition by session interaction,  $p=0.006$ ). Furthermore, there was a session by Gf-group by block interaction ( $p=0.048$ ). Those with relatively high Gf improved across sessions on the second block ( $p=0.037$ ), but this was evident only in rested subjects ( $p < 0.001$ ).

**Conclusions:** Premorbid Gf predicted sleep-deprived performance on a task conceptually related to Gf, such that the benefit of Gf to speed of semantic decision processing persisted across sessions. Regarding cognitive flexibility, higher Gf did not confer resilience to TSD; only higher Gf subjects who were rested showed a benefit in session 2. This work suggests that investigating premorbid individual differences may clarify our understanding of task-specific resilience during sleep deprivation.

**Acknowledgements:** Research supported by NIH grant CA167691 and CDMRP grant W81XWH-20-1-0442.

#### EXPLORING THE ASSOCIATION BETWEEN SLEEP AND COGNITIVE PERFORMANCE IN A HEALTHY AND REAL-WORLD COGNITIVELY IMPAIRED POPULATION

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**Introduction:** Poor sleep is a risk factor for cognitive decline. Multiple mechanisms link sleep and brain health, including pathological accumulation of amyloid and changes in synaptic plasticity during acute sleep deprivation. However, there has been conflicting evidence as to which aspects of sleep are associated with different stages of dementia progression and healthy ageing. We aim to explore this association in both a healthy and real-world cognitively impaired population.

**Materials and Methods:** This cross-sectional study involves two cohorts: a healthy volunteer and a clinical one. Healthy participants completed a web-based study (SleepQuest) comprising validated questionnaires: Pittsburgh Sleep Quality Index (PSQI), General Anxiety Disorder (GAD7), Patient Health Questionnaire (PHQ8), Dysfunctional Beliefs and Attitudes about Sleep (DBAS-16) and an online cognitive assessment- Cambridge Cognition Paired Associates Learning (PAL) task through the Great Minds research registry ([www.greatmindsfordementia.uk](http://www.greatmindsfordementia.uk)). The clinical cohort, comprising attendees to the Cognitive Disorders Clinic at Southmead Hospital, completed PSQI (to measure sleep quality) and STOP-BANG (to gauge sleep apnoea risk) questionnaires to assess sleep, with the Montreal Cognitive Assessment (MoCA) used to assess cognition.

**Results:** 446 healthy participants completed the SleepQuest survey and PAL task and were categorised into two groups: good sleepers ( $PSQI \leq 5$ ) and poor sleepers ( $PSQI > 5$ ). Anxiety and depression scores were higher in poor sleepers compared to good sleepers [(GAD7: 3.67 vs 1.60,  $p < 0.0001$ ); (PHQ8: 5.78 vs 2.18,  $p < 0.0001$ )]. Age ( $\beta = 0.184, p < 0.001$ ), gender (female vs male;  $\beta = 0.236, p < 0.001$ ) and quality of life ( $\beta = -0.363, p = 0.048$ ) significantly predicted cognitive performance, but sleep quality and attitudes towards sleep did not.

109 clinic participants completed the PSQI, STOP-BANG and MoCA. Overall sleep quality was poor ( $PSQI > 5$ ,  $n=67$  (65.1%), mean PSQI 7.54) with 63 participants (61.1%) scoring  $\geq 3$  on STOP-BANG. STOP-BANG significantly correlated with cognitive performance ( $r_s = -0.233, p < 0.01$ ). Overall sleep quality (PSQI) did not significantly correlate with cognitive performance ( $r_s = -0.058, p > 0.05$ ).

**Conclusions:** Poor sleep quality was associated with increased symptoms of depression and anxiety in healthy participants. Meanwhile, in the memory clinic population, risk of sleep apnoea was negatively associated with cognitive performance, suggesting a potential role for sleep apnoea treatment in improving cognitive outcomes in a clinic population; future clinical trials should evaluate this possibility. Although average sleep quality in the memory clinic group was poor, we did not find a clear link between subjective sleep quality ratings and cognition. This mirrored the lack of an association between self-rated sleep and cognition in the healthy group. Future longitudinal studies with molecular classification of neurodegenerative disease and objective sleep markers of micro- and macro-architecture would aid our understanding of the role that sleep may have as a modifiable risk factor for dementia.

#### INCREASED VARIABILITY IN TOTAL SLEEP TIME IS ASSOCIATED WITH REDUCED PSYCHOMOTOR VIGILANCE IMPAIRMENT FOLLOWING EXPERIMENTAL SLEEP CONTINUITY DISRUPTION

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**Introduction:** Sleep deprivation, restriction, and disturbance typically result in impairments of psychomotor vigilance and sustained attention. However, there is a large degree of trait interindividual variability in these impairments. Previous evidence suggests that increased variability in habitual Total Sleep Time (TST) is associated with adverse health outcomes including reduced subjective sleep quality, subjective wellbeing, and increased depressive symptoms. Therefore, we sought to test the hypothesis that variability in TST might represent a trait phenotype of individual response to sleep disruption, using a novel sleep continuity disruption paradigm (Forced Awakenings) which aims to mimic the kind of sleep loss experienced in those with insomnia.

**Materials and Methods:** We performed secondary data analysis from a previously published clinical trial, where 100 healthy sleepers were randomized (stratified by age, sex, BMI) to receive two nights of sleep continuity disruption (Forced Awakenings/ FA: consisting of eight random awakenings lasting 20–60mins) and two nights of undisturbed sleep (US: 8-hour sleep opportunity) in a within-subjects crossover design, separated by a minimum two-week washout period. Participants were rigorously screened to ensure they were healthy sleepers, free of psychiatric, medical or occult sleep disorders. Prior to undergoing the inpatient sleep protocols, participants underwent seven days of at-home actigraphy, from which we derived actigraphic measures of habitual sleep variability. Variability in TST was calculated from actigraphy using two standardized measures of variability: Intra-individual Standard Deviations (iSD) and Mean Square of Successive Differences (MSSD). In accordance with previously published analyses, we assessed the degree to which variability in TST was associated with change in psychomotor vigilance (Both lapses and reciprocal reaction times), from US to FA conditions. The PVT was performed at days one and two of the respective conditions. Analyses were performed using linear regression models and controlled for age and average TST across the seven days of actigraphy.

**Results:** Following one day of forced awakenings, variability in TST was not significantly associated with change in PVT lapses or reciprocal reaction times between FA and US conditions. Following two days, contrary to our hypotheses, increased variability (iSD) in total sleep time was associated with a smaller increase in lapses between undisturbed sleep and sleep disruption (unstandardized beta =  $-0.027$ , SE = 0.12,  $p = 0.03$ ), signifying reduced psychomotor impairment. MSSD of TST was not significantly associated with PVT lapses, despite trending close to significance (unstandardized beta =  $-0.0001$ , SE = 0.0003,  $p = 0.05$ ). There was no association between TST variability and reciprocal reaction time for iSD or MSSD.

**Conclusions:** Contrary to the literature linking increased TST variability to adverse health outcomes, increased TST variability may represent a phenotype which is protective against the effects of sleep disruption on psychomotor vigilance. Future studies should continue to probe the association between this phenotype and other measures of cognitive-emotional impairment following sleep disruption.

## INVESTIGATING THE ROLE OF EXCESSIVE DAYTIME SLEEPINESS IN NEGATIVE EMOTION BIAS IN HIGHER EDUCATION STUDENTS

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**Introduction:** A review article by Tempesta et al (2018) identifies a clear link between sleep and emotional phenomena such as emotional reactivity, emotional memory formation, empathic behaviour, fear conditioning, threat generalisation and extinction memory. This study investigates the relationship between excessive daytime sleepiness, emotional reactivity, and a bias towards negative visual stimuli within a higher education population. This study aims to investigate the role of sleepiness on emotional recognition.

**Materials and Methods:** Data from 93 participants was collected. Participants were aged between 18 and 59 and enrolled within higher education institutions across the United Kingdom. There was a total of, 77 Cisgender Female, 15 Cisgender male, and 1 non-binary participant. The average age of participants was 25.

Participants were given three self-report daytime sleepiness scales: the Epworth Sleepiness Scale (ESS; Johns, 1991), Stanford Sleepiness Scale (SSS; Shahid et al, 2011), and the Pittsburgh Sleep Quality Index (Smyth, 1999).

The OASIS image set (Kurdi, 2017) was chosen as the visual stimuli to be presented as these images are free to use online, are non-specific, and are high quality standardized images. In the presentation block of the study 180 random images were chosen, within these images 60 were positive ( $M_{\text{valence}} = 6.0$ ;  $SD_{\text{valence}} = .215$ ;  $M_{\text{arousal}} = 5.03$ ;  $SD_{\text{arousal}} = .512$ ), 60 images were neutral ( $M_{\text{valence}} = 4.34$ ;  $SD_{\text{valence}} = .207$ ;  $M_{\text{arousal}} = 2.59$ ;  $SD_{\text{arousal}} = .770$ ) and the final 60 images were negative ( $M_{\text{valence}} = 2.52$ ;  $SD_{\text{valence}} = .523$ ;  $M_{\text{arousal}} = 4.01$ ;  $SD_{\text{arousal}} = .460$ ).

Participants were asked to fill in the ESS, SSS, PSQI in a random order. After this, Participants were shown the 180 OASIS images, one image at a time. Participants were asked to make a decision as to whether these images were positive neutral or negative using the 'k' 'l' or 'j' keys.

**Results:** Overall, the regression model was significant  $F(4, 88) = 4.76$ ,  $p < .002$ ,  $R^2 = .178$ , with 18% of the variance in accuracy of emotion recognition being explained by ESS, SSS, Global PSQI and Sleep duration.

**Conclusions:** These results suggest that sleep parameters significantly impact emotional recognition within a higher education sample. Nevertheless, further research is required to investigate how sleepiness impacts higher level components of emotional intelligence, such as emotional understanding. The results of this study suggest that hypersomnolence is detrimental to emotional recognition, however it is not certain whether their understanding of visual stimuli is impacted.

### Acknowledgements:

Supervisors: Dr Abbie Millett, Dr Alexander Latinjak and Professor Brian McCook.

Dr Jo-Anne Johnson

## IS OPTIMAL ALWAYS OPTIMAL? CHRONOTYPE, TIME-OF-DAY, AND CHILDREN'S COGNITIVE PERFORMANCE IN REMOTE NEUROPSYCHOLOGICAL ASSESSMENT

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**Introduction:** Chronotype and time-of-day are important variables to consider in multiple dimensions of human functioning, including cognitive performance. However, chronotype in children has received little attention

in comparison to adolescents and adults, possibly due to the a priori simplistic supposition that children are essentially oriented towards morningness. We investigated potential interactive effects of chronotype and time-of-day on children's cognitive performance (i.e., memory, language, and executive functions), hypothesizing that it may differ when comparing optimal vs. suboptimal times-of-day.

**Materials and Methods:** Seventy-six morning-type (M-Type;  $n = 37$ ) or evening-type (E-Type;  $n = 39$ ) children (48.7% girls; 51.3% boys; 7 to 10 years old;  $M$  age = 8.05;  $SD$  age = .51), identified through the Children ChronoType Questionnaire, from the 3<sup>rd</sup> and 4<sup>th</sup> grades of elementary school completed two remote neuropsychological assessment sessions. These two 30-minute evaluations were conducted via videoconference, either on the first or last hour of the school day (9:00 vs. 16:00, according to Portuguese school schedules), depending on a randomized allocation. The protocol included remote-friendly adapted versions of neuropsychological tests targeting memory, language, and attention/executive domains.

**Results:** The results showed a statistically significant moderate interactive/asynchrony effect between chronotype and time-of-day on a Rapid Alternating Stimulus task [ $F(1,72) = 5.78$ ,  $p = .019$ ,  $\eta^2 = .07$ ]. If tested at their suboptimal time-of-day (i.e., morning for E-types, afternoon for M-types), M- and E-type children were faster when compared to an optimal time-of-day (i.e., morning for M-types, afternoon for E-types). There was also a nearly statistically significant small interactive/synchrony effect between chronotype and time-of-day on a Stories Memory Long-term Retrieval task [ $F(1,72) = 3.79$ ,  $p = .055$ ,  $\eta^2 = .05$ ]. If tested at their optimal time-of-day, M- and E-type children retrieve more story components when compared to a suboptimal time-of-day. There was also a main effect of chronotype on a Backward Digit Span task, with E-type children performing better than M-type children [ $F(1,72) = 5.98$ ,  $p = .017$ ,  $\eta^2 = .08$ ]. Additionally, there was a main effect of time-of-day on an Alternating Verbal Fluency task, with both M- and E-type children performing better in the morning when compared to the afternoon session [ $F(1,72) = 8.85$ ,  $p = .004$ ,  $\eta^2 = .11$ ].

**Conclusions:** Chronotype and time-of-day, individually or in interaction, appear to be relevant variables in primary school children's cognitive performance, namely verbal memory retrieval, working memory, processing speed, and verbal fluency. Children tested in their suboptimal time-of-day can sometimes perform better than in their optimal time-of-day depending on the cognitive area considered (i.e., more automatic processing). We are pursuing further studies to help to disentangle which cognitive processes are more susceptible to synchrony or asynchrony effects and which ones are more resistant to chronotype and/or time-of-day effects.

**Acknowledgements:** Work developed under the larger research project True Times - Morningness-eveningness and time-of-day effects on cognitive performances and emotional states: New lessons from children and adolescents (PTDC/PSI-ESP/32581/2017; CENTRO-01-0145-FEDER-032581), funded by Portugal 2020, Centro 2020, FEDER (UE), and FCT.

## K-COMPLEXES MODULATE THE PROCESSING OF RELEVANT SENSORY INFORMATION DURING NREM SLEEP

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**Introduction:** In as much as the sleeping brain responds differently to auditory stimuli of distinct characteristics, the role of such differential responses is not fully understood. K-complexes represent the most prominent brain response to sensory perturbations during non-rapid eye movement (NREM) sleep. Latest research proposes that K-complexes reflect both sleep protecting as well as arousal inducing processes. We sought to investigate the role of the evoked K-complex to different auditory stimuli, in order to disentangle the function of brain responses to external stimuli during NREM sleep, whether they reflect inhibition and sleep protection or rather sensory processing.

**Materials and Methods:** We recruited 17 healthy humans (14 females) to sleep for a full night (~8h) in the laboratory while acquiring polysomnography data using high-density electroencephalography (EEG). During the night, we presented subjects with their own names as well as

two unfamiliar names. These names were spoken by either a familiar voice to the subject (FV) or an unfamiliar one (UFV). We used an automatic algorithm to detect K-complexes, and performed event-related, time-frequency, and phase coherence analyses to unravel the ongoing brain processes during the auditory-evoked K-complex. Finally, we utilized a machine learning approach to differentiate between brain responses to different stimuli during NREM sleep.

**Results:** We show that UFVs evoked more K-complexes than FVs; however, there was no difference in the number of evoked K-complexes between the names. The difference in the number of evoked K-complexes between FVs and UFVs appeared as early as 100ms post-stimulus and disappeared right after the stimulus presentation ends (mean stimulus duration 808ms). Moreover, by contrasting FV and UFV stimuli that evoked K-complexes, we observed that UFVs evoked a larger amplitude of the N550 component of the K-complex. Further analysis revealed that this difference in the amplitude of the N550 does not demonstrate larger amplitudes of the UFV-evoked K-complexes but rather stronger phase synchronization of brain responses to the onset of UFVs as shown by inter-trial phase coherence analysis. Spectral analysis revealed in the presence of the evoked K-complex, UFVs evoked stronger arousal-like response ( $>16\text{Hz}$ ) relative to FVs. Finally, by training a linear discriminant analysis (LDA) classifier to decode between FV and UFV stimuli from post-stimulus brain activity, we show that only in the presence of evoked K-complexes, the classifier was able to decode the presented voice.

**Conclusions:** Our results suggest the presence of time windows in NREM sleep during which the brain continues to respond preferentially to relevant sensory information. Central to such responses is the K-complex which, when evoked by sensory stimuli, reflects underlying brain processes that serve to extract and process relevant information. We propose that such dynamic reactivity to the environment entails the presence of a sentinel-processing mode where the brain remains connected to the environment while engaging in the vital processes that are ongoing during sleep.

**Acknowledgements:** MA is supported by the Austrian academy of sciences (OEAW), and the Austrian Science Fund (FWF).

#### LAPSES OF REACTION TIMES DURING COGNITIVE AND PSYCHOMOTOR TESTING ARE THE MOST DELICATE INDICATOR OF POOR SLEEP ASSESSED WITH PITTSBURGH SLEEP QUALITY INDEX IN MEDICAL STUDENTS

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**Introduction:** Numerous studies supported the idea that sleep has important roles in regulation of cognitive and affective brain functions. Even though the overall sleep quality contributes to cognitive performance, distinction of various components of subjective sleep quality might provide more precise insight into the aforementioned association, specifically in the student population. The aim of this study was to elucidate the relationship between components of sleep quality and reaction times on simple and complex cognitive and psychomotor tests in medical students. We hypothesized that sleep quality components are more precise indicators of sleep than overall subjective sleep quality and that poor sleep can be detected even by subtle deteriorations in cognitive performance.

**Subjects and Methods:** A total of 164 students (49 men) enrolled in the Basic neuroscience course at the University of Split School of Medicine, participated in the study. All subjects completed Pittsburgh Sleep Quality Index (PSQI), a self-reported general measure of sleep quality and disturbances over the past one-month period. From the 19 items of the PSQI questionnaire, 7 components are created indicating subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction. Cognitive and psychomotor abilities were assessed using Complex Reactionmeter Drenovac (CRD-series), a battery of computer-based psychomotor tests, measuring reaction times and speed of information processing. Three CRD-series test were used: CRD11, assessing solving simple arithmetic operations, CRD311, assessing discrimination of the light signal position, and CRD411, assessing complex psychomotor coordination of

upper and lower limbs. In each test, several variables were analyzed: total test solving time (TTST), minimum single task solving time (MinT), maximum single task solving time (MaxT) and start to end ballast ratio (SB/EB).

**Results:** There was no significant correlation between TTST and MinT with the total PSQI score on CRD11 ( $P=0.633$  and  $P=0.881$ ), CRD311 ( $P=0.446$  and  $P=0.951$ ) and CRD411 tests ( $P=0.464$  and  $P=0.412$ ). However, SB/EB ratio was correlated with total PSQI score on the CRD311 test ( $r=0.201$ ,  $P=0.01$ ). Regression analysis using 7 components of the PSQI questionnaire as predictors revealed that there was an association between use of sleeping medication and MaxT on CRD11 test ( $\beta=0.167$ ,  $P=0.037$ ). On CRD311 test, prolonged MaxT was associated with increased sleep latency ( $\beta=0.379$ ,  $P<0.001$ ), prolonged sleep duration ( $\beta=-0.439$ ,  $P<0.001$ ), decreased habitual sleep efficiency ( $\beta=0.404$ ,  $P<0.001$ ), and less frequent sleep disturbances ( $\beta=-0.370$ ,  $P<0.001$ ). On the CRD411 test, prolonged MaxT was associated with shorter sleep duration ( $\beta=0.174$ ,  $P=0.03$ ) and less frequent reports on daytime dysfunctions ( $\beta=-0.165$ ,  $P=0.039$ ).

**Conclusions:** Our results suggest that precise analysis of sleep quality components might provide a better insight into sleep of students in comparison to overall subjective sleep quality. Maximum single task solving time, as a measure of cognitive performance on the tests of simple arithmetic operations, discrimination of the light signal position, and complex psychomotor coordination was associated with the sleep quality components. Thus, one might presume that this measure, possibly indicating lapses of concentration, is the most sensitive to discriminate impairments of sleep quality components.

**Acknowledgements:** All the students participated in the study.

#### MINIMALLY INVASIVE NASAL AIRWAY SURGERY CAN REVERSE ADHD IN CHILDREN

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**Introduction:** Attention Deficit Disorder (ADD) and Attention Deficit Hyperactivity Disorder (ADHD) are increasingly diagnosed in children, and estimated to occur in nearly 10% of children in the US. While their etiology can be varied and complex, ADD and ADHD are known to occur in up to 50% of children who exhibit sleep disordered breathing (SDB). The mechanism of hyperactivity in these children is directly related to 2 phenomena of SDB: (a) the secretion of adrenaline during sleep to assist children to breath through their airway obstruction, and (b) the build up of “toxins” in the brain during the day that are not appropriately cleared during interrupted sleep. Sleep patterns in children with SDB are characterized by intermittent airway obstruction resulting in episodic hypoxia, sleep fragmentation due to repeated arousal, mouth breathing, and sleep deprivation. In the past decade, medical and behavioral treatment of ADHD has been extensively studied, however no one has yet evaluated the effect on ADD/ADHD behavior after correcting SDB in these children. In our study, we compare the changes ADHD behavior before and after targeted upper airway surgical treatment for SDB in children.

**Materials and Methods:** A prospective pilot study designed to evaluate the effect of targeted nasal surgery on improving ADHD symptoms in children with SDB. 72 children with ADHD symptoms who demonstrated SDB as determined by history, physical exam, and sinus CT-scan were included. The validated Barkley Deficits in Executive Functioning Scale was obtained at baseline and 6 months after surgery. Data from this ADHD evaluation tool was analyzed and compared for each patient using the reliable change index scale (RCI). Parents completed the assessment tool during the child’s clinic visits.

**Results:** 72 patients aged 6-17 years (M 91%; F 9%) completed the study. For ages 6-11 years, 44% of children showed “highly significant” improvement in their RCI, and another 20% improved between 75-99% of the “highly significant” threshold. For children ages 12-17 years, these numbers were 17% and 67%, respectively. 5% of children in both age groups showed slightly worse RCI scores after surgery. Combined, 37.7% of children exceeded the RCI threshold for “highly significant change”, and another 26% improved to between 75-99% of the “highly significant” threshold. There were no surgical complications in this study cohort.

**Conclusions:** Targeted minimally invasive upper airway surgery in children with SDB and ADHD symptoms can significantly improve their executive functioning. This pilot study shows the importance of restoring upper airway breathing and normal sleep as part of ADHD management in a majority of children with SDB and ADHD.

**Acknowledgements:** The patients and their families who trusted in us along the way.

#### MODERATOR EFFECT OF PHYSICAL ACTIVITY ON STRESS AND SLEEP RELATIONSHIP IN DAILY LIFE: AN OBSERVATIONAL STUDY USING WEARABLE DEVICES

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**Introduction:** Daily sleep may be affected by several conditions, including stress. Stress has been shown to impact our physical and mental health. Perceived stress can affect sleep quantity, quality, and architecture, with a detrimental effect on emotional responses to daily stressors. Moreover, poor quantity/quality sleep can increase the risk of severe medical and mental disorders that in turn can have a negative effect on sleep. However, some beneficial sleep/stress management interventions seem to have a mediator impact on a stress-sleep relationship. Physical activity (PA) is reported to prevent the negative effects of perceived stress on sleep, in stress conditions, as COVID-19 pandemic lockdown.

The study aimed to conduct a preliminary analysis on the relationship between PA, perceived daily stress (pdStress), and sleep parameters from data collected through Garmin and Apple wearable devices by LUCA app, a psychophysiological well-being application, helping to recognize and manage stress.

**Materials and methods:** Data from Australian users have been collected for 14 consecutive days. No inclusion and exclusion criteria were applied. PA and sleep parameters were selected if present on both Garmin and Apple devices.

We assessed: PA by daily calories consumption during active daily periods, and total steps; sleep as time spent asleep; pdStress as the total score obtained from four specific daily, day-framed questions investigating the ability to relax, the presence of somatic, and emotional/cognitive symptoms [total score range: 0-12; the higher is the score the higher is the pdStress.]

Statistical analysis included linear mixed models, with pdStress total score as independent variable and sleep duration as dependent variable. PA parameters were added separately as moderators of pdStress and sleep relationship, with age, sex, and the brand of the wearable devices as covariates.

**Results:** Sample: 46 Australian users (19 from Garmin and 27 Apple wearable devices), including 27 females (58.7%); age between 20 and 60 years (years;  $m=40.8$ ,  $sd=\pm 9.1$ ). On average, the sample was characterized by: low to moderate levels of PA; mild levels of pdStress; and sleep duration as WHO's recommendations.

The analyses showed a statistically significant inverse association between level of pdStress and sleep duration ( $p < 0.001$ ). This relationship was moderated by PA measured by active calories consumptions ( $p = 0.015$ ) and total steps ( $p = 0.038$ ), with higher activity levels resulting in a reduction of the strength of the inverse association between pdStress and sleep.

**Discussion:** Our results confirm the detrimental relationship between pdStress and nighttime sleep duration, as reported by the literature. Moreover, our data show that high levels of PA can reduce the negative effect of pdStress on sleep duration.

Despite the limitations concerning the limited number of subjects, device-related recording errors, indirect sleep parameters, and non-sophisticated PA measures, our results underline the importance of PA programs when daily stress conditions and sleep alterations occur.

**Acknowledgment:** Data collection was sponsored by Mebidio LTD. We thank all participants involved in the study.

#### PREDICTING AGE, COGNITIVE SCORES, AND SLEEP STAGES FROM SLEEP EEG WITH A MULTI-TASK DEEP NEURAL NETWORK USING THE FRAMINGHAM HEART STUDY

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**Introduction:** Impaired sleep quality, quantity and timing are associated with neurological and mental health disorders, potentially through disruption of functional and anatomical neuronal pathways. Sleep state oscillations likely encode brain health, therefore, sleep may provide accessible biomarkers for estimating brain health. One potential biomarker is sleep electroencephalogram (EEG)-based brain age, which if elevated above chronological age, could indicate abnormal or accelerated aging. Another potential method to build a biomarker is to directly estimate cognitive function from sleep data. Here, we investigate how well age and neuropsychological test scores can be predicted from EEG using an artificial deep neural network.

**Materials and Methods:** We used data from 735 participants of the Framingham Heart Study (FHS). Each participant had at a minimum one polysomnographic recording (PSG) and one neuropsychiatric evaluation for fluid intelligence (Wechsler Adult Intelligence Scale, NPS). Additionally, age at evaluation was available for each participant, resulting in 1244 PSG-age-NPS triplets. We solely used EEG data from C3 electrodes for this analysis. The EEG signal, recorded in 125 Hz, was bandpass-filtered between 0-20Hz and transformed into the time-frequency domain with the multitaper method (2 second window length, 1 second step size). The resulting spectrograms were all zero-padded to 11 hours, harmonizing the numerical dimensions of the sleep representations across subjects.

We developed an artificial deep neural network with a "U-Net"-like architecture, i.e., consisting of an encoder and decoder part. The network's input was a subject's EEG spectrogram, and its tasks were to predict sleep stages for 30-second epochs, the subject's age, and the subject's neuropsychological test score (NPS). The model mainly consisted of convolution-batch normalization-max pooling/upsampling layers, with a total of 11 million parameters. Fully connected layers for the age and NPS prediction tasks consisted of 15,600 parameters. The loss functions used were cross entropy for the sleep staging task and mean squared error for the age and NPS tasks. We evaluated the model's performance with 10-fold cross-validation.

**Results:** Sleep staging: The accuracies (means and standard deviations across folds) per sleep stage were Wake 0.64 (0.02), N2 0.61 (0.02), N3 0.59 (0.04), NREM combined 0.79 (0.01), and REM 0.53 (0.06). Cohen's Kappa was  $k=0.54$  (0.02). Predicting age: Pearson correlation between chronological age and predicted age was  $r=0.60$  (0.06). Predicting neuropsychological test score: Pearson correlation between the NPS and the predicted cognitive score was  $r=0.25$  (0.07).

**Conclusions:** A multi-task deep learning network was able to predict sleep stages, age, and cognitive scores from sleep EEG with varying performance precision. While there was a strong correlation between predicted age and chronological age, predicted cognition scores correlated weakly to moderately with the actual scores. It is likely that prediction performance for all tasks can be increased with larger and more variable datasets. The sleep-based, subject-specific estimates for age and cognition may serve as biomarkers for brain health, a hypothesis we will test in future studies.

**Acknowledgements:** Research was supported by the National Institute of Neurological Disorders and Stroke of the National Institutes of Health, 1R01AG062989.

#### PROCESSING OF RANDOM AND PREDICTABLE TONE SEQUENCES IN WAKEFULNESS AND SLEEP

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**Introduction:** It is well established that human perception relies on top-down representations, such as expectations. The extent to which such representations influence the processing of upcoming stimuli in sleep has been only recently investigated. Some studies report disruption of hierarchical predictive coding in sleep, whereas others argue for limited but preserved detection of violation of predictions, with profound implications to studies showing effective learning during sleep. Here, we present preliminary results of how higher-order stimulus statistics modulate the neural responses during sleep.

**Materials and Methods:** We presented participants (N=24) with four different auditory tones presented at a fixed presentation rate (3 Hz). We manipulated the tone transition probabilities creating random and predictable tone sequences. Participants listened to the tones in wakefulness and during a 2.5 hour afternoon nap. We collected simultaneous Electroencephalography (EEG) and Magnetoencephalography (MEG) data. We used the EEG data for sleep staging, and we analyzed the MEG data using multi-level pattern analysis (MVPA) to decode low-level tone properties.

**Results:** Preliminary results indicate that low-level stimulus properties are decodable in N1 and N2, although decoding accuracies drop significantly. This is in line with previous studies showing attenuated cortical activations related to the processing of low-level stimulus properties in sleep. In addition, decoding of ordered tones yield significant and above chance pre-stimulus decoding accuracies, whereas this was not observed for the random tones. This effect was present also in N1 and N2 but decoding accuracies appeared less pronounced and stable than in wakefulness.

**Conclusions:** Detection of stimulus predictability seems to be preserved, at least to some extent, in sleep.

**Acknowledgments:** We would like to thank the Doctoral College “Imaging the Mind” for their financial support (FWF, Austrian Science Fund:W 1233-B).

#### PULSE RATE VARIABILITY PREDICTS DEMENTIA IN PATIENTS WITH OBSTRUCTIVE SLEEP APNEA

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**Objective:** We have shown in previous studies that indices of pulse rate variability (PRV) are associated with the incidence of atrial fibrillation (AF) and the occurrence of stroke in patients with obstructive sleep apnea patients (OSA). Given the strong associations between AF, stroke, and dementia, we evaluated in these patients whether PRV indices are also associated with the risk of dementia.

**Patients and methods:** This retrospective study was conducted on OSA patients from the French Pays de la Loire sleep cohort database. Clinical and sleep recording data from 3283 patients aged 60 years and older, without a history of AF were merged with health administrative data to identify the occurrence of dementia (Alzheimer’s or other). Time and frequency-domain parameters of PRV were extracted from photoplethysmography signals. Cox proportional hazard models were used to assess the association between PRV parameters and dementia risk. Association of dementia with clinical parameters as well as OSA severity indices was also assessed.

**Results:** After a median follow-up of 6.8 years, 70 patients had been diagnosed with dementia. Incident dementia was independently associated ( $p < 0.05$ ) with older age, depression, stroke, hypertension, and temporal and frequency indices of PRV. In multivariate analysis only age, depression, and 2 temporal indices of PRV (ln RMSSD: HR [95%CI] = 1.36 [1.08-1.71] and ln SNND: HR [95%CI] = 1.34 [1.05-1.72]) were associated with risk of dementia. However, there was no association between OSA severity indices and dementia.

**Conclusion:** In patients with OSA, older age, depression and increased pulse rate variability assessed by sleep oximetry derived RMSSD and SNND indices may help identify patients at high risk for dementia.

**Acknowledgements:** We thank the IRSR, promoter of the cohorts from

which the data for this study were obtained and the sleep technicians in Sleep Medicine of Angers University Hospital.

#### QUANTITATIVE AND QUALITATIVE FEATURES OF DREAMING ACTIVITY DURING THE PANDEMIC

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**Introduction:** The COVID-19 pandemic has crucially influenced daily habits, mental health, and sleep. Several findings reveal that dreams are affected by waking experiences and sleep patterns. The lockdown could have provoked strong modifications in dreaming activity. This study aimed to assess dream features during the Italian lockdown. Furthermore, we also investigated the impact of the end of COVID-19 confinement on dream activity through a longitudinal investigation.

**Materials and Methods:** We used a web survey to collect demographic, clinical, sleep, and dream data during the lockdown. The sample included 1091 participants. After filling out the survey, 90 subjects participated in the longitudinal protocol lasting two weeks: (a) the first week (April 28–May 4) of full lockdown; and (b) the second week (May 5–May 11) of easing of restrictions. Participants were asked to record at home their dream experiences and complete a sleep-dream diary each morning.

**Results:** Results obtained from the first protocol showed an increase in quantitative and qualitative dream features during the lockdown, compared to a pre-lockdown period. Higher dream frequency and specific qualitative features were found in females and individuals with poor sleep quality, nocturnal disruptive behaviors, and depressive symptoms. Most of the dream features collected during the lockdown were predicted by age, gender, depressive symptoms, presence of other people at home, and territorial area. Sleep duration and several sleep quality indexes were the best predictors of dream variables. During the lockdown, dreams were also characterized by increased negative emotions, particularly frequent in females, younger adults, and people with poor sleep quality, nocturnal disruptive behaviors, anxiety, and depressive symptoms. Regarding the longitudinal protocol, the analyses showed that participants had higher numbers of awakenings, lower ease of falling asleep, higher dream recall, and lucid dream frequency during lockdown than post-lockdown. Subjects reported more dreams, including “being in crowded places” during post-lockdown than lockdown.

**Conclusions:** Our results confirm the strong influence of the pandemic on dreaming, supporting both the continuity-hypothesis between waking experience and sleep mentation and the view of a key influence of sleep patterns on dreaming. The poorer sleep quality during lockdown is consistent with previous studies. The relationship between traumatic events and dream recall frequency supports the idea of the pandemic as “collective trauma”. Moreover, we hypothesized that the greater lucid dreams frequency during confinement could reflect the attempt to cope with the waking pandemic experiences. The crowded places into dream scenarios during the second week of our protocol are also consistent with the continuity-hypothesis: the possibility to access places frequented by other people could represent a relevant experience after a long period of confinement. Finally, we believe that investigations on COVID-19 infected subjects experiencing the long-COVID-19 syndrome should be carried out since preliminary findings on COVID-19 patients showed strong associations between increased nightmares and the infection severity. This evidence suggests that the more that people were affected by COVID-19, the greater the impact on dream activity and quality of life.

#### RELATIONSHIP BETWEEN OBJECTIVE SLEEP QUALITY AND AGGRESSIVENESS

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**Introduction:** Sleep is linked to different emotions and behaviors, but despite this, studies relating sleep quality or sleep problems with

antisocial behaviors or with aggressiveness and anger are scarce and with contradictory results. Therefore, the study aimed to analyze the relationship between aggressiveness and sleep, evaluated objectively. It is expected to obtain a negative relationship between sleep quality and aggressiveness and anger.

**Materials and Methods:** The subjective assessment consisted of a socio-demographic survey, the Spanish version of the Aggressiveness Questionnaire (Andreu et al., 2002), and the Spanish adaptation of the State-Trait Anger Expression Inventory (STAXI; Miguel-Tobal, Cano-Vindel, Casado, & Spielberger, 2001). The objective evaluation of sleep was performed by polysomnography. For this purpose, the participants were summoned at the same time to the Sleep Laboratory of the University of Granada. Light, noise, and temperature conditions were controlled and were the same in all evaluations. The subjects received instructions on sport, napping, food, and stimulant consumption on the day of the test. Upon arrival at the laboratory, electrodes were placed in the lateral pathways as recommended by the AASM, concerning the opposite preauricular area. The sleep signals were analyzed manually. Participants had a code to link their responses to the questionnaires, thus maintaining anonymity. The questionnaires were applied in a computerized form.

**Results:** The prediction models of the anger and aggression variables explained by the sleep variables were not statistically significant. Nevertheless, the adjusted coefficient of determination was high in some cases: trait anger (R2adjusted = .38); anger expression and control (R2adjusted = .24); verbal aggressiveness (R2adjusted = .47;  $p = .035$ ) and anger (R2adjusted = .2). The variables with the greatest explanatory power were sleep efficiency, REM latency, and total sleep time.

**Conclusions:** The results seem to go in the direction of the hypothesis: the higher the sleep efficiency, the lower the aggression and anger. Nevertheless, the results are not significant, perhaps because of the low sample size or because some subjects reported a poorer sleep quality due to the discomfort of the evaluation. Despite the lack of significance in most of the models, we analyzed the most explanatory variables and observed that the most explanatory variables were sleep efficiency, time the subject spent awake after first falling asleep, total sleep time, and REM latency. This means that surely a larger sample size would give statistically significant results since some of the correlations are high.

**Acknowledgements:** The LoMonaco Group for financing the second author's contract.

## RELATIONSHIP BETWEEN SUBJECTIVE SLEEP QUALITY AND AGGRESSIVENESS

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**Introduction:** Sleep is associated with different emotions and behaviors. However, studies relating sleep quality or sleep problems with antisocial behaviors or with aggressiveness and anger are scarce and with contradictory results. Therefore, this study aimed to analyze the relationship between perceived sleep quality and levels of aggression. The working hypothesis was that poorer sleep quality would be related to higher levels of aggressiveness and anger

**Materials and Methods:** A total of 130 participants of Spanish nationality (39 men; 30%) were evaluated, with a mean age of 31 years (SD = 12.88). A total of 80.76% had university studies. The evaluation involved a socio-demographic survey, the Spanish version of the Aggressiveness Questionnaire (Andreu et al., 2002), the Spanish adaptation of the State-Trait Anger Expression Inventory (STAXI, Miguel-Tobal, Cano-Vindel, Casado and Spielberger, 2001). A one-week sleep diary was used to assess subjective sleep quality. The data were averaged for each person. The entire evaluation was applied online, using two Google Forms: one for the questionnaires and another for the sleep diary (since it had to be completed seven nights).

**Results:** Different simple linear regression models were performed using anger and aggressiveness as dependent variables and sleep variables (sleep efficiency, number of awakenings, mean duration of awakenings, and latency to sleep). In no case were models found whose fit was statistically relevant. In fact, at the clinical level, the models did not seem to

have a high percentage of explained variance. Similarly, in the Pearson correlations between variables, no statistically significant relationships were observed beyond isolated relationships. Even so, it was observed that the variables with the greatest explanatory capacity were the mean number of awakenings and the mean sleeping time.

**Conclusions:** The results obtained do not support the hypothesis put forward. It should be noted that the results in the literature are inconsistent and this may be due to the use of subjective measures of sleep quality assessment. It may also be because this relationship only occurs in people with sleep problems or disturbances, whose sleep quality is severely affected for sustained periods.

**Acknowledgements:** The LoMonaco Group for financing the second author's contract.

## SELF-AWARENESS BY WATCHING OWN POLYSOMNOGRAPHY FOR CONTINUOUS POSITIVE AIRWAY PRESSURE

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**Introduction:** Patients with obstructive sleep apnea (OSA) are suspected by observation of the surroundings rather than subjective symptoms, and continuous positive airway pressure (CPAP) is started according to the test results. This results in a lack of insight into the OSA and lowers CPAP compliance.

**Materials and Methods:** This is a randomized controlled study in patients with OSA of an apnea-hypopnea index over 15. All patients with OSA were confirmed through polysomnography and divided into group A in which the patients watched the event of their own sleep apnea and group B without watching the video. After a CPAP titration, all patients had cognitive behavior therapy from the doctor in charge of the sleep center. Then, patients were randomly assigned to either group A or group B and received a CPAP machine. The patients in group A watched their own sleep apnea events that occurred during polysomnography and went home. The patients of group B went home without watching the video. The usage of CPAP was assessed on day 90, and patients were considered as adherent when using their CPAP machine for more than 4 hours per day for 70% of the observed days.

**Results:** A total of 60 patients (30 in each group) were investigated. Group A and group B were compared. On day 90, the average usage per day of groups A and B were  $5.72 \pm 1.02$  and  $5.31 \pm 1.07$ , respectively ( $p = 0.131$ ). The number of used days was more in group A than group B ( $84.77 \pm 7.52$  vs.  $79.70 \pm 10.78$ ,  $p = 0.040$ ). The number of days with more than 4 hours used was more in group A than B ( $73.47 \pm 12.82$  vs.  $64.13 \pm 17.08$ ,  $p = 0.044$ ). The number of CPAP adherence was more in group A than group B ( $n = 29$ , 96.7% vs.  $n = 22$ , 73.3%,  $p = 0.011$ ).

**Conclusions:** To see is to believe. Showing patients their own apnea events can be a plausible option to enhance CPAP adherence.

**Acknowledgements:** This study was registered in the Clinical Trial Registry of Korea (<https://cris.nih.go.kr>): KCT 0005250.

## SLEEP AND THE OPTIMISATION OF MUSICAL LEARNING AND PERFORMANCE

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**Introduction:** This in-progress study aims to quantify the impact that changes in measurable sleep markers have on key objective aspects of musical learning and performance. A growing body of research shows that both quality and quantity of sleep affect memory and learning. Sleep, and specifically certain stages of sleep, are believed to be necessary to consolidate a memory so that it can be successfully accessed in the future. Chronic sleep deprivation degrades the ability to learn, process, and absorb novel information.

The impact that chronic sleep deprivation has on memory and fine motor skills has been looked at in the context of sports performance and within the general population in elegant studies including Dr. Walker's "Practice with sleep makes perfect: sleep-dependent motor skill learning." (Neuron,

2002). In the context of optimising performance capacity, this area is only beginning to be addressed by scholars in the field of music. However, research in this field has not adequately addressed the detrimental effects of chronic low-grade sleep deprivation on musical learning and performance.

**Materials and Methods:** The empirical testing of musical skills has long been problematic. This is due to elements of subjectivity that are present to varying degrees throughout the assessment process. This paper relies upon a combination of established best practices and novel techniques to introduce and develop a new battery of tests designed to quantitatively measure musical ability in three key areas: rhythmic stability, sight-reading, and memorisation. Freshly conceived testing protocols and materials designed to minimise subjectivity in scoring have been incorporated, as have measures to reduce confounding factors. This new battery of tests includes elements drawn from assessment tools as old as the Watkins-Farnum Performance Scale, which was published in 1954, to modern technology such as Korg's BEATLAB Rhythm Trainer, the first iteration of which was produced in 2016. In the case of musical memorisation, recent research developed in non-musical disciplines has been re-purposed and adapted for application in musical research. This new collection of tests and protocols better aligns with the goal of empirically measuring important musical skill sets. It does this whilst minimising the need for expensive and cumbersome equipment. Sleep stages and other parameters of sleep will be tracked with the recently validated Somnofy system (Toften, 2020).

**Results:** Validation trials are currently underway with promising preliminary results.

**Conclusions:** Filling the current gap in knowledge within the fields of sleep research and music and the quantification of the role sleep has on musical skill acquisition has the potential to contribute to the way sleep researchers understand the impact sleep has on human performance, and revolutionise the way music students approach their learning, music educators optimise their teaching, and professional performers execute their concerts.

#### Acknowledgments:

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#### SLEEP DISORDERS AND AWARENESS OF CARDIOVASCULAR PREVENTIVE MEASURES IN GENERAL POPULATION AGED 25–64 YEARS IN RUSSIA/SIBERIA: WHO INTERNATIONAL PROGRAM MONICA-PSYCHOSOCIAL

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**Objective:** to establish associations of awareness and attitude towards cardiovascular diseases (CVDs) prevention in people with sleep disorders in an open population of Novosibirsk aged 25–64 years.

**Materials and Methods:** We carried out screening surveys of representative samples of the 25–64 years old population: in 2013–2016 – V screening (427 men, mean age – 34±0.4 years, response rate – 71%; 548 women, mean age – 35±0.4 years, response rate – 72%); in 2015–2018 – VI screening (275 men, mean age – 49±0.4 years, response rate – 72%; 390 women, mean age – 45±0.4 years, response rate – 75%) using the protocol of the WHO international program «MONICA-psychosocial». Jenkins sleep evaluation questionnaire was used to evaluate sleep disorders.

**Results:** Participants with sleep disorders believed that they were «not entirely healthy» (men – 65.5%,  $\chi^2 = 57.825$ ,  $df=8$ ,  $p<0.001$  and women – 69.6%,  $\chi^2 = 96.883$ ,  $df=4$ ,  $p<0.001$ ); had health related complaints (men – 78.2%,  $\chi^2 = 24.179$ ,  $df=2$ ,  $p<0.001$  and women – 85.2%,  $\chi^2 = 55.144$ ,  $df=2$ ,  $p<0.001$ ), and clearly did not care enough about their health (men – 32.7%,  $\chi^2 = 29.31$ ,  $df=4$ ,  $p<0.001$  and women – 34.1%,  $\chi^2 = 28.116$ ,  $df=4$ ,  $p<0.001$ ). Men with sleep disorders more often assumed that they were

more likely to get a serious illness within the next 5–10 years ( $\chi^2 = 12.976$ ,  $df=4$ ,  $p<0.01$ ). Participants with sleep disorders were confident that modern medicine can prevent (men – 10.9%,  $\chi^2 = 19.079$ ,  $df=2$ ,  $p<0.001$  and women – 13.3%,  $\chi^2 = 21.944$ ,  $df=2$ ,  $p<0.01$ ) and successfully treat (men – 3.6%,  $\chi^2 = 24.142$ ,  $df=8$ ,  $p<0.01$  and women – 3.7%,  $\chi^2 = 15.538$ ,  $df=8$ ,  $p<0.05$ ) only some heart diseases. Men and women with sleep disorders are more likely to seek medical attention in case of severe pain or discomfort in the heart area, but do not seek medical advice if this pain or unpleasant sensation is mild (men – 63.6%,  $\chi^2 = 14.867$ ,  $df=6$ ,  $p<0.05$  and women – 60%,  $\chi^2 = 17.872$ ,  $df=6$ ,  $p<0.01$ ). Among the participants with sleep disorders men more often believe that the doctor «knows more than me» (36.4%), and women (48.1%) chose an answer: «I will not necessarily agree with the opinion of the doctor after a general examination, until a thorough evaluation has been carried out by specialists» ( $\chi^2 = 5.917$ ,  $df=2$ ,  $p<0.05$ ). Women with sleep disorders were more likely to continue to work if they did not feel very well (54.1%,  $\chi^2 = 12.455$ ,  $df=4$ ,  $p<0.05$ ) or their body temperature rose (37.8%,  $\chi^2 = 12.937$ ,  $df=4$ ,  $p<0.05$ ).

**Conclusions:** Persons with sleep disorders generally have a more negative attitude towards their health and are skeptical about the possibilities of modern medicine to prevent and treat CVDs, which is reflected in their attitude to work and preventive check-ups.

#### SLEEP DISORDERS IN ADULTS WITH TUBEROUS SCLEROSIS COMPLEX: A QUESTIONNAIRE-BASED STUDY

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**Introduction:** Tuberous Sclerosis Complex (TSC) is a rare systemic disease with an almost constant neurological involvement, and in which epilepsy and TSC-associated neuropsychiatric manifestations (TAND) represent the major burden. Also sleep disorders (SD) are highly prevalent, yet still largely under-recognized and under-treated. The objective of this study was to assess the prevalence of SD in adult patients with TSC, and to evaluate the relationship between sleep, epilepsy and TAND.

**Materials and Methods:** we administered Pittsburgh Sleep Quality (PSQI) and Insomnia Severity Index (ISI) to adult patients referring to different Italian centers. We also collected information on epilepsy and TAND.

**Results:** We analyzed 114 questionnaires (mean age 31.7 years). An epilepsy diagnosis was reported by 82.3%, with persistent seizures in 67.7% of them. At least one TAND was reported by 73.4% of participants. An existing SD diagnosis was reported by 24 subjects (21.2%).

PSQI and ISI revealed a positive score, respectively, in 52 (46.0%) and 30 patients (26.5%).

PSQI was positive in 26.7% seizure free patients versus 61.9% patients with active epilepsy ( $p=0.003$ ), and the association remained significant ( $p=0.01$ ) even applying a multivariate logistic model considering age, antiseizure medications (ASM), TAND and nocturnal epileptic seizures. ISI positive scores have been detected in 1/30 (3.3%) seizure free patients and in 26/63 (41.3%) of those with persistence of seizures ( $p=0.0004$ ). This association was also confirmed by a univariate logistic regression analysis, estimating that active seizures increased the risk of having a positive ISI score ( $p=0.004$ ,  $OR=3.01$ ). After adding in a multivariate logistic model the independent variables listed above, the association remained significant ( $p=0.007$ ,  $OR=2.98$ ).

PSQI was positive in 43/83 patients (51.8%) with the presence of TAND and in 9/30 of patients (30%) without ( $p=0.06$ ). A univariate logistic regression analysis estimated that a comorbid neuropsychiatric condition increased the risk of having a positive PSQI score ( $p=0.04$ ,  $OR=0.92$ ). However, after adding in a multivariate logistic model the independent variable of active epilepsy, TAND ceased to be a significant risk factor for positive PSQI ( $p=0.12$ ,  $OR=0.75$ ). As for ISI, it resulted positive in 27/83 patients (32.5%) with TAND and in 3/30 (10%) of those without ( $p=0.03$ ). This association was also confirmed by a univariate logistic regression analysis, which estimated that TAND increased the risk of having a positive ISI score ( $p=0.02$ ,  $OR=1.47$ ). After adding in a multivariate logistic model the

independent variable of active epilepsy, TAND ceased to be a significant risk factor for positive PSQI ( $p=0.09$ ,  $OR=1.85$ ).

**Conclusions:** our results confirmed that SD are highly prevalent in adults with TSC, affecting almost half of individuals. Surprisingly, neuropsychiatric comorbidity did not appear to significantly impact the presence of a SD, that appeared to be mostly influenced by the presence of active epilepsy independently from the presence of nocturnal seizures. A bad sleep quality and sleep fragmentation is recognized as a possible triggering factor for seizures, therefore identifying and treating SD might have an impact in reducing the risk of frequent daily seizures.

**Acknowledgements:** we thank the Italian TSC Association for supporting us in performing this study.

### SLEEPING WHILE AWAKE: SLEEP-LIKE SLOW WAVES IN WAKEFULNESS PREDICT MODULATIONS OF PERFORMANCE AND SUBJECTIVE EXPERIENCE

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**Introduction:** Sleep and wakefulness are not mutually exclusive states and when individuals are prevented from sleeping for extended periods of time, a subset of brain regions can start displaying electroencephalographic (EEG) signatures of non-rapid eye-movement (NREM) sleep in the form of sleep-like slow waves. These sleep-like slow waves have been interpreted as a form of sleep intrusions within wakefulness. However, it is unclear if such slow waves are everyday life events, and whether they could impact behaviour in well-rested individuals. Here, we sought to characterise the occurrence of these slow waves in regular wakefulness, determine their link with vigilance and establish their effect on behaviour and subjective experience.

**Materials and Methods:** To understand the neural mechanisms underlying attentional lapses, we studied the behaviour, subjective experience and neural activity of 25 healthy well-rested participants performing a task requiring sustained attention (sustained attention to response task, SART). To quantify the modulations in participants' subjective experience and attentional focus, random interruptions prompted participants to indicate their mental states as task-focused, mind-wandering or mind-blanking. We recorded high-density electroencephalography and pupil diameter throughout the task to monitor vigilance and allow the detection of sleep-like slow waves.

**Results:** Spatially and temporally localized slow waves, a pattern of neural activity characteristic of the transition toward sleep, accompany behavioural markers of attentional lapses and preceded reports of mind wandering and mind blanking. The location of slow waves could distinguish between different types of attentional lapses: for example, between sluggish and impulsive behaviours, and between mind wandering and mind blanking.

**Conclusions:** Our results suggest attentional lapses share a common physiological origin: the emergence of local sleep-like activity within the awake brain.

### SLEEP RESTRICTION IMPAIRS THE ABILITY TO INTEGRATE MULTIPLE PIECES OF INFORMATION INTO A DECISION

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**Introduction:** Sleep deprivation impacts overall decision-making, though the impact on specific components of decision-making are less well studied, especially outside of total sleep deprivation. Here, we examine the effects of sleep restriction on the ability to integrate multiple pieces of information into a decision.

**Materials and Methods:** Healthy adults ( $n=41$ ;  $age=27.9\pm 6.0$  years, 20F) lived in the sleep lab for 2 counterbalanced conditions: well-rested (WR: 9-hour sleep opportunity for 4 nights) and sleep restriction (SR: one 9-hour night, followed by three 3-hour nights). Following the last night of

each condition, participants performed the decision task. Across 48 trials, participants first saw two containers, with different numbers of black and white balls. Eight balls were randomly drawn, with replacement, from one unknown container. Participants decided which container was used, based on the "odds" each container was used and draw results ("evidence"). Mathematical modelling determined the amount of weight given to odds/evidence. The "best" decisions integrate both pieces of information.

**Results:** When WR, participants utilised both pieces of information to make their decisions, though odds were given slightly more weight. During SR, the amount of weight given to the odds did not change, and the weight given to the evidence decreased significantly.

**Conclusions:** SR impaired the ability to integrate multiple pieces of information into a decision. Instead, participants focused on a single piece of easy-to-understand information and did not fully utilise a harder-to-understand piece of information. This has implications for complex applied environments where individuals have large amounts of information with which to make decisions.

**Acknowledgements:** Study funded by the Office of Naval Research Global

### SNAPSHOTS OF THE SLEEPY BRAIN: HIGH-DENSITY EEG AND SUBJECTIVE SLEEPINESS UPON AWAKENING

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**Introduction:** Why do we sometimes feel sleepy as we wake up? Why is it sometimes harder to get active in the morning? Sleep inertia has been suggested to be a consequence of a desynchronized awakening of brain regions, but little is known about the relationship between these local variations, the sleep stage from which one awakes and perceived sleepiness upon awakening.

**Materials and Methods:** In the present study, we investigated the awakening brain regional activity prior and upon awakening and the determinants of subjective sleepiness upon awakening (546 awakenings) in 20 healthy subjects who were recorded with high-density electroencephalography (EEG).

**Results:** Surprisingly, we found that subjective sleepiness was higher upon awakening from REM sleep as compared to NREM sleep, even when adjusting for time spent asleep before the awakening. Sleepiness at awakening correlated with subjective sleep depth before the awakening and was highest when subjects did not report conscious experiences. At the EEG level, we found that awakenings from both REM and NREM sleep were characterized by the persistence of 'sleep-like' low-frequency activity (delta and theta power) in posterior brain regions while only upon awakening from NREM it was associated to an increase of high-frequency activity above wake levels. Furthermore, subjective sleepiness negatively correlated with high-frequency activity and positively with low-frequency activity immediately after awakening. The effect of 'EEG activation' was not localized, but rather diffuse.

**Conclusions:** These results challenge the common assumption that subjective sleepiness is strongest upon awakening from 'deep' slow wave sleep. They also suggest that the awakening process displays distinctive regional activity patterns, with anterior and central brain regions 'waking up' before posterior regions. Finally, these results provide an objective correlate of subjective sleepiness.

**Acknowledgements:** This work was supported by the Swiss National Science Foundation (Ambizione Grant PZ00P3\_173955 to F.S.), the Divesa Foundation Switzerland (F.S.) and the Pierre-Mercier Foundation for Science (F.S.).

### TARGETED MEMORY REACTIVATION DURING REM SLEEP: IMPLICATIONS IN THE TREATMENT OF SOCIAL ANXIETY DISORDER

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**Introduction:** Social anxiety disorder (SAD) is characterized by a significant amount of fear when confronted to social situations and can cause considerable distress in daily life. Exposure therapy, based on fear extinction, is a popular treatment for anxiety disorders, although it does not often lead to full remission. Based on previous research showing that rapid eye movement (REM) sleep strengthens extinction memory consolidation, we tested whether we could enhance exposure therapy by using targeted memory reactivation (TMR) during REM sleep, associated with positive feedbacks and virtual reality (VR), to increase extinction learning.

**Materials and Methods:** 46 subjects with SAD were randomly assigned to a control or TMR group. All participants took part in VR exposure sessions during which they gave presentations in front of a virtual jury, following which they received positive feedback. For the TMR group, a sound was paired with the feedback phase, representing the extinction memory to be consolidated during sleep. During the 8 nights following the first presentation, this sound was administered during REM sleep for all participants, using a wearable headband device. Anxiety levels were assessed using subjective (Subjective Units of Distress Scale) and objective (electrodermal activity and heart rate variability) measures during the preparation phases of the presentations at baseline (T1), after one night of sleep (T2), and after eight nights of sleep (T3).

**Results:** A difference in anxiety levels between groups, assessed with the heart rate measurement (RMSSD), was observed during the last preparation phase (T3), with higher anxiety levels for the TMR group compared to the control group ( $p = .037$ ), while no such difference was observed at baseline (T1).

**Conclusions:** Surprisingly, our protocol led to higher anxiety in the TMR group. While this result was only observed in one out of the three anxiety measures, a possible explanation could be that the TMR sound was associated with the stressful VR situation as a whole, instead of the positive feedback only. Previous studies using fear conditioning and TMR protocols in NREM sleep showed contradictory results, resulting in either a reduction (Hauner et al., 2013; He et al., 2015) or an increase of fear responses (Barnes & Wilson, 2014; Rolls et al., 2013). These findings bring attention to the necessity of testing new experimental protocols to identify the mechanisms that would allow TMR to successfully enhance extinction, which could lead to the development of new therapies.

**Acknowledgements:** This study was supported by the University of Geneva and the University Hospitals of Geneva.

#### TESTING PREDICTIONS OF THE EMOTIONAL AND STRESS REGULATION THEORIES OF DREAM FUNCTION

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**Introduction:** Prevailing modern theories of dream function focus on mood and stress regulation. Typically, it would be achieved through desensitization to negative experiences within dreams. Support comes from the observation that dreamers tend to evaluate emotions felt in their dreams more positively than independent judges based on dream narratives (i.e., positivity bias), which may consequently lead to more positive morning mood even if the content of the dream is objectively more negative. The present study examined the relationship between evening, dream, and morning mood and stress to evaluate the potential desensitization function of dreams and its effects on morning mood and stress levels.

**Materials and Methods:** Male and female participants ( $N = 175$ ) between the age of 12–24 years old recorded at least two dreams (dreams  $N = 350$ ) over a period of ten days and self-reported their mood and stress at bedtime and upon waking, and their emotions in their dream retrospectively. Additionally, an independent judge evaluated the subjects' dream mood. Subjects' positivity bias of their dreams was defined as the difference between the subjects and an independent judge's evaluation of levels of positive emotions in the dream. Participants' dreams were categorized as positive or negative based on their perceptions of the positive and negative emotions in their dreams. After computing an affective balance score of participants' dream emotions, 171 (49%) had more negative dream

nights and 164 (47%) had more positive dream nights; a few had neutral dream nights (4%). Neutral dreams were omitted from the analyses.

**Results:** A t-test revealed that subjects were more likely to perceive their dreams on any given night as more positive than an independent judge ( $p = < .001$ ) but not less negative ( $p = .88$ ), suggesting a positivity bias. Results of a multigroup structural equation model, where a unified model was tested across positive and negative dream nights, demonstrated that bedtime mood and stress were the strongest predictor of morning mood and stress, respectively. However, the second strongest predictor of morning mood, specifically positive morning mood and stress, was subjects' positivity bias. This positivity bias explained why those who had positive dream nights had more positive morning mood above and beyond the objective positivity of the dream. The positive relationship between dream positivity bias and positive morning mood was strongest in those who had negative dream nights. Despite this finding, dreamers' positivity bias did not negatively relate to morning stress in those who had more negative dream nights. This finding suggests that the positivity bias may be one pathway in which a desensitization function of dreams operates for mood regulation but not for stress regulation.

**Conclusions:** These results offer support for the notion of a desensitization function of dreams and its potential for mood regulation. These results also highlight potential distinct mechanisms and functions of dreams for mood and stress regulation. These results are correlational in nature. Experimental manipulation of dream mood and stress would be required to test this theory.

**Acknowledgements:** Social Sciences and Humanities Research Council Canada

#### THE LACK OF AMBULATION IN REM SLEEP BEHAVIOUR DISORDER - WHY DO THEY STAY IN BED?

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**Introduction:** REM Sleep Behaviour Disorder movements often reflect mentation involving frightful situations requiring defensive actions, and the lack of typical REM-like atonia, creating unique potential to study dreams. Whilst commonly described as vivid and engaging, RBD movements almost never involves leaving the bed.

**Study aim and hypothesis:** The goal of this observational study on a large iRBD population is to further investigate the semiology of RBD through video analysis. The brain uses two main "frames" representing spatial information and environmental interactions. *Egocentric* – subject body centred representation. *Allocentric* – a world centred representation. Utilising a philosophical allegory of people in Plato's Cave, we hypothesise that spatial perception and spatial co-ordinates of RBD remain predominantly guided by the (*allocentric*) brain-generated virtual space-map, and thus, no, or very limited, truncal/lumbar axial ambulation will occur during RBD events across the yz-octant of the sagittal plane of the sleeping body.

**Methodology:** A retrospective analysis of clinical and video polysomnographic findings of all patients diagnosed with iRBD during 2019 in GSTT Centre, London, UK. The semiology of each RBD-event was visually analysed and entered into a statistical database. RBD events were classified into distinct groups according to the predominant motor manifestation. To test our hypothesis concerning the movement of the trunk in the sagittal plane, we included an additional category "plane change" and registered the movements that involved a shift from horizontal to upright position.

**Results:** 38 patients were eligible for the study. Body movement identified in 675 RBD events and the 62 solely associated with vocalisation or/and orofacial events. 531 RBD episodes were not complex and subcategorized in the following elementary types: myoclonic (6.59%), simple (72.50%), stereotype (2.63%), simple & myoclonic (16%), simple & stereotype (1.88%), myoclonic & stereotype (0.18%) and mixture of all types (0.18%). self-oriented body movement events (5.3%) scenic (16.29%), violent (4%), vocalisations (4.29%), orofacial (9.77%) and 3.40% had both. Topographical distribution categorisation: head and neck (19.85%), upper limbs (80.30%), lower limbs (44.74%), and trunk (4.88%). Spatial distribution: focal (35.41%), multifocal (40.59%), proximal (67.70%) and distal (71.7%). Bilateral body movement was present in 58% of the limb involving events.

**Discussion:** The additional explicit relevance of our VPSG study is that, for the first time, primary focus is on categorization and demonstration of the paradoxically restricted semiology of truncal/thoraco-lumbar movements during RBD events, which persists even during complex dream re-enactments. Possible theory suggesting the primary somatosensory cortex may present a novel spatial navigation system outside the hippocampal formation. This taken together with our findings, raise the possibility that paradoxical reductions in truncal movements during RBD events may originate from phasic REM replays across primary somatosensory cortex. The phasic REM-related replay in the primary somatosensory spatial navigation system may account for most features of RBD movements in our patients. Most notably, it might underlie the limited truncal mobilisation during RBD events, and as such it may present a useful biomarker that differentiates the RBD events from other (e.g.

**Acknowledgement:** This work was supported by the Wellcome Trust.

#### THE MATTER DREAMS ARE MADE OF: A DICTIONARY-BASED ANALYSIS AND CATEGORIZATION OF DREAM REPORTS

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Verbal reports represent the primary source of insight into oneiric activity. Crucially, computational linguistic methods could be used to extract and objectively quantify information about dream contents in an automatized and reproducible manner. Aim of this study was to investigate similarities and differences in linguistic features between reports of dream experiences and the possible existence of dream prototypes. The study involved 70 healthy Italian native language speakers (40F, 21-64y). Participants filled out an anamnestic questionnaire and questionnaires measuring sleep quality, and mental imagery during wakefulness and sleep. Trait anxiety levels were measured through the STAI-Y2 scale. Then, subjects were asked to record a report of their last dream experience each morning upon awakening for 14 days. Dream reports were automatically transcribed and manually cleaned of any information that did not directly concern the experience (e.g., subjects' comments and digressions). False starts, repetitions and self-corrections were also removed. Misspelled words, regionalisms and dialectal words/phrases were manually corrected. Afterwards, we automatically pre-processed textual data by converting it to lower-case, and removing stop words, punctuation, and finally tokenized it. A dictionary-based content analysis was performed on 605 dream reports through the Italian dictionary of *Linguistic Inquiry and Word Count* (LIWC), allowing for a word-by-word classification of lexical items into distinct categories: first-person perspective, third-person perspective, affective processes, cognitive processes, sensory processes, inhibition, social interactions, time, space, movements, and body. Reports were classified and clustered according to the word frequency count for those categories. We applied a k-means clustering algorithm using cosine distance. The optimal number of clusters was evaluated according to the silhouette criterion. Dream reports clustered around ten semantic dimensions independently of subjects' linguistic idiosyncrasies. Six clusters polarized to the specific dimensions: positive emotions (9%), negative emotions (10%), first-person plural (10%), third-person plural (9%), body (10%), and time (7%). We also found clusters polarized to multiple dimensions: past and movements (13%), space and social interactions (9%), past and third-

person singular (12%), present and first-person singular (10%). Spearman correlation analyses were used to investigate the potential relationship between the frequency of each category and individual variables derived from questionnaires. We observed a negative correlation of participants' age with body and third-person singular perspective ( $p < 0.01$ ), a negative correlation of education level with movements and body ( $p < 0.01$ ), and a positive correlation between trait anxiety levels and references to present time ( $p < 0.01$ ). Further analyses revealed a positive correlation between third-person singular perspective and references to the past ( $p < 0.0001$ ), while first-person singular perspective correlated with references to the present ( $p < 0.0001$ ). Therefore, in describing a dream experienced in the first-person perspective, volunteers tended to represent the events in the present time, while they tended to represent the events experienced by others in the past. Present results indicate the existence of specific dream prototypes according to objective and generalizable semantic dimensions. We found that particular linguistic categories in dream reports are related to trait anxiety, suggesting a possible link with mental well-being. The same analyses could allow to identify and quantitatively characterize alterations of dream experiences in clinical populations.

#### THE ROLE OF DREAMING IN AFFECT REGULATION

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**Introduction:** A key theory of dreaming proposes that dreams function to regulate affect. Research investigating change in emotions across sleep often does not consider the contribution of dreaming mentation to affect regulation, but rather focuses on the association between sleep physiology and affect regulation. We hypothesise that if dreams are responsible for affect regulation, there will be a change in self-reported emotion (both positive and negative) within a dream, leading to less emotionality towards the end of a dream. We also hypothesise that affect will be regulated across the night, with less emotionality in dreams towards the end of the night.

**Materials and Methods:** 24 healthy UCT students (age range 19 – 34 years) were selected to spend 3 non-consecutive nights at a sleep laboratory for PSG monitoring, collection of dream reports, and self-reported emotions experienced during these dreams. The first night was an adaptation night, followed by two experimental nights. During the first experimental night participants were awoken in REM sleep during the early night (dream-point: Early REM) and on the second experimental night they were awoken in REM sleep towards the end of the night (dream-point: Late REM) to record their dreams, using voice recordings, and collect self-reported emotions experienced during these dreams using Visual Analogue Mood Scales (VAMS). Participants completed mood scales for emotions experienced in both the first part (1<sup>st</sup> dream-half) and last part (2<sup>nd</sup> dream-half) of their dream. Each recorded dream was transcribed and assessed for affective content using the Linguistic Inquiry and Word Count program (LIWC). Furthermore, the change in mood of participants across each experimental night was measured using the Positive and Negative Affect Schedule (PANAS).

**Results:** Analysis of the VAMS did not reveal a significant difference in self-reported emotion between the first and second half of dreams, or between early and late REM dreams. There was, however, a significant interaction between dream-half and dream-point, indicating a decline in emotionality from the first half to the second half of early REM dreams, followed by an increase in emotionality from the first to the second half of late REM dream, although still below that of early REM levels. Analysis of the LIWC showed a significant decrease in objectively scored emotional content of dreams from early to late REM.

**Conclusions:** These results suggest that there is an initial decrease in dream affect during the night, followed by an increase in the early morning. We hypothesize that dream affect decreases towards a homeostatic settling point during the night, before rising again to meet this homeostatic point in the early morning hours, which may be required for next-day readiness. This change towards a homeostatic point, and the overall attenuation of dream affect across the night, support the notion that dreaming plays a role in affect regulation.

**Acknowledgments:** This study was supported by the South African National Research Foundation (NRF) through the Competitive Support for Unrated Researchers (CSUR) fund.

### TRAIT PREDICTORS OF DREAM RECALL FREQUENCY IN HEALTHY ADULT INDIVIDUALS

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Understanding potential sources of inter-subject variability in dream recall frequency (DRF) has fundamental implications for the study of dream neurophysiology. Indeed, several physiological, psychological, and cognitive factors have been suggested to influence DRF in the adult population and may act as confounds in studies aimed at investigating the correlates or functions of dreaming. Here we set out to investigate the possible impact of demographic variables, attitude towards dreaming, and memory abilities on DRF. The study involved 87 healthy Italian native language speakers (33M, 21–65y). Participants filled out questionnaires assessing their general health, sleep quality, mental imagery, dream recall frequency, and attitude towards dreaming. In this last questionnaire, participants were asked to provide their degree of agreement with six statements regarding the general meaning and significance of dreams (Bulkeley, K., & Schredl, M., *Int. J. Dream Res.*, 2019). Then, they were asked to record a report of their last dream experience each morning upon awakening for 14 days. If subjects woke up with the perception of having dreamt but could not remember any feature of the experience, they were asked to refer this perception ('white dream'). If they neither could remember any detail of the experience nor had the feeling of having dreamt, they just had to record this ('no recall'). Cases in which participants did not produce a report upon awakening were regarded as 'missing data.' At the end of the 14-day period, participants underwent a neuropsychological assessment. On this occasion, visuospatial and verbal memory abilities were evaluated through the administration of the Rey-Osterrieth Complex Figure and the Babcock Story Recall Test, respectively. We performed a multiple linear regression analysis including DRF as the dependent variable and subjects' age, gender, education level, attitude towards dreaming, and visuospatial and verbal memory scores as independent variables. Based on provided reports we estimated a daily DRF of  $0.60 \pm 0.25$  (range 0.13–1.00). The daily frequency of 'no recall' was  $0.29 \pm 0.22$  (range 0–0.78), while it was  $0.09 \pm 0.11$  (range 0–0.42) for white dreams. A comparison of DRF estimated from provided reports and self-reported DRF based on a 6-point scale revealed a significant correlation between the two measures (Spearman's correlation;  $r=0.49$ ,  $p<0.0001$ ). Interestingly, a stronger statistical association was found when white dreams were counted in the report-based estimates ( $r=0.54$ ,  $p<0.0001$ ), suggesting that measures of self-reported DRF might be influenced by both recalled and white dreams. The multiple regression analysis ( $F_{(5,81)}=4.62$ ,  $p<0.001$ ,  $R^2=0.22$ ) revealed a significant association between attitude towards dreaming and DRF ( $p<0.001$ ). Marginally significant effects were also found for both visuospatial and verbal memory ( $p<0.05$ ), while no significant effects were observed for sex ( $p=0.64$ ) and age ( $p=0.22$ ). Present results indicate that attitude towards dreaming is a strong predictor of DRF. Given that this factor can be easily and rapidly measured using brief questionnaires, its assessment should be considered in studies for which inter-subject variability might represent a relevant confound. When feasible, an evaluation of visuospatial and verbal memory functions might also be advisable.

### TREATMENT OF NIGHTMARES WITH IMAGERY REHEARSAL THERAPY AND TARGETED MEMORY REACTIVATION

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**Introduction:** Nightmare disorder (ND) is characterized by dreams with strong negative emotions occurring during rapid-eye movement (REM) sleep. With a prevalence of around 4% in the general population, this

disorder can disrupt considerably sleep and daytime functioning of patients. ND is mainly treated by imagery rehearsal therapy (IRT), where the patients are asked to change the negative story line of their nightmare to a more positive one.

**Materials and Methods:** Here, we used targeted memory reactivation (TMR) during REM sleep to strengthen IRT-related memories, and accelerate remission of ND. Thirty-six patients with moderate or severe ND were asked to perform an initial IRT session, and while they generated a positive outcome of their recurrent nightmare, half of the patients were exposed to a sound (TMR group, N=18), while no such pairing with a sound took place for the other half (control group, N=18). During the next two weeks, all patients performed IRT every evening at home, and were also exposed to the sound during REM sleep with a wireless headband, which automatically detected sleep stages. Nightmares were assessed with the Nightmare Frequency Questionnaire (NFQ) before the IRT session, at 2 weeks and at a 3-month follow-up. Emotions in dreams were also assessed with a dream diary prior to and during the IRT period.

**Results:** We found that the TMR group had significantly less frequent nightmares and more positive emotions in their dreams compared to patients of the control group after 2 weeks of IRT, and a sustained decrease of nightmares after 3 months.

**Conclusions:** By demonstrating the effectiveness of using TMR during sleep to potentiate IRT, these results have clinical implications for the management of ND, with plausible relevance for learning-based therapies in other psychiatric diseases. Additionally, these findings show that TMR applied during REM sleep can modulate emotions in dreams.

**Acknowledgements:** This study was supported by the Swiss National Foundation.

### Chronobiology/Circadian Disorders

#### A HYBRID EXPERIMENTAL/INFORMATIC APPROACH IDENTIFIES RHYTHMS AND TARGETS IN BREAST CANCER

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**Introduction:** Cancer therapies must kill neoplastic cells while sparing normal tissue. Basic research and clinical experience suggest that both efficacy and toxicity are often modulated by time-of-day. In mice, thousands of genes, including many chemotherapeutic targets, oscillate in a tissue specific manner. Meanwhile, the cell cycle – a system fundamental to neoplasia – is coupled to the circadian clock across phylogeny, sharing molecular components and signaling pathways.

But knowledge of molecular rhythms comes mostly from animal models. Our inability to describe the molecular rhythms in both normal and neoplastic human tissues has been a key barrier in clinical translation and in identifying targets for human chronotherapy. Here we develop a cost efficient, hybrid informatic/experimental protocol and use it to describe the rhythms in human breast tissue and the circadian alterations in breast cancer subtypes.

**Materials and Methods:** We modified CYCLOPS (CYClic Ordering by Periodic Structure), an established methodology for unsupervised circadian data ordering, so that it can both account for confounding variables (e.g. batch collection site or gender) and make use of a limited number of time-stamped samples. After sequencing 26 time-stamped clinical breast biopsies including both neoplastic tissue and the non-cancerous margin, we combined these data with public RNA-Seq data from the Genotype-Tissue Expression (GTEx) project and the Tissue Cancer Genome Atlas (TCGA). The combined dataset included 299 non-cancerous samples and 379 neoplastic samples and was analyzed with the modified CYCLOPS protocol. **Results:** For the time-stamped samples, the ordering inferred from CYCLOPS was well correlated with known collection time. Moreover, the acrophases predicted for core circadian genes in non-cancerous breast

tissue were in good accord with known circadian molecular physiology. We identified >1000 transcripts that showed statistically significant rhythms using Cosinor regression in the non-cancerous samples (FDR < 0.05). Gene set analysis revealed cycling of pathways relating to adipogenesis, hormone responsiveness, and various pathways related to both cancer and therapy including DNA repair, MYC and P53 signaling. Analysis of the cancer samples using the model derived from non-cancerous breast tissue predicts a loss of rhythms in some cancer subtypes and provides testable hypotheses for molecular alterations that correlate with rhythm loss.

**Conclusions:** Our findings demonstrate the utility of hybrid experimental/informatic strategies in identifying clinically relevant rhythms and potential chronotherapeutic targets in a time and cost-efficient manner. We have identified strong rhythms in normal breast tissue which can guide chronotherapy to minimize local toxicity. We also find that histological subtype, when combined with select molecular features, can predict circadian incompetence in individual cancers.

**Acknowledgements:** This work was supported, in part, by NIH grant 5R01CA227485

### A MODEL-BASED INVESTIGATION OF PHYSIOLOGICAL FACTORS THAT PROMOTE IRREGULAR SLEEP/WAKE PATTERNS

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**Introduction:** Irregular sleep/wake patterns have recently been recognized as an adverse risk factor for health. However, we currently have a poor understanding of physiological factors that would contribute to individuals having irregular sleep/wake patterns. We used a validated mathematical model of sleep-wake and circadian physiology to systematically examine potential mechanistic factors, including circadian, sleep homeostatic, and light sensitivity parameters.

**Materials and Methods:** Sleep-wake patterns were generated by a computational model, assuming (i) a 5-day work schedule with enforced wakefulness between 7:00–19:00; and (ii) a fast-forward rotating shift schedule involving night shifts. We introduced daily random variation  $\sigma$  in the model's sleep-onset threshold to mimic observed intra-individual variability in sleep/wake patterns. To quantify sleep regularity, the Sleep Regularity Index (SRI) was calculated, ranging from 0 (random sleep/wake pattern) to 100 (perfectly regular pattern). Eight model parameters were varied to determine their effects on SRI: circadian period ( $\tau$ ); circadian amplitude (nu\_vc); sleep homeostatic time constant ( $\chi$ ); and five light sensitivity parameters: delay bias of the phase response curve (b), sensitivity of the dose response curve (p), retinal output strength (G), photoreceptor activation rate ( $\alpha 0$ ), and photoreceptor recovery rate ( $\beta$ ).

**Results:** Sleep regularity was meaningfully affected by six of the eight parameters. Responses occurred in three clusters: (1) light sensitivity parameters G and  $\beta$  had no effect on SRI; (2) circadian amplitude nu\_vc modulated the effect of  $\sigma$ , such that weaker amplitude resulted in lower SRI (less regular patterns) for the same  $\sigma$ ; and (3) the remaining five parameters  $\tau$ ,  $\chi$ , b, p, and  $\alpha 0$  all showed highest SRI scores (most regular patterns) for default parameter values, with lower SRI scores when parameters deviated from that default. The reason for the default-value peak was a beneficial “anchoring” effect by work hours: default-model sleep times were late enough to not vary freely between work end and start time, and early enough to not be severely restricted by a 7:00 wake time. Results of the shift work simulation were similar to those of the day work schedule.

**Conclusions:** This is the first study to systematically investigate potential mechanisms of irregular sleep using mathematical modeling. Our findings suggest that irregular sleep can result from an interaction between environmental restrictions and individual physiological factors, including individual differences in the sensitivity to the timing and intensity of light exposure.

**Acknowledgements:** N/A.

### AN OBSERVATIONAL STUDY TO INVESTIGATE CRY1 VARIANTS ASSOCIATED WITH FAMILIAL DELAYED SLEEP-WAKE PATTERNS

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**Introduction:** The association of the cryptochrome circadian clock 1, CRY1 $\Delta$ 11 c.1657+3A>C splicing variant with familial delayed sleep-wake phase disorder (DSWPD) was initially described by Patke et al., 2017. We conducted a rigorous observational research study to collect information on sleep-wake patterns and metabolic output from participants with a confirmed status of this splicing variant.

**Materials and Methods:** Study participants included carriers of this CRY1 variant and their controls, defined as wild-type family members. Altogether, 67 participants enrolled and completed the observational study. Participants were recruited in Turkey from families with at least one CRY1 gene variant-confirmed member. We measured the sleep-wake patterns of CRY1 gene variant and control participants by daily post-sleep diaries for a period of 28 days. Additionally, we collected information on daily metabolic output, specifically the time and frequency of bowel movements for all participants. The sleep diary measured self-reported bed time, wake time, midpoint of sleep, and latency to persistent sleep (LPS), and accounted for naps and awakenings for religious purposes.

**Results:** Results demonstrated a significant difference in wake time, bed time, and midpoint of sleep on work nights between carriers of a CRY1 gene variant and their familial controls. Wake time and midpoint of sleep were both significantly later in the CRY1 variant group versus wild-type (wake time: mean,  $p_{\text{ttest}} = 0.03$ ,  $p_{\text{wilcoxon}} = 0.02$ ; midpoint: mean,  $p_{\text{ttest}} = 0.05$ ,  $p_{\text{wilcoxon}} = 0.03$ ). LPS was also significantly greater in participants in the CRY1 variant group (mean,  $p_{\text{ttest}} = 0.01$ ,  $p_{\text{wilcoxon}} = 0.001$ ). The bed time on all nights of sleep (work and free nights) was later in participants with a CRY1 variant versus wild-type (mean,  $p_{\text{ttest}} = 0.11$ ,  $p_{\text{wilcoxon}} = 0.07$ ). The metabolic effects of a sleep delay were determined by the time of a participant's first daily bowel movement. Participants with a CRY1 variant had significantly later bowel movements than wild-type participants (mean,  $p_{\text{ttest}} = 0.01$ ,  $p_{\text{wilcoxon}} = 0.001$ ).

**Conclusions:** These results demonstrate that, on average, individuals with the studied CRY1 variants experience pronounced delays in sleep period and circadian-related metabolic processes.

**Acknowledgements:** Vanda would like to acknowledge the Investigator and participants who contributed to this study.

### ASSOCIATION OF DELAYED SLEEP/WAKE RHYTHM WITH DEPRESSION DURING THE FIRST COVID-19 LOCKDOWN IN FRANCE

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**Introduction:** The containment of the population during the COVID-19 pandemic had major health consequences, including the emergence or recurrence of psychiatric conditions and sleep disorders. The influence of sleep/wake rhythm on mental health is well known. The objective of our study was to evaluate the link between the shift in sleep/wake rhythm and the presence of depressive symptoms during the March to May 2020 lockdown in the French population.

**Materials and Methods:** Participants were recruited via newspapers advertisement and social networks in March 2020. Of the 2612 participants who completed an online questionnaire, data from 2530 subjects could be analyzed to evaluate i) sleep-wake rhythm before and during the lockdown, assessed by the change in mid-sleep time on work-free days corrected for sleep debt on workdays (delta MSFsc); ii) circadian rhythm type, defined by a morning (moderately and definitely), evening (moderately or definitely) or neutral chronotype (Horne & Ostberg questionnaire); and iii) depressive symptoms (Patient Health Questionnaire-9, PHQ-9).

The delta MSFsc and the PHQ-9 score were compared between morning,

neutral, and evening chronotypes using the Kruskal-Wallis test. A multivariate model adjusted for age, sex and circadian rhythm type was used to assess the influence of delta MSFsc on the PHQ-9 score in the whole population.

**Results:** Our population consisted of 77% women, and the median age was 39 (30–48) years. Compared with the pre-lockdown period, the median (IQR) MSFsc was shifted by 29 (0–61) min during the lockdown, with a significant difference between evening [60 (15–120) min], morning [15 (0–46) min] and neutral [30 (0–69) min] chronotype individuals,  $p < 0.001$ . One-third of the participants had moderate to severe depressive symptoms on the PHQ-9. People with evening chronotype had higher PHQ-9 score [10.0 (6.0–15.0) vs 6.0 (2.0–9.0) for morning chronotype and 7.0 (4.0–11.0) for neutral chronotype,  $p < 0.001$ ]. A 1-hour shift in MSFsc was associated with a 0.51-point increase [95% CI (0.29; 0.73),  $p < 0.001$ ] in PHQ-9 after adjustment for age, sex, and circadian rhythm type.

**Conclusions:** In a containment situation, a phase delay in the sleep-wake rhythm is observed in the general population. Such disruption is associated with depressive symptoms, with a greater vulnerability in people with an evening circadian rhythm type. The direction of the link remains hypothetical because depression can also influence the sleep/wake rhythm. The impact on mental health of preventive measures targeting the sleep/wake rhythm in this context remains to be evaluated.

**Acknowledgements:** None

#### AYU-RHYTHM: APPLICABILITY OF TRIDOSHA CONCEPT TO UNDERSTAND THE CHRONOBIOLOGY OF SLEEP

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**Introduction:** Sleep is a physiological activity that has an impact on a variety of biological functions. It is a natural physiological process that occurs in a cycle, allowing the body and mind to completely relax and restore the individual's potential. The organism's general functioning depends on the repetition of this biological phenomena happening. All living species have an internal time clock that is controlled by genes and is influenced by the earth's rotation on its axis. The sleep-wake cycle is one of the physiological processes regulated by this internal biological clock. The sleep-wake cycle is a natural occurrence in all living things and crucial for the body's healthy functioning since it replenishes and heals it. Proper sleep (Samyak nidra) was defined by Ayurveda as necessary for living a normal and healthy life, which is today accepted by modern science. It is a necessary occurrence for all living creatures on the planet's existence, preservation, and healing of both body and mind. The Acharyas believe that Nidra (Sleep) is responsible for happiness and sadness, growth and ageing, strength and weakness, virility and impotence, knowledge and ignorance, as well as life's survival and termination. Sleep is divided into several periodic events in terms of timing, phases, and duration, all of which are guided by an inner rhythm known as the Ayurveda-tridosha rhythm.

**Discussion:** The chronology of tridosha in distinct phases of the day, night, and season was defined by Ayurveda. Tridosha "the body building block" are made up of three elements: Vata, Pitta, and Kapha, which are often interconnected and responsible for the internal and external processes of the human body in order to maintain homeostasis. All main pathophysiological activities, such as immunity, metabolism, growth, and development, are controlled by the tri-dosha. According to the Acharyas, vata, pitta, and kapha are most prevalent in old age, middle age, and childhood, as well as during the final, middle, and initial portion of the day, sleep, and the entire digestive process. This denotes the autorhythmicity of tridosha in different phases which may be coined as Ayu-rhythm. However, in today's technological age, peoples involving in many businesses, including health care, require nonstandard working hours to preserve society's continuity of care and work, which causing shift workers to sleep in the typical rising phase of the circadian rhythm (Diwa Swapana), and awake at night (Ratri Jagarana) resulting in Desynchronized sleep circadian rhythm (Nidra Viparyaya) ultimately leads to disruption of the cycle and resulted in the emergence of ailments. As a result, the majority of the world's

population is getting less sleep hours than they require, which causes metabolic, immunological, neurological, and psychological problems. In turn, the Ayu-rhythm strategy is advantageous in chrono-pharmacological treatment.

**Conclusion:** The goal of this review is to look at how the Ayurvedic idea of Tridosha may be used to maintain inner biological rhythms and how the Ayu-rhythm notion can be used in clinical practice.

#### CHRONOTYPE PREDICTS SPORT PERFORMANCE IN ADOLESCENT MALE BASKETBALL PLAYERS

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**Introduction:** Evening types are more likely to reduce the time devoted to sleep during working days to adhere to their social schedule, compensating during the weekend by oversleeping (i.e., social jetlag). Little is known on how cumulative sleep debt secondary to social jetlag might affect athletes' performance. Given the role sleep plays in motor learning and performance stabilization, it is likely that the impact of sleep restriction would be higher in participants in a training phase as compared to participants that have already learned a motor scheme. We hypothesized that chronotype could predict sport performance, and that it may interact with the day of the week. We also hypothesized that an externally imposed routine (i.e., attending school) would modify the predictive power in participants with a higher propensity towards eveningness and would be detrimental for participants in a training phase.

**Materials and Methods:** Eighty male basketball players (mean age 15.49 years; range 13–17) performed multiple 10-free throw sessions in different days of the week (number of free throws = 6960), both during the school period ( $n = 2180$ ) and the summer holidays ( $n = 4780$ ). The probability of scoring was considered as an index of sport performance, whereas a high standard deviation (i.e., an unstable performance) was treated as a proxy for being in a training phase. Chronotype was assessed through the reduced version of the Morningness/Eveningness Questionnaire. Likelihood Ratio Test was used to compare nested random effects logistic regression models with and without the variables of interest (chronotype, day of the week, and their interaction; school/holidays, standard deviation, and their interaction). Models were adjusted for age, sport expertise, chronotype and time of day.

**Results:** Chronotype and its interaction with the day of the week significantly predicted probability of successful throw in the whole sample ( $p = 0.008$ ) and when regularly attending school ( $p = 0.04$ ), but not on holidays ( $p = 0.15$ ). Moreover, during the school period, participants with the highest propensity towards eveningness reached their peak performance on Mondays, whereas their probability of scoring gradually decreased throughout the week reaching the minimum on Fridays. The interaction between school/holidays period and the standard deviation also significantly predicted sport performance ( $p = 0.0007$ ), which was worse during the school period as compared to summer holidays in participants with a more unstable performance.

**Conclusions:** The impact of chronotype and day of the week on sport performance is tightly related to the presence of an externally imposed sleep/wake schedule and is consistent with evening individuals' increased likelihood of experiencing social jetlag. Possibly due to chronic sleep restriction, attending school significantly worsened performance of participants in a training phase. Results confirmed the relevance of sleep for motor learning and performance in a naturalistic setting. Further investigations are required to assess whether reducing the mismatch between biological and social clocks might improve sport performance along with other aspects of adolescents' life.

**Acknowledgements:** We are grateful to Dr. Di Galante for the excellent technical support.

## CIRCADIAN DISADVANTAGE WHEN TRAVELING WESTWARD IN THE NATIONAL FOOTBALL LEAGUE

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**Introduction:** National Football League (NFL) games have historically been played between 9AM and midnight. Teams can travel up to 3 time zones away, either westward or eastward. Many studies have shown a circadian disadvantage in evening games when traveling westward in multiple sports due to jetlag and circadian misalignment that is disadvantageous for their performance. However, most of the past studies have analyzed wins and losses. Few studies have investigated specific game statistics in professional football following a team's travel. Thus, the objective of this study is to investigate the effect of the direction and the number of time zones traveled on the game statistics of performance.

**Materials and methods:** All evening (after 6PM) away games in the NFL from 2000 to 2020 ( $n = 5360$ ; excluding playoffs and games outside the U.S.A.) were analyzed. Statistics were retrieved from nflpenalties.com and profootballreference.com. Wins/losses, score differential, % pass completion made and allowed to opposing teams, yards per catch, yards per rush, % of successful field goals, total penalties, sacks, interceptions, and taking a risk on fourth down by running an offensive play instead of kicking the ball were extracted from these databases. One-way ANOVAs and linear regressions were computed to evaluate the effects of the circadian disadvantage, its direction (westward, same time zone, eastward) and the number of time zones traveled on each of these game statistics.

**Results:** As expected, results from the ANOVAs show significant differences depending on the direction of travel (westward, same or eastward) for wins ( $F=3.23$ ,  $p=.04$ ,  $\eta^2=.01$ ), but also score differentials ( $F=4.01$ ,  $p=.02$ ,  $\eta^2=.01$ ), yards allowed per pass ( $F=4.50$ ,  $p=.01$ ,  $\eta^2=.01$ ), yards made per pass ( $F=3.51$ ,  $p=.03$ ,  $\eta^2=.01$ ), pass completion percentage ( $F=6.41$ ,  $p<.01$ ,  $\eta^2=.01$ ) and risks on fourth down ( $F=4.35$ ,  $p=.02$ ,  $\eta^2=.01$ ). ANOVAs comparing each time zone traveled (-3 to 3) show differences in % pass completion made ( $F=4.27$ ,  $p<.001$ ,  $\eta^2=.03$ ), % pass completion allowed ( $F=2.15$ ,  $p<.05$ ,  $\eta^2=.01$ ), yards per catch ( $F=2.74$ ,  $p=.01$ ,  $\eta^2=.02$ ), yards per rush ( $F=2.43$ ,  $p=.02$ ,  $\eta^2=.02$ ) and risks on fourth down ( $F=3.55$ ,  $p<.01$ ,  $\eta^2=.02$ ). Post hoc t-tests comparisons for all these ANOVAs indicate a disadvantage for the teams travelling westward. Results from the linear regression analyses show relationships between the number of time zones traveled and wins/losses ( $\beta=-.09$ ,  $p<.01$ ,  $Ra2=.01$ ,  $p<.01$ ), score differential ( $\beta=.10$ ,  $p=.001$ ,  $Ra2=.01$ ,  $p<.01$ ), % pass completion allowed ( $\beta=.09$ ,  $p<.01$ ,  $Ra2=.01$ ,  $p=.01$ ), yards per catch ( $\beta=-.12$ ,  $p<.001$ ,  $Ra2=.01$ ,  $p<.001$ ), yards per rush ( $\beta=.08$ ,  $p=.01$ ,  $Ra2=.01$ ,  $p=.02$ ), and risks on fourth down ( $\beta=-.11$ ,  $p<.001$ ,  $Ra2=.01$ ,  $p<.001$ ).

**Discussion:** These results confirm that there is a circadian disadvantage for NFL teams traveling westward in the evening games. In addition to the known effect on the wins/losses, our results also show that this disadvantage can be observed in several aspects of performance. Also, the number of time zones traveled is associated with performance statistics when teams are traveling westward. Future studies should focus on ways to minimize the effects of jetlag and circadian misalignment during the competition hours of professional athletes.

## CIRCADIAN TYPOLOGY AND COGNITIVE FLEXIBILITY

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**Introduction:** Cognitive Flexibility (CF) is the ability to switch from a task to another, involving high-level activities related to planning and goal-directed behaviour. Switching from task to task requires a high cognitive effort (switch cost), directly influencing the final performance. As for many

other cognitive functions, the influence of sleep-wake cycle on CF has been extensively studied. However, studies on the effect of circadian synchronisation on cognitive performance led to controversial results. Some authors reported better cognitive performances when the tasks are run at the best time of the day for participants, based on their circadian typology (chronotype). This study explores the possible association between time of the day, CF, and chronotype in a sample of healthy participants.

**Materials and Methods:** We recruited 73 participants (avg. age 26.11 ± 7.77, 52% females), who filled a questionnaire assessing socio-demographics, chronotype (reduced Morningness/Eveningness Questionnaire, rMEQ), and autistic traits (Autism-spectrum Quotient, AQ). CF was tested in a lab setting using a well-established behavioural experimental paradigm of task-switching, i.e., Wisconsin Card Sorting Test (WCST), whose peculiarity is that rules change over time. As final outputs, the WCST provides measures of reaction time (RT), number of trails required before completing the task (i.e., ten correct consecutive answers), and the number of perseverative errors (i.e., when the same error occurs instead of adopting a change in strategy). To test the effect of the time of the day and chronotype on CF, we invited 50% of morning (MT, rMEQ score > 18) and evening (ET, rMEQ score < 11) types to undergo the lab session between 6 and 10 a.m., while the other half performed between 6 and 10 p.m. Neutral types (NT) completed the lab session between 10 a.m. and 6 p.m. Finally, we asked to repeat the task from remote after the lab session. MT and ET repeated the test twice (12 and 24 h after). NT repeated only 24 h after.

**Results:** CF (measured as number of trails required to complete the task) is greater in MT compared to ET and NT (median values of 2.434, 2.518 and 2.595, respectively; Kruskal-Wallis,  $p$ -value = 0.038). No synchronisation effect emerged as significant, although a remarkable reduction in the variability of RT in the desynchronised group was observed between the lab session and the two sessions run from remote (Bartlett's test,  $p$ -value = 0.012). A positive correlation was reported between RT and AQ domain "communication skills" ( $r = 0.147$ ,  $p$ -value = 0.052). A weak difference was observed in AQ domain "imagination skills" between chronotypes (Wilcoxon test,  $p$ -value = 0.068), so that ET showed a higher impairment in imagination compared to other chronotypes.

**Conclusions:** Our findings are in line with a vast body of literature. As CF is crucial in work routines, practical implications are immediate. Our results might be considered when planning work and educational activities, e.g., assigning suitable working schedules to different chronotypes.

**Acknowledgements:** The authors thank all the participants who joined this study.

## CLOCK GENES EXPRESSION AND OTHER SLEEP-WAKE RHYTHM BIOMARKERS PROFILES AMONG ACUTE ISCHEMIC STROKE PATIENTS

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**Introduction:** Sleep-wake rhythm disturbances are one of the possible and modifiable risk factors for stroke. Sleep-related breathing disorders are most widely investigated in stroke onset and follow-up studies, supporting evidence for early investigation and treatment of sleep apnea. However, data about non-breathing-related sleep disorders and circadian disturbances among stroke patients are scarce. Circadian-based studies on neurodegenerative disorders such as Parkinson's, Alzheimer's and Huntington's diseases show a global circadian desynchrony features, such as alterations in cortisol, melatonin and clock genes expression profiles. The aim of our study was to investigate clock genes expression profiles among ischemic stroke patients and their relations to other sleep-wake rhythm biomarkers, sleep structural and clinical stroke features.

**Materials and Methods:** This prospective study included patients that were investigated in the acute period of stroke (2-10 days after stroke onset) with neurological and objective examination, questionnaires, polysomnography, actigraphy, skin temperature thermochrones and 24-h blood sampling for melatonin and clock genes profiles (samples taken at five time points: 7, 11 p.m., 3 and 7 a.m., 12 p.m.). Control group consisted of age and sex matched relatively healthy controls without stroke or other neurodegenerative disorder anamnesis.

**Results:** 27 patients (20 males) with the age median [min ÷ max] of 56 [34÷82] years and primary NIH stroke scale value of 4 [0÷21] were diagnosed with an acute ischemic medial cerebral artery stroke (19, 70.4%) or vertebrobasilar stroke (8, 29.6%). Control group consisted of 25 gender and age matched participants (17 males) with the median age of 55 [33÷83] years. According to actigraphy-based rest-wake rhythm analysis, there were no significant differences between two study groups regarding average bed times and get up times, total sleep time, sleep efficiency, sleep onset, total number of awakenings, except that controls had shorter wake after sleep onset time than stroke patients (median of 44.25 vs. 62.88 minutes,  $p=0.01$ ). Median melatonin plasma concentrations at four time points at 7, 11 p.m., 3 a.m. and 12 p.m. did not differ significantly between patients and controls, only early morning melatonin concentration at 7 a.m. was significantly lower among stroke patients (median 18.98 vs. 33.22,  $p=0.041$ ). Additionally, cortisol plasma concentration at 7 a.m. was significantly higher in the patient group (median 522.47 vs. 425.57,  $p=0.038$ ). All four clock genes (*ARNTL* (*BMAL1*), *NR1D1* (*Rev-erba/β*), *PER1*, and *PER3*) showed significant time-of-day variation in both patient and control groups. According to the genes expression comparisons between patients and controls, only expression of *NR1D1* (*Rev-erba/β*) at 7 a.m. and *PER1* at 12 p.m. differed significantly (respectively, median 0.2407 vs. 0.3202,  $p=0.034$ , and 0.2431 vs. 0.6733,  $p=0.04$ ).

**Conclusions:** Acute ischemic stroke patients tend to preserve diurnal variation of sleep-wake rhythm biomarkers such as actigraphy measures, melatonin and clock genes expression profiles, except early morning time point showing higher cortisol and lower melatonin concentrations and lower *NR1D1* (*Rev-erba/β*) expression, as well as lower *PER1* midday expression in comparison with controls, that might reflect peculiar circadian desynchrony features in different loops of the molecular circadian clock system.

**Acknowledgements:** None.

#### COGNITIVE ALTERATIONS IN PATIENTS WITH ALTERATIONS IN SLEEP ARCHITECTURE IN A COURT OF COLOMBIAN PATIENTS

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**Introduction:** Increasing evidence suggests that sleep disorders precede the onset of Alzheimer's disease by years, which is why it has been proposed that patients with alterations in sleep architecture have some degree of cognitive impairment (subjective complaint of memory or cognitive level impairment).

In neurological clinical practice, we observe that sleep studies ordered to rule out OSAHS generally do not show severe alterations in this aspect, but they do show alterations in sleep architecture, mainly low sleep efficiency and N3 sleep proportion. Patients with memory problems may have alterations in the structure of sleep, however it remains unclear if having an affection in the organization of sleep affects the cognition of the subjects. With this work we want to describe the results of cognitive tests in patients with results in sleep architecture.

**Materials and methods:** Descriptive cross-sectional study, where 160 polysomnographies were reviewed, 68 patients met the inclusion criteria and 31 agreed to the Montreal Cognitive Assessment (MOCA) cognitive test to detect level cognitive impairment and the Hopkins test. For memory evaluation, they cannot have moderate or severe sleep apnea syndrome and cannot be taking medications that cause the sleep-wake cycle.

**Results:** 77% presented the MOCA test below the normal values validated for the Colombian population, without finding significant differences between patients without OSAHS and with mild OSAHS, with delayed recall being the most affected domain.

**Conclusions:**

1. 77% of the patients included in the study presented MOCA test values below the normal values validated for the Colombian population.
2. There were no significant differences between patients with AHI <5 and AHI 5 - 15.
3. The Hopkins test was used in the majority of patients with alterations in

the architecture of sleep.

4. Alterations in sleep architecture could be a factor associated with cognitive disorders and thus could motivate a complete neuropsychological assessment.

**Acknowledgements:** To my mother Alma Luz, my teachers and patients who inspire us to study every day.

#### COMPARISONS OF SUBJECTIVE AND ACTIGRAPHIC MEASUREMENTS OF SLEEP BETWEEN SHIFT-WORKING AND DAYTIME PSYCHIATRIC NURSES

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**Introduction:** Shiftwork is known to be one of the common causes of sleep and health problems and finally causes the decreased quality of life. The purpose of this study was to investigate the sleep patterns of shift-working and daytime psychiatric nurses using actigraphy and compare it with subjective assessment for sleep.

**Materials and Methods:** Twenty-three shift-working and 25 daytime nurses were enrolled. They rated their sleep quality using Pittsburgh Sleep Quality Index (PSQI) and other self-rating scales were measured for psychosocial aspects. Actigraphy was applied to the subjects for a total of 7 days to measure the sleep parameters. They also wrote sleep diaries during the period of wearing actigraphy. Sleep-related parameters of actigraphy, global score and components of PSQI, and the results of other self-rating scales were compared between shift-working and daytime nurses.

**Results:** Although the global score of PSQI did not show significant difference, the PSQI components showed significant differences between two groups: the shift-working nurses showed lower sleep quality, more sleep disturbance and hypnotic medication use, and worsened daytime dysfunction than daytime nurses. The shift-working nurses showed significantly shorter total time in bed and total sleep time, lower sleep efficiency, and longer average awakening time than those of daytime nurses in actigraphy.

**Conclusions:** The results showed that shift-working nurses experienced more sleep disturbances in both subjective and objective aspects of sleep than daytime nurses. This study also suggests that actigraphy may be useful to measure the objective aspects of sleep that are difficult to assess with subjective questionnaires alone.

#### DEVELOPING A MULTIDISCIPLINARY PEDIATRIC CIRCADIAN MEDICINE CLINIC: THE CIRCADIAN AND COMPLEX SLEEP DISORDERS CLINIC

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**Introduction:** Complex sleep and circadian disorders are common in pediatric populations in the US. However, to date, no pediatric-specific circadian clinics have been established. Due to high referral volume and a multidisciplinary faculty with strong interests in sleep and circadian rhythm disorders, the Circadian and Complex Sleep Disorders Clinic (CCSDC) was established in 2020 at Cincinnati Children's Hospital Medical Center to diagnose and treat the biobehavioral determinants of these disorders in the pediatric population. Our objective is to review our experience developing the first dedicated multidisciplinary pediatric circadian medicine clinic.

**Methods:** To establish this clinic, translational research funding was obtained through internal grant mechanism. Consultations were made with other institutions with established circadian medicine programs. IRB permission was obtained to establish a data registry for our patient population and to aid in future translational research studies. Staff members were selected based on their specific roles, which included sleep boarded psychologists, sleep boarded medicine providers, a medical assistant, dedicated nurse, and clinical research coordinator. A dedicated clinical space was established in a multidisciplinary space in the hospital.

**Results:** There are two facets to this clinic: clinical care and translational research. Concurrent clinical evaluations with a board-certified sleep physician and a board-certified sleep psychologist informs multidisciplinary treatment, providing patients with comprehensive sleep management that addresses the biobehavioral determinants of their circadian disorders. Institutional funding provides for certain diagnostic resources at no additional cost to the families. Through an individualized approach, the care team works with the family to create a treatment plan that may include medication, surgical therapies, and/or cognitive-behavioral treatment. Our data registry collects clinical research outcomes including actigraphy, sleep diaries, and validated questionnaires that measure demographics, sleep habits and disturbances, chronotype, psychological functioning, health related quality of life, and pain characterization. Such validated clinical measures provide baseline characterization of sleep and health status as well as prospective measurements of treatment outcomes during and after treatment. Currently, we have recruited over 100 patients to our circadian patient registry. We also have recruited over 25 families to our family-centered project to identify genetic markers for circadian disorders, which has translated to genetic experiments in mice to better understand the functionality of certain genetic mutations.

**Conclusions:** Since the inception of this clinic, patients have benefitted from individualized care informed by evidence-based treatment. Registry data demonstrates patient outcomes reflect significantly improved sleep quality. Through our research, we found that clinics can effectively evaluate treatment outcomes during the initial diagnostic workup, which could change the treatment course entirely. Working together with the patient and family to transition to new treatment options significantly improves the patient's overall understanding of the process, which translates to a significantly higher likelihood that the patient will respond well to therapies and continue follow-up care. Through this clinic's multifaceted approach to clinical directives and research perspectives, we have demonstrated that individually directed circadian disorder therapies show strong improvements in our patients based on their symptomatology.

**Acknowledgements:** Academic and Research Committee (ARC) funding, Cincinnati Children's Hospital Medical Center

#### DYNAMIC EXPRESSION OF *DDC* MEDIATES THE MELATONIN BIOSYNTHESIS RHYTHMS IN THE MOUSE: A VIRTUAL KNOCKOUT APPROACH

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**Introduction:** Sleep is inevitable for overall healthy living. Periodical exposures of light/dark (LD)-cycles coupled with the circadian rhythms are crucial determinants for sleep health. Melatonin (MT), an essential natural hormone that regulates the circadian rhythms in mammals. It is primarily synthesized in the pineal gland during the dark phase and temporally distribute across different tissues. Hence, the tissue-specific abundance of MT used to vary. Studies suggested that the MT-biosynthesis occurs rhythmically in four steps subjected to the LD exposures. The tissue-specific distribution also follows a rhythm. MT-biosynthesis initiates with an essential amino acid, Tryptophan (Trp), that gets converted to Serotonin (5-HT) through an intermediate, 5-hydroxytryptophan. Then, in the pineal gland, 5-HT is converted to MT through an intermediate, N-acetyl-serotonin. Tryptophan hydroxylase (TPH), Aromatic amino acid decarboxylase (AADC/DDC), 5-HT-N-acetyl transferase (SNAT/AANAT), and 5-hydroxyindole-O-methyltransferase (HIOMT) are the enzymes involved in MT-biosynthesis. The mRNA encoding those enzymes are assumed to have a rhythmic expression. However, their functional relationships, inter-dependencies, and the spectrum of factors influencing their expressions are not extensively exposed. Their multiplexed interactome may elucidate the intricacy of MT-biosynthesis. And it may offer a clue to modulate it dynamically to intervene in targeted therapeutics related to MT depletion and sleep. Here, we have introduced a quantitative approach to investigate the dynamic transcriptional regulatory landscape of those genes and their influence on MT-biosynthesis rhythms.

**Methods:** We introduced a tuning-responsive robust ODE- and SDE-based quantitative model for MT-biosynthesis. Different kinetic parameters associated with its genetic circuits were analyzed. They were further transcriptionally perturbed to estimate the impact on the MT-biosynthesis at a dynamic scale. Our model combines the whole-liver transcriptome data as input and predicted the regulatory TF-logics to decode the tuning-responsive transcriptional regulatory networks for MT-biosynthesis. We further devised transcriptional simulations with virtual-knockout mutants of those identified TF-logics to quantify the extent of perturbation.

**Results:** Our results indicated that the reconstructed quantitative transcriptional regulatory networks were able to predict several crucial transcriptional controls for the enzymatic regulations involved in MT-biosynthesis. It also decoded their transcriptional regulatory interaction patterns and expression dynamics. We have found that the gene, *Ddc* critically controls MT-biosynthesis, and follow a rhythmic expression across the time series. It essentially suggests that the expression of that gene is regulated transcriptionally by the molecular clock mechanisms, and plausibly considered as a clock-controlled gene. It was also supported with the network analyses predicted with core circadian TFs. Further, the *Ddc* transcriptional simulations with different circadian TFs mutants were also able to influence the dynamic fluctuations of the MT concentrations reflected through our tuning-responsive quantitative model.

**Conclusions:** This study infers an indication to devise scalable, robust, and iterative strategies to control the MT-biosynthesis at a dynamic scale by regulating its transcriptional controls. It may further enhance the progression of circadian and sleep medicine.

**Keywords:** Melatonin dynamics, Virtual knockout, Transcriptional Regulatory Networks

**Acknowledgements:** Research Grants Council of Hong Kong (12201818); National Natural Science Foundation of China (31871315); Natural Science Foundation of Guangdong, China (2018A030310693); Shenzhen Science and Technology Innovation Commission of China (JCYJ20170817115152903, JCYJ20170817173139249).

#### EFFECT OF NIGHT AND SHIFT WORK WITH METABOLIC SYNDROME AND ITS COMPONENTS IN AN ACTIVE MIDDLE-AGED POPULATION-BASED SAMPLE

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**Introduction:** While night and shift work has become highly prevalent in modern societies, the impact of shift work on metabolic syndrome is not yet completely understood. Moreover, the specific effect of shift work and permanent night work remains largely unknown. This study aimed to examine the effects of work schedules on metabolic syndrome and its components in active middle-aged workers.

**Materials and Methods:** A cross-sectional analysis including active workers from the population-based CoLausPsyCoLaus study (Lausanne, Switzerland) was performed. Work schedule was self-reported and defined as follows: permanent day, day shift, night shift, and permanent night work. Associations between work schedule and the risk of metabolic syndrome and its components were analyzed using multivariable-adjusted logistic regressions.

**Results:** A total of 2301 active workers (mean age  $56.2 \pm 6.9$  years, 50.1% women) were included. Of these, 1905 were permanent day workers, 220 were day shift workers, 134 were night shift workers and 42 were permanent night shift workers. There were significant interactions between sex and work schedule for metabolic syndrome, high triglycerides and visceral obesity. Men but not women permanent night workers had a higher prevalence of metabolic syndrome than permanent day workers in multivariable-adjusted analyses (OR 4.45 [95% CI 1.36–14.56]). Analysis of metabolic syndrome subcomponents showed that the association between work schedule and metabolic syndrome in men was mainly driven by visceral obesity (OR 3.35 [95% CI 1.04–10.76]). Conversely, women but not men working in night shift were at increased risk of having high triglycerides compared with permanent day workers (OR 2.92 [95% CI 1.03–8.27]).

**Conclusions:** The risk of metabolic syndrome is higher in men working in permanent night shift compared with permanent day work and this association could be mediated by visceral obesity.

**Acknowledgements:** The HypnoLaus and the CoLaus/ PsyCoLaus studies were and are supported by research grants from GlaxoSmithKline, the Faculty of Biology and Medicine of Lausanne, the Swiss National Science Foundation, Leenaards Foundation, and Vaud Pulmonary League.

#### ENRICHMENT OF THE VNTR PER3 VARIANT IN DSWPD PATIENTS: A LARGE WHOLE GENOME SEQUENCING ANALYSIS

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**Introduction:** We have conducted a rigorous observational research study in suspected delayed sleep-wake phase disorder (DSWPD) patients. The objective was to measure sleep-wake patterns and to conduct exploratory genetic analyses to delineate the genetic landscape of the DSWPD phenotype.

**Materials and Methods:** We measured the sleep-wake patterns (self-reported bed time, wake time, midpoint of sleep, and sleep latency) of participants by daily post-sleep diaries for 10 weeks. Participants completed questionnaires on demographics, medical and surgical history, sleep history, and concomitant medications. Altogether, 119 participants were consented and 76 participants provided samples for whole genome sequencing. Seventy-eight participants were females and the mean age was 44 years. Principal component analysis defined ancestry as 29.3% AFR, 17.3% AMR, and 53.4% EUR.

**Results:** We observed a significant enrichment of the minisatellite 54bp (1: 7829913–7829966 (GRCh38)) variable number of tandem repeat (VNTR) PER3 rs57875989 4 allele. We observed significantly higher frequencies of the 4/4 variant: 59.2% when compared to the super control population frequency of 42.2% ( $n = 315$ ; recessive: OR 1.9, CI 1.07 to 3.65,  $p < 0.02$ ). Super controls were defined as participants without reported sleep issues or diagnosed sleep disorders. The MAF in the DSWPD group was 0.74 versus 0.62 in matched super controls. Allelic frequency varied across ancestries, with the highest MAF reported in East Asian populations and the lowest MAF reported in the Ashkenazi Jewish population. We have

analyzed adjusting for population stratification.

This variant is of particular interest as it is located in the coding region of VNTR (exon 18). Functionally, PER3 is phosphorylated by casein kinase 1 (CK1) and translocates to the nucleus to inhibit CLOCK/BMAL1 in the presence of PER1. The VNTR motif contains clusters of potential phosphorylation sites for CK1. Given the VNTR PER3 variant could change protein phosphorylation levels in addition to tertiary protein structure and also have interactions with binding partners, it is hypothesized that the VNTR would cause functional changes in PER3. The observed accumulation of the PER3 VNTR 4/4 supports prior literature describing evening-types and DSWPD patients as having greater frequencies of PER3<sup>4/4</sup> homozygotes; this effect can be as high as 75% homozygotes in DSWPD.

**Conclusions:** These results demonstrate that, on average, DSWPD individuals are more likely to harbor variants within their core clock genes with particular enrichment of the VNTR variant, potentially leading to a pronounced delay in sleep period. This variant can further impact the response to treatment across carriers of the 4/4.

**Acknowledgements:** Vanda would like to acknowledge the participants who contributed to this study.

#### EVENINGNESS IS ASSOCIATED WITH SEDENTARY BEHAVIOR AND INCREASED CARDIOVASCULAR RISK – DATA FROM THE SCAPIS PILOT COHORT

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**Introduction:** Chronotype reflects individual preferences for timing activities throughout the day and is determined by the circadian timing system, environment, and behavior. We studied the association between chronotype and physical activity patterns as well as cardiovascular risk in the Swedish CARDioPulmonary bioImage Study (SCAPIS) pilot cohort.

**Materials and Methods:** A cross-sectional analysis was performed in a random population sample aged 50 to 64 years ( $n=812$ , 48% male). Chronotype was classified as extreme morning, moderate morning, intermediate, moderate evening, or extreme evening based on a multiple-choice question. Physical activity patterns were determined by hip accelerometer worn for seven days. Time spent sedentary and in moderate to vigorous physical activity (MVPA) was analyzed. 10-year risk of fatal cardiovascular event was calculated according to the 2015 European Systematic Coronary Evaluation (SCORE) charts.

**Results:** We found that extreme evening chronotypes exhibited the most sedentary and least MVPA ( $55.3 \pm 10.2$  and  $5.3 \pm 2.9$  % of wear-time, respectively). As chronotype shifted towards extreme morning, time spent sedentary decreased, and MVPA increased in a dose-dependent manner (ANOVA,  $p < 0.001$  and  $0.001$ , respectively). This pattern was most pronounced in the morning. In a generalized linear regression model, extreme evening chronotype was associated with increased cardiovascular risk compared to extreme morning type independent of physical activity levels and other confounders ( $\beta=0.50$ ,  $SE=0.20$ ,  $p=0.013$ ).

**Conclusions:** Evening chronotype is associated with unhealthy lifestyle and poor cardiovascular health. We argue for the importance of avoiding phase delay of the circadian timing system and suggest that chronotype should be considered in lifestyle counseling and primary prevention programs.

**Acknowledgements:**

The SCAPIS was supported by the Swedish Heart and Lung Foundation, the Knut and Alice Wallenberg Foundation, the Swedish Research Council and VINNOVA (Sweden's Innovation agency). The SCAPIS pilot study received

support from the Sahlgrenska Academy at University of Gothenburg and Region Västra Götaland.

### EXPOSURE TO SHORT PHOTOPERIOD HELPS TO RESTORE THE VENTRAL SUBICULAR LESION INDUCED ALTERATIONS IN SLEEP WAKE BEHAVIOR IN RATS

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**Introduction:** ventral subiculum is important for both cognition and affective behaviors. Ventral subicular lesion (VSL) has shown to alter the sleep wake (S-W) behavior in rats. exposure to short photoperiod ameliorates the anxiety- and depressive-like symptoms in ventral subicular lesion (VSL) rats. The effect of short photoperiod on sleep wake behaviors in VSL rats is discussed.

**Materials and Methods:** Adult male Wistar rats were housed in the Central Animal Research Facility (CARF) at NIMHANS with a constant temperature at  $26 \pm 2^\circ\text{C}$ , humidity at 50%-55% and on a 12 h light-dark cycle (lights on at 6:00 a.m.). Rats were subjected to chemical lesioning of Ventral subiculum (VS) under anesthesia using stereotaxic surgery and were chronically implanted with electrodes for 24-h S-W recordings. The VC (vehicle control rats) received only PBS in the VS. Post surgical care was given for 7 days and Food and water were provided *ad libitum* in the home cage and the rats were maintained in 12/12 LD cycle. The baseline sleep wake recording was done under normal photoperiod regime (NPR; 12/12 h light-dark cycle; lights-on at 6:00 a.m., lights off at 6:00 p.m.). Divided randomly into VSL-NPR (n=7), VSL SPR (n=7) and VC-NPR (n=7) and VC SPR (n=7) groups. The NPR groups were exposed to normal 12/12 h light-dark cycle; lights-on at 6:00 a.m., lights off at 6:00 p.m.) and the SPR groups were exposed to 06/18 h light-dark cycle; lights-on at 10:00 a.m. lights off at 4:00 p.m.) for 21 days.

The sleep wake data were acquired using 16 channel Brain Electro Scan System (B.E.S.S.; Axonon solutions, Bangalore). All signals were amplified ( $\times 200$ ) and bandpass filters (0.1 Hz – 490 Hz), digitized (1KHz) using 24-bit A/D converter, and notch-filtered (50 Hz). 24 h S-W recording data was stored in a computer and later processed offline for classification of S-W stages.

**Conclusions:** VSL led to an enhancement of total sleep time due to significant increase in NREM and REM sleep. Following 21 days of the SPR exposure, the VSL-SPR rats showed comparable total sleep time due to decrease in NREM sleep compared to VC rats exposed to NPR. The VC rats exposed to SPR maintained sleep homeostasis as the sleep duration was comparable to VC rats exposed to NPR. However, they showed a deviation from the normal S-W behavior as they demonstrated a phasic sleep pattern with sharp peaks of sleep alternating with wakefulness across dark period. This could be due to the acute sleep debt imposed by SPR that shortened the light period by six hours.

The study demonstrates the effectiveness of photoperiod manipulation as a non-pharmacological treatment to reverse S-W alterations reported in mood and neuropsychiatric disorders such as Alzheimer's disease, bipolar disorder and major depressive disorder.

**Acknowledgements:** The study was funded by Science and Engineering Research Board (SERB), New Delhi, India. Grant/Award Number: EMR/2017/001237. NIMHANS, Bengaluru for providing support to carry out the study.

### LO SMART WORKING DURANTE LA PANDEMIA DI COVID-19 RIMUOVE LA VULNERABILITÀ AI PROBLEMI DI SONNO DELLE PERSONE CON CRONOTIPO SEROTINO E NE ALLEVIA LA PREDISPOSIZIONE ALLA DEPRESSIONE

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**Introduzione:** Il disallineamento tra ritmi circadiani e sociali, il cosiddetto "jet-lag sociale", è un fenomeno particolarmente pronunciato tra le persone con cronotipo serotino, che tendono a sperimentare una durata di sonno più breve nei giorni lavorativi, disturbi del sonno più gravi e conseguenti sintomi depressivi. La progressiva imposizione dello *smart working* durante la pandemia di COVID-19 ha rappresentato uno scenario ideale per valutare se orari lavorativi più flessibili potessero influenzare la qualità/quantità di sonno delle diverse tipologie circadiane, permettendo, inoltre, di chiarire il ruolo del sonno nella predisposizione alla depressione dei serotini.

**Metodologia:** 610 lavoratori in presenza (età media  $\pm$  deviazione standard,  $34.73 \pm 10.11$ ) e 265 lavoratori da casa ( $39.54 \pm 10.75$ ) hanno partecipato ad un'indagine online durante la seconda ondata di contagi da COVID-19 (28 novembre–11 dicembre 2020). Sono stati valutati: cronotipo (Morningness-Eveningness Questionnaire-versione ridotta, MEQR), qualità/durata del sonno (Pittsburgh Sleep Quality Index, PSQI), insonnia (Insomnia Severity Index, ISI) e sintomatologia depressiva (Beck Depression Inventory-seconda edizione, BDI-II). Sono stati eseguiti tre modelli di mediazione moderata per valutare l'effetto di mediazione di ciascuna variabile di sonno (qualità del sonno, gravità dell'insonnia, durata di sonno) nella relazione tra continuum mattutino-serotino e sintomi depressivi, utilizzando la "modalità di lavoro" (*smart working*, lavoro in presenza) come moderatore dell'associazione tra cronotipo e variabili di sonno.

**Risultati:** Lo *smart working* ha determinato un postcipo di ~30 minuti nell'orario di addormentamento ( $p < 0.001$ ) e di risveglio ( $p < 0.001$ ). La "modalità di lavoro" modera l'effetto del cronotipo sulle variabili di sonno, in quanto l'interazione tra i punteggi del MEQR e il fattore "modalità di lavoro" è risultato significativo in ciascun modello (PSQI:  $B = 0.15$ ,  $p = 0.03$ ; ISI:  $B = 0.23$ ,  $p = 0.02$ ; durata del sonno:  $B = -2.87$ ,  $p = 0.01$ ). Mentre nei lavoratori in presenza la serotinità si associa ad una peggiore qualità del sonno ( $B = -0.25$ ,  $p < 0.001$ ), a sintomi di insonnia più gravi ( $B = -0.37$ ,  $p < 0.001$ ) e a una minore durata del sonno ( $B = 3.02$ ,  $p < 0.001$ ), nei lavoratori da casa non è emersa alcuna relazione significativa tra i punteggi del MEQR e le variabili di sonno (PSQI:  $B = -0.10$ ,  $p = 0.07$ ; ISI:  $B = -0.14$ ,  $p = 0.09$ ; durata del sonno:  $B = 0.15$ ,  $p = 0.88$ ). Inoltre, la "modalità di lavoro" modera l'effetto di mediazione dei punteggi del PSQI (Indice di Mediazione Moderata, IMM=0.18, 95% IC:[0.01, 0.36]), dell'ISI (IMM=0.23, 95% IC:[0.03, 0.43]) e di durata di sonno (IMM=0.11, 95% IC:[0.02, 0.22]) nella relazione tra i punteggi del MEQR e del BDI-II. Mentre le variabili di sonno mediano parzialmente l'effetto del cronotipo sulla depressione nel gruppo di lavoratori in presenza (PSQI: Effetto Indiretto,  $EI = -0.31$ , 95% IC:[-0.42, -0.21]; ISI:  $EI = -0.36$ , 95% IC:[-0.49, -0.24]; durata di sonno:  $EI = -0.12$ , 95% IC:[-0.19, -0.06]), tale mediazione svanisce nel campione di lavoratori da casa (PSQI:  $EI = -0.13$ , 95% IC:[-0.27, 0.02]; ISI:  $EI = -0.14$ , 95% IC:[-0.30, 0.03]; durata di sonno:  $EI = -0.01$ , 95% IC:[-0.08, 0.07]).

**Conclusioni:** Lo *smart working* rimuove la ben nota vulnerabilità ai problemi di sonno delle persone con cronotipo serotino, eliminando il ruolo del sonno nella predisposizione ai sintomi depressivi. Un ambiente lavorativo che rispetti il cronotipo individuale potrebbe garantire un'adeguata quantità/qualità di sonno alle persone serotine, promuovendone il benessere psicologico.

### MIGRATION, MENTAL HEALTH AND SLEEP

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**Introduction:** Last year, about 1 million refugees came to Germany. Many of the refugees are in makeshift accommodation. Doctors and nurses are involved in support activities and the health care of these immigrants. The participating sleep physicians, psychologists and nurses have a good insight into the life situation.

In addition to the general medical conditions, the sleep medical conditions are also rather bad and necessarily improvable. Narrow spatial conditions, poor acoustic and light-related conditions, poor bedding conditions and possible posttraumatic stress disturbances increase sleep disturbances and sleep disorders and can trigger them.

In this course, sleep disorders are very common in migrants and refugees. There could be many different predictors for sleep disturbances in these vulnerable groups: pre-migration stress in the home country, acculturation, trauma before, while and after migration, integration and life style in the host country.

Often they are suffering under comorbid disorders: somatic or psychiatric diagnoses and/or psychological disturbances (like metabolic syndrome, post-traumatic stress disorder, depression, and anxiety disorders).

**Methods:** In our actual study, we could include nearly 150 participants from different countries – around 100 migrants and around 50 refugees. We researched:

1. relationship between migration and sleep disorders
2. influence of PTSD, depression and anxiety on sleep
3. chronobiology and sleep disorders in refugees and peoples with migration background
4. pathophysiology in sleep of refugees and peoples with migration background
5. treatment possibilities in refugees and peoples with migration background.

All participants were examined by psychiatric anamnesis and sleep anamnesis; they even were tested with different sleep questionnaires.

The first fully evaluated 33 participants include 17 women (51.52 %) and 16 men (48.49 %).

**Findings:** In the until now evaluated population, we found 32 patients with PTSD (96.96 %), mostly coupled with Depression and/or Panic disorder. 32 patients of our patients are suffering under Insomnia (96.96 %), 25 have had Nightmares (75.75 %), 6 Sleep Apnea Syndrome (18.18 %), 2 Restless Legs Syndrome (0.06 %) and one of them have had Pavor nocturnus, Somnambulism, Hypnotic Hallucinations and / or Sleep Wake Rhythm Disorder (0.03 %).

**Summary:** We can conclude that migration is an important factor, which influenced the mental status and the good sleep in refugees and resulted in many different psychiatric and sleep disorders.

## MI RELOJ INTERNO (MY ENDOGENOUS CLOCK): AN EVIDENCE-BASED MOBILE-APP TO IMPROVE SLEEP AND CIRCADIAN RHYTHMS

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**Introduction:** The human circadian clock is daily entrained by both light exposure and daily social schedules, which were severely affected during the pandemic-associated lockdown. In a previous work we found that after one month of lockdown, Argentinian residents exhibited later chronotypes compared with a pre-pandemic situation, despite they slept longer and showed less social jetlag (Leone M.J. et al, *Current Biology*). In this study, we collected an independent set of local data with the aim to develop an evidence-based mobile app that offers customized recommendations to improve and maintain healthy sleep and circadian rhythms.

**Materials and methods:** Data was collected throughout a phone/website survey between July and September 2020 (n=4460, after 4–6 months into lockdown) in Argentina. The survey included questions about demographic factors, habits, and previously standardized and validated questionnaires (MEQ, MCTQ, PSQI). Data from Buenos Aires city and suburbs (n=3246) was calibrated to match the population distribution and it was used to run the main analyses. The rest of the database was used to validate results. We conducted a cross validation process using linear models, which included a feature selection process to find the most relevant regressors to fit each chronotype and sleep-related variable. For a given age and gender, each model predicted a set of optimal values for the regressors (e.g. sunlight exposure, regular activities) where the dependent

variable is maximized (or minimized). Finally, the recommendation system is based on the comparison between optimal and actual values for each predictor, considering the most affected variables.

**Results:** The final calibrated sample (age: 41.3±15.5, 67% female) shows late chronotypes (MSFsc: 06:00±11min, MEQ score: 49.42±11.3), low levels of social jetlag (0.99h±1.09) and considerable long sleep duration on weekdays (7.31h±1.43). The regressors which significantly affect at least one variable were light exposure, use of alarm, naps and regular activities (and its timing, i.e. work, study, dinner, other activities) as well as age and gender (and interactions). We found no effects of cohabitation, exercise timing and use of screens. The optimal levels of the selected regressors were used to build the recommendation system (i.e. algorithm) on which the mobile app MiRelojInterno is based (available for both Android and iOS platforms, www.mirelojinterno.org).

**Conclusions:** We developed a mobile app based on local evidence that inquires about habits, chronotype and sleep, returns to its users an overview of their current state -including all variables and predictors- along with customized recommendations with the aim to create awareness and improve and maintain healthy sleep and circadian rhythms depending on the age, gender and habits.

**Acknowledgements:** This research project was supported by CONICET and Agencia I+D+i (IP-COVID19-679).

## MULTI-OMICS BASED CHRONOBIOLOGICAL SIGNATURES OF HEALTH RISKS ASSOCIATED WITH NIGHT SHIFT WORK

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**Introduction:** Circadian misalignment associated with night shift work increases risks of long-term health problems, including metabolic disorders, cardiovascular disease, and cancer. In this simulated night shift study, we investigated circadian disruptions in the temporal patterns of multi-omics data to find chronobiological signatures of the molecular underpinnings of these health risks.

**Materials and Methods:** N=14 healthy volunteers (aged 22–34; 10 males, 4 females) participated in a 7-day (6-night) laboratory study. Participants underwent three days of either a simulated night shift schedule (n=7) with daytime sleep opportunities (10:00–18:00), or a simulated day shift schedule (n=7) with nighttime sleep opportunities (22:00–06:00). This was followed by a 24-hour constant routine protocol with blood sampling at 1- to 3-hour intervals. Laboratory conditions were strictly controlled and light levels during scheduled wake periods including the constant routine protocol were fixed at <50 lux. In plasma extracted from blood samples collected during the constant routine protocol, 132 metabolites implicated in metabolic processes and energy metabolism were quantified using liquid chromatography/mass spectrometry (LC-MS/MS) based targeted metabolomics, and 405 lipids were quantified using LC-MS/MS based lipidomics, and melatonin was assessed using radioimmunoassay. From circulating leukocytes 770 mRNA targets (including 40 internal controls) of the PanCancer Pathways panel were assessed with NanoString nCounter transcriptomics, and 1,388 proteins with two or more unique peptides (derived from 32,455 unique peptides) were identified from peripheral blood mononuclear cells (PBMCs) using LC-MS/MS based proteomics. Multi-omics data were analyzed for circadian rhythms with mixed-effects cosinor regression analysis, enrichment analyses were performed, and an

association network was inferred from the combined proteomics and targeted metabolomics data.

**Results:** The simulated night shift schedule, compared to the simulated day shift schedule, caused a significant but small (<2 hours) delay in the timing of the central circadian pacemaker, as measured by dim light melatonin onset. However, 95% of circulating metabolites and 33% of PBMC based proteins with significant rhythmicity showed profound changes during the constant routine protocol, exhibiting temporal profiles driven by behavioral time cues during the prior shift schedule rather than the central pacemaker. Circulating lipids with low between-subjects variation in each shift condition showed generally increased triglycerides and decreased phospholipids, with triglycerides containing odd chain fatty acids peaking earlier after the night shift condition. In leukocytes, transcripts of the DNA repair pathway were significantly enriched for genes exhibiting circadian rhythmicity after the simulated day shift schedule, but not after the simulated night shift schedule. The inferred association network identified bottleneck proteins implicated in dysregulation of mitochondrial function and insulin resistance.

**Conclusions:** As observed during constant routine, a three-day simulated night shift schedule caused widespread disruption of endogenous circadian rhythmicity in the multi-omics data, indicating profound misalignment of peripheral oscillators and internal desynchrony. Our findings revealed candidate markers of metabolic disturbance, insulin resistance, cardiovascular disease, and cancer risk.

**Acknowledgements:** NIH grants R00ES022640, R01ES030113, R01MD014035 and R21CA227381, UK BBSRC grant BB/I019405/1, EU FP7-HEALTH-2011 EuRhythDia grant 278397, CDMRP awards W81XWH-16-1-0319, W81XWH-18-1-0100 and CA171123, and PNNL LDRD program under BRAVE Agile.

#### MULTI-TISSUE DISRUPTION OF MOLECULAR CIRCADIAN RHYTHMS AFTER INTENSIVE CARE

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**Introduction:** Molecular circadian rhythms influence much of physiology. Both critical illness and current intensive care protocols have been hypothesized to upset daily rhythms and impair function. However, the influences of critical illness and critical care on molecular clock function in different tissues are unknown. Here we evaluate the effect of intensive care on transcription, focusing on circadian output genes and on the transcriptional organization of the core circadian oscillator.

**Materials and Methods:** We downloaded RNAseq count data from Genotype-Tissue Expression (GTEx) project. Analyzing each tissue separately and treating the use of a ventilator as a marker for intensive care, we stratified samples into Acute and Intensive Care groups based on the Hardy Death Scale. We restricted our analysis to 25/53 tissues with greater than 50 samples in both groups. Using the EdgeR package and controlling for collection site, gender, and age, we identified transcripts significantly modulated by intensive care. Over-representation and enrichment methods were used to identify gene sets modulated by intensive care across tissues. We then calculated the delta clock correlation distance (dCCD), a measure of circadian oscillator function, in the both the acute and ventilator groups in each tissue. The statistical significance of the dCCD was assessed by permutation, modifying a pre-existing R package to control for confounding variables.

**Results:** Intensive care, as marked by mechanical ventilation, significantly modulated the expression of thousands of genes at a Bonferroni corrected p value <.05. The set of transcripts that were modulated in >66% of tissues was enriched for genes involved in mitochondrial energetics, cellular stress, amino acid metabolism, immune function, and notably circadian regulation. A list of established, robust clock output genes was strongly affected across tissues. Oscillator function, as assessed by the dCCD, was significantly reduced in the intensive care group in 15/25 tissues.

**Conclusions:** Our findings support the hypothesis that patients in intensive care have impaired molecular circadian rhythms. Tissues involved in metabolism and energetics demonstrated the most marked changes in

oscillator organization. In skeletal muscle and adipose tissue, there was a significant overlap between those transcripts previously established to be modulated by sleep deprivation in those tissues with the transcripts modulated by critical care. This work suggests that ICU protocols that restore cycles in sleep and nutrition may be of benefit.

**Acknowledgements:** This work was supported by NIH grants 5R01CA227485 and NIH 5R01AG068577. JNF was supported by the Diversity Action Plan in Genomics.

#### OUTCOMES OF PRE-TREATMENT AND POST-TREATMENT MEASURES AFTER THERAPY FOR PEDIATRIC CIRCADIAN DISORDERS

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**Introduction:** There are no published reports of clinical outcomes following multidisciplinary treatment of complex sleep disorders in youth. Cincinnati Children's Hospital has established a multidisciplinary Circadian and Complex Sleep Disorders Clinic that provides evidence-based care to children presenting with complex sleep disorders that involve significantly disturbed sleep. Some patients have completed their treatment and have been observed through research from start to finish. This is a retrospective case series discussion of two exemplar patients that demonstrate the effectiveness of multidisciplinary care for pediatric complex circadian rhythm disturbances.

**Methods:** Patient 1 presented to our clinic with chief complaints of sleep-related anxiety and insomnia. On average, sleep onset occurred 3-4 hours after attempting sleep. This patient was diagnosed with a delayed sleep-wake phase disorder, insomnia associated with sleep anxiety, and excessive daytime sleepiness. Initial management for patient 1 included phase advance chronotherapy, melatonin therapy used for phase shifting, and cognitive-behavioral therapy for sleep-related anxiety. This patient was enrolled in our research data registry and was asked to wear an actigraphy watch and keep a sleep diary.

Patient 2 presented to our clinic with chief complaints of difficulty falling asleep, persistent snoring, nocturnal enuresis presenting after a previous cleft repair surgery, and restless sleep. Sleep onset occurred 2-3 hours after attempting sleep. This patient was diagnosed with delayed sleep-wake phase disorder, sleep disordered breathing, insomnia, and had clinical symptoms of periodic limb movement disorder. Initial management for patient 2 involved iron and ferritin supplements, phase advance chronotherapy, melatonin therapy, and a diagnostic polysomnogram (PSG). This patient was also enrolled in our research data registry and was asked to wear an actigraphy watch and keep a sleep diary.

**Results:** After treatment, patient 1 responded well to melatonin and phase advancing. Sleep onset latency significantly improved from 3-4 hours to 5-30 minutes and a clinically significant reduction in insomnia symptoms. Based on an in-house sleep outcomes questionnaire, called the Status of Sleep Outcomes (SSO), patient 1's insomnia score decreased from an initial score of 15 to a post-treatment score of 6 (possible range 0 to 30 where higher scores signify greater insomnia symptoms). Comparisons of pre-treatment and post-treatment actigraphy and sleep diaries indicate more consolidated sleep with fewer nighttime awakenings.

For patient 2, PSG findings informed discontinuation of ferrous sulfate supplements and initiation of gabapentin for sleep consolidation and treatment of PLMD, which significantly improved symptoms. Imipramine

was prescribed to combat nocturnal enuresis. Patient 2 also responded well to melatonin and phase advancing. Sleep onset latency significantly improved from 2-3 hours to 30 minutes. Comparisons of pre-treatment and post-treatment actigraphy and sleep diaries indicate more consolidated sleep with fewer nighttime awakenings.

**Conclusions:** Based on the comparisons of pre-treatment and post-treatment actigraphy, sleep diaries, and subjective reports, patients 1 and 2 responded well to their individualized treatments and have successfully completed their courses of treatment. These case studies demonstrate the utility of phase stabilization and phase shifting for pediatric circadian disorders.

**Acknowledgements:** Academic and Research Committee (ARC) funding, Cincinnati Children's Hospital Medical Center

### PREDICTORS OF SUICIDAL IDEATION AND PREPARATORY BEHAVIORS IN INDIVIDUALS WITH BIPOLAR DISORDER: THE CONTRIBUTION OF CHRONOBIOLOGICAL DYSRHYTHMICITY AND ITS ASSOCIATION WITH HOPELESSNESS

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**Introduction:** Circadian sleep alterations are key factors influencing the trajectory of bipolar disorders and may increase suicidal risk.

**Objective:** To examine the role of chronobiological dysrhythmicity in suicidal ideation and behaviors in bipolar disorders we examined, its relationship with mood disorders severity and with hopelessness, an important predictor of suicidal risk

**Methods:** One hundred twenty-seven patients (77 females, mean age of  $47.4 \pm 12.5$  years) with a major depressive episode and bipolar disorder (BD) type I or II (according to Structured Clinical Interview for DSM-5 assessment) were recruited in 2019 and assessed for depressive and manic symptoms (Beck Depression Inventory-II, Young Mania Rating Scale) and with the Biological Rhythms Interview of Assessment in Neuropsychiatry for evaluating chronobiological risk, Beck Hopelessness Scale for evaluating Hopelessness and Scale for Suicide Ideation. Univariate regression and mediation analyses were performed.

**Results:** Forty-one patients (32.3%) showed clinically significant suicidal ideation and were more frequently affected by BD type I ( $P = .029$ ) with mixed features ( $P = .022$ ). Compared to nonsuicidal individuals, they had significantly more depressive symptoms ( $P = .019$ ), higher emotional component of hopelessness ( $P = .037$ ), and higher dysrhythmicity of sleep ( $P = .009$ ), activities ( $P = .048$ ), and social life ( $P = .019$ ). Passive and active suicidal ideation and suicidal plans were best predicted by dysrhythmicity of sleep and social life. Dysrhythmicity of sleep and social life mediated the direct effect of depressive symptoms on passive and active suicidal ideation and also of active ideation on suicidal plans. The emotional component of hopelessness was related to dysrhythmicity of social life and mediated its effect on suicidal plans ( $P = .010$ ).

**Conclusions:** Chronobiological alterations directly contributed to passive and active suicidal ideation and to suicidal preparation, with a key role of dysrhythmicity of sleep, activities, and social life. Chronobiological alterations also impacted the emotional component of hopelessness, hence indirectly contributing to suicidal ideations and plans. These findings call for the systematic screening of these dysrhythmicity dimensions when considering suicidal risk in individuals with BD.

### PROCEDURE FOR CHARACTERIZATION OF PERSONALIZED CIRCADIAN PHENOTYPE (CHRONOME) FROM AMBULATORY CIRCADIAN MONITORING (ACM)

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**Introduction:** Personalized medicine has aroused increasing interest over the last years. Wearable devices allow the assessment of sleep and circadian rhythms related to personal habits under normal-living conditions. The phenotypic manifestation of circadian rhythms results from the interaction of biological clocks, life habits acting as external synchronizers, and possible pathologies. In turn, chronodisruption increases the risk of many diseases. In line with other "omics", we propose a procedure to characterize the circadian phenotype of a subject (Chronome) from multivariate records for early and automated detection of reversible alterations that help disease prevention and personalized therapies.

**Methods:** 244 volunteers (144 women, ages ranging from 14 to 86; mean = 46.29; SD = 13.43) were monitored during a full week with the Kronowise device (KW). The procedure for getting a Chronome was as follows: 1. Data collection. The KW device records 14 complementary variables, including: skin temperature (T), motor activity (A), light exposure (L) and body position (P) at 10Hz, stored at 30" epochs.

2. Filtration and preliminary data analysis, including variable normalization, TAPL integration and sleep detection (Madrid-Navarro et al., 2019).

3. Non-parametric time series analysis. For radar charts, five dimensions for each circadian variable were calculated: 1) Interdaily stability; 2) Day-night contrast as normalized relative amplitude; 3) Synchronization between internal and environmental time; 4) Circadian robustness as a circadian health score 5) Restfulness index as indicator of sleep depth.

4. Generation of individual Chronomes basing on this five dimensions. Future steps will be aimed to generate population Chronomes for circadian healthy phenotype and for different chronodisrupted phenotypes through clustering techniques, in order to estimate the risk of belonging to a pathological phenotype and establish personalized intervention strategies.

**Results:** Personalized circadian profiles are to be characterized in the form of radar charts, with 5 radios each representing a circadian dimension: regularity, day-night contrast, environmental synchronization, robustness and restfulness index, the minimum score (0) being at the center of the radar and the maximum score (1) at the outer end. The normal population values (between 25th and 75th percentiles) of each parameter are indicated with a thicker bar on each radio. A subjects specific score in each parameter is represented by a point along the radius, so that the union of the five corresponding points constitutes a pentagon that allows visually characterizing the global state of a subject based on these five parameters. The individual score in each of these five dimensions allow to design a personalized strategy through lifestyle intervention.

**Conclusions:** The automatic generation of a chronome allows condensing >250,000 data from each subject in five circadian dimensions. This facilitates characterizing personalized circadian profiles for early detection of chronodisruption and selecting personalized therapies based on habits modification.

**Acknowledgements:** Ministry of Economy and Competitiveness, Instituto de Salud Carlos III through CIBERFES (CB16/10/00239), Ministry of Science Innovation and Universities RTI2018-093528-B-I00 (co-financed by FEDER), Call H2020-sc1-BHC-2018-2020 (Grant agreement 825546, Diafrail-Latam) and Spanish Sleep Society (SES), Ministry of Economy and Competitiveness through 2017 Torres-Quevedo Aids for the Recruitment of PhD Researchers, granted to Kronohealth SL

### REMOTE WORKING DUE TO THE COVID-19 PANDEMIC ELIMINATED THE VULNERABILITY TO SLEEP DISTURBANCES OF EVENING-TYPE PEOPLE RELIEVING THEIR PREDISPOSITION TOWARD DEPRESSION

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**Introduction:** The issue of the misalignment between the daily social/working schedule and the endogenous biological clock is a long-standing controversy, the so-called "social jetlag". This phenomenon is especially

pronounced among the evening-type people, leading them to experience shorter sleep duration, more severe sleep disturbances, and related depressive symptoms. During the COVID-19 pandemic, there was an upsurge of remote working worldwide. This scenario emerged as an ideal context to address whether a more flexible working routine influenced the sleep quality/quantity of the different circadian typologies, clarifying the role of sleep in explaining the predisposition toward depression of late chronotypes.

**Materials and Methods:** A total of 610 Italian office workers (mean age  $\pm$  standard deviation, 34.73 years  $\pm$  10.11) and 265 remote workers (39.54 years  $\pm$  10.75) participated in a web-based survey during the second contagion wave of COVID-19 (28 November–11 December 2020). We evaluated chronotype, sleep quality/duration, insomnia, and depression symptoms through the following questionnaires: Morningness-Eveningness Questionnaire-reduced version (MEQr), Pittsburgh Sleep Quality Index (PSQI), Insomnia Severity Index (ISI), and Beck Depression Inventory-second edition (BDI-II), respectively. Three moderated mediation models were performed, testing the mediation effect of each sleep variable (sleep quality, insomnia severity, sleep duration) between the morningness-eveningness continuum and depression symptoms, with working modality (office working, remote working) as a moderator of the association between chronotype and sleep variables.

**Results:** Remote working led to  $\sim$ 30 minutes delayed bedtime and get-up time (both  $p < 0.001$ ). The interaction between MEQr scores and working modality factor was significant in each model (PSQI:  $B = 0.15$ ,  $p = 0.03$ ; ISI:  $B = 0.23$ ,  $p = 0.02$ ; sleep duration:  $B = -2.87$ ,  $p = 0.01$ ), indicating that working modality moderated the effect of chronotype on sleep variables. Specifically, eveningness was associated with poorer sleep quality ( $B = -0.25$ ,  $p < 0.001$ ), more severe insomnia symptoms ( $B = -0.37$ ,  $p < 0.001$ ), and shorter sleep duration ( $B = 3.02$ ,  $p < 0.001$ ) in the office working group. On the other hand, no significant relationship between MEQr score and sleep variables among the remote workers emerged (PSQI:  $B = -0.10$ ,  $p = 0.07$ ; ISI:  $B = -0.14$ ,  $p = 0.09$ ; sleep duration:  $B = 0.15$ ,  $p = 0.88$ ).

Finally, working modality factor moderated the mediation effect of PSQI score (moderated mediation index = 0.18, 95% CI: [0.01, 0.36]), ISI score (moderated mediation index = 0.23, 95% CI: [0.03, 0.43]), and sleep duration (moderated mediation index = 0.11, 95% CI: [0.02, 0.22]) between MEQr and BDI-II scores. While sleep variables partially mediated the effect of chronotype on depression in the office working group (PSQI: indirect effect = 0.31, 95% CI: [-0.42, -0.21]; ISI: indirect effect = -0.36, 95% CI: [-0.49, -0.24]; sleep duration: indirect effect = -0.12, 95% CI: [-0.19, -0.06]), the above mediation vanished among the remote workers (PSQI: indirect effect = 0.13, 95% CI: [-0.27, 0.02]; ISI: indirect effect = -0.14, 95% CI: [-0.30, 0.03]; sleep duration: indirect effect = -0.01, 95% CI: [-0.08, 0.07]).

**Conclusions:** Working from home due to the COVID-19 pandemic abolished the well-documented vulnerability to sleep problems of evening-type subjects, extinguishing the sleep role in accounting for the relationship between morningness-eveningness continuum and depression. A working environment complying with individual circadian preferences might ensure an adequate sleep quantity/quality to late chronotypes, also relieving their tendency to depression disorder.

#### SEASONAL VARIATIONS IN OBJECTIVE SLEEP DURATION AND QUALITY: A LONGITUDINAL BIG-DATA ANALYSIS

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**Introduction:** Seasonal effects on sleep-wake patterns attributed to altered environmental zeitgebers including light and temperature remain poorly characterized. Recent advancements in consumer sleep technologies allow for large-scale and continuous measurement of ambulatory and objectively measured sleep throughout the year. The purpose of the present analysis was to examine the association between seasonal variations and objective changes to sleep-wake schedules, sleep duration, and sleep quality.

**Materials and Methods:** Sleep data were captured using the PSG-validated SleepScore mobile application, which uses a non-contact sonar-

based sensor to objectively capture sleep-related metrics. The dataset included 548,005 nights across 29,191 users residing in the US (age range: 18–85, mean age: 45.2  $\pm$  16.7 years, 52.9% female). Sleep data were captured from 01/01/2019–3/12/2019. Seasons were defined according to the Northern Hemisphere's meteorological calendar and included the following: fall (September, October, November), winter (December, January, February), spring (March, April, May), and summer (June, July, August)

The relationships between objectively measured sleep and the month of the year were examined using a mixed-effect model controlling for age and gender.

**Results:** Bedtimes were earlier during wintertime, reaching a minimum of 23:05 pm in November and shifts later in summertime, peaking in July at 23:19 ( $p < 0.001$ ). Wakeup times were observed to be earliest between January and May, with a minimum in May of 06:47 am; Wakeup times then shifted later in the summer months, reaching 6:55 am in July ( $p < 0.001$ , vs May). Wakeup times then gradually shifted earlier in the fall and winter, with the exception of December, where the average wakeup time was 6:54 am. Total sleep time (TST) was lower in the summer months, with a minimum of 368 minutes in June. TST increased in the fall and winter months, peaking at 378 minutes in December ( $p < 0.001$  vs June). Sleep efficiency was lowest during the late summer and early fall, reaching a minimum of 82.1% in August before increasing in the winter months, peaking in December at 83.1% ( $p < 0.001$ ). Across the year weekends are associated with an increase in TST compared to weekdays, this difference was larger in the winter and early spring months, reaching a peak of 20.1 minutes in February, and decreasing in the summer to a minimum of 12.8 minutes in July ( $p < 0.001$ ).

**Conclusions:** The present study identified a phase delay in sleep schedules with a shift to later bedtimes and waketimes during the brighter, longer summer months which were accompanied by significant reductions to total sleep time and sleep efficiency compared to wintertime. Of particular interest is the fact that there is less of a difference between weekend and weekday sleep patterns in the summertime, suggesting that sleep schedule changes are likely due to both social and chronobiological factors.

#### SETTING YOUR CLOCK: ASSOCIATIONS OF PHYSICAL ACTIVITY TIMING WITH CARDIOVASCULAR DISEASE RISK

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**Introduction:** Little is known about the impact of daily physical activity timing (here referred to as “chronoactivity”) on cardiovascular disease (CVD) risk. For the present study, we examined the associations between timing patterns of physical activity and multiple CVD outcomes in the UK Biobank.

**Materials and Methods:** Objective physical activity data was collected through triaxial accelerometer over a 7-day measurement period. We used K-means clustering to create groups of participants with similar chronoactivity irrespective of the mean daily intensity of the physical activity. Multivariable-adjusted Cox proportional hazard models were used to estimate hazard ratios (HRs) comparing the different clusters adjusted for age and sex (model 1), and baseline cardiovascular risk factors (model 2). Additional stratified analyses were done by sex, mean activity level, and self-reported sleep chronotype.

**Results:** We included 86 657 individuals (57.6% female, mean age: 55.9 [SD: 7.8] years, mean BMI: 26.6 [4.5] kg/m<sup>2</sup>). Over a follow-up period of 6 years, 3707 CVD cases were reported. Overall, participants with a tendency of late morning physical activity had a lower risk of incident coronary artery disease (CAD) (HR: 0.84, 95%CI: 0.76, 0.92) and cerebrovascular disease (HR: 0.82, 95%CI: 0.69, 0.98) compared to participants with an

average (“midday”) pattern of acceleration with accompanying evidence that these effects were more pronounced in women ( $p$ -value for interaction = 0.00). We did not find evidence favouring effect modification in the stratified analyses for total activity level and sleep chronotype.

**Conclusions:** Our findings suggest that, irrespective of total physical activity, morning physical activity associates with lower risk of incident CVD, stressing the importance of chronoactivity in disease prevention and treatment.

#### SEX DIFFERENCES IN THE EFFECTS OF SLEEP RESTRICTION AND SCHEDULED SHORT NAPS ON VIGILANCE, COGNITION AND SLEEP ARCHITECTURE IN HEALTHY ELDERLY ADULTS.

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**Introduction:** Sleep and waking cognition are modulated by the dynamic interaction between sleep-wake homeostasis and the circadian phase. There is evidence that age and biological sex modulate these sleep-wake regulatory effects. Younger people and women present increased vulnerability to sleep loss compared to older people and men, respectively. However, it is not known how biological sex modulates the effect of sleep restriction and time-of-the-day on vigilance and cognition in the elderly population. This is an important aspect considering sex bias in neuroscience and biomedical research. Moreover, female sex is suggested to increase the risk of Alzheimer's that has a well-established bidirectional relationship with sleep and circadian alterations.

**Materials and Methods:** Thirty-five healthy elderly participants (16 males(M), age:(Mean±SD)63.25±7.26; 19 females(F), age: 64.53±9.42) underwent a 2.5-days-long laboratory session in dim light condition (<10lx) and followed a modified constant routine protocol in the Sleep and Brain Research Unit at the University of East Anglia. After a baseline night, the participants were randomly assigned to either a 40-h sleep deprivation(SD) or a multinap(MN) experimental condition followed by recovery night. Nine 80-min-long naps were scheduled every 160-minutes. Comprehensive cognitive test battery including Psychomotor Vigilance Task(PVT), measures of memory, and spatial navigation were administered every 4 hours. Karolinska Sleepiness Scale(KSS) served as a subjective measure of sleepiness.

**Results:** Women compared to men, reported worse subjective sleep quality( $p=0.012$ ) with a lower number of self-reported hours of sleep( $p=0.001$ ). During laboratory sessions, time spent awake was associated with a gradual increase in subjective sleepiness (KSS)( $p<0.0001$ ) and a decrease in objective vigilance (PVT)( $p=0.01$ ) in SD compared to MN. Objective vigilance was affected by SD significantly more in women than men( $p=0.03$ ). Episodic memory and spatial navigation showed neither a clear sleep deprivation nor a circadian effect but a practice-dependent gradual improvement throughout the protocol across both experimental conditions. Analysis of melatonin concentration has revealed significant differences for neither biological sex nor protocol. At baseline night, females had significantly more slow-wave sleep (SWS)( $p=0.041$ ). During the recovery night that followed MN protocol, females spent considerably more time in SWS( $p=0.011$ ), whereas men in N2( $p=0.012$ ). Sleep parameters in the MN condition (naps) showed a circadian pattern with longer total sleep time(TST)( $p<0.0001$ ), higher sleep efficiency(SE)( $p<0.0001$ ), shorter sleep latency(SL)( $p<0.0001$ ), and more SWS( $p=0.02$ ) during the circadian night. Men and women had similar TST(M=57.9±3.76min; F=50.9±3.32min), SE(M=0.67±0.05, F=0.60±0.04) and SL (M=21.9±2.18min; F= 24.5±1.95min) with women spending significantly longer time in SWS( $p<0.0001$ ;M=6.51±1.27min; F= 16.15±1.12min), and less time in N2( $p=0.003$ ; M=32.2±2.43min; F=20.6±2.14min) compared to men across the naps.

**Conclusions:** We show that previously reported sex differences in sleep architecture and the deleterious effects of sleep loss on vigilance shown in younger people are also present in healthy older adults. Sleep loss and time of the day had minimal effects on memory and spatial navigation performance in this age group. Our results suggest that biological sex should be considered when studying the effect of sleep impairment, jet lag or

shiftwork on daytime vigilance in the older age group.

**Acknowledgements:** This study was supported by the Wellcome Trust to Dr Lazar (207799/Z/17/Z).

#### STUDY ON EFFECT OF CHRONOTHERAPY IN DEPRESSIVE PHASE OF BIPOLAR DISORDER

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Bipolar disorder is a mental health condition that affects your moods, and it can go from one extreme to the other. It was previously called Manic Depression. The affections of bipolar disorder are the following ones:

- Depression- feeling very low and lethargic.
- Mania- feeling very excited and overactive.

Symptoms of bipolar disorder depend on the emotions that are experienced.

Unlike simple mood swings, each extreme episode of bipolar disorder can last for weeks (or longer). Initially it is possible to be diagnosed with clinical depression before a manic episode (sometimes several years later), after that you may be diagnosed with bipolar disorder.

During a depression episode, it is possible to experience an overwhelming sense of worthlessness, which can lead to suicidal thoughts.

During the manic phase of bipolar disorder, it is likely to feel very happy, energetic, having ambitious plans and being impulsive. It is often interpreted as a positive experience due to burst of creative ideas. Insomnia and aggressiveness are also commonly experienced.

But there is the possibility to experience symptoms of psychosis, wherein patients see or hear things that are not real and believe in them.

The high and low stages of bipolar disorder are often so extreme that they interfere with daily life. But there are several options for treating bipolar disorder that can make a difference. Their goal is to manage the effects of the episodes and help people with bipolar disorder live as normally as possible.

The following treatment options are:

Medications to prevent episodes of mania and depression- these are called mood stabilizers. Learning to recognize triggers and signs of depressive or manic episodes from the psychotherapy, and lifestyle changes; such as exercising regularly, planning activities one enjoys to give a sense of accomplishment, along with suggestions for improving the diet are often accompanied with the medication.

Lifestyle changes which are often what gets people through depressive phase, is the focus of our research. Two cases of bipolarity have been studied through the changes in their routines as suggested by the psychiatrist, and they ended up having a positive improvement in the quality of life.

The specific change has been to introduce a Chronobiology Therapy. In the mornings, for a small period of time patients are exposed to a daylight spectrum with high quantity of blue light, which is caught by the circadian system. The results of the study show an improvement under the clinical observation and a stabilisation of the circadian rhythm thereby enhancing the sleep quality.

#### THE ASSOCIATION OF SHIFT WORK SCHEDULE CHARACTERISTICS WITH MENTAL HEALTH AMONG NURSES AND PHYSICIANS IN POLAND

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**Introduction:** Health care professionals often work in the shift system which includes working at night or having 24-hour shifts. Circadian misalignment associated with working outside the standard wake phase of sleep-wake cycle or working excessive hours may affect not only sleep, but

also other mental health dimensions. The aim of the study was to investigate the association of work schedule and work experience with mental health of nurses and physicians working in the public sector in Poland.

**Materials and Methods:** The participants filled in a demographic survey and questions regarding work schedule characteristics. Standardized measures were used to assess insomnia symptoms (Insomnia Severity Index), daytime sleepiness (Epworth Sleepiness Scale), depression (Patient-Health Questionnaire-9) and anxiety (Generalized Anxiety Disorder-7). Statistical analyses included the Mann-Whitney test and Spearman's correlations.

**Results:** The study included 111 nurses and 173 physicians working 12-hour or 24-hour shifts or combination of both. They had at least one year of work experience and at least one year of shift work experience. The sample was predominantly female. There was no age difference between nurses and physicians in this study. We found differences in work schedule characteristics. Physicians worked significantly more hours per week, but fewer nights per month. They had the same number of days off in the previous four weeks. Nurses had significantly longer experience working night shifts than physicians.

Nurses and physicians did not differ in their scores on Insomnia Severity Index. Their scores differed in Epworth Sleepiness Scale, Patient Health Questionnaire-9 and Generalized Anxiety Disorder-7 scale. Physicians scored higher on all three measures.

Among nurses the number of hours per week was moderately negatively correlated with insomnia symptoms. Length of shift work experience and number of night shifts per month were weakly positively associated with daytime sleepiness. None of the work characteristics significantly correlated with depression or anxiety scores of the nurses. Among physicians the number of hours per week was weakly to moderately positively correlated with insomnia symptoms, daytime sleepiness, anxiety and depression. The number of night shifts in the previous four weeks was moderately positively associated with insomnia and daytime sleepiness, but only weakly positively linked to depression and anxiety. Depression and anxiety symptoms were moderately negatively associated with the number of days off in the previous month and weakly positively with the length of shift work experience.

**Conclusions:** The results of this study point to physicians experiencing more symptoms of mental health disturbance than nurses when it comes to daytime sleepiness, depression and anxiety. The work schedule characteristics and work experience showed to be associated with mental health variables among doctors. Work characteristics were not associated with depression and anxiety among nurses, only with sleep disturbances.

**Acknowledgements:** The research was supported by a grant no. 2019/33/N/HS6/02572 from the National Science Centre in Poland.

### THE COST OF FAST-ROTATING BACKWARD-SHIFT WORK AMONG NURSES

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**Introduction:** 24-hour rotating shifts are common among hospital nursing staff to ensure continuity of care. There is mounting evidence that night shift work significantly impacts health and performance due to the alteration of natural homeostatic and circadian sleep processes.

Nurses' adaptability to night shifts is often affected by the speed and direction of the shift rotation (i.e., clockwise [forward] or counterclockwise [backward]). In forward-rotating shifts (FRSs), morning shifts are followed by afternoon and then night shifts. In contrast, backward-rotating shifts (BRSs) consist of night shifts followed by afternoon and then morning shifts. It is commonly assumed that forward rotation is easier to adapt physiologically because the human circadian rhythm moves forward. The association of BRSs with subjective and objective measures of sleep quality, daytime vigilance, sleepiness, and tiredness of health care workers has not yet been established. The present study aimed to investigate the

association of shift rotation direction with tiredness, sleepiness, and sustained attention among two large samples of nurses working 8-hour FRSs or BRSs.

**Materials and Methods:** Data of this cohort study were collected from nurses working at five Italian hospitals. The nurses had either a forward-rotating schedule (i.e., morning to afternoon to night) and or a backward-rotating schedule (i.e., afternoon to morning to night).

Sleep quality was evaluated using the Pittsburgh Sleep Quality Index. Tiredness and Sleepiness data were collected using the Tiredness Symptom Scale and the Karolinska Sleepiness Scale. Sustained attention was measured using the Psychomotor Vigilance Task (PVT).

**Results:** A total of 144 nurses (mean [SE] age, 41.3 [0.8] years; 92 women) participated in the study; 80 nurses working FRSs and 64 nurses working BRSs. Both groups showed similar poor sleep quality rates (57.5% in FRSs group; 57.8% in BRSs group). Otherwise, there were significant differences between the BRS and FRS groups for sleepiness and all PVT variables. Specifically, nurses working BRSs demonstrated greater subjective sleepiness ( $F_{1,139}=41.23$ ,  $P<.001$ ) and significantly worse attentional performance on PVT (e.g., longer median reaction times:  $F_{1,139}=42.12$ ,  $P<.001$ ) than those working FRSs. Moreover, subjective tiredness and sleepiness were higher during the night shifts than the morning and afternoon shift (tiredness:  $F_{2,278}=67.91$ ,  $P<.001$ ; sleepiness:  $F_{2,278}=43.29$ ,  $P<.001$ ). Night shifts were also associated with worse performance on the PVT (i.e., median reaction times:  $F_{2,278}=7.78$ ,  $P<.001$ ; fastest 10%:  $F_{2,278}=10.18$ ,  $P<.001$ ; minor lapses:  $F_{2,278}=4.37$ ,  $P=.01$ ; reaction time distribution:  $F_{2,278}=8.88$ ,  $P<.001$ ). Importantly, these differences were not affected by age, years of employment, and quality of sleep.

**Conclusions:** In conclusion, this cohort study confirmed the well-established negative effects of night shifts and found that fast FRSs for nurses were associated with lower levels of sleepiness and higher levels of sustained attention compared with BRSs. Optimization of shift rotations should be implemented to decrease the combination of the negative outcomes associated with shift work and reduce the related risk of medical errors in health care systems.

**Acknowledgements:** Our gratitude to all the nurses who took part in the study.

### THE IMPACT OF OBSTRUCTIVE SLEEP APNEA TREATMENT WITH CONTINUOUS POSITIVE AIRWAY PRESSURE ON THE BIOLOGICAL CLOCK

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**Introduction:** Obstructive Sleep Apnea (OSA) is one of the most common sleep disorders worldwide. Untreated, OSA has been associated with multiple comorbidities, among which hypertension, cardiovascular and metabolic diseases. Recent studies show that OSA disrupts the biological clock, which might contribute to the large spectrum of comorbidities observed. Yet, the interplay between OSA, the clock, and OSA treatment is not fully understood. In this context, we aim to explore the impact of OSA and OSA treatment with Continuous Positive Airway Pressure (CPAP) on clock-associated physiological and molecular markers.

**Materials and Methods:** The levels and temporal profile of clock physiological markers, namely, plasma melatonin, cortisol and body temperature, and the expression of core-clock genes in peripheral blood mononuclear cells (PBMCs), were monitored in 34 OSA patients (age:  $55 \pm 2$ ), before and

after CPAP treatment, and 7 controls of the same sex and age group (age:  $50 \pm 3$ ), at four time points along 24 hours. Machine-learning methods were applied for a detailed data analysis. This study was approved by the ethical committee of the Faculty of Medicine of the University of Coimbra and of Coimbra Hospital and University Centre.

**Results:** OSA patients show alterations in levels and circadian profiles of melatonin ( $p < 0.01$ ) and several clock genes mRNAs relative to control subjects ( $p < 0.05$ ). Two years of CPAP treatment re-established the levels and profiles of melatonin and of some of the impaired clock genes mRNAs. Machine-learning clustering approaches, based on clock-markers, can distinguish controls from untreated OSA patients and show that long-term CPAP-treated patients better resemble controls than untreated/short-term (4 months) treated patients.

**Conclusions:** OSA disturbs the biological clock and although CPAP does not fully re-establish all clock molecular alterations, it promotes evident ameliorations long-term. Our results reinforce the need of new/complementary strategies for a more effective OSA treatment. Machine-learning approaches, based on clock-associated markers, show potential applications in OSA diagnosis, patient stratification and treatment response monitoring.

**Acknowledgements:** Work in CNC was supported by the European Regional Development Fund (ERDF) through the Operational Programme for Competitiveness and internationalization - COMPETE 2020 - and Portuguese national funds via FCT - Fundação para a Ciência e a Tecnologia, under the projects noOSAnoAGEING (POCI-01-0145-FEDER-029002, PTDC/MEC-MCI/29002/2017), HealthyAging 2020 (CENTRO-01-0145-FEDER-000012) and UIDB/04539/2020; and by the European Social Fund through POCH - Human Capital Operational Programme and Portuguese national funds via FCT under PD/BD/135497/2018. Work in Charité was supported by the German Federal Ministry of Education and Research (BMBF) – eBio - CIRSPICE - [FKZ031A316], the Dr. Rolf M. Schwiete Stiftung, the Einstein Foundation and the graduate school Berlin School of Integrative Oncology (BSIO), Charité Berlin.

## Dental

### A COMPARISON OF IN PERSON VS. TELEMEDICINE DELIVERIES OF MANDIBULAR ADVANCEMENT DEVICES (MAD) FOR TREATMENT OF OBSTRUCTIVE SLEEP APNEA (OSA)

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**Introduction:** Between March 13, 2020 and December 31, 2021, 920 patients diagnosed with obstructive sleep apnea were treated with MADs; with insertion (fitting of the device in the patient's mouth) in-office in person, or by synchronous telemedicine delivery. This study evaluated whether patients who received their MAD by a telemedicine visits were more likely to need follow up adjustments for poor fit, compared to those patients who received their oral appliance in person in the office.

**Materials and Methods:** This is a retrospective study of all inserts of MADs between March 13, 2020 and December 31, 2021. A total of 920 patient MAD inserts were performed. Insert appointments consist of presenting the MAD to the patient, fitting the appliance, instructing the patient in titration and care; and fitting the patient with a thermoplastic molded morning repositioner. The patient demographics include: average age of 43 (no patients under age 18 were treated). 67.9% males and 32.1% females. All patients had a home sleep test (HST) and a medical diagnosis of sleep apnea with a prescription for a MAD. These patients were then referred for examination and to obtain dental records for fabrication of a MAD. Dental records were taken by 3D digital technology (Carestream 3600) in the office, or by synchronous telemedicine home impressions by sending dental impression kits to the patients. The dental records were sent to third party dental laboratories for fabrication of MADs. Once the MAD was ready, an insert appointment was scheduled for either in-office or telemedicine insert. A follow up visit with the patient's medical practitioner was scheduled 4 weeks after the insert appointment to allow time for titration of the MAD, and depending on the subjective results of decreased snoring and decreased daytime sleepiness; the patient was instructed by

the medical practitioner to complete a sleep test for efficacy evaluation. Patients were scheduled for adjustments either in-office or via telemedicine to adjust the device for comfort or retention or to help titrate the MAD.

**Results:** 920 patients received a MAD to treat OSA. 60.5% percent of patients had the insert of a MAD via telemedicine while 39.5 % had the insert of a MAD in office.

39.6% of patients were diagnosed with mild OSA, 39.6% with moderate, and 20.8% with severe. The odds of an adjustment were 0.96 (95% CI=0.37, 2.44) times as likely among patients who had a telemedicine insert compared to patients who had an in-office insert. .

**Conclusions:** Telemedicine deliveries of MADs is feasible, and adopting this workflow allows greater access to MAD treatment for OSA, and decreased expenses due to travel and work absences.

### ADHERENCE TO THE MANDIBULAR ADVANCEMENT DEVICE IN PATIENTS WITH INTOLERANCE TO CPAP AFTER 3 YEARS OF FOLLOW-UP

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**Introduction:** Obstructive Sleep Apnea (OSA) is a major health problem. An adequate treatment in order to obtain a good control of the disease and an improvement of the quality of life, supposes a challenge for its good management. In patients with intolerance to CPAP, the mandibular advancement device (MAD) is positioned as an appropriate therapeutic alternative. The objective of this study was to analyze the adherence to treatment of these patients at 3 years of follow-up.

**Materials and Methods:** A descriptive study was carried out in which 62 patients diagnosed and followed up by OSA were analyzed in the Sleep Unit of the Ramón y Cajal Hospital, between 2018 and 2021.

According to Shapiro Wilk's test, the population distribution was non-parametric. The Wilcoxon test was used for comparisons of related samples in quantitative variables and the Chi Square test in qualitative variables.

**Results:** The participants included were 45 men (72.6%) and 17 women (27.4%). The mean age of the sample was 55 years. Regarding cardiovascular risk factors, 24 patients (38.7%) were hypertensive while 38 (61.3%) of them were not. The average Body Mass Index (BMI) was 26.7. 30 patients (48%) were overweight, 17 patients (27.4%) were obese and 15 patients (24%) were normal weight. The mean follow-up time of the sample was 695 days. We analyze the Hypoapnea Apnea Index (AHI) prior to the start of treatment with MAD of those patients who persisted with the treatment at the date of last revision. Of the total, 16 patients (32.65%) had been diagnosed with mild OSA, 22 patients (44.89%) with moderate OSA and finally, 11 patients (22.44%) with severe OSA. The mean AHI prior to the start of treatment was 24/h while the mean AHI in the subsequent respiratory polygraphy control was 11.9/h, with an improvement in AHI of 50.7%.

Prior to the use of MAD, 68.9% (42 patients) had an AHI  $\geq 15$  and with the use of MAD, only 19.4% (12 patients) persisted with an AHI  $\geq 15$ .

At the end of the follow-up, 49 of the patients (79.03%) maintained the treatment with MAD of which all showed preference for the MAD with respect to the CPAP. 54 patients (90%) had compliance greater than 5 hours while 6 patients (10%) had less than 5 hours. On the other hand, there were 13 patients (20.96%) who had abandoned treatment. The causes that motivated the abandonment of treatment were: in 5 patients (38.46%) the cure of the disease (due to weight loss), in 4 patients (30.76%) intolerance to the device (discomfort in temporo-mandibular joint, gingival hemorrhage, displacement of teeth) and in 2 patients (15.38%) the absence of response to treatment (persistence of symptoms: daytime sleepiness, multiple night awakenings). One patient was exitus due to other causes (pancreatic cancer) and a patient's follow-up was lost due to a unilateral decision.

**Conclusions:** MAD is an adequate alternative therapy in patients with OSA

who refuse the use of CPAP, observing good compliance and adherence in the long term, along with adequate clinical control of the disease.

### A RETROSPECTIVE COMPARISON OF CEPHALOMETRIC LANDMARKS BETWEEN PATIENTS WITH SIMPLE SNORING AND OBSTRUCTIVE SLEEP APNEA

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**Introduction:** Snoring and obstructive sleep apnea (OSA) are defined as two different severity kinds of sleep disordered breathing (SDB). Currently, the data concerning the craniofacial characteristics of subjects who snore but do not exhibit OSA are limited. The study aimed to compare the differences of craniofacial and pharyngeal anatomy between groups of OSA and snoring subjects.

**Materials and Methods:** A total of 51 patients (30 males, 21 females) were enrolled in this study. There were 34 patients (20 males, 14 females) in the OSA group, with an average age of 42.18 ± 10.37 year, body mass index (BMI) as 24.49 ± 2.81 kg/m<sup>2</sup> and apnea-hypopnea index (AHI) as 25.65 ± 16.36 /h. The snoring group was matched with OSA group by age, gender and BMI, which included 17 patients (10 males, 7 females) with the average age, BMI, AHI of 42.29 ± 11.04 year, 24.49 ± 2.81 kg/m<sup>2</sup>, 1.75 ± 1.47 /h, respectively. All participants undergone overnight polysomnography (PSG) and lateral cephalograms. Differences of craniofacial structure, upper airway and its surrounding tissues between two groups were then evaluated. Paired T-test was practiced on all coordinates we collected and a two-sided p-value of <0.05 was considered to be statistically significant.

**Results:** The OSA group showed smaller bony nasopharynx (PNS-R: 21.44 ± 2.62 vs 23.14 ± 2.30, P = 0.034) and lower hyoid position (H-MP: 17.28 ± 5.30 vs 13.73 ± 6.45, P = 0.041). Pearson correlation showed that AHI was negatively correlated with posterior airway space (PAS) and mandible length (MAN) and positively correlated with hyoid position (H-MP). Multiple linear regression results showed that after adjusting for confounding factors, AHI was correlated with PAS ( $\beta = -0.427$ ,  $t = -3.635$ ,  $P = 0.001$ ) and H-MP ( $\beta = 0.415$ ,  $t = 3.533$ ,  $P = 0.001$ ).

**Conclusions:** While the cephalometric measurements of snoring patients resembled those with OSA, some differences in soft tissue and hyoid orientation were apparent. OSA subjects may demonstrate a gradation trend in the size of the airway and its associated structures.

**Acknowledgements:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

### AUTOMATED MANDIBULAR MOVEMENT MONITORING DURING RAPID MAXILLARY EXPANSION

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**Objectives:** To evaluate mandibular movement (MM) and possible changes in respiratory effort (RE) derived from mandibular position and motion during sleep following rapid maxillary expansion (RME) treatment.

**Methods:** This pilot prospective cohort study included 14 patients treated at two orthodontic practices. Inclusion criteria were patients with mild to moderate obstructive sleep apnea, between the ages of 7–15 years-old with no previous history of orthodontic treatment, craniofacial anomalies or missing teeth outside of third molars. The orthodontic treatment of all patients included RME to correct transverse maxillary deficiency. MM measurements (Frequency of MM, percent change, and variance) and sleep variables (Duration of obstructive event, Total Sleep Time [TS], Sleep Efficiency [SE], Micro Arousal Index [Micro AI], Respiratory Effort-Related Arousal Index [RERA]) were assessed using the Sunrise® automated MM sensor placed on the chin at night below the mentolabial sulcus area. Data were analyzed using machine learning algorithms. Additionally, sleep disordered-breathing was subjectively determined using the pediatric

sleep questionnaire (PSQ). Outcomes were compared at pre-expansion with RME (T1) and immediately post-expansion (T2). The Wilcoxon Rank sum test was performed to analyze median difference in MM and sleep variables pre- and post-expansion.

**Results:** The sample mean age at T1 was 11.72±2.28 years. For MM variables, there was no statistically significant difference between T1 and T2 in percentage of MM change or variance ( $p=0.583$ , and  $p=0.530$  respectively). However, there was a statically significant decrease in MM Frequency from T1 (18.43) to T2 (12.33), ( $p=0.009$ ). For sleep variables, the duration of obstructive event was significantly reduced from T1(10.92s) to T2 (6.75s), ( $p=0.008$ ). SE was significantly increased from T1 (74.14%) to T2 (80.79%), ( $p=0.014$ ). There were no statistically significant changes in mean TST, Micro AI, AHI, and PSQ. Maxillary intermolar width increased from 36.76mm to 48.53mm, ( $p=0.001$ ).

**Conclusions:** Following RME, the frequency of MM decreased, SE improved, and the duration of obstructive event decreased. The results of this paper showed similar results to previous studies that investigated the association between maxillary expansion and sleep variables, but none looked at the effects of RME on MM as it relates to RE and sleep. This study has shown that RME does have an effect on MM pattern during sleep. Further research is warranted to determine MM changes during a longer treatment period and analyzing MMs at the different sleep stages.

### BIOMIMETIC ORAL APPLIANCE THERAPY (BOAT): NOVEL ORAL APPLIANCE TREATMENT FOR OBSTRUCTIVE SLEEP APNEA ADMINISTERED BY DENTISTS

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**Introduction:** Obstructive sleep apnea (OSA) is a rising source of morbidity worldwide with myriad health consequences. Although the airway and oral cavity are the primary domains of dentists and many dentists currently screen for and treat OSA, there is little physician awareness of the growing specialty of dental sleep medicine. There is an ever increasing array of oral appliances that treat OSA, many of which are mandibular advancement devices. Biomimetic Oral Appliance Therapy (BOAT; Vivos Therapeutics, USA) consists of a series of dental devices that treat OSA by expanding the airway through 3-D maxillary expansion. The difference between BOAT and conventional oral appliance therapy is that the former is designed to obviate the need of lifelong oral appliance used to treat OSA. This retrospective study evaluated patient data collected by Vivos from dentists using BOAT to determine its efficacy in treating OSA.

**Materials and Methods:** After IRB review (exempted by WCGIRB 11/1/2021) we conducted a retrospective database review of patients 18 years and older with OSA who underwent BOAT for a minimum of 6 months. Demographics and pre-, mid-, or post-treatment sleep study parameters were reviewed to generate descriptive statistics. Of note, the pre-treatment and mid-/post-treatment sleep studies were conducted without the BOAT oral appliance in the patients' mouths.

**Results:** Overall, 170 charts from 6 dental practices across the United States and Canada were reviewed with 58 charts meeting the above criteria for analysis. Out of 58 patients with OSA, 49 (84.4%) had their OSA parameters (AHI or ODI or both) improve, 38 (65.5%) improved by >50%, 20 (34.4%) had clinical cure (normal post-treatment OSA parameters), and 11 (19.0%) clinically worsened. Patients with OSA were observed to improve their OSA parameters regardless of baseline OSA severity or BMI.

**Conclusions:** This retrospective showed that OSA patients treated with BOAT showed improvement in their OSA, irrespective of baseline OSA severity or BMI. Further analyses of these data, as well as future clinical trials and multidisciplinary collaboration are needed to better understand this novel treatment for OSA.

## COMPARISON OF CEPHALOMETRIC PARAMETERS IN PEDIATRIC PATIENTS WITH AND WITHOUT OBSTRUCTIVE SLEEP APNEA

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**Introduction:** Pediatric obstructive sleep apnea (POSA) is a type of sleep-disordered breathing that affects 1 to 5% of all children, and its incidence peaks are seen between 3 and 8 years of age. Pharyngeal, palatine and lingual tonsil hypertrophy are the main predisposing factors. Current studies have shown the role of dentoalveolar anomalies in the development of respiratory disturbances during sleep. The aim of our study was to study the role of different craniofacial measurements in connection to POSA.

**Materials and Methods:** Pediatric patients with complaints of breathing difficulties were referred by ENT specialists to a tertiary sleep disorders center and for orthodontic assessment. The participants were studied by using home sleep apnea test (HSAT) or in-lab polysomnography. The sleep events were scored according to AASM recommendations. Apnea-hypopnea index (AHI), oxygen desaturation index (ODI) and average oxygen saturation (SatO2) parameters were utilized. The patients were divided into two groups based on the presence or absence of clinically significant POSA. Growth factors of craniofacial complex were assessed by an experienced orthodontist. Angular and linear measurements were traced manually and studied on lateral computed cephalograms. SNB - shows horizontal position of lower jaw related to anterior cranial base, MxPIMnPI - angulation of the palatal plane with the mandibular plane, airway dimension PAS1 - nasopharyngeal, PAS2 - oropharyngeal and evaluation of adenoid parameters AD1 and AD2. Mann-Whitney U test was used for statistical analysis.

**Results:** Overall 45 participants were involved in our study (mean age  $6.7 \pm 3.1$  (3-13); females - 26.7%) with subsequent classification into two groups: no or mild OSA (NOSAG) (n= 23 (51.1%)) and moderate-to-severe OSA (MSOSAG) (n=22 (48.9%)). Mean values for the position of the lower jaw related to the anterior cranial base (SNB): NOSAG -  $77.8^\circ$  vs MSOSAG -  $75.3^\circ$  ( $p < 0.05$ ). Angulation of the cranial base with the mandibular plain (MnPISN) was significantly larger in the MSOSAG compared to the NOSAG:  $38.8^\circ$  vs  $33.0^\circ$  ( $p < 0.05$ ). Angulation of the cranial base with the palatal (maxillary) plain (SNPP) was not significantly different between groups: NOSAG -  $8.4^\circ$  vs MSOSAG -  $10.3^\circ$  ( $p = 0.18$ ). Angulation of the palatal (maxillary) plane with the mandibular plane (MxPIMnPI) was larger in the MSOSAG -  $29.7^\circ$ , while in the NOSAG it was  $25.5^\circ$  ( $p < 0.05$ ). The volume of adenoid tissue for AD1 and AD2 parameters for the groups NOSAG/MSOSAG was as follows respectively: AD1 - 12.2mm vs 8.19mm, AD2 - 14.3mm vs 10.0mm ( $p < 0.05$ ). Sizes for NOSAG/MSOSAG were 11.9mm vs 7.7mm for nasopharyngeal ( $p < 0.05$ ), and 7.6mm vs 4.5mm for oropharyngeal ( $p < 0.05$ ) linear measurements, representing smaller sizes within the MSOSAG group. The mean AHI and ODI values were as follows (NOSAG/MSOSAG): AHI - 1.7/15.2 ( $p < 0.001$ ), ODI - 1.8/16.0 ( $p < 0.001$ ).

**Conclusions:** We found that dentofacial measures like SNB (shows the distal position of mandible) found to have clinically useful correlations especially in the group with moderate-to-severe form of POSA. The higher obturation of the nasopharynx and oropharynx and adenoid size also have a significant correlation connected with OSA groups in growing patients. Regarding the obtained data analyses, we can assume the highly important role of different craniofacial measures in connection to POSA.

## COMPLICATIONS ASSOCIATED WITH MINI-SCREW ASSISTED RAPID PALATAL EXPANSION

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## Complications associated with mini-screw assisted rapid palatal expansion

Audrey Yoon, Jacqui Payne, Heeyeon Suh, Angela Chan, Heesoo Oh

**Introduction:** One of the craniofacial features of obstructive sleep apnea (OSA) is the underdevelopment of the naso-maxillary complex. Mini-screw assisted rapid palatal expansion (MARPE) has recently been advocated as an option for treating older adolescents and adult patients with OSA. The purpose of this study is to identify the possible oral, dental, and facial complications associated with MARPE treatment and their frequency of occurrences.

**Materials and methods:** A retrospective analysis was conducted on 256 patients (mean age  $18 \pm 8$ , 125 female and 131 male) who underwent MARPE at a specific private practice office or University of the Pacific Orthodontic Clinic between August 2014 and June 2021 (success or failure of expansion was not considered). The following clinical complications were identified: inflammation around the appliance, pain, broken screw, breakage of the appliance, loss of tooth vitality, temporary hearing loss, numbness, swelling, severe gag reflex, and sinus infection. Dental tipping and asymmetry were measured from patients who had CBCT scans taken prior to the start of MARPE treatment (T1) and immediately following expansion (T2). Inflammation degree was measured from clinical photographs taken after expansion and before removal.

**Results:** Mid-palatal suture was separated in 88% of total cases. The most common complication of gingival inflammation around the appliance was found in 81.94% of patients. 47.8% of patients showed more than 1 mm asymmetric expansion. 42% of patients reported some form of pain. After MARPE, a palatal expansion of  $7.75 \pm 2.39$  mm was achieved. The difference in molar inclination from T1 to T2 was statistically significant with an average of  $3.57 \pm 3.76$  degrees of buccal tipping. Breakage of appliances occurred in 19 cases. Rare complications included tooth vitality loss, temporary hearing loss, numbness, swelling, severe gag reflex, and sinus infection. There were no cases of tooth loss or necrosis observed.

**Conclusions:** The data analysis reveals that major, long-term complications are rare with MARPE. It is proposed that patients should be informed of the possible inflammation and pain that may occur with MARPE. Even though asymmetry expansion was common after the palatal split, most cases were managed with orthodontic treatment. Further studies should aim to identify risk factors that may predispose patients to specific complications

## CORRELATION BETWEEN NASOMAXILLARY COMPLEX DIMENSIONAL CHANGES AND RESPIRATORY IMPROVEMENT AFTER MAXILLARY SKELETAL EXPANSION TREATMENT IN PEDIATRIC OBSTRUCTIVE SLEEP APNEA PATIENTS

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**Introduction:** After use of nasomaxillary skeletal expander (NMSE) for expansion of the upper airway including the nasal cavity, the reduction of upper airway resistance can be expected in pediatric obstructive sleep apnea (OSA) with maxillary constriction. The purpose of this study was to investigate the relationship between respiratory functions and dimensional changes of the nasomaxillary complex (NMC) and upper airway (UA) compartments after NMSE treatment for pediatric OSA patients with maxillary transverse deficiency.

**Materials and Methods:** A total of 26 pediatric OSA patients with a mean age of  $13.6 \pm 2.9$  years who were treated with NMSE at Kyung Hee University Dental Hospital from May 2016 to June 2019 were included. Patients were diagnosed with OSA based on the apnea-hypopnea index (AHI) criteria ( $\geq 2$  for children,  $\geq 5$  for adolescents and post adolescents), presenting with difficult breathing during sleep, and maxillary transverse constriction as indicated by a transverse discrepancy index less than -2 mm. CBCT morphometric analysis were performed to evaluate dimensional changes in NMC by 5 parameter (anterior maxillary width, posterior maxillary width, nasal cavity width, nasal floor width, and maxillary base width) and UA by 4 compartments (nasal airway, nasopharynx, velopharynx, and glossopharynx). Home sleep test (HST) and modified pediatric sleep questionnaire (m-PSQ) were evaluated for functional analysis.

**Results:** After NMSE treatment, NMC dimensions significantly increased except glossopharyngeal airway volume. Transverse nasomaxillary dimensions significantly increased after NMSE at all tested levels ( $P < 0.01$ ). In sleep breathing function tests, m-PSQ results (subjective symptoms such as snoring and mouth breathing) and HSAT result (apnea-hypopnea index, oxygen desaturation index, lowest O<sub>2</sub> saturation, flow limitation, and snoring events) showed significant improvement. AHI reduction was correlated with UA dimensional increase, displaying no correlation with NMC expansion amount, whereas flow limitation (FL) reduction was only affected by NMC expansion amount. The only parameter affecting the increase of lowest O<sub>2</sub> saturation (LSaO<sub>2</sub>) was the minimum cross-sectional area (MCA). The improvement in m-PSQ had the most correlations with dimensional parameters except anterior maxillary width, velopharynx volume, and glossopharynx volume.

**Conclusions:** Regardless of the amount of expansion with NMSE treatment, improvement of AHI and volume increase of UA were proved to have a significant correlation. The MCA of the above degree was the most important morphological feature showing a significant correlation with the decrease of AHI and the increase of LSaO<sub>2</sub>. Therefore, combined treatment with NMSE should be considered for the complicated patients to allow the prevention and interruption of the secondary craniofacial deformation to OSA. The m-PSQ score was found to be clinical diagnostic value as much as HST in growing patients.

**Acknowledgements:** The authors received no specific funding for this work.

#### COVID-19, SYMPTOMS OF ANOSMIA AND CONNECTIONS WITH OSA

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**Introduction:** Coronavirus disease (COVID-19) is a respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. The most common clinical presentation of severe COVID-19 is viral pneumonia, acute respiratory failure consistent with the acute respiratory distress syndrome. Symptoms, typical for the disease, are: fever, cough, dyspnea, hypoxemia, reduction of smell and taste, bilateral infiltrates on chest radiographs. Although anosmia and hyposmia were not initially recognized as typical symptoms of COVID-19, due to the number of COVID-19 new variants and newer insights on the relevant virus entry proteins, this has changed. Frequent risk factors for a severe COVID-19 case are: advanced age, obesity, cardiovascular diseases, diabetes mellitus, and poor lung function. In patients with obstructive sleep apnea (OSA), these risk factors and combinations of them, are more common and thus, patients are endangered of severe forms of COVID-19 and hospitalization.

**Materials and Methods:** Scientific databases – PubMed and SCOPUS were used to find studies in English and other languages on the topic, with the following keywords – COVID-19, nasal breathing, anosmia, OSA. A time period of 2020–2021 was set.

Twenty-five patients diagnosed and recovered from mild, medium and severe forms of COVID-19 (in the period May–August 2021) visited Audio-vestibular laboratory of the University medical and dental center, Medical University – Varna in the time period September 2021–November 2021 for an otorhinolaryngologic and sleep check-up. Patients filled out questionnaires and signed written informed consents.

**Results:** Of the 25 patients, 5 (3 male and 2 female) up to the moment have not regained their proper taste and smell feelings. Sixteen of the patients fully regained their taste and smell. Four patients (2 male and 2 female) had differently expressed dysosmia and dysgeusia, after recovering from the COVID-19 infection. Some of the patients reported for arising symptoms of the vestibular and hearing systems (tinnitus, vertigo, dizziness), others – for aggravating of the already present symptoms of vestibular or hearing deficits at the time of infection. One fourth of the patients reported for difficulties breathing even after recovering from COVID-19 and as well as arising of sleep problems.

**Conclusions:** More investigations in the field of COVID-19, part of rehabilitation programmes, need to be executed. Patients have to receive consistent and interdisciplinary care.

**Acknowledgements:** This study was able to be undertaken thanks to the joint efforts by Medical University – Varna, University medical and dental center and the clinicians involved.

#### DEVELOPMENT OF A SMARTPHONE APPLICATION FOR EARLY DIAGNOSIS OF MANDIBULAR RETRUSION

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**Introduction:** This presentation will describe the development of a first-generation smartphone application (Gnathic-Click™), designed to evaluate and follow undiagnosed retrognathic mandibles in infants and toddlers. The co-existence of micrognathia and mandibular retraction with other conditions has received little attention in non-syndromic patients including feeding difficulty, myofunctional problems, cranio-facial-respiratory development and airway concerns. Clinical diagnosis of mandibular retrognathia is often reduced to a "clinical impression" as clinicians attempt to avoid invasive diagnostic procedures such as radiographs, CAT scans and other 3D imaging. Most screening indices depend on invasive diagnostics help to define the maxillo-mandibular relationship because the use of a single soft tissue index has limitations.

**Materials and Methods:** The Gnathic-Click™ app's algorithm incorporates published evidence-based indices commonly utilized to define the retrognathic mandible. Its development will provide a useful screening tool to predict a possible retrognathic grower from infancy. By using facial-recognition technology, the app correlates known biometric correlations to define the retrognathic mandible, by incorporating goniomaxillary/goniomandibular length ratios, mandibular volumes, and other mandibular anthropometrics (references).

**Results:** By using a concurrence from grouped indices, we propose to provide an accurate prediction of whether an infant/toddlers' mandible is retruded in position, within normal limits or possibly prognathic.

**Conclusions:** The use of the Gnathic-Click™ smartphone app will help in building a data base for clinicians to identify non-syndromic retrognathic patients that will benefit from multidisciplinary, early interceptive treatment modalities.

**Acknowledgements:** David A Tesini DMD, MS, Associate Clinical Professor TUSDM, Tesini Pediatric Dentistry, Toothprints PC 13 Norcross Rd, Hopkinton MA 01748; tesini22@gmail.com

#### IMPACT OF RAPID MAXILLARY EXPANSION ON ADENOTONSILLAR HYPERTROPHY IN CHILDREN

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**Introduction:** Adenoid and tonsillar hypertrophy in children often leads to adverse respiratory symptoms and obstructive sleep apnea (OSA). Current clinical guidelines from the American Academy of Pediatrics and the American Academy of Family Physicians recommend tonsillectomy as the first line of pediatric OSA treatment for children with tonsillar hypertrophy. Rapid maxillary expansion (RME) performed by orthodontists is known to improve obstructive sleep apnea in children by reducing nasal airway resistance, increasing nasal volume, raising tongue posture, and enlarging pharyngeal airway. However, the role of RME in alleviating tonsillar hypertrophy remains elusive. This study evaluates the effectiveness of RME in attenuating adenoid and palatine tonsil sizes using 3D volumetric analysis of CBCT scans.

**Materials and Methods:** In this retrospective cohort study, a total of 60 pediatric patients (mean age: 9.79, range: 5–17, 36 females and 24 males) with tonsillar hypertrophy (size 3 and 4) were included divided into a control group (n=20) and RME group (n=40). The control group did not receive any treatment. The RME group underwent expansion using a conventional Hyrax expander, activated 0.25mm per day for 4 to 6 weeks. Final CBCT scans (T2) were performed 9–12 months after the initial scan (T1). Sleep questionnaire and BMI were obtained at each timepoint. Volumetric analysis of adenoid and palatine tonsils was performed using a combination of bony and soft tissue landmarks in CBCT scans with Anatomage Invivo 6 imaging software. Student t-tests were used to

evaluate the difference between the initial and final adenoid and tonsil volumes. *p* values less than 0.05 were considered statistically significant. The inter-rater reliability was evaluated using Pearson Correlation between two investigators.

**Results:** Compared to the control group, the RME group experienced a statistically significant decrease in both adenoid and tonsil volume. There was non-statistically significant increase in volume from T1 to T2 for the control group. 87.5% of patients in the RME group experienced a reduction in adenoid volume and 94.7% of RME patients experienced a reduction in tonsil volume. The average volume decrease of adenoid volume was 23.1% while that of tonsils was 42.1%. The RME patients had up to 60.0% and 75.4% reduction in adenoid and tonsil size, respectively, following orthodontic intervention. Pearson correlation of inter-rater reliability ranged from 0.96–0.99 for each measurement, representing excellent internal consistency.

**Conclusions:** To our knowledge, this is the first study to quantify the changes of adenoids and tonsils following RME. Our results demonstrated that RME significantly reduced the size of both adenoid and palatine tonsils, thus revealing another long-term benefit of RME treatment. This study suggests orthodontic intervention with RME may be a potential treatment consideration before proceeding to adenotonsillectomy for pediatric OSA population with narrow maxilla and adenotonsillar hypertrophy.

**Acknowledgements:**

#### LONG-TERM DENTOSKELETAL SIDE EFFECTS OF MANDIBULAR ADVANCEMENT THERAPY IN PATIENTS WITH OBSTRUCTIVE SLEEP APNEA: DATA FROM THE PAYS DE LA LOIRE SLEEP COHORT

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**Introduction:** Mandibular advancement devices (MADs) are the main therapeutic alternative to continuous positive airway pressure for obstructive sleep apnea. Our aim was to evaluate the long-term dentoskeletal side-effects of MADs and to identify the predictive factors for these side-effects.

**Materials and Methods:** Patients from the Pays-de-la-Loire cohort treated with a custom-made MAD for at least 1 year were included in this retrospective study. Digital cephalometric analyses were performed at baseline and at follow-up.

**Results:** We included a total of 117 patients, treated with a MAD for a median [interquartile range] of 4.6 [2.6–6.6] years. The main significant side-effects were a decrease in overbite ( $-0.5 \pm 1$  mm), overjet ( $-0.7 \pm 1$  mm) and maxillary incisor inclination ( $-2.5 \pm 2.8^\circ$ ), and an increase in mandibular incisor inclination ( $+2.2 \pm 2.7^\circ$ ). Subjective side-effects were not linked to the observed dentoskeletal changes. Current smokers were at higher risk of overjet modifications. A pre-existing anterior open-bite was associated with a greater decrease in overbite. Treatment duration was associated with a more pronounced mandibular incisor proclination. Propulsion was negatively associated with maxillary incisor retroclination.

**Conclusions:** Long-term dentoskeletal side-effects were mainly moderate dental side-effects. Some predictive factors were shown to be associated with more pronounced changes. Subjective side-effects did not appear to be reliable tools to detect dentoskeletal side-effects. Regular follow-up with clinical examination and regular radiographs is mandatory. The predictive factors could be of interest for a better selection of patients and to individualize follow-up.

#### PERCEPTION OF NASAL FUNCTION AND COSMESIS AFTER MAXILLARY EXPANSION FOR OBSTRUCTIVE SLEEP APNEA

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**Introduction:** Distraction osteogenesis maxillary expansion (DOME) is a procedure that addresses nasal obstruction as well as posterior tongue displacement in patients with high arched and narrow palates. Widening of the maxilla in a transverse discrepancy has been shown to be highly

efficacious in facilitating nasal breathing as well as creating more space for the tongue to move forward. Taken together, patients often report better nasal breathing during sleep as well as better CPAP compliance with lower pressures. Due to the required skeletal movements of the midface, nasal form and function are therefore important considerations for the surgeon and patient. To evaluate both function and cosmesis following DOME, we use a validated tool such as SCHNOS to quantify the degree of change in nasal function and esthetics.

**Methods:** This is a prospective study evaluating subjects undergoing DOME from September 2020 to 2021 at the Stanford Sleep Surgery Division. The outcome measure used to assess nasal function and cosmesis was the validated Standardized Cosmesis and Health Nasal Outcomes Survey (SCHNOS) and the Epworth sleepiness Scale (ESS). Inclusion criteria were subjects with available scores and who underwent maxillary expansion

**Results:** Fourteen patients met the inclusion criteria. The SCHNOS-O (obstruction) and SCHNOS-C went from 36.7 to 17.2 ( $p < 0.05$ ) and from 12.3 to 9.4 ( $p < 0.05$ ) after an average of 57 days. ESS showed significant improvement ( $p < 0.05$ ) from 13.4 to 7.1

**Conclusion:** OSA patients with narrow high arched palates benefit tremendously from maxillary expansion. This study shows that despite significant maxillary transverse widening, nasal function significantly improves without any cosmetics or esthetic repercussions.

#### POLYGRAPHY IN CHILDREN WITH MALOCCLUSION: ANALYSIS OF THE CORRELATION BETWEEN OSAS AND RME

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**Introduction:** Obstructive sleep apnea syndrome (OSAS) is a sleep respiratory disorder caused by a partial (hypopnea) or total (apnea) obstruction of the upper airways, disrupting normal ventilation during sleep and normal sleep patterns. Each apnea can be accompanied with changes in heart rate, arterial oxygen desaturation and awakenings. Prevalence in children is between 1% and 5%. Diagnosis of OSAS in children is commonly based on the presence of sleep disordered breathing symptoms associated to an Apnea Hypopnea Index (AHI)  $\geq 1$  episodes per hour.

The orthodontic treatment with a rapid maxillary expansion (RME) is an option for the treatment of OSAS in children with malocclusion.

The aim of this study is to compare AHI index and mean SaO<sub>2</sub> value by using home respiratory polygraphy (HRP) in patients with malocclusion before and after orthodontic treatment using RME.

**Materials and Methods:** Our sample included 18 children between 5 and 13 years old with clinical signs of malocclusion (ogival palate often associated with unilateral, bilateral or anterior crossbite). Each patient completed the orthodontic treatment with RME. All the children underwent an overnight home respiratory polygraphy at the baseline (before treatment with RME device, T0) and after the active expansion phase before removing the device (T1). Furthermore, the mean SaO<sub>2</sub> value was also calculated for each patient.

**Results:** Out of the 18 children with malocclusion, 6 (33,3%) were diagnosed with OSAS (AHI  $\geq 1$ ) at T0. At T1 the AHI index decreased in 4 of the 6 subjects with OSAS (66,6%): 3 dropped to an AHI  $< 1$ , while the fourth one had a significant decrease from 15,9 to 7,5 events/h. In the other 2 subjects (33,3%) with OSAS, AHI remained unchanged after RME treatment. The mean SaO<sub>2</sub> value showed a tendency to improve after treatment.

**Conclusions:** RME could be an useful approach for the management of children with malocclusion and OSAS. Therefore, orthodontists should have an important role in the early diagnosis and treatment of children with OSAS, in order to intervene as soon as possible on the malocclusion.

#### SELECTION OF CUSTOM ORAL APPLIANCE FABRICATION SETTINGS IMPACT TREATMENT EFFICACY

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**Introduction:** In a previously published Study-1, custom oral appliances (Custom-OA) fabricated using a conventional dental protocol provided inferior apnea-hypopnea index (AHI) reductions compared to the Apnea Guard® trial appliance (AG). In this comparison, Study-2 Custom-OAs were fabricated using the AG bite registration applied to one of two randomly assigned design types, with controlled vertical-mouth-opening (VMO).

**Materials and Methods:** CPAP-intolerant patients completed a two-night home-sleep-apnea study; Night-1 at baseline, Night-2 with the AG. The AG vertical dimension of occlusion (VDO) was based on tongue-scallop (women=5.5/6.5 mm; men=6.5/8.0 mm), and “AG target protrusion” set to 70% of the neutral-maximum range, while in situ.

The Custom-OAs for Study-1 were fabricated with VDO dependent on sex (women=2.5 mm; men=5 mm), with protrusion set using a George-Gauge measured 70% from maximum retrusion-protrusion, and dentist-directed advancement. In Study-2, the Custom-OAs were fabricated to the AG VDO and target protrusion. In Study-1, 50% of the Custom-OAs were fitted with a Herbst (CA-Herbst) and 14% with a ProSomnus® [IA], vs. randomly assigned Study-2 distributions of 51% vs. 49%, respectively. Efficacy studies were conducted after completion of the Custom-OA titration in Study-1 and at the AG target protrusion in Study-2. With the CA-Herbst, vertical elastics were optional in Study-1 and mandatory in Study-2. In Study-2, five patients at-risk for temporomandibular joint complications were excluded, i.e., <7% of patients fitted with a Custom-OA, to avoid delivery at the AG target protrusion. Statistics included Mann-Whitney, Chi-squared, Bland-Altman, and multiple logistic regression analyses.

**Results:** The Study-1 (n=84) and Study-2 (n=51) Patients who completed efficacy studies had similar distributions of logistic regression variables, including scalloped tongues (64% vs. 67%), sex (women 45% vs. 43%), age (53.8±11.9 vs. 54.9±15.2 years), body mass index (29.4±5.7 vs. 27.8±4.2 km/m<sup>2</sup>), and pre-treatment AHI severities (24.6±14.4 vs. 27.7±17.4 events/hour).

Bland-Altman plots highlighted significant differences between the AG and the Custom-OA overall AHI values in Study-1 vs. Study-2 (4.2±7.8 vs. 1.2±6.7; P=0.023). The significant differences between the Custom-OA vs. AG AHI values in Study-1 (Overall: 12.3±9.2 vs. 8.2±5.9; P<0.002; Supine: 17.0±13.6 vs. 10.8±7.8; P<0.003) were no longer apparent in Study-2 (Overall: 11.1±7.7 vs. 9.9±6.8; P=0.58; Supine: 16.0±13.0 vs. 12.4±8.6; P=0.37).

The Study-1 vs. Study-2 protocol (Odds ratio=3.34; 95%CI: 1.19–9.36; P=0.022), pre-treatment AHI (Odds ratio=0.95; 95%CI: 0.91–1.00; P<0.036), and AG AHI (Odds ratio=0.73; 95%CI: 0.62–0.85; P<0.0001) were predictive of those who achieved a Custom-OA AHI<10. The AG AHI also predicted those with a Custom-OA AHI reduction >50% (Odds ratio=0.91; 95%CI: 0.83–1.00; P<0.05), and both an AHI reduction >50% and an AHI<10 (Odds ratio=0.77; 95%CI: 0.67–0.88; P=0.0002).

With Study-2 temporomandibular joint screening, no side effects were reported in the patients delivered Custom-OAs at 70% AG target protrusion (n=69).

**Conclusions:** These findings confirm Custom-OA fabrication settings impact treatment efficacy. Custom-OA outcomes were equivalent to the AG when fabricated with the AG bite-registration, i.e., VDO and protrusion, and VMO was controlled.

**Reference:** Validation of a Novel Trial Oral Appliance Protocol vs. a Conventional Custom Oral Appliance Protocol for the Treatment of OSA. Levendowski DJ, et al. *J Den Sleep Med.* 2021;8(2).

**Acknowledgements:** None

## SNORING AND OBSTRUCTIVE SLEEP APNEA AMONG PRE- AND POST-MENOPAUSAL WOMEN AND THEIR RELATIONSHIP TO SYMPTOMS OF NOCTURNAL MASTICATORY MUSCLE ACTIVITY

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**Introduction:** Obstructive sleep apnea (OSA) is characterized by repetitive collapse of the upper airway during sleep, often associated with oxygen

desaturation and/or arousal from sleep. It is associated with snoring, excessive daytime sleepiness and sleep bruxism (SB).

**Materials and Methods:** In the present study 112 Arab women at the age of 20–40 years old (pre-menopause, PreM) and 116 Arab women at the age of ≥ 50 years old (post menopause, post-M) were requested to complete questionnaires regarding demographic variables, risk of OSA (STOP-BANG questionnaire), daytime sleepiness (Epworth sleepiness scale – ESS) and symptoms of nocturnal masticatory muscle activity (possible SB, headache and stiffness of the oral and/or neck musculature upon awakening).

**Results:** The risk of OSA was significantly higher among the older PostM group as compared to their younger PreM counterparts. There were no differences between the age groups in their ESS scores.

Women who reported snoring showed higher risk of OSA but not higher risk of daytime sleepiness than non-snoring women. Snoring women experienced more headache (33.3% versus 19.3%, p<0.05) more muscle stiffness upon awakening (34.3% versus 16.3%, p<0.005), and more SB (35.8% versus 20.6%, chi square, p<0.05) than their non-snoring counterparts. 11% of the snoring women showed high risk for OSA as compared to only 1% among the non-snoring ones (p<0.000).

**Conclusions:** Snoring is often regarded as a “masculine” phenomenon which women tend to under-report, often reporting less direct non-specific symptoms such as headache and sleep disruption. As dentists are among the most often visited caregivers who focus their examination on the oro-facial area they should develop higher awareness to snoring and to additional symptoms of OSA, especially among their post-menopausal female patients.

**Acknowledgements:**

## THE EFFECTIVENESS OF MORNING REPOSITIONING SPLINTS FOLLOWING MANDIBULAR ADVANCEMENT DEVICE USE – A PILOT STUDY

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**Introduction:** There are several side-effects associated with mandibular advancement devices (MAD) used to treat obstructive sleep apnea (OSA). Some providers advocate the use of morning repositioning splints (MRS) to minimize these side effects despite the lack of evidence supporting their use.

**Objectives:** The main objective of this randomized controlled pilot study is to evaluate MRS-use as a means of mitigating MAD-associated short-term side-effects.

**Materials and Methods:** 9 subjects with OSA requiring MAD-use were included in this study and were randomized into a control group (n=5) and a treatment group (n=4). All participants were treated with a customized adjustable MAD (SomnoDent Flex, SomnoMed, USA) and received morning exercise instructions for comfort. Subjects in the treatment group also received an MRS that was to be used every morning for 1 hour after removal of their MAD. Follow-up consisted of 6 appointments over approximately 8 months. During this time, variables including occlusal changes, side effects and treatment adherence were evaluated.

**Results:** A tendency for overjet, overbite and maxillary intermolar distance reduction as well as maxillary arch length shortening was observed in the control group only (p=0.063). 6 months after completion of MAD titration, masticatory problems were more frequently reported by subjects in the control group. 60% of these subjects reported masticatory problems on a weekly basis whereas subjects in the treatment group never or rarely reported these issues.

**Conclusions:** Our results suggest that MRS-use can minimize short-term side effects associated with MADs used to treat OSA. Additional, well-constructed, studies are needed to confirm these findings.

## Excessive Daytime Sleepiness (not Narcolepsy)

### A GLOBAL CONSENSUS REGARDING THE EVALUATION AND MANAGEMENT OF SLEEPINESS IN OBSTRUCTIVE SLEEP APNOEA: RESULTS OF A DELPHI PROCESS

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**Introduction:** Obstructive sleep apnoea (OSA) is thought to affect up to 1 billion people worldwide. Excessive daytime sleepiness (EDS) is a common symptom of OSA, although its evaluation and management are variable. One benefit of treating OSA is improvement in EDS; however, many patients experience residual EDS despite efforts to optimise therapy for the underlying OSA. The literature lacks consensus recommendations regarding current definitions and management approaches towards EDS in OSA; therefore, this study sought to reach a global consensus of experts using the Delphi process.

**Materials and Methods:** A panel of 10 international experts was convened to undertake the Delphi process, which involved literature searches to collect current data regarding identified topics on EDS in OSA, followed by the development of recommendation statements (NCT05055271). The following topics were covered: 1) EDS: definition, evaluation/assessment, and tools, 2) definitions of residual EDS in patients with OSA treated with primary airway therapy, 3) practical recommendations, and 4) management. Consensus of the panelists was achieved through iterative rounds of blinded survey voting and revision to the statements until a pre-determined level of agreement was met (80% agreement). At least 3 rounds of virtual review (2 asynchronous and 1 live) were held to achieve consensus on each topic of interest and finalise consensus statements.

**Results:** The literature synthesis and panel consensus resulted in 32 recommendations. First, the panelists agreed that EDS is a patient-reported symptom and recognised the importance of subjective and objective evaluation of EDS, both in the initial evaluation and subsequent management of OSA. Second, the importance of optimising OSA therapy, including troubleshooting potential issues affecting efficacy, was emphasised. Third, the differential diagnosis of residual EDS in optimally treated OSA and the need to evaluate patients for underlying causes were discussed at length. Fourth, the potential role of pharmacotherapy in the management of residual EDS in OSA following individual risk-to-benefit assessment was recognised. Finally, the panelists agreed that the utility of wake-promoting agents in this case is increasingly supported based on published literature, although further investigation is highly supported. All consensus statements were accepted based on the 80% agreement threshold: 25/32 final statements were accepted with 100% (10/10 panelists) of experts voting "strongly agree"; 6/32 statements were accepted with 90% (9/10 panelists) voting "strongly agree" and 10% (1/10 panelists) voting "agree with reservation"; and 1/32 statements was accepted with 80% (8/10 panelists) voting "strongly agree" and 20% (2/10 panelists) voting "agree with reservation."

**Conclusions:** EDS in patients with OSA is a major public health issue that requires increased awareness, recognition, and attention. The described Delphi process may be a useful way to reach global consensus on diagnosis and management of EDS in OSA, and could help guide subsequent studies. Implementation of the consensus recommendations may be helpful to patient care and could facilitate improvement in long-term management and clinical outcomes of patients with OSA.

**Acknowledgements:** Under direction of the authors, medical writing and editorial assistance were provided by Peloton Advantage, LLC, an OPEN Health company, and funded by Jazz Pharmaceuticals.

### ASSESSMENT OF DAYTIME SLEEPINESS IN OBSTRUCTIVE SLEEP APNEA PATIENTS USING PUPILLOGRAPHIC SLEEPINESS TEST

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**Introduction:** Since 1940s, infrared pupillography in darkness has been investigated as a potential tool for the objective measurement of daytime sleepiness, with the pupil displaying specific behavior (slow pupillary diameter oscillations) in excessively sleepy individuals. This concept was revitalized in 1970s with the advent of digital era, leading to further development in the 1980s and 1990s, with several sleep deprivation studies comparing the pupillography with subjective sleepiness scales and Multiple Sleep Latency Test (MSLT). These efforts culminated in the development of Pupillographic Sleepiness Test (PST), which introduced a novel approach to the quantification of pupillary diameter changes. The main output parameter - the Pupillary Unrest Index (PUI) was further validated against modified MSLT and reference population data were acquired. The recent Standards for Pupillography (2019) suggest Pupillographic Sleepiness Test as an objective and validate method for measuring daytime sleepiness. To date, only two studies were carried out in patients with obstructive sleep apnea (OSA), comparing PST findings in patients before and three days (1998) and three months (1999) after the initiation of the therapy with positive airway pressure (PAP) ventilation. These studies concluded that PST may be a welcome tool for objective measurement of sleepiness in OSA patients, especially in the context of longitudinal observation. However, despite PUI being able to statistically discriminate patients with apnea-hypopnea index (AHI) over 55, the PUI did not closely correlate with AHI.

**Materials and Methods:** In our study, we aim to follow on the first of the two studies performed by German authors Wilhelm et al in 1998. The major difference in the design will be the employment of the now commercially available head-mounted PST measuring device (F2D2, AMTech). Furthermore, our study is being conducted in a semi-controlled clinical setting, rather than the fully controlled laboratory setting in the original studies. The study is still in progress, we aim to include 30 patients with newly diagnosed OSA. Each subject has the PST measured twice, prior and two nights after the initiation of therapy with PAP. Epworth Sleepiness Scale and Visual Analog Scale will be used to gauge subjective sleepiness before each PST measurement. The resulting parameter PUI will be compared between the testing sessions and correlated with Epworth Sleepiness Scale and Visual Analog Scale.

**Results:** The preliminary results show a trend towards significant reduction of PUI after two nights of PAP.

**Conclusions:** Small sample size as of writing this abstract does not permit drawing any definitive conclusion. We aim to answer the following question: Can PST measured by head-mounted device be used to measure objective sleepiness in patients with OSA in a realistic clinical setting?

**Acknowledgements:** Authors have no affiliation to the manufacturer of the PST device (AMTech). The study is supported by the Internal Grant Agency of Palacky University Olomouc, Czech Republic (IGA LF UPOL), grant ID: IGA\_LF\_2021\_041.

### ASSOCIATION BETWEEN EXCESSIVE DAYTIME SLEEPINESS AND CORONARY PLAQUE BURDEN IN PATIENTS WITH OBSTRUCTIVE SLEEP APNEA

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**Introduction:** Excessive daytime sleepiness (EDS), a common symptom among patients with obstructive sleep apnea (OSA), is associated with cardiovascular disease. However, evidence for its association with coronary plaque burden among OSA patients is limited. We therefore aim to examine the association of EDS with coronary plaque burden, and the modification effects of age, gender, obesity among OSA patients.

**Materials and Methods:** Consecutive patients with OSA, who underwent coronary CT angiography within 6 months of sleep study between September 2015 and August 2019, were included. EDS was defined as Epworth sleepiness scale  $\geq 11$ . Multivariable linear regression models were used to evaluate the associations of EDS with volume of total plaque, as well as its subcomponents (non-calcified plaque (NCP), low density non-calcified plaque (LD NCP), and calcified plaque (CP)).

**Results:** In the overall cohort, there was no evidence for significant associations between EDS and total plaque volume or any subcomponents (all  $P > 0.05$ ). However, tests for the interaction between EDS and obesity in relation to coronary plaque volume were significant. We found that the associations between EDS and total plaque volume, NCP volume, and LD NCP volume were significant in the obese patients ( $P = 0.015, 0.018, 0.021$ , respectively), but not in the non-obese patients ( $P = 0.740, 0.637, 0.672$ , respectively) after adjusting for confounders. In addition, there was a significant association between EDS and LD NCP volume in the younger ( $\beta \pm SE, 36.067 \pm 17.619$  mm<sup>3</sup>) but not older participants ( $5.154 \pm 10.414$  mm<sup>3</sup>;  $P$  for interaction = 0.354).

**Conclusions:** EDS was associated with coronary plaque burden in obese but not in non-obese patients with OSA, suggesting that obesity may moderate the association between EDS and plaque burden in patients with OSA

**Acknowledgements:** The authors gratefully thank the staff at Sleep Medical Center, Beijing Anzhen Hospital, China, for scoring the sleep studies according to the updated AASM scoring guidelines and the staff at department of Radiology, Beijing Anzhen Hospital, China, for Coronary CTA images scan. In addition, we also thank VoxelCloud Technology Co., Ltd., Suzhou, China for providing the plaque analysis software program.

## EEG BIOMARKERS OF INSUFFICIENT SLEEP IN CHRONIC OPIOID USERS

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**Introduction:** Chronic pain patients on long-term opioids frequently complain of excessive daytime sleepiness<sup>1</sup>. These complaints are non-specific and correlate poorly with conventional objective measures. Sleep disorders are prevalent among these patients<sup>2</sup>. Several EEG biomarkers that are sensitive to insufficient sleep have recently become available. These are derived from the odds ratio product (ORP), which is a highly validated continuous measure of sleep depth.<sup>3-5</sup> The markers of interest<sup>5</sup> are ORP during stage wake (ORP<sub>w</sub>), agreement between sleep depth in right and left hemispheres (R/L ICC), and decrease in sleep depth across the night as sleep pressure decreases (DORP). We wished to determine if these indices provide objective evidence of the patients' symptom of excessive sleepiness.

**Materials and Methods:** 167 chronic pain patients on a stable dose of opioid for  $\geq 3$  months, who were referred from five university affiliated pain clinics, and underwent in-lab polysomnography (PSG). This was a planned post-hoc analysis of a prospective cohort study conducted at five pain clinics.<sup>6</sup>

PSGs were scored for the three indices of insufficient sleep. Sleepiness was assessed by the Epworth Sleepiness Scale (ESS).

**Results:** ESS had a statistically significant negative correlation with right/

Left ORP difference ( $P$ -value = 0.016) and Wake ORP ( $P$ -value = 0.003) but not with DORP ( $P$ -value = 0.363). Opioid dose had a marginally significant correlation with R/L ORP ICC ( $P$ -value = 0.031) and ORP<sub>w</sub> ( $P$ -value = 0.024), but not with DORP (correlation coefficient = 0.08,  $P$ -value = 0.312).

**Conclusions:** The negative association between ESS with Wake ORP and R/L correlation provides objective evidence for the presence of sleepiness. This study also shows that these abnormalities are opioid dose-dependent.

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## POST-COVID SYNDROME: OBJECTIVE SLEEP-WAKE CHANGES IN PATIENTS WITH FATIGUE AND EXCESSIVE DAYTIME SLEEPINESS

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**Introduction:** Post-COVID syndrome affects approximately 10% of patients with SARS-CoV2 infection. It is characterized by multiple symptoms including headache, anosmia, dyspnoea, fatigue and sleep-wake disturbances. In the absence of systematic data in the literature, the aim of the study was the assessment of objective sleep-wake changes in post-COVID patients reporting fatigue and excessive daytime sleepiness (EDS).

**Materials and Methods:** A consecutive series of patients with Post-COVID-19 and fatigue and EDS seen at our institution between March and October 2021 were included. A standardized assessment included questionnaires ( $n=14$ , e.g. Fatigue Severity Scale (FSS), Epworth Sleepiness Scale (ESS), and Beck Depression Index (BDI)), conventional video-polysomnography (PSG,  $n=14$ ), vigilance tests (multiple sleep latency test (MSLT),  $n=7$ ; maintenance of wakefulness test (MWT),  $n=5$ ), actigraphy ( $n=13$ ) and laboratory tests. Differences between groups were analyzed using the Mann-Whitney U and Fischer Exact tests.

**Results:** Patients were mostly female (9/14, 69%), young (mean age 45 years, 95% Confidence Interval (95%CI 37-53) and had a history of mild acute SARS-CoV2 infection (11/13, 85%). All but one (13/14, 93%) had a positive PCR test. The mean scores were 6.0 for the FSS, 14.0 (13/14 > 10) for the ESS, and 19.2 (11/14 > 12) for BDI 19.2. The mean apnoea-hypopnea index (AHI) was 18/h (6/14 > 20/h, 2/14 > 30/h). PSG documented a mean sleep efficiency of 84.5% (5/14 < 85%), a mean sleep duration of 384 min and a mean arousal index of 31.9/h. The mean percentage of N1, N2, N3 and REM (%) was 14%, 34%, 21% and 15%, respectively (3/14 had NREM < 15% and 6/14 a REM < 15%). The mean sleep latencies were 12.0 min (1/7 < 5) on MSLT and 24.6 min (1/5 < 14) on MWT. There were no sleep onset REM episodes. No patient had a high PLMS-index (>15/h) or REM-sleep behaviour disorder (RBD).

**Conclusions:** Preliminary findings of this ongoing study (actigraphy data was not analyzed so far) show that in post-covid patients reporting fatigue and EDS only a minority has abnormal vigilance (MSLT, MWT) tests and/or clear-cut sleep disorders. Conversely, a mild acute covid infection, female gender, depression, moderate SDB, and sleep architecture changes are

frequently found. More data are needed to confirm these observations and to identify predictors of objective and treatment-relevant sleep-wake changes in post-covid patients.

**Acknowledgements:** Nothing to disclose related to this work.

### PREDICTION OF RISK FACTORS OF SLEEPINESS AT THE WHEEL AMONG PATIENTS WITH OBSTRUCTIVE SLEEP APNEA

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**Objective:** Our objective was to determine risk factors for drowsy driving in patients with obstructive sleep apnea (OSA) and to identify factors independently associated with drowsy driving accidents.

**Patients and methods:** This retrospective study was conducted on 843 patients with OSA from the French Pays de la Loire cohort sleep database. Each patient completed questionnaires including anthropometric data, medical history, professional status, and data on alcohol and tobacco use. Questionnaires on the Epworth Sleepiness Scale (ESS) and on sleep quality were administered. Regarding driving, data were collected on the occurrence of a "near miss" or a drowsiness-related accident in the past year, as well as on the distance driven per year. The primary dependent variable of interest was self-reported drowsiness while driving.

**Results:** A multivariate regression analysis showed that self-reported drowsiness while driving (n=298) was independently associated with younger age (p=0.02), male gender (p=0.009) marked nocturnal hypoxemia (p=0.006), lower BMI (p=0.03), absence of cardiovascular disease (p=0.022), managerial or high degree jobs (p=0.003) and insomnia (p=0.03). Only experience of drowsy driving (OR 12.18, [6.38-23.25]) and an ESS ≥ 11 (OR 4.75 [2.73-8.27]) were independently associated with self-reported traffic accidents (n=30) or "near misses" (n=137).

**Conclusion:** In newly diagnosed OSA patients, the risk of traffic accidents appears to be multifactorial, and its assessment should include multiple parameters such as self-reported drowsiness while driving, occurrence of drowsiness-related accidents, anthropometry, occupational status, and insomnia complaints. Thus, it is possible to assess this risk and advise patients at the first diagnostic examination for OSA without waiting for the results of the sleep study.

**Acknowledgements:** We thank the IRSR, promoter of the cohorts from which the data for this study were obtained and the sleep technicians in Sleep Medicine of Angers University Hospital.

### SLEEP DISORDERS AND MORTALITY: A PROSPECTIVE STUDY IN THE CANADIAN LONGITUDINAL STUDY ON AGING

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**Introduction:** Sleep problems are among the most common complaints in the aging population. In addition to impairing quality of life, sleep problems may lead to physical and psychological complications, such as cardiovascular problems, diabetes, cognitive decline, depression, anxiety, and fatigue. However, it is unclear whether the risk of mortality is also increased in sleep disorders. This study aimed to compare mortality in different sleep disorders in a large population-based prospective study.

**Materials and Methods:** Participants completed a questionnaire at baseline (collected during 2011–2015) for overall sleep satisfaction, hours of daily sleep, sleep-onset and sleep-maintenance insomnia disorder (according to DSM V criteria), daytime somnolence disorder (according to DSM V criteria), REM sleep behavior disorder (RBD, according to RBD1Q), restless leg syndrome (RLS, according to 4-item minimal IRLSSG criteria) and obstructive sleep apnea (OSA, according to STOP questionnaire). The

vital status of participants up to July 2019 was released after the second wave of data collection. Baseline sleep problems of participants who were died (cases) were compared to those who survived (controls). For each case, five age/sex-matched controls were selected. Binary logistic regression was used to estimate the association between sleep symptoms and mortality, adjusting for age, sex, marital status, province, education, alcohol consumption, smoking, caffeine, and body mass index. In a complementary model, we added anxiety and depression to the model.

**Results:** Among 30,097 participants at baseline, 974 deaths were reported in 2019 (60.7% male, age=72.31 years, SD=9.4). 4,870 age/sex-matched controls were selected (60.7% male, age=72.10 years, SD=9.3). On the initial analysis, mortality cases reported more baseline sleep-maintenance insomnia (12.1% vs. 8.0%, Adjusted OR [95%CI]=1.62 [1.15,2.29]), daytime somnolence (2.4% vs. 1.1%, AOR=2.70 [1.34,5.44]), and higher possible RLS (16.4% vs. 12.4%, AOR=1.50 [1.09,2.05]). They were also more likely to screen positive for possible OSA (33.8% vs. 24.2%, AOR=1.32 [1.07,1.64]). Long duration sleep (≥10 hours per day) was also associated with increased mortality (3.4% vs. 1.9%, AOR=1.83 [1.04,3.24]). Other sleep symptoms/disorders, such as sleep-onset insomnia (7.3% vs. 4.3%, AOR=1.54 [1.00,2.37]), possible RBD (5.3% vs. 5.1%, AOR=1.02 [0.62,1.69]), and sleep dissatisfaction (26.5% vs. 22.6%, AOR=1.14 [0.93,1.41]) were not different among these groups. However, because of a large discrepancy in sleep disorder prevalence in mood disorders, along with the increased risk of mortality in those with mood disorders, we added anxiety and depression to the adjustment model. After adding these variables, all differences attenuated and became statistically nonsignificant, with the exception of daytime somnolence disorder and OSA. After stratifying by sex, we found a mortality relationship only among women, with no link between sleep problems in men and mortality.

**Conclusions:** We confirm a relationship between numerous sleep disorders and mortality (i.e., sleep-maintenance insomnia, daytime somnolence, possible RLS, possible OSA, and long sleep duration). However, this effect appears to be primarily related to co-existing anxiety and depression.

**Acknowledgements:** We would like to thank CLSA for providing the data and thank Webster Foundation for funding this project.

### TACKLING LONG COVID USING INTERNATIONAL HOST GENETICS RESEARCH COLLABORATION

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**Introduction:** While the world is still fighting the spread and casualties of the acute disease caused by SARS-CoV-2 virus, there is also a need for mitigating the long-term effects of this pandemic. WHO has estimated that 10–20% of coronavirus disease 2019 (COVID-19) patients suffer from lingering symptoms, termed Long COVID (Post-acute sequelae of COVID-19, PASC / Post COVID-19 conditions). Various symptoms have been reported in virtually all organs, with debilitating fatigue, exercise intolerance, cognitive dysfunction, anxiety, depression, loss of smell or taste, and sleep difficulties among the most prevalent.

Several pathophysiological mechanisms ranging from prolonged infection to tissue damage and autoimmunity have been proposed. Studying human genetic variants predisposing to Long COVID can provide hypothesis-free information on the underlying biology.

**Materials and methods:** We have established an open world-wide collaboration for elucidating genetic risk factors for Long COVID. Currently, the Long COVID Host Genetics Initiative comprises 46 studies across 23 countries with genotype data combined to questionnaire information of symptoms and/or electronic health record (EHR) data of diagnoses.

Using questionnaire data, we have defined Long COVID as 'any symptoms that cannot be explained by alternative diagnoses, or impact on everyday functioning, 3 months after the onset of COVID'. With EHR data, we have used specific diagnosis codes for Post COVID-19 conditions (ICD-10: U09) or Coronavirus as the cause of other diseases (B97.2).

In the first data freeze, we have data from 11 studies from 8 countries, with

1,534 Long COVID cases and 800,353 controls, of which 96,692 have had COVID but not Long COVID. Each contributing study has performed genome-wide association analyses (GWAS) comparing Long COVID to individuals who have recovered from COVID within 3 months, and to population controls. Also lifestyle measures and other diagnoses have been broadly assessed in some of the participating cohorts. This allowed us to examine the phenotypic associations with Long COVID using logistic regression.

**Results:** GWAS of individual cohorts have suggested potential variants associated with Long COVID but without genome-wide statistical significance. We are currently running meta-analyses to increase statistical power by combining data from these studies.

Using registry follow-up of 12 months in the FinnGen study after the beginning of the COVID-19 pandemic in Finland identified 2,018 participants with a PCR-verified SARS-CoV-2 infection. 50 (2.5%) of them had received a diagnosis for long COVID. Long COVID associated with autoimmune diseases ( $p = 0.026$ ,  $OR[se] = 2.15[1.41]$ ) but not with depression ( $p = 0.71$ ,  $OR[se] = 1.20[1.75]$ ) or asthma ( $p = 0.43$ ,  $OR[se] = 1.55[1.74]$ ).

**Conclusions:** Our findings indicate that Long COVID may be related to autoimmunity. The joint effort of the international Long COVID Host Genetics Initiative combining phenotypic and genetic data will allow us to identify genetic risk factors and test causality between autoimmunity and Long COVID.

**Acknowledgements:** We acknowledge the work of clinicians, healthcare professionals, technicians, patients and researchers working hard together to tackle this pandemic and its long-term consequences. The current list of authors contributing to the Long COVID Host Genetics Initiative can be found in <https://tinyurl.com/LongCOVIDHGIAuthors>

#### WAKE UP AND LEARN - A SCHOOL BASED SLEEP EDUCATION AND SURVEILLANCE PROGRAM: EXCESSIVE DAYTIME SLEEPINESS A COMMON CONCERN

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**Introduction:** "Wake Up and Learn" (WUAL) is a population based preventative sleep screening and education program for 7th to 12th graders through an asynchronously delivered virtual platform. The program was intentionally developed to be completely virtually delivered for scalability, which was of advantage during COVID allowing for the program to continue to be implemented with modest delays related to school schedule changes. This is a descriptive summary of excessive daytime sleepiness over two time points during the academic school year.

**Materials and Methods:** The 7th to 12th grade students of Montgomery school district (Pennsylvania) were given an opt-out option for participation in the WUAL program. The surveys were generated using REDcap and included the Epworth sleepiness scale-CHAD (ESS-CHAD) and the childhood sleep habits questionnaire (CHSQ). The surveys became available online via the WUAL website ([wakeupandlearn.org](http://wakeupandlearn.org)) and the students were instructed to access the website and complete the surveys as part of class time. Surveys were completed in December 2020 for the first time and then again in April 2021 as part of the planned three times per year surveillance. Due to school schedule changes experienced related to COVID the first survey planned for beginning of the academic year was skipped.

**Results:** A total of 344 students completed ESS-CHAD in December 2020. There were 57 students with ESS scores greater than 10 (16.5%). In April, a total of 321 students completed ESS-CHAD with 49 students (15%) having ESS scores greater than 10. Of those with abnormal scores in December 15 (26%) had persistent sleepiness, 28 (49%) improved, and 14 (25%) did not provide a completed survey in April 2021. With this said, 34 (69%) of the respondents in April 2021 were newly identified to have pathologic sleepiness. 31% with persistent EDS from December 2020.

**Conclusions:** Excessive daytime sleepiness is common in this adolescent high school cohort, but may not remain persistent over time. The majority of students who provided follow up responses had resolution of complaints of excessive daytime sleepiness between the two time points. Alarming, however, 34 additional students endorsed new complaints of

EDS. Further examination of trends of EDS over time in this age group is required to better determine if this pattern is replicated in different school districts. If this is replicated it will be important to further explore factors that contribute to development, persistence and recovery from EDS. It is important to note that COVID and varying school structures (i.e in-person, virtual, hybrid) may have played a role in these findings. Wake Up and Learn is an on going program with plans for further expansion into additional school districts that may provide further insights into these trends.

**Acknowledgements:** Thank you to Jazz pharmaceuticals and Janet Weis Children's Hospital for their support of the development and growth of this program.

#### Sleep Health

#### A COMPARISON OF ESTIMATED SLEEP-WAKE PATTERNS OBTAINED FROM A LARGE U.S. SAMPLE BY HOME-BASED UNDER-MATTRESS MONITORING DEVICES BEFORE AND AFTER THE START OF THE COVID-19 PANDEMIC

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**Introduction:** The COVID-19 pandemic has affected sleep in multiple ways. Technological advances in home sleep monitoring have provided the opportunity to analyze sleep-wake patterns on a scale much larger than previously imaginable. This study compares the estimated sleep-wake patterns in the time before and after the start of the pandemic in a large U.S. sample.

**Materials and Methods:** Sleep parameters [estimated total sleep time (TST), bedtime (BT), and morning rise time (RT)] were analyzed by a commercially-available home sleep monitoring device (Sleeptracker-AI Monitor, Fullpower Technologies, California, USA). The device passively monitors sleep using piezo-electric sensors that register the forces exerted through the mattress by features such as the individual's motion, respiration, heartbeats, and snoring vibrations. The de-identified data obtained from the devices were analyzed, following review and exemption of the study (#57681) from the Stanford University IRB. Data from the calendar years of 2019 and 2020, from 62,152 individuals with 20,255,441 recorded nights, were available. Individuals who had at least 300 nights of sleep each year were included in the analytic dataset, with Sunday nights through Thursday nights analyzed since sleep on weekend nights was expected to have more variability.

**Results:** A total of 8,580 individuals (4,459 men,  $51 \pm 13$  years; 3,982 women,  $50 \pm 13$  years) with 5,681,087 recorded nights met the inclusion criteria for data analysis. In preparation for time-series analysis, we analyzed key timepoints. Each timepoint comprised a week of nights ending on weekdays (Sunday night through Thursday night), with a given week in 2020 compared with a week 52 weeks (364 days) earlier in 2019. The weeks selected were: (A) 1/5/2020-1/9/2020 (pre-pandemic baseline, first full week of 2020); (B) 4/5/2020-4/9/2020 (first wave zenith: 218,581 new U.S. weekly cases), and (C) 5/24/2020-05/28/2020 (nadir between first and second waves: 147,228 new U.S. weekly cases). The differences between 2019 and 2020 in estimated mean TST, BT, and RT for each of the timepoints, in minutes, were: (A) TST -0.7, BT +0.9, RT -1.0; (B) TST +17.2\*, BT +22.8\*, RT +41.1\*; (C) TST +10.6\*, BT +13.9\*, RT +26.1\*; a (+) indicates an increase and (-) a decrease in the sleep parameter from 2019 to 2020, and (\*) signifies  $p < 0.05$  by paired t-test. Weekend data followed similar but less pronounced trends compared to the weekday data, with an average difference of +9.0\*, +13.4\*, and +22.1\* in estimated TST, BT, and RT, respectively, for the weekend preceding timepoint (B).

**Conclusions:** An estimated increase in TST and delayed BT/RT was associated with the pandemic's first wave zenith vs. the prior year for the same individuals. At the nadir between waves 1 and 2, differences between the individuals' sleep parameters were still greater compared to pre-pandemic levels. The causes of these changes are likely multifactorial, including possible factors such as the coronavirus's clinical/subclinical effects and comorbidities, social isolation, stress, and variability in work-from-home schedules. Home sleep monitoring enables analysis of longitudinal trends,

and further work will focus on studying the evolution of sleep architecture/patterns over the pandemic's course.

### A CROSS-SECTIONAL STUDY ON THE SLEEP QUALITY AND EXCESSIVE DAYTIME SLEEPINESS OF FILIPINO MEDICAL STUDENTS IN A STATE-RUN UNIVERSITY DURING THE CORONAVIRUS DISEASE (COVID-19) PANDEMIC

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**Introduction:** Movement restrictions and changes in medical education around the world due to the coronavirus 2019 pandemic have been sources of stress, which affects sleep and compounds the demands of medical education. In the Philippines, stay-at-home orders were implemented in the National Capital Region on 15 March 2020, and remain in effect to date, July 2021. This cross-sectional study aims to determine the sleep quality and daytime sleepiness of Filipino medical students during prolonged stay-at-home orders.

**Materials and Methods:** The medical student population of a state-run university in the City of Manila was included, and comprises 2 pre-medicine and 4 medicine proper year levels. Those on a leave of absence and those without consent were excluded. The Epworth Sleepiness Scale and the Pittsburgh Sleep Quality Index, which measure excessive daytime sleepiness and sleep quality respectively, were disseminated via Google Forms from April to May 2021.

**Results:** Response rate was 87.75% (709) with a mean age of  $22.9 \pm 2.0$  years and a 0.92 male-to-female ratio. Among all the respondents, 41.18% had varying levels of excessive daytime sleepiness and was significantly higher for the first-year pre-medicine students (52.50%) and first-year medical students (46.48%). A decrease in daytime sleepiness was noted for all year levels relative to pre-pandemic scores, with statistical significance noted for the pre-medicine students, first-year medical students, and clinical clerks. On the other hand, 62.34% of all the respondents had poor sleep quality with global scores being significantly higher for the first-year pre-medicine students (82.50%), second-year pre-medicine students (70.59%), and first-year medical students (70.42%). Statistical analysis of the component scores further support that the lower year levels, particularly the first year pre-medicine students and the first year medical students, have greater affectation of the different dimensions of sleep, namely sleep duration, day dysfunction, and sleep quality. Furthermore, in both excessive daytime sleepiness and poor sleep quality, a greater percentage of females were affected.

**Conclusions:** To the authors' knowledge, this is the first study in a Filipino medical student population examining daytime sleepiness and sleep quality during the pandemic. Both poor sleep quality and excessive daytime sleepiness remain prevalent during prolonged stay-at-home orders. These highlight the demands of medical education, online or not, and represent opportunities for more effective future policy making and curricula development with sleep as a main consideration.

**Acknowledgements:** The authors would like to acknowledge the contribution of our research assistants and fellow medical students: C. Bagsic, J. Vergara, I. Legaspi, and A. San Diego; and our statistician, Professor M. Albis.

### ADOLESCENT CHRONIC SLEEP RESTRICTION PROMOTES ALCOHOL BINGE DRINKING AND ESCALATES ALCOHOL CONSUMPTION IN MSP RATS

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**Introduction:** In modern society, chronic sleep restriction (CSR), defined as gaining less than 8–10 hours of sleep per night for consecutive nights, has become epidemic among adolescents worldwide. Sleep is critical for our health and sleep disruption is associated with an incremental deterioration of a variety of cognitive functions, altered emotional regulation,

increased psychosis, and enhanced propensity to engage into risk-taking behaviors. Poor sleep relates to altered functioning of the meso-corticolimbic system and to increased risk of developing neuropsychiatric disorders, higher consumption of substances of abuse, including alcohol use and expression of related comorbidities. In this study, we aim to determine the short- and long-term effects of adolescent CSR on alcohol consumption, development of alcohol use disorder, and related neuropsychiatric comorbidities in two rat lines.

**Materials and Methods:** Male Sardinian alcohol-preferring (msP) rats and its control Wistar line were used. MsP rats have been genetically selected for high propensity to excessive alcohol consumption and preference. Through selection, hyper-anxiety and depressive-like traits co-segregated with excessive drinking, such that this animal line is now considered an ideal model to study these comorbidities. Both lines were divided into controls and sleep-restricted (CSR) groups and subjected to 6hrs or 20-22hrs of sleep restriction, respectively, for 4 consecutive days. On the fifth day, rats were exposed to a 2-bottle choice paradigm (choice between 10% alcohol solution and water) to measure alcohol drinking. This cycle was repeated across the entire adolescent period (postnatal day 23 to 60). CSR was achieved using an automated sleep-deprivation device mimicking gentle handling. Behavioral tests were carried out 1 and 5 weeks after the end of the CSR protocol to assess short- and long-term effects, respectively.

**Results:** At the end of the sleep restriction, adolescent CSR msP rats showed increased binge drinking ( $p < 0.0001$ ) and alcohol consumption ( $p < 0.001$ ) relative to controls ( $n = 14$  CSR;  $n = 10$  controls), whereas no significant effect was found in Wistar rats ( $n = 29$  CSR;  $n = 26$  controls). In both strains, CSR was associated with signs of hedonic imbalance, as suggested by the attenuated reduction to sucrose preference in the sucrose negative-contract test in CSR rats relative to controls (Wistar  $p = 0.0001$   $n = 10$  CSR;  $n = 10$  controls; msP  $p = 0.003$ ,  $n = 6$  CSR;  $n = 4$  controls). Furthermore, in a Novelty-suppressed feeding test, CSR rats approached food with a shorter latency and consumed higher amount of pellet relative to controls (latency: Wistar  $p = 0.02$ , msP  $p = 0.009$ ), suggesting a propensity towards undertaking more risky behaviors in an unfamiliar environment. However, when exposed again to alcohol and behavioral tests after 5 weeks of recovery from sleep restriction, both Wistar and msP adult rats showed similarly high levels of alcohol drinking with no statistically significant differences between CSR and controls in the behaviors measured.

**Conclusions:** These experiments show that adolescent CSR promotes binge drinking and the escalation of alcohol consumption in young adult msP rats. Moreover, CSR favors risky behaviors and increases the value of an anticipated reward in both rat lines. However, after 5 weeks these maladaptive behaviors are no longer evident, suggesting spontaneous recovery from the CSR.

ADVANCING ADOLESCENT BEDTIME BY USING MOTIVATIONAL INTERVIEWING AND TEXT REMINDERS – A RANDOMIZED CONTROLLED TRIAL R.N.Y. CHAN<sup>1,2</sup>, S.X. LI<sup>3,4</sup>, C.C. TSANG<sup>1,2</sup>, M.W.M. YU<sup>1,2</sup>, J. ZHANG<sup>1,5</sup>, Y.K. WING<sup>1,2</sup>. <sup>1</sup>THE CHINESE UNIVERSITY OF HONG KONG, PSYCHIATRY, SHATIN, HONG KONG; <sup>2</sup>THE CHINESE UNIVERSITY OF HONG KONG, LI CHIU KONG SLEEP ASSESSMENT UNIT, SHATIN, HONG KONG; <sup>3</sup>THE UNIVERSITY OF HONG KONG, PSYCHOLOGY, HONG KONG, HONG KONG; <sup>4</sup>THE UNIVERSITY OF HONG KONG, THE STATE KEY LABORATORY OF BRAIN AND COGNITIVE SCIENCES, HONG KONG, HONG KONG; <sup>5</sup>GUANGDONG ACADEMY OF MEDICAL SCIENCES, GUANGDONG MENTAL HEALTH CENTER, GUANGDONG PROVINCIAL PEOPLE'S HOSPITAL, GUANGDONG, CHINA

**Introduction:** Chronic sleep deprivation is a prevalent sleep problem in school-aged adolescents. The natural delay of circadian rhythm combined with early school schedule leading to significant sleep loss during school days. In particular, adolescents in Hong Kong not only sleeping less than their Shanghai counterparts but also having later bedtime. Delaying school start time is an effective strategy but has met numerous constraints. While previous sleep education programs have successfully improved sleep knowledge but failed to increase sleep practice. Intervention with specific focus on late bedtime might be an potential approach to improve adolescent sleep. Current study explores the possibility of advancing adolescent bedtime by group-based motivational enhancement approach and text message reminders.

**Materials and Methods:** Healthy adolescents (12–18 yrs old) with schoolday sleep duration <7 hours and without other sleep disorders such as insomnia and delay sleep phase disorder were randomly allocated to intervention or non-active control group. The intervention consists of four weekly, group-based therapy delivered using motivational interviewing approach and 3 week daily text reminders. Assessments were conducted at baseline, post-intervention, 3-month and 6-month follow up. The primary outcomes were sleep-wake pattern captured by 7-day sleep diary. The intervention effect was evaluated by linear mixed model. The trial was registered with the Clinical Trial Registry (NCT03614572).

**Results:** A total of 212 adolescents (mean age:  $15.8 \pm 0.98$ ; female:60.1%) were recruited from Aug 2018 to Apr 2021. Approximately 80% of the adolescents attended all the follow up assessments. Adolescents in the intervention group have significantly earlier schoolday bedtime at post-intervention (intervention vs. control: (-14 mins vs +19 mins) and 6-month follow up (-14 mins vs +21 mins) compared to the control group ( $F=4.6$ ,  $P=0.004$ ). They also had a tendency of increased sleep duration throughout the follow up period, but the difference was not significant ( $F=2.22$ ,  $P=0.089$ ). This is explained by the difference in schoolday wakeup time as control group had a significant later wakeup time at post-intervention (intervention vs. control: -2 mins vs +23 mins) in relative to the intervention group. It is not common to observe a change in schoolday wakeup time as wakeup time is largely determined by early school schedule. The outbreak of Coronavirus in 2020 has forced schools to close and adopted an online study mode. The online class schedule varied significantly between schools, which might explain the difference in wakeup time at follow up assessment. Despite there is no significant difference in schoolday sleep duration, adolescents in the intervention group reported greater intention to behavioral changes ( $P=0.043$ ), and lower level of daytime sleepiness ( $P=0.001$ ). However, there is no difference observed in sleep knowledge, mood symptoms and quality of life.

**Conclusions:** This study supports that motivational interviewing in combined with text reminders are effective approach in advancing adolescent bedtime, improving their motivation and daytime functioning. Adolescents were able to maintain earlier bedtime regardless of the school schedule. We suggest that advancing bedtime protocol should be incorporated at school-level to benefit more adolescents.

**Acknowledgements:** Supported by Health Medical Research Fund (#15163071), Hong Kong SAR, China.

#### AMERICAN LIFE IN REALTIME (ALIR): PERSON-GENERATED HEALTH DATA FROM FITBITS TO ASSESS THE MULTI-LEVEL INFLUENCE OF SOCIAL DETERMINANTS ON SLEEP AND OTHER HEALTH OUTCOMES IN VULNERABLE AND UNDERSERVED POPULATIONS

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**Introduction:** Social and structural determinants of health—including economic/educational inequalities, healthcare access, systemic racism, and lifetime stress—account for 60–80% of modifiable risk factors that contribute to sleep health disparities. Many sleep interventions use population averages to create “one-size-fits-all” approaches, but are limited by individual heterogeneity in number, magnitude, interplay, and amplification of social determinants. Person-generated health data (PGHD) derived from consumer digital technologies (including wrist-worn monitors, such as Fitbits) are invaluable and rapidly emerging tools for “precision public health,” a field that aims to develop personalized digital interventions targeting unique needs of specific populations. PGHD can continuously measure everyday lived experiences and health in a continuous manner outside of intermittent clinical settings and are increasingly being used to assess sleep health. However, PGHD are typically captured from convenience samples through “bring-your-own-device” designs, and thus, have systematically underrepresented high-risk groups, including Black or American Indian/Alaska Native individuals, and low-income populations. To address this significant gap, the American Life in Realtime (ALiR) was developed to provide the first-in-kind holistic and sociodemographically representative registry of continuously-collected Fitbit and health data. The current study provides preliminary data on the ALiR sample, study

methods, recruitment, and multi-level social, behavioral, and environmental correlates of sleep health.

**Materials and Methods:** Participants were recruited from existing members of a nationally-representative survey panel of American adults from USC’s Understanding America Study, with oversampling of racial/ethnic minorities and low-socioeconomic status individuals. Individual-level longitudinal data include: (1) raw sensor PGHD from provided Fitbits worn continuously by participants for at least 1 year (transformed through machine learning into “features” including sleep duration and efficiency); (2) sociodemographics and geolocation, collected every 3 months; (3) all elements from the Health and Retirement Survey, collected annually; (4) social determinants (e.g., food security, adverse childhood events) from validated scales collected annually; (5) validated health scales (e.g., depression, anxiety, disability) collected monthly; and, (6) contextual data from public data sets (e.g., air quality, crime, ambient noise).

**Results:** To date, 1007 individuals consented to participate between August 3rd and November 23rd, 2021. Racial/ethnic distributions include 65% White, 13% Black, 4% American Indian / Alaska Native, 9% Asian, 1% Hawaiian / Pacific Islander, 8% Mixed, and 26% Hispanic/Latino, with relatively even gender and age distributions. Seventy percent of individuals are without a bachelor’s degree, and 20% have at least one chronic condition (e.g., obesity, cardiovascular disease). Overall response rates exceed 87%, averaging 90% for surveys and 82% for Fitbits. Planned analyses will also examine the association between social, environmental, and behavioral factors with sleep duration and efficiency.

**Conclusions:** ALiR establishes a generalizable research infrastructure to use PGHD to explore the influence of population-specific lived-experiences on sleep and other health outcomes in virtually any population. This novel and ongoing research infrastructure which will ultimately be publicly available, providing an invaluable resource to better understand and intervene on sleep health disparities.

#### ANALYSIS OF SLEEP AND SEDENTARY LIFESTYLE HABITS AMONG ITALIAN WOMEN DURING COVID-19 PANDEMIC: A PILOT STUDY

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**Introduction:** COVID-19 pandemic has drastically reduced physical activity levels. Sedentary behaviors are strictly associated with higher risks of developing diseases, including cardiovascular diseases, obesity, type II diabetes, some specific cancers, cognitive alterations, neurodegenerative diseases, etc. (Allen et al., 2017). Severe lockdown periods and personal quarantine had influenced the quality and quantity of sleep, eating behaviors, the physical activity levels, inducing increased stress and anxiety among the population. Our study aimed to analyze lifestyle habits in a group of 14 volunteer women aged from 40 to 50 years with the scope of analyzing specific lifestyle and anthropometric changes induced by COVID-19 pandemic

**Materials and Methods:** Semi-Structured questionnaires on lifestyle habits, anthropometric measures, sleep were administered with Google modules. Physical activity monitoring by smartphone was recorded. All data were collected three times: before, during, and after lockdown. Data are reported as mean  $\pm$  standard deviation (S.D.). Before using parametric tests, the normality assumption was verified using the Shapiro-Wilk W test. Variables association was assessed using Pearson’s product-moment correlation coefficients (i.e.,  $r$ ). An analysis of variance (ANOVA) for repeated measures with the Newman-Keuls test was used to compare the physiological parameters among the different recording sessions. Comparisons between PSQI variable means were performed using the Student’s paired t-test.

**Results:** During the lockdown, the daily number of steps shows a reduction of ~65%. The number of weekly walking kilometers was drastically reduced by ~70%. No statistically significant improvements were registered in the Pittsburgh Sleep Quality Index (PSQI), although the number of steps had returned to pre-COVID levels. The PSQI global score seems to normalize after lockdown, but the data are not statistically significant. We observed an inverse correlation between daily dissipated kilocalories and

latency of falling asleep in the lockdown phase ( $r=-0.56$ ;  $p=0.04$ ). The correlation is not maintained in the post lockdown phase, suggesting that other stressogenic factors influence the latency of falling asleep ( $r=0.53$ ;  $p=0.06$ ). The PREDIMED questionnaire revealed a sufficient adherence to the Mediterranean diet (mean score=7.5). The mean quantity of daily sleep hours during the lockdown was  $6.64\pm 0.74$  versus  $6.89\pm 0.56$  of the post lockdown phase. Anthropometric parameters like waist circumferences were found to significantly increase between pre-COVID-19 and post lockdown phases (waist circumference pre versus post lockdown observation  $80.4\pm 8.5$  cm versus  $83.4\pm 9.9$  cm ( $p=0.013$ )). The waist/Hip ratio increased after lockdown ( $p=0.033$ ). No significant changes were observed in body mass index ( $p=0.487$ ). However, an increasing trend was observed for weight.

**Conclusions:** The study highlights that educational strategies are necessary to avoid the risks of prolonged sedentary behaviors in women. COVID-19 pandemic has dramatically reduced daily steps and caloric dissipation by movements, leading to an increased waist circumference, associated with visceral fat accumulation, silent inflammation, and increased risk of cardiovascular disease. Correct sleep hygiene, promoting adequate and monitored physical activity levels, and increased adherence to the Mediterranean diet are achievable goals advocating adult women's health.

**Acknowledgments:** We acknowledge the volunteers who kindly participated in the study

#### ASSOCIATION BETWEEN SCHOOL START TIME AFFECTED BY EXTRACURRICULAR ACTIVITIES AND SLEEP DURATION: NATIONAL QUESTIONNAIRE SURVEY IN JAPAN

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**Introduction:** Long extracurricular activities are observed in adolescents, but their associations with sleep habits and daytime sleepiness are unclear. This study aimed to evaluate how basic age and gender, extracurricular activity time, and lifestyle habits are associated with school start time, sleep duration, and daytime sleepiness.

**Materials and Methods:** An online survey was conducted throughout Japan from October 7 to December 31, in 2020. The questionnaires were distributed by parents to their children through Parent-Teacher Association (PTA) and answered via cell phones or personal computers. Participants were from the first to the third year of junior high school. Grade (1 to 3), gender (male, female, unspecified), Pediatric Daytime Sleepiness Scale (PDSS), sleep duration on weekdays, basic lifestyle (TV/mobile phone use, morning sunlight, caffeine use, nighttime brightness), and prefecture of residence were collected. From the residence, the average weekly extracurricular time was calculated and used for analysis (>900, 800-900, and <800 min/week). Regression and multiple regression analyses were performed with sleep duration and PDSS as outcomes, using R.

**Results:** There were 3419 participants in the study (1774 males, 1580 females, 65 unspecified). Those who started school before 7:30 and after 9:00 had longer extracurricular activities ( $p<0.001$ ). Regression analysis of gender, grade, school start time, extracurricular activity time, and lifestyle on sleep duration in weekdays showed that school start time before 7:30 a.m. was associated with a decrease in weekday sleep time ( $\beta=-0.096$ ,  $p<0.001$ ) even after adjusting for lifestyle factors. Extracurricular activity time was not associated with weekday sleep duration, but the analysis of covariance structure showed that long extracurricular activities affected weekday sleep time through school start time. Regression analysis of school start time and these variables on PDSS showed that long extracurricular activity time was associated with daytime sleepiness ( $\beta=0.035$ ,  $p<0.05$ ), even in the model after adjusting for weekday sleep duration.

**Conclusions:** It might be necessary to set a school start time that is not too early and to prevent extracurricular activities from being too long to take appropriate sleep duration in adolescence.

**Acknowledgments:** We appreciate PTA members, parents, and children

conducting the survey.

#### ASSOCIATION OF SLEEP MICROSTRUCTURE WITH INCIDENT HYPERTENSION IN A POPULATION-BASED SAMPLE: THE HYPNOLAUS STUDY

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**Introduction:** Although evidence suggests that altered sleep quality is associated with increased incident hypertension (HTN), few studies have investigated the impact of objective parameters of sleep structure on HTN. This study aimed to determine the association between sleep macro- and microstructure and incident HTN in a middle-to-older aged sample of the general population.

**Materials and Methods:** Participants from the HypnoLaus population-based cohort without HTN at baseline and with HTN status at 5-year follow-up were included. All participants had an at-home polysomnography at baseline allowing to assess sleep macrostructure (N1, N2, N3 and REM sleep stages) and microstructure (power spectral density of electroencephalogram [EEG] in non-REM sleep and spindles characteristics (density, duration, frequency, amplitude) in N2). Associations between incident HTN and sleep macro- and microstructure were assessed with multiple-adjusted logistic regression including adjustment for age, sex and body mass index, alcohol consumption, systolic blood pressure, diabetes, dyslipidemia, obstructive sleep apnea, and sleep efficiency.

**Results:** A total of 1172 participants (42% men,  $55\pm 10$  years) without HTN at baseline were included. Of them, 198 (17%) developed HTN over a mean follow-up of 5.2 years. Although the percentage of N3 was lower in the incident HTN group in bivariate analysis, no sleep macrostructure features were associated with incident HTN after multiple adjustments. Low absolute delta and sigma power were significantly associated with incident HTN; participants in the lowest quartile of delta and sigma had a  $\approx 1.7$ -fold increased risk of incident HTN than those in the highest quartile. Moreover, higher spindle density (adjusted odds ratio [ORa]: 0.87, 95% confidence intervals: 0.76-0.99) and spindle amplitude (ORa: 0.98 [0.95-1.00]) were associated with a lower incidence of HTN.

**Conclusions:** Sleep microstructure but not macrostructure is associated with the development of HTN. Slow-wave activity and sleep spindles, two hallmarks of objective sleep continuity and sleep quality, were inversely associated with incident HTN after multiple adjustments. This reinforces the protective role of sleep continuity in the development of HTN and further cardiovascular diseases.

**Acknowledgments:** HypnoLaus was supported by grants from Leenards Foundation, the Faculty of Biology and Medicine (FBM) of Lausanne and the Swiss National Science Foundation (SNSF).

#### ASSOCIATIONS BETWEEN SLEEP-RELATED CHARACTERISTICS AND NEO-FIVE PERSONALITY TRAITS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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**Introduction:** Adequate sleep is essential for physical and mental health. Given the high prevalence of sleep disturbances and their significant negative impacts, a growing body of research has been conducted to

understand the predisposing factors that may be associated with changes in sleep-related characteristics and the risk of sleep problems. Whilst there has been some evidence suggesting a relationship between personality traits and sleep features, the results remained controversial. This current review aimed to explore whether personality, especially NEO-Five personality traits, are associated with sleep-related characteristics (i.e., sleep quality and sleep duration) in adults.

**Methods:** After a systematic search in four major databases from inception to Apr 2021, 37 studies that included the key outcome measures were identified and included in this review. The inclusion criteria comprised of articles written and published in English, with a mean age of sample size over 18-year-old and reported the association between any of the NEO-Five personality traits and sleep-related characteristics (i.e. sleep quality and sleep duration) as measured by standardized measurement, either subjectively or objectively.

**Results:** Better sleep quality was associated with a higher level of openness ( $r=-0.01$ ; 95%CI: -0.07, 0.05;  $p=0.02$ ), conscientiousness ( $r=-0.11$ ; 95%CI: -0.20, -0.03;  $p<.01$ ), extraversion ( $r=-0.10$ ; 95%CI: -0.15, -0.04;  $p<.01$ ) and agreeableness ( $r=-0.20$ , 95%CI=-0.42, 0.05;  $p<.01$ ), and a lower level of neuroticism ( $r=0.29$ , 95%CI=0.17, 0.40;  $p<.01$ ). Shorter sleep duration was found to correlate with a higher degree of neuroticism ( $r=0.13$ ; 95%CI: 0.06, 0.20;  $p<.01$ ) while not significantly with conscientiousness ( $r=-0.03$ ; 95%CI: -0.10, 0.04;  $p=0.76$ ) and extraversion ( $r=-0.03$ ; 95%CI: -0.10, 0.04;  $p=0.57$ ). Qualitative analysis suggested that longer sleep duration was associated with higher degree of openness but not with the level of agreeableness trait.

**Discussion:** Most of the included studies utilized self-report measures and recruited participants from the general population with a cross-sectional design. Future studies may consider utilizing objective measures and exploring the observed associations in the clinical populations. There is also a need for longitudinal studies to examine the prospective association between personality traits and sleep-related characteristics. Further exploration of how personality traits affect the outcome of prevention and intervention of sleep problems in future research may potentially inform clinical practice and the design of personalized treatment plans.

#### A SYMPTOM OF PERIODIC LIMB MOVEMENT DURING SLEEP IS NOT ASSOCIATED WITH EXCESSIVE DAYTIME SLEEPINESS IN ADOLESCENTS WITH SUGGESTIVE SYMPTOMS OF RESTLESS LEGS SYNDROME

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**Introduction:** Although periodic limb movement during sleep (PLMS) and restless legs syndrome (RLS) are not rare sleep-related symptoms in children and adolescents, they are relatively overlooked. In clinical field experience, PLMS has been evaluated as having a lower clinical significance than RLS. This study was designed to study the relationship of socio-behavioral factors of PLMS symptom on Korean adolescents and to check whether PLMS symptom is related to excessive daytime sleepiness (EDS), depending on whether RLS accompanies.

**Materials and Methods:** In this cross-sectional study, we evaluated 25,789 adolescents between 12 and 18 years of age (mean  $15.76 \pm 1.73$  years; female 51.49%) by using an online survey. Global Sleep Assessment Questionnaire and self-report questionnaires were used to assess PLMS, RLS, EDS, sleep habits, and various socio-behavioral factors.

**Results:** The prevalence of PLMS and RLS symptom were 903 (3.50%) and 1,311 (5.08%) each. 399 participants of 1,311 participants with RLS symptoms have PLMS. Odds ratios for the presence of symptoms of PLMS in participants with RLS symptom were followings: males (OR = 1.528; 95% CI: 1.145–2.040), usually/always witnessed apnea (OR, 3.006; 95% CI, 1.954–4.624), with increased internet addiction proneness (OR = 1.013; 95% CI: 1.001–1.025), sometimes/often consuming coffee (OR = 1.312; 95% CI:

1.015–1.695), EDS (OR = 0.826; 95% CI: 0.488–1.398), and insufficient sleep (OR = 1.143; 95% CI: 0.835–1.565).

**Conclusions:** Male, experiencing sleep apnea, consuming coffee, and being prone to internet addiction were identified as factors significantly associated with PLMS symptoms in RLS symptom. However, EDS and insufficient sleep were associated with PLMS symptom in absence of RLS symptom.

#### BEDTIME PROCRASTINATION AND CHRONOTYPE HAVE A DIFFERENTIAL IMPACT ON OBJECTIVELY MEASURED SLEEP AMONG ADOLESCENTS ON SCHOOL NIGHTS AND NON-SCHOOL NIGHTS

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**Introduction:** The tendency to delay sleep beyond an intended bedtime (bedtime procrastination; BTP) is prevalent and has been associated with negative sleep outcomes in survey studies (e.g. delayed sleep timing, shorter sleep duration, poorer sleep quality). Currently, there is a lack of studies verifying this relationship using objective sleep measures. Furthermore, it is unclear how the effects of BTP on delayed sleep timing can be distinguished from the effects of circadian preference i.e. chronotype. This study examined how BTP and chronotype relate to objectively measured sleep in an adolescent sample.

**Materials and Methods:** 121 adolescents aged 14–19 years completed a survey on sleep quality, chronotype, bedtime procrastination, and mental health. Subsequently, habitual sleep was objectively measured with actigraphy across 1–2 weeks. Associations between BTP, chronotype, and actigraphy-measured sleep were examined for school nights and non-school nights separately.

**Results:** Greater BTP was associated with poorer sleep quality, more symptoms of chronic sleep reduction, higher levels of daytime fatigue, as well as eveningness chronotype and higher anxiety/depression scores. On school nights, greater BTP predicted later bedtimes and shorter sleep duration. In contrast, on non-school nights, eveningness chronotype, but not BTP, predicted later bedtimes and wake times but not sleep duration.

**Conclusions:** BTP is associated with poorer subjective and objective sleep outcomes. Notably, BTP and chronotype have differential effects on sleep for school nights which are bounded by school schedules, and non-school nights which allow for alignment of sleep schedules with one's chronotype.

**Acknowledgements:** This work was supported by the National Medical Research Council Singapore (STAR19may-0001).

#### BENEFICIAL EFFECTS OF TELEMEDICINE-BASED FOLLOW UP IN SLEEP APNEA - A RANDOMIZED CONTROLLED MULTI-CENTER TRIAL

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**Introduction:** Clinically relevant obstructive sleep apnea (OSA) is treated with positive airway pressure ventilation (PAP). Telemedicine in PAP treatment is based on the transfer of data from the patient's PAP equipment to a central server. This enables continuous surveillance and remote therapy adjustment. The efficacy, clinical usefulness and patient acceptance of this technology is not sufficiently explored. The aim of the study was to evaluate the clinical utility and patient satisfaction of a telemedical solution in PAP follow-up.

**Materials and methods:** Randomized, controlled multi-center study conducted at four sleep clinics within the Region of West Sweden. Treatment naive OSA patients (N=409, 24.3% women, mean age  $59 \pm 12$  years, body mass index  $31.9 \pm 6$  kg/m<sup>2</sup>, number of respiratory events during sleep

41.5±21 apneas/h), recently started on PAP therapy using outpatient routines, were randomized to (A) standard follow up (203 patients with fixed follow-up procedures) or B) telemedicine-based follow-up (Air View, Resmed; 206 patients, continuous follow-up) for 3 months. Evaluated variables included PAP adherence at 3 months, treatment efficacy, patient-related outcome measures (ESS, SF36), and staff time. Between group difference were analysed with linear mixed regression models adjusting for baseline disease severity and anthropometrics as confounders. (ClinicalTrials.gov, VGFOUREG-663941).

**Results:** The study groups were comparable in terms of OSA severity and clinical data at baseline and were representative when compared with data from the national Swedish Sleep Apnea Registry ([www.SESAR.se](http://www.SESAR.se)). PAP adherence, the primary study outcome variable, was higher in the telemedicine compared to the control group (4.3±2.4 and 4.1±2.6 hours/night,  $P=0.01$ , respectively). In sensitivity analysis, hypertensive patients tended to benefit more from telemedicine surveillance compared to normotensives (+0.54 hours vs +0.085 hours,  $p=0.051$ ). Relevant mask leakage (>24 l/min) was lower in the telemedicine group ( $N=5.5\%$  versus  $N=11.3\%$ ,  $P=0.047$ , respectively). Residual apnea, daytime sleepiness, and staff time spent on follow-up were equivalent between groups. Health related quality of life (SF 36) improved substantially by CPAP treatment without significant differences between the follow-up procedures. Similarly, patient satisfaction with treatment and follow-up was high and equivalent between the groups.

**Conclusions:** Telemedical management of the initial follow up of PAP treatment was superior in terms of adherence and other treatment outcomes to conventional follow up at four sleep clinics using slightly different clinical routines. We found that hypertensive patients as a subgroup may particularly benefit from telemedicine based follow up. Specific clinical routines are required to establish this novel practice in sleep clinics and long term follow-up studies are warranted.

**Acknowledgements:** The study was supported by the Swedish Heart and Lung Foundation (2018-567) and the West Sweden Research Foundation (VGR-FoU227161).

#### BETTER SLEEP HEALTH AT BASELINE IS ASSOCIATED WITH GREATER WEIGHT LOSS AT 6 MONTHS IN A TECHNOLOGY-SUPPORTED BEHAVIORAL WEIGHT LOSS INTERVENTION TRIAL

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**Introduction:** Sleep is related to weight outcomes. Specifically, getting less than the recommended amount of sleep is associated with being overweight or obese. However, less is known about the role of sleep health on intentional weight loss. The purpose of this investigation was to examine the association between baseline sleep health and weight outcomes in a trial testing mHealth strategies.

**Materials and Methods:** This study was a secondary analysis of the SMARTER trial which tested the efficacy of two technology-supported behavioral interventions for weight loss: self-monitoring + feedback (SM + FB) vs self-monitoring without feedback (SM). At baseline, all participants received a one-on-one counseling session with a dietitian on behavioral changes to target weight loss. Participants used a smartphone app to self-monitor dietary intake, a Fitbit to track physical activity, and a digital Bluetooth-enabled scale for weight tracking. Individuals in the SM + FB group received three personalized messages per day, based on their self-monitoring entries. Messages addressed diet, physical activity, and weight, but not sleep. At baseline, four dimensions of sleep health were calculated from objective Fitbit data: regularity, timing, efficiency, and duration. Each dimension was given a score of 0 (poor) or 1 (good) based on current recommendations and summed for a sleep health score. Weight was

measured using a Tanita digital scale. Linear and logistic regression analyses were used to examine the associations between baseline sleep health, both individual sleep dimensions and sleep health score, and percent weight loss from baseline to 6 months controlling for treatment group, sex, race, and age.

**Results:** Of the 180 SMARTER trial participants with complete sleep and weight data, most were female (79.4%) and white (86.7%) with a mean ( $\pm$  SD) age of  $48.5 \pm 14.6$  years and body mass index of  $33.1 \pm 3.6$  kg/m<sup>2</sup>. The prevalence of good sleep dimensions was 47.2% for regularity (SD of wake time < 60 minutes), 63.9% for timing (sleep midpoint between 0200 and 0400), 96.7% for efficiency ( $\geq 85\%$ ) and 80.0% for duration (6 to 8 hours). Baseline mean sleep health score was  $2.9 \pm 0.9$  (range 1 - 4). At 6 months, mean weight loss was  $4.3\% \pm 5.4\%$ . In the adjusted model, good sleep duration was associated with 2% greater weight loss ( $b = 2.01$ , 95% CI: 0.03 - 4.07,  $p = .046$ ). No other individual sleep dimension was associated with weight loss. Higher sleep health scores were associated with greater weight loss ( $b = 1.12$ , 95% CI: 0.26 - 1.99,  $p = .011$ ). Participants with a sleep health score of 4 lost 3.4% more weight compared to those with a sleep health score of 1 after controlling for treatment group, sex, race, and age.

**Conclusions:** Better sleep health at baseline was associated with greater weight loss at 6 months. Interventions aimed at identifying and improving poor sleep health prior to the start of weight loss interventions may result in improved weight outcomes.

**Acknowledgements:** National Institutes of Health Grant #HL131583 (PI: LE Burke)

#### BILATERAL HYPOGLOSSAL NERVE STIMULATION IMPROVES MODERATE TO SEVERE OBSTRUCTIVE SLEEP APNOEA IN PARTICIPANTS WITH AND WITHOUT COMPLETE CONCENTRIC COLLAPSE (BETTER SLEEP)

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**Introduction:** Obstructive sleep apnea (OSA) is a chronic medical condition, characterised by recurrent episodes of partial and complete collapse of the upper airway during sleep. Untreated, OSA is associated with long-term health consequences. Recently, the use of hypoglossal nerve stimulation (HGNS) has shown promise in addressing OSA through dose-titratable electrical stimulation to reduce disease severity and provide symptom relief. However, current HGNS systems are contraindicated for OSA patients with complete concentric collapse (CCC) of the retropalatal airway. Therefore, a multicentre, prospective, open-label, two group study was designed to assess the safety and performance of a bilateral HGNS system in adult patients with moderate-to-severe OSA with and without CCC.

**Methods:** Participants with moderate-to-severe OSA and body mass index  $\leq 32$  kg/m<sup>2</sup> who failed, refused or did not tolerate positive airway pressure therapy were enrolled, provided they met additional inclusion/exclusion criteria. At screening, polysomnographies (PSGs) and drug induced sleep endoscopies (DISEs) were performed. DISE recordings were assessed for presence of CCC by an independent core laboratory. Eligible participants received a bilateral HGNS system (Genio®, Nyxoah SA, Belgium) via placement of an implantable stimulator through a single-incision under the chin. Devices were activated six weeks post-implant with monthly in-laboratory PSGs and therapy titrations performed up to the primary endpoint visit.

Safety endpoint included the incidence of device-related serious adverse events (SAEs) from consent to 6 months post-implant. Safety events were adjudicated by an independent clinical events committee (CEC).

Primary and exploratory efficacy endpoints were defined as a mean reduction in AHI (4% oxygen desaturation, AHI4) at 6 months post-implant for the entire cohort and for the CCC subgroup, respectively, as determined

by an independent statistician. Scoring followed the American Academy of Sleep Medicine 2014 acceptable guidelines. Secondary endpoints included the oxygen desaturation index scored at 4% desaturation (ODI4). Statistical significance was assessed at  $p < 0.05$  using paired t-tests.

**Results:** Forty-two (31/11-Males/Females, 24/18-non-CCC/CCC) of the 45 enrolled participants received an implant at 8 research sites in Australia. Results from the full analysis cohort, defined as all implanted participants, are presented.

No device-related SAEs up to 6 months post-implant were reported by the site investigators. The CEC identified two device-related SAEs (device migration, infection).

Mean AHI4 values decreased significantly from  $27.5 \pm 11.9$ ,  $28.9 \pm 11.9$  and  $26.5 \pm 12.1$  to  $16.9 \pm 16.0$ ,  $18.9 \pm 17.6$  and  $15.5 \pm 15.0$  events/hr at 6 months post-implant in the entire cohort, CCC and non-CCC cohorts, respectively, with mean improvements of  $10.7 \pm 11.6$ ,  $10.1 \pm 12.3$  and  $11.0 \pm 11.3$  events/hr ( $p \leq 0.001$ ). The ODI4 also decreased significantly from  $21.9 \pm 12.1$ ,  $23.9 \pm 12.5$  and  $20.5 \pm 11.9$  events/hr at baseline to  $14.1 \pm 13.6$ ,  $16.2 \pm 14.9$  and  $12.6 \pm 12.7$  events/hr at 6 months post-implant in the entire cohort, CCC and non-CCC cohorts, respectively, with mean improvements of  $7.9 \pm 10.6$ ,  $7.7 \pm 12.1$  and  $7.9 \pm 9.5$  events/hr ( $p \leq 0.01$ ).

**Conclusions:** Statistically significant reductions in AHI4 and ODI4 were observed in the full cohort of participants. While not designed to compare sub-cohorts, the study showed similar improvements in AHI4 and ODI4 for both CCC and non-CCC participants.

#### CARDIORESPIRATORY FITNESS IS ASSOCIATED WITH PHASE ADVANCED CIRCADIAN RHYTHMS IN HEALTHY ADOLESCENTS

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**Introduction:** Adolescence is often accompanied by delayed sleep/wake patterns and circadian activity rhythms (CAR). Regular participation in exercise facilitates entrainment of circadian rhythms and has positive impacts on sleep and overall health. However, the relationship between cardiorespiratory fitness (CRF), an important marker of health, and circadian rhythms has not been explored. The present study aimed to examine the associations between CRF as measured by peak  $VO_2$  with behavioral and endogenous circadian rhythm variables in healthy adolescents.

**Materials and Methods:** Eighteen adolescents (10 females) aged 11-17 years ( $M_{age} = 14.6 \pm 2.3$  years) participated during summer vacation. The study involved two laboratory visits bracketing an ambulatory assessment. Peak  $VO_2$  was assessed during visit 1 following standardized cardiopulmonary exercise testing (CPET) protocol by using a ramp-type progressive cycle ergometry with a breath-by-breath measurement of gas exchange. Sleep/wake patterns and CAR were estimated with 7-14 days of actigraphy between the two laboratory visits. CAR characteristics, an indication of behavioral circadian rhythmicity, were parameterized using cosinor (i.e., acrophase, amplitude and mesor) and a graphical approach. Graphical approach yields UP time (time of activity rise in the morning), DOWN time (time of activity decrease in the evening), and last activity peak (LAP) time (time of the last peak of daytime activity prior to decrease of activity in the evening time). Salivary melatonin was sampled hourly during visit 2 at a sleep laboratory to determine dim light melatonin onset (DLMO) phase, a marker of endogenous circadian phase. Bivariate correlations adjusting for sex, pubertal status, and amount of engagement in physical activity were performed to evaluate the associations between CRF with rhythm variables. Mixed models using longitudinal actigraphic activity data that were aggregated hour-by-hour over a single 24-hour period were conducted to examine the association between CRF and actigraphy-derived circadian activity patterns.

**Results:** Greater peak  $VO_2$  was significantly associated with earlier mid-sleep time ( $r = -0.698$ ,  $p = 0.004$ ) and circadian phase parameters, including acrophase ( $r = -0.631$ ,  $p = 0.012$ ), UP time ( $r = -0.603$ ,  $p = 0.017$ ), DOWN time ( $r = -0.548$ ,  $p = 0.035$ ), and LAP time ( $r = -0.531$ ,  $p = 0.042$ ). Peak  $VO_2$  trended towards an association with earlier DLMO phase ( $r = -0.533$ ,  $p = 0.060$ ),

exhibiting a large effect size. All these associations were independent of sex, pubertal status, and amount of engagement in physical activity. We also observed a significant interaction between peak  $VO_2$  and hour-by-hour circadian activity patterns [ $F(23, 368) = 3.16$ ,  $p < 0.000$ ], with strongest interactions noted around morning waking hours (6:00 – 10:00).

**Conclusions:** These data amongst healthy adolescents suggests that better CRF is associated with favorable behavioral manifestations of circadian rhythms, i.e., earlier sleep/wake patterns and a more phase advanced CAR. Future studies are needed to investigate the longitudinal effects of the interaction between CRF and advanced rhythms on health outcomes.

**Acknowledgements:** NCATS grant #UL1TR001414 & PERC Systems Biology Fund

#### CHANGES IN SLEEP BEFORE AND DURING COVID-19 IN URBAN AMERICAN INDIAN/ ALASKA NATIVE ADOLESCENTS

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**Introduction:** COVID-19 has profoundly affected sleep, although little research has focused on high-risk populations for poor sleep health, including American Indian/ Alaska Native (AI/AN) adolescents.

**Materials and Methods:** This is the first longitudinal study to examine changes in sleep with surveys completed before the pandemic and during the early months of COVID-19 in a sample of urban AI/AN adolescents ( $N = 118$ ; mean age = 14 years at baseline; 63% female). We use a mixed-methods approach to explore how COVID-19 affected urban AI/AN adolescents' sleep, daily routines, and interactions with family and culture. Quantitative analysis examined whether pandemic related sleep changes were significant, and explored potential moderators of COVID-19's effect on sleep, including family and community cohesion and engagement in traditional practices.

**Results:** Findings demonstrate changes in sleep, including increases in sleep duration, delays in bedtimes and waketimes, and increases in sleep-wake disturbances ( $p$ 's  $< .001$ ). Higher levels of family cohesion and higher levels of engagement in traditional practices moderated pandemic-related increases in weekday sleep duration. Qualitative analyses revealed changes in adolescents' sleep and daily behaviors, as well as strategies adolescents used to cope with pandemic-related disruptions in sleep and routines.

**Conclusions:** We found evidence for both positive and negative changes in sleep during COVID-19 stay-at-home orders, including simultaneous increases in sleep duration and sleep-wake disturbances. Results highlight the importance of considering multi-level influences on adolescent sleep, such as early school start times, family dynamics, and cultural factors. A multi-level approach may help guide prevention and intervention efforts to improve adolescent sleep health.

**Acknowledgements:** This work was supported by the National Center on Minority Health and Health Disparities under Grant R01MD012190 (MPIs: Troxel, D'Amico, Dickerson).

#### CHARACTERING AIRWAY COLLAPSE FROM PSG TRAINED ON SNORING SOUND

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**Introduction:** Characterizing the pattern of upper airway collapse can help direct treatment for patients with obstructive sleep apnea (OSA). One approach to visualizing the dynamic collapse of airway is drug-induced sleep endoscopy (DISE). While it has been shown to direct alternative treatment to positive airway pressure (PAP) therapy, the intrusive procedure is not practical for all patients nor is it conducted in natural sleep. Ideally, there is a way to predict sites of airway collapse based on readily available parameters from polysomnography. Combining DISE and snoring sound, we present early findings from our machine learning algorithm correlating snoring sound with sites of airway collapse.

**Materials and methods:** The dataset used in this study was obtained from Taipei Tzu-Chi Hospital. For model training and testing, we primarily used a dataset consisting of 23 subjects with mean AHI: 40.18 and mean BMI: 27.99. The snores of 19 men and 4 women OSA patients (mean age: 40.5 years old) who were diagnosed via full-night polysomnography (PSG). All 23 subjects received DISE to evaluate their upper airways and whose upper airway obstruction sites were classified under the VOTE classification system (Vellum, Oropharynx, Tongue-base, and Epiglottis). The sound collected simultaneously during the procedure was further matched with the video and annotated under the VOTE classification system. Based on the video recordings, the locations of sound generation were categorized as "V", "O", "T", "E", "VO", "VT", "OT". In total, 2256 seconds, 2137 seconds, 801 seconds, and 63 seconds of recordings were collected for the obstruction areas of vellum, oropharynx, tongue-base, and epiglottis, respectively. We compared three machine learning models including the support vector machine (SVM) paired with the bag of audio words (BoAW), long-short term memory (LSTM), and ResNet50 trained with the spectrogram of the snores.

**Results:** The ResNet50 model achieved a weighted average recall (WAR) of 86% and was therefore our best-performing model. The SVM, paired with the bag of audio words (BoAW) demonstrated similar results, with a WAR of 81%. The LSTM model showed the lowest performance with a 78% WAR.

**Conclusions:** Our SVM model performs significantly better on categories with more extensive data (i.e., vellum and oropharynx) than on the less representative category (epiglottis). The SVM-based model is offered as a visualization tool online at <https://disa.csie.ntu.edu.tw:7759/> to enable doctors to "see" the airway collapse pattern of snoring sounds from either PSG or DISE. The visualization tool could be helpful for an audio-based diagnosis of OSA patients, which could significantly improve the management of this pathology.

**Acknowledgments:** The authors thank the All Vista Healthcare Center, Ministry of Science and Technology, Taiwan for the support.

#### COMPLIANCE WITH NOCTURNAL CONTINUOUS POSITIVE AIRWAY PRESSURE (CPAP) THERAPY IN MODERATE TO SEVERE OBSTRUCTIVE SLEEP APNEA (OSA), AN OBSERVATIONAL STUDY

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**Introduction** Therapy with nocturnal continuous positive airway pressure (CPAP) is the "Gold Standard" treatment for Obstructive Sleep Apnea Syndrome (OSAS), a breathing disorder during sleep. OSAS has serious adverse health effects, resulting from impaired breathing, noisy snoring, poor quality of sleep, and cardio-cerebrovascular sequelae. When used appropriately, CPAP treatment is highly effective in normalizing breathing and sleep, improving symptoms and reducing the risk of adverse events. However, patients do not necessarily accept or respect the treatment.

**Aim of the study:** To evaluate which anthropometric parameter, anamnestic data and tests, which investigate sleep disorders, could be predictive of adherence to therapy.

**Materials and methods:** From 2017 to 2021, 200 patients with moderate to severe OSAS who were eligible for therapy with CPAP were referred to the outpatient clinic for sleep disorders of the UOC of Geriatrics of the

Policlinico Umberto I in Rome. 51 patients were not eligible for the study because some data were missing; 149 patients were eligible: 64 of them were adherent to the therapy while 85 patients were non-adherent to the therapy, therefore used as a control group.

The complete medical history was collected for all patients, questionnaires were administered to investigate daytime sleepiness, snoring and sleep quality. In addition, for each of them, anthropometric parameters such as weight, height and body mass index (BMI) were measured.

**Results:** From our study it emerged that the only characteristics capable of approaching the appropriate statistical weight in predicting CPAP compliance were age and smoking habit, while other parameters, such as the patient's subjective symptoms than in other studies they proved valid, they did not lead to the same result in our work.

**Conclusion:** the need to increase adherence to treatment and the results of this study suggest focusing interventions on psychological and behavioral factors.

#### CORRELATES OF SLEEP DISTURBANCE AMONG PEOPLES LIVING IN JEJU ISLAND, KOREA

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**Introduction:** Individuals dissatisfied with their sleep are more likely to seek medical help, to report daytime impairment functioning, and to be diagnosed with a sleep or a mental disorder. However, none of the previous studies has examined the relative importance of the various factors correlated to sleep disturbance. This study aims to investigate the prevalence of sleep disturbance and to find the associated factors contributing to sleep disturbance in the general population of Jeju Island, the largest island in the part of South Korea.

**Materials and Methods:** Seven hundred thirteen people who consented to participated in this study and completed questionnaires were analyzed. The questionnaires were used to assess the participants' sleep satisfaction and general characteristics (sex, age, marital status, occupation, monthly household income, self-perceived health, smoking, drinking status, etc.); in addition, for the clinical evaluation, depression was assessed through the Center for Epidemiologic Studies Depression Scale (CES-D) and social support through Functional Social Support Questionnaire (FSSQ). CES-D cutoff score of 21 was used to define depressive disorder. The collected data were analyzed using t-test, chi-square test and logistic regression analysis according to data properties and the purpose of analysis.

**Results:** In 713 subjects, the mean age was 58.6±17.3 years, and overall, 24.9% of the subjects reported being sleep disturbance. The prevalence of sleep disturbance was higher in women than in men (60.9% vs 39.1%, crude OR=1.49, 95% CI=1.05-2.12, p=0.028) and increased with age (crude OR=1.03, 95% CI=1.02-1.04, p<0.001). The multiple logistic regression analysis demonstrated that the associated factors for the sleep disturbance were age (adjusted OR=1.04, 95% CI=1.02-1.07, p=0.001), smoking (adjusted OR=2.54, 95% CI=1.33-4.86, p=0.005) and depressive symptoms (adjusted OR=6.08, 95% CI=3.47-10.64, p<0.001).

**Conclusions:** Sleep disturbance was related to increasing age, smoking, and more depressive symptoms. The sleep symptoms are often unresolved by treatment, and confer a greater risk of depression. Previous epidemiological studies have pointed out that sleep problem is a risk factor for depression. There is, therefore, a need for more successful management of sleep disturbance, in order to improve quality of life and reduce an important factor in depression.

**Acknowledgments:** None

#### CORRELATION BETWEEN PHYSICAL ACTIVITY, SLEEP COMPONENTS

## AND QUALITY : IN THE CONTEXT OF TYPE AND INTENSITY : A CROSS-SECTIONAL STUDY AMONG MEDICAL STUDENTS

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**Introduction:** Physical activity during the day is composed of different domains, specifically work related, transportation, and recreation, physical activity. We aimed at studying the correlation between energy expenditure and the corresponding metabolic equivalent of task and sleep in the context of type of physical activity, general level of activity as to be low, moderate and vigorous and the intensity of activity either moderate or vigorous physical activity.

**Materials and Methods:** A cross-sectional study, participants were n= 273 enrolled from al-Neelain university faculty of medicine between January and April 2021 we used the global physical activity questionnaire to measure standard metabolic equivalent of task for participants for vigorous and moderate work MET, Transportation MET, Vigorous and moderate leisure MET, and sedentary time. we used Pittsburgh sleep quality index to assess different components of sleep (subjective sleep quality, sleep latency, habitual sleep efficiency, sleep duration, sleep disturbances, use of medications, daytime dysfunction) and sleep quality. Daytime sleepiness was further assessed with (epworth sleepiness scale) and psychological distress with (kessler 10-item questionnaire).

**Results:** The Mean of Total-MET was (3533.36min/week) predominantly moderated work-MET (33%). Poor sleepers prevalence was high (62%). Moreover there was significant difference between good and poor sleepers in moderate work MET mean (876.36,1334.2 min/week) (P<0.01), respectively. There was a significant difference between categories of activity in sleep duration (P<0.05) being higher for low activity group(7.2h) more than high and moderate categories (6.9h-6.3h) respectively. The use of sleep medications was significantly higher among the higher level of activity group (P<0.05) compared to low activity group. There was significant positive correlations between moderate work MET and roughly all sleep components namely (sleep latency, sleep disturbances, use of medications, daytime dysfunction) rho=(0.196, 0.182, 0.132, 0.149)(P<0.01, P<0.01, P<0.05, P<0.05) respectively and sleep quality rho=(. 211 P<0.001). Vigorous-leisure MET positively correlated with increased sleep latency rho=(0.134 P<0.01). Total MET correlated with increased sleep latency, use of medications, and poor sleep quality in general. (0.134, 0.124, 0.133) (P<0.05). Psychological distress significantly correlated with both moderate work MET (0.135)(P<0.05) and increased sleep latency (0.229 P<0.001) severe daytime sleepiness (0.295 P<0.001)and overall poor Sleep quality (0.330 P<0.001).

**Conclusions:** Our results show that poor sleep quality is primarily influenced by the type and intensity of physical activity. Eliciting a dose-response effect of different domains, being deleterious for work related physical activity as work MET is of too low intensity or too long duration for maintaining or improving cardiorespiratory fitness and cardiovascular health subsequently imposing its deleterious effect. So in order to improve quality of life for university students, special strategies and policies that leverage 'good sleep' quality are warranted by limiting work related physical activity and adding on well structured early morning exercises for University students thus improving cardiorespiratory fitness and subsequently sleep.

**Acknowledgements:** With all gratefulness and compassion I would like to thank Allah for blessing me with the strength to finish my project, then i would like to show my gratitude for my parents and family as they helped me throughout my journey.

## COVID-19 PANDEMIC'S IMPACT ON THE STUDENT'S SLEEP PATTERNS AT THE UNIVERSITY OF GEORGIA

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**Introduction:** It is shown that international students, isolated from families and native culture, experience more stress and sleep difficulties.

Therefore, it could be expected that COVID-19 pandemic induced sleep disorders and corresponding mental problems among international students would be stronger. The present study aimed to assess sleep quality among the international (Int. Stud.) and Georgian students (Geo. Stud) of the University of Georgia (UG) during the COVID-19 pandemic.

**Materials and Methods:** A cross-sectional online survey was conducted among the Int. Stud. and Geo. Stud. at the UG, during the COVID-19 fifth wave from October 24th to November 3rd, 2021. The survey was administered by using a Google form hosted by the University of Georgia. The survey collected the data of age and sex of the students. Respondents were asked to fill out the Pittsburgh Sleep Quality Index scale (PSQI), a widely used questionnaire that assesses 7 components of DETERIORATING SLEEP WAKE HEALTH PATTERNS AMONG sleep quality: as subjective sleep quality (SSQ), sleep latency (SL), sleep duration (SD), habitual sleep efficiency (HSE), sleep disturbances (SDs), use of sleeping medication (USM), and daytime dysfunction (DDS).

**Results:** Out of the 500 participants, 360 students were Georgian and 140 were international. The number of female participants were more in both groups. The Georgian participants under 20 years of age (50.8%) were more than the rest of the age categories, which were 21-30 (48.1%) and more than 31 years old (1.1%). Among Int. Stud. the group of age between 21 and 30 (74.3%) was more than the rest, as <20 years (22.1%) and >31 years (3.6%).

The distribution of PSQI components among UG Students: The obtained results showed that Geo.Stud (48.6%) according to PSQI, reported poor subjective sleep quality, while Int. Stud. had less complaints (only 31.4% of the participants). Although in 53.6% of Int. Stud., SL was longer (versus 44.2% of Geo. Stud.). Sleep duration more than 7 hours was persistent for 65.8% of Geo. Stud. and for 50.7% of Int. Stud. While sleep disturbances in 27.2% of Geo. Stud were less versus 36.4% of the Int. Stud. The component of DDS (44.7%) among Geo.Stud. and in the fewer number of participants of Int.Stud. was less substantial (24.3%). Most Geo.Stud. showed low SDs (72.5%) and for the Int.Stud. this parameter was even lower (63.6%). Only few students in both Georgian (8.1%) and international (6.4%) groups reported using medications. 51.9% of Geo.Stud. had indicated poor sleep and fewer participants of Int.Stud. (40.7%) noted the same. Poor SSQ was high among the females of both Georgian and International students. There was significance relation between SSQ and age among Georgian students (p<0.05).

**Conclusions:** Conducted survey revealed that the poor sleep quality and the higher sleep disturbances have a prevalence among Int.Stud. Only fewer participants of the both groups use of sleeping medication. Although the poor sleep quality was high among females of both Georgian and International students. The participants, especially among Geo.stud., under 20 years old were more vulnerable.

**Acknowledgements:** This study was supported by the University of Georgia, Tbilisi

## COVID-19-RELATED SLEEP QUALITY, STRESS, HEALTH BEHAVIORS AND MENTAL HEALTH SYMPTOMS AMONG ISRAELI AND U.S. ADULTS

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**Introduction:** Social isolation and changes in daily routine prompted by the COVID-19 pandemic, led to adverse changes in health behaviors, such as physical activity, smoking, alcohol use, diet habits and sleep quality. The current study had two hypotheses:

1) Participants with more COVID-related stress will report significantly more adjustment difficulties, depression and anxiety symptoms, and poorer sleep quality; and 2) Sleep quality will mediate the associations between stress and depression and anxiety symptoms.

**Material and Method:** The current study combined data from two large, diverse samples of adults collected via online platforms in the early stages of the pandemic in the United States (N=572;) and Israel (N=1,969). Participants completed measures of COVID-related stress, anxiety and depression using the DASS-21, adjustment difficulties using the Ultra Brief

ADNM-4, sleep quality using the PSQI, and self-reported unhealthy behaviors including changes in sleep, exercise and eating habits, and use of tobacco and alcohol.

**Results:** Participants from Israel were significantly older (40 vs. 37yrs); more likely to be female (55% vs 45%); and less likely to be employed (74% vs. 91%), and married (63% vs. 76%). American participants reported poorer sleep quality than Israelis on total PSQI ( $9\pm 3.9$  vs.  $4.9\pm 3.3$ ), as well as higher depression, anxiety, and adjustment difficulties due to COVID-19. Overall, a significant portion of respondents reported mental health problems, including 15% moderate to severe levels of depression symptoms, 20% moderate to severe levels of anxiety symptoms, and more than half (54.5%) difficulty adjusting to the pandemic. With regard to sleep health, 56% reported a sleep disturbance and 70% reported engaging in at least two of five unhealthy behaviors. Multiple regression was used to examine COVID-19-related health behaviors as a predictor of adjustment problems, depression, anxiety, stress, and poorer sleep quality, controlling for demographic variables (including site). Participants who reported more unhealthy behaviors experienced significantly poorer adjustment, more depression, anxiety, and COVID-19-related stress, and poorer sleep quality. In addition, a significant portion of the association between stress and psychological symptoms was accounted for by sleep quality in both samples.

**Conclusion:** It is clear from this early COVID-19 study that sleep quality mediated associations between COVID-related stressors and mental health outcomes on both depression, anxiety, and between health behaviors and mental health outcomes. This finding speaks to the central role that subjective sleep quality plays in promoting resilience in the face of stress or adversity.

#### DETERIORATING SLEEP WAKE HEALTH PATTERNS AMONG NEW AMERICAN RESIDENT PHYSICIANS AT ORIENTATION AND AT 6 MONTHS OF TRAINING

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**Introduction:** Sleep-wake disorders (SWD) among medical professionals are common. They are at high risk for the development of SWD during residency training. In response to this high risk, the ACGME mandates fatigue and sleeplessness counseling and awareness advocacy. During Geisinger's physician residency orientation, there is a standard sleep and fatigue educational lecture, but no other proactive interventions provided. To better understand the prevalence of sleep issues among residents and determine the best mitigation strategies for fatigue and sleepiness, Geisinger residents were invited to complete a standard sleep survey prior to the start of orientation and at 6 months. Insufficient sleep was determined by self-reported number of hours of sleep and self-reported difficulties with sleep initiation, as well as maintenance of early awakenings. Daytime dysfunction related to sleep difficulties are characterized by self-reported tiredness, fatigue, or sleepiness during the day and sleep difficulties impacting their daytime performance at least once a week.

**Materials and Methods:** Since the start of the 2019-2020 academic year, all incoming residents could complete 2 sleep screening tools, Sleep Disorders Symptoms Checklist 25 (SDS-CL-25) and the Alliance Sleep Questionnaire (ASQ) at orientation and 6 months. The residents were emailed an invitation to complete these surveys online. SDS-CL-25 is a comprehensive brief 25-item sleep survey that can screen for 13 different sleep disorders and be completed in 3-5 minutes. ASQ is a detailed online questionnaire that can provide specific characterization of SWD. This data is based on the responses acquired through the SDS-CL-25. Since 2019, 333 residents completed SDS-CL-25 surveys and 93 residents completed follow up surveys.

**Results:** Young adults should achieve 7-9 hours of sleep per night. The results of this survey demonstrated that at orientation, 12.2% had less than

7 hours of sleep per night, 21% had 7 hours of sleep, 33.8% had 7.5 to 9 hours of sleep, and 2% had greater than 9 hours of sleep (31% did not respond). When repeated, there was a significant trend towards increased sleeplessness with 19.4% having less than 7 hours of sleep per night and 26.9% having 7 hours of sleep. One quarter to almost half of the respondents described difficulties falling asleep, staying asleep or waking earlier than desired. At baseline, 35.6% described feeling that their sleep problems interfered with daytime activities. This percentage grew to 44% when re-evaluated 6 months later. An additional concerning trend is that at baseline, 19.5% of respondents rated themselves as being tired, fatigued, or sleepy during the day and 34.5% at 6 months into training. At baseline, 11.6% of respondents described that their sleep difficulties impacted daytime performance at least once a week, which grew to 21.4% at 6 months. **Conclusions:** This data illustrates a concerning pattern of deterioration in sleep and increase in daytime dysfunction during residency. This program may be useful to expand across residency programs nationally to promote consistent sleep screening and provide opportunity for behavior change to improve sleep health and daytime function and performance.

#### DETERMINANTS OF INFANT SLEEP HEALTH: BEDTIME BEHAVIORAL FACTORS, SOCIOECONOMIC STATUS AND PARENTAL PERCEIVED STRESS BUT NOT INFANT RACE/ETHNICITY ARE ASSOCIATED WITH INFANT SLEEP.

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**Introduction:** The burden of poor sleep health is not experienced equally across the U.S. population, starting as early as infancy, with parents of racial/ethnic minoritized communities reporting worse sleep for their children compared to parents of White children. Several factors have been hypothesized to contribute to these disparities, including parental mental health, sleep environment, bedtime routines, and socioeconomic status (SES). A few studies have investigated racial/ethnic disparities accounting for these factors, but often their uneven distribution across racial/ethnic groups has limited in depth understanding. This warrants further investigation since sleep health negatively affects multiple health domains and could contribute to racial/ethnic health disparities. In this study, we examine ethnic sleep differences in a sample of non-Hispanic White (NHW) and Hispanic infants, accounting for SES, parental stress, and parent-infant bedtime behavioral factors (PIBBF).

**Materials and Methods:** Ethical approval was obtained by the New York State Psychiatric Institute and Advarra Institutional Review Boards. Parents of US infants were recruited from the customer base of Nanit sleep monitoring system (77.7% mothers, 21.9% fathers) and were asked to complete on REDCap the Brief Infant Sleep Questionnaire-Revised, Perceived Stress Scale and demographic questions. Infant sleep metrics were captured via Nanit videosomnography (nights recorded  $11.8\pm 2.2$ ). We performed linear regressions with infant sleep duration, quality and night awakenings as dependent variables and ethnicity as an independent variable. Infant age, how the child falls asleep, parental education and perceived stress were included as covariates, while sleeping environment and parental confidence in sleep management were not included due to minimal variability.

**Results:** The sample includes 427 NHW and 62 Hispanic infants (age  $9.1\pm 1.8$  months, 49.9% male). PIBBF: 31% of the infants fell asleep while being held/with an adult in the room vs 69% alone in the room. 90% of the parents reported feeling very/somewhat confident in managing their infant's sleep. 98% of the infants slept in their own crib/bed.

Parental education: 5% High school/secondary, 50% College University, 45% Graduate.

Perceived stress score was  $14.4\pm 6.4$ .

In none of these domains were there differences by ethnicity.

Infant sleep duration was  $10.5\pm 1.1$  hr, it increased with infant's age ( $\beta=0.06\pm 0.03, p=0.02$ ), was shorter for infants who fell asleep while being held/with an adult in the room ( $\beta=-1.07\pm 0.1, p<0.001$ ), and if parental perceived stress was higher ( $\beta=-0.02\pm 0.008, p=0.02$ ).

Infant sleep quality was  $92\pm 0.06$ , it increased with infant's age ( $\beta=0.06\pm 0.03, p=0.02$ ) and with parental education (college

$\beta=0.27\pm 0.01, p=0.04$ ; graduate  $\beta=0.03\pm 0.01, p=0.02$ ), and was lower for infants who fell asleep while being held/with an adult in the room ( $\beta=-0.03\pm 0.006, p<0.001$ ).

Number of night awakenings was  $3.1\pm 1.4$  and decreased with the infant's age ( $\beta=-0.3\pm 0.04, p<0.001$ ).

There were no significant differences in any sleep domain by ethnicity.

**Conclusions:** These results highlight that in this relatively high SES sample, with no differences by ethnicity in SES, parental stress, sleep environment and PIBBF, ethnic disparities in infant sleep were not observed. This supports the hypothesis that socioeconomic barriers and structural influences found in the general population, particularly in racially/ethnically minoritized communities, may interfere with families' ability to optimally support infants' sleep health.

#### DETERMINANTS OF UNHEALTHY SLEEP PRACTICES AMONG BELGIAN UNIVERSITY STUDENTS: AN APPLICATION OF THE THEORY OF PLANNED BEHAVIOR

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**Introduction:** University students often show unhealthy sleep practices, including irregular sleep habits, daytime napping, alcohol use, or using phone before going to sleep. Poor sleep hygiene is related to a variety of ill-health effects, including metabolism dysregulation, cardiovascular problems, memory and attention problems and poor academic performance. However, research on sleep practices mostly focuses on the consequences of poor sleep behavior, and seldom addresses its determinants. The purpose of this study was to test if the constructs of the Theory of Planned Behavior (TPB) predicted unhealthy sleep behaviors of Belgian university students.

**Materials and Methods:** An online questionnaire was used to assess the frequency of irregular sleep times, daytime napping, alcohol use before sleep, and engaging in activities that keep awake such as being on the internet or video watching before bedtime, as well as the attitudes, perceived norms, perceived control and intentions towards these behaviors, amongst 1006 university students enrolled at a French-speaking university (70% females). The sample was also divided according to the type of study (i.e. humanities, health sciences or sciences and technology), the year of study (i.e. bachelor level, master level or other such as PhD students or complementary master students) and type of residence (i.e. living with parents, shared housing, studio apartment or other). Principal Component analysis (PCA) and internal consistency analysis (Cronbach alpha) was used to establish the validity and reliability of the scales representing the dimensions of the TCP for each behavior.

**Results:** Multiple regression analyses showed that perceived advantages and disadvantages, perceived norms and perceived control significantly predicted 21% of the intention to avoid irregular sleep patterns, 74% of the intention to take daytime naps, 27% of the intention to engage in activities that keep awake, and 45% of the intention to consume alcohol before bedtime. Intentions and perceived behavioral significantly predicted self-reported irregular sleeping times ( $R^2=.15$ ), daytime napping ( $R^2=.36$ ), performing activities keeping awake before bedtime ( $R^2=.23$ ), and alcohol use before bedtime ( $R^2=.51$ ). Multivariate analysis of variance revealed significant for the four sleep hygiene behaviors with regard to gender, study type and type of residence.

**Conclusions:** The TPB dimensions provide a useful framework to predict healthy sleep intentions and behaviors of university students. Their role can be taken into account when developing healthy sleep promotion campaigns for students. Moreover, results from the multivariate analysis providing alternative perspectives for new interventions.

**Acknowledgements:** We would like to thank Observatoire de la vie Étudiante (OVE) from UCLouvain for their help in disseminating our survey to students and for their support throughout the process.

#### DIAGNOSTIC VALIDITY OF NOCTURNAL RECORDING OF OXYGEN

#### SATURATION COMPARED WITH POLYSOMNOGRAPHY IN PATIENTS WITH SUSPECTED OBSTRUCTIVE SLEEP APNOEA

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**Introduction:** To determine the correlation of nocturnal pulse oximetry compared with respiratory events obtained in polysomnography in the presence of clinical suspicion of obstructive sleep apnea (OSA).

**Materials and Methods:** Prospective study of diagnostic test comparison performed in the sleep disorders respiratory unit of a University Hospital. Patients who consecutively met the inclusion criteria and none of the exclusion criteria were included. The inclusion criteria were: (1) clinical suspicion of OSA; (2) Age between 18 and 75 years; (3). Signing of the informed consent. The exclusion criteria were: (1) Thoracogenic or neuromuscular disease; (2) Chronic respiratory failure; (3) Psychogenic disorder; (4) Insomnia. All patients underwent simultaneous pulse oximetry and polysomnography.

**Methods.** An overnight polysomnography was performed. The usual neurological and respiratory signs were recorded. In these last: apnea-hypopnea index (AHI), average and minimum SpO<sub>2</sub> reached during sleep, percentage of sleep time with SpO<sub>2</sub> < 90% (T90), oxygen desaturation index > 3% ODI3) and > 4% (ODI4) defined as the number of decreases per hour of sleep in SpO<sub>2</sub> > 3% or at 4%, respectively. OSA was ruled out if polysomnography showed an AHI ≤ 5 and was diagnostic if AHI > 5. Pulse oximetry results (Konika-Minolta Pulsox-300i) were analyzed according to recording time. Pearson's statistic was applied to determine the correlation between AHI and SpO<sub>2</sub> results in pulse oximetry. To evaluate which nocturnal SpO<sub>2</sub> variables have greater diagnostic accuracy in relation to an AHI ≥ 5 and to an AHI ≥ 30 obtained in polysomnography, a ROC (receiver operator characteristic) curve was constructed.

**Results:** A total of 123 patients were studied, 91.1% diagnosed with OSA (44.7% with severe OSA). Significant correlation ( $p < 0.001$ ) was observed between AHI and T90 ( $r = 0.658$ ), ODI3 ( $r = 0.925$ ), ODI4 (0.897). For these variables, the area under the curve (AUC) was calculated observing that the highest diagnostic performance (AHI > 5) was for ODI3 with a value in the AUC = 0.962 (95% CI = 0.924-1) and also for the diagnosis of severe OSA (AHI ≥ 30) with an AUC = 0.971 (95% CI = 0.941-1).

**Conclusions:** There is a good correlation between the results of nocturnal pulse oximetry and polysomnography. ODI3 is more accurate for diagnosis and identification of severe OSA. Nocturnal pulse oximetry is a valid alternative to prioritize the diagnosis and treatment of patients with OSA

#### Acknowledgements:

#### DO CHANGES IN SLEEP MICROENVIRONMENT TEMPERATURES INFLUENCE SLEEP QUALITY IN ADULTS?

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**Introduction:** Human body temperature follows a circadian rhythm with a 0.8-1°C oscillation between a diurnal maximum near the end of the day and nocturnal minimum in the early morning hours. Body temperature decreases as humans enter deeper stages of sleep; the greatest rate of decline is associated with NREM, where the body responds to temperature changes through responses, physiological (eg. sweating, shivering) and behavioural (eg. changing body position). Sleep is most sensitive to disruption through either heat or cold exposure during REM sleep when thermoregulatory functions are the most limited. This review investigated the current understanding of the effects of temperature manipulations of the sleep microenvironment on sleep quality.

**Materials and Methods:** A systematic literature search screened articles for inclusion criteria, yielding a total of 80 articles for review.

**Results:** We found that raising skin temperature prior to sleep onset has

the most evidence for improving sleep quality, followed by cooling skin temperatures in the early stages of sleep and decreasing ambient temperatures. The limited number of inclusion studies that involved temperature modifications and measured outcomes, reflects the need for more research in this domain, nevertheless, data analysis yielded valuable information.

**Conclusions:** Moving forward, a multi-disciplinary approach considering the multitude of factors influencing the sleep microenvironment, will enable innovative designs to counter the poor sleep epidemic.

**Acknowledgements:** There are no conflicts of interest to report. All authors have completed the International Committee of Medical Journal Editors Conflicts of Interest Form. This study received no funding.

### DOES AN ACUTE BOUT OF BREATHING AWARENESS MEDITATION IMPROVE BREATHING STABILITY CORRELATED WITH REGULATORY PREFRONTAL CORTEX NEURAL ACTIVITY IN OBSTRUCTIVE SLEEP APNEA?

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**Introduction:** Obstructive sleep apnea (OSA) is accompanied by breathing instability, reflected as higher breathing rate (BR) variability (BRV) compared to healthy controls during wakefulness. Prefrontal cortical (PFC) dysfunction is common in OSA. We predict that an acute bout of BA meditation will reduce BRV, stabilizing the breathing pattern in OSA. Furthermore, we hypothesized that the BRV change will correlate with functional changes in medial PFC regulatory neural activity differently in OSA compared to healthy controls.

**Materials and Methods:** Breathing was measured using a thoracic respiratory belt from BIOPAC. Simultaneously, neural activity associated with PFC oxygenation was measured using functional near-infrared spectroscopy. Physiological and neural recordings during the last 5 minutes of a 10-minute BA meditation task was compared to 5 minutes of rest in 5 OSA patients (all males, Respiratory Event Index, mean±S.E.M.= 14±1 events/hour, age=40±5 years, BMI=28±2 kg/m<sup>2</sup>), and 5 healthy controls (all males, age=32±3 years, BMI=26±1 kg/m<sup>2</sup>). The effect sizes of the BA responsive changes relative to rest were calculated in OSA and controls for BR, BRV, right, medial and left PFC oxygenation. Additionally, changes in BRV was correlated with changes in right, medial and left PFC oxygenations separately in OSA and controls.

**Results:** In response to BA relative to rest, we found BR decreased by 30±13% in OSA and 21±6% in controls, both significantly different at  $p<0.05$ ; BRV changes in both OSA (decrease by 18±23%) and controls (increase by 0.9±16%) were not significant; right PFC oxygenation decreased by 3±2 times in OSA (not significant) and by 1±0.3 times in control (significant at  $p<0.05$ ), medial PFC oxygenation decreased by 2±0.6 times in OSA (significant,  $p<0.05$ ) and 0.8±0.2 times in controls (significant,  $p<0.01$ ), left PFC oxygenation decreased by 0.8±0.4 times in OSA (not significant) and 0.8±0.5 times in controls (not significant). Medial PFC oxygenation changes correlated significantly differently ( $p<0.05$ ) with BRV changes in controls ( $R=0.96$ ) and in OSA ( $R=-0.6$ ). Right PFC oxygenation changes correlated with BRV changes in controls ( $R=0.8$ ) and in OSA ( $R=-0.3$ ), left PFC oxygenation changes correlated similarly with BRV ( $R=-0.3$ ) in both OSA and controls.

**Conclusions:** In response to an acute bout of BA meditation- BR and neural activity at the medial PFC declined for both OSA and controls, although BRV changes were ambiguous with the majority of OSA subjects (3 out of 5) showing decreases in BRV and the majority of control subjects (3 out of 5) showing increased BRV. Moreover, changes in BRV correlations with alterations in medial PFC oxygenation significantly differed in OSA (negative) and controls (positive). In OSA, together with previous finding of instable breathing pattern with high BRV, our findings indicate that regular BA meditation practice may stabilize breathing pattern by reducing BRV after considerable stress reduction. Furthermore, consistent with previous findings, BRV seems to be an indicator of physiological stress

correlated with medial PFC neural regulatory activity.

**Acknowledgements:** NR-017435, HL135562.

### EEG SPECTRAL PROPERTIES AND ASSOCIATED ECG-BASED HEART-RATE VARIABILITY IN PEOPLE WITH INSOMNIA VERSUS HEALTHY SLEEPERS

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**Introduction:** Sleep disorders may disrupt normal central and autonomic nervous system function, as measured by electroencephalogram (EEG)/ electrocardiogram (ECG) coupling. People with insomnia have increased EEG  $\alpha$  (8–12 Hz) and  $\sigma$  (11–16 Hz) power during rapid eye movement (REM) sleep, and decreased  $\delta$  (0.5–4 Hz) power and increased  $\theta$  (4–8 Hz),  $\alpha$ , and  $\sigma$  power during non-REM (NREM) sleep. People with insomnia also have notably lower ECG-based heart-rate variability (HRV) during NREM and REM sleep compared with healthy sleepers.

This study aimed to compare the sleep architecture, central and autonomic nervous system functions, and EEG/ECG coupling of healthy sleepers versus people with insomnia using polysomnography.

**Materials and Methods:** This study used publicly available, de-identified polysomnography data from 9 people with insomnia (PhysioNet CAP database) and 12 age-matched, healthy sleepers (obtained from an IRB-approved sleep study conducted by Sleep Number Corporation). Sleep architecture was characterized for all study participants and the following variables were measured for REM and NREM sleep: spectral EEG power in the  $\delta$ ,  $\theta$ ,  $\alpha$ , and  $\beta$  (15–30 Hz) bands; heart rate; and HRV. A generalized linear model approach was used to assess the degree of coupling between EEG power and ECG-derived metrics in REM and NREM sleep for all participants.

**Results:** The cohorts were similar in demographic characteristics, baseline sleep architecture, and cardiovascular parameters during sleep. EEG power was significantly higher for healthy sleepers across all bands (all  $P\leq 0.01$ ), so all EEG values for each band were normalized by total power (power in each band divided by total power). After normalization, healthy sleepers had significantly higher NREM  $\theta$  power versus people with insomnia ( $P=0.005$ ); power results in all other bands were not significantly different. Analysis for EEG/ECG coupling revealed that the HRV high-frequency (HF; 0.15–0.4 Hz) band, HRV low-frequency (LF; 0.04–0.15 Hz) band, and LF:HF ratio were predictors of EEG  $\alpha$  power during NREM sleep in people with insomnia (adjusted  $R^2=0.705$ ,  $P=0.113$ ). Notably, HF and LF:HF decreased, and LF increased, with increasing  $\alpha$  power. A second analysis was performed to account for collinearities and interactions, which significantly increased model predictability (adjusted  $R^2=0.974$ ,  $P=0.02$ ).

**Conclusions:** This analysis found that  $\alpha$  power in NREM, likely a marker of restlessness, negatively correlated with HRV-HF—reflecting parasympathetic activity—and positively correlated with HRV-LF, reflecting baroreflex activity. These results suggest that, in people with insomnia, the parasympathetic dominance in NREM sleep is challenged by higher  $\alpha$  power, which may decrease sleep quality. Adding the interaction between the standard deviation of normal-to-normal intervals (time domain metric of HRV) and LF/HF (frequency domain HRV metric) significantly increased adjusted  $R^2$ . A limitation of this study was the small sample size; further research with a larger population is needed to confirm these results.

**Acknowledgments:** The authors wish to thank the MIT Laboratory for Computational Physiology for generously providing freely accessible insomnia PSG data via the PhysioNet database. Medical writing support was provided by Sandra Page, PhD, of Oxford PharmaGenesis, Inc, Newtown, PA, USA, and was funded by Sleep Number Corporation.

### EFFECTS OF AIR POLLUTION EXPOSURE PREDICTING SLEEP EFFICIENCY IN CHILDREN MODIFIED BY EXPOSURE TO VIOLENCE, 4-7 YEARS, IN THE PROGRESS BIRTH COHORT

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**Introduction:** A growing body of literature on sleep shows increasingly diverse effects on childhood health. Studies suggest that exposure to both air pollution and violence may alter development trajectory, as it may disrupt

the HPA-axis which plays an important role in how the human body reacts to environmental stressors affecting sleep. We propose that prenatal air pollution exposure may interact with violence to affect the efficiency of sleep, as this effect maybe modified by exposure to violence.

**Methods:** We studied 412 children enrolled in Programming Research in Obesity, Growth, Environment and Social Stressors (PROGRESS), a birth cohort study in Mexico City. To estimate ambient air pollution, we used a spatio-temporal model to estimate individual daily prenatal PM<sub>2.5</sub> exposure at each participant's residential address. We assessed the sleep efficiency (defined with time awake divided by time in bed) of all kids at age 4-7 years with assigned accelerometer worn during sleep, and recorded sleep patterns for a week. Exposure to violence is estimated with questionnaires and scored using a RASCH model. To examine the association between PM<sub>2.5</sub> exposure and sleep efficiency and test effect modification from exposure to violence, we fitted a varying coefficient model, that relaxes the constant effect assumption on PM<sub>2.5</sub> to sleep efficiency and estimated as a function of violence exposure.

**Results:** Participants are mostly low SES families (54.6%) with slightly lower proportion of low maternal education (42.1%) and are racial/ethnicity uniformed. Sleep efficiencies are normally distributed and ranging from 63.5 to 91.8. At age 4, children who were exposed to low-to-mid violence are more likely to have their sleep efficiency disrupted by prenatal PM<sub>2.5</sub> exposure (ETV at 10%tile,  $\beta=-0.26$ , CI:-1.19,0.68; peak PM effect at ETV at 58%tile,  $\beta=-0.96$ , CI:-1.9,-0.001; ETV at 90%tile,  $\beta=-0.27$ , CI:-1.4,1.9; ). The effect of PM<sub>2.5</sub> is then attenuated as the exposure to violence increases. However, at age 6, we found that PM<sub>2.5</sub> reduced sleep efficiency at even lower levels, but again we observed an U shape change of effect estimate (ETV at 10%tile,  $\beta=-0.26$ , CI:-1.05,0.54; peak PM effect at ETV at 36%tile,  $\beta=-0.71$ , CI:-1.5,0.09; ETV at 90%tile,  $\beta=0.28$ , CI:-1.1,5.5; ), as the exposure to violence increases.

**Conclusion:** This research study adds to the literature by addressing the main effect of prenatal air pollution on sleep and examine effect modification between ambient air pollution and exposure to violence on sleep patterns among children, 4-7 years old. As the literature expands on sleep and sleep disparities, the sparseness of studies on children's sleep highlights a research void that if addressed could mitigate the adverse impact of child sleep disparities on long term health.

## EFFECTS OF LONG COVID ON SLEEP HEALTH

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**Introduction:** COVID-19 has infected millions of people worldwide with growing evidence showing that those individuals may continue to show persistent post-COVID symptoms (long COVID). The aim of this study was to investigate sleep health in an international sample of individuals who reported previously testing positive for COVID-19.

**Materials and Methods:** 1001 individuals who reported a positive diagnosis of COVID-19, across different geographical regions, including North and South America, Sub-Saharan Africa, and Europe, completed an online survey between March 4–June 15, 2021. Self-reported sleep health was assessed using the RU-SATED scale, as recalled before a COVID-19 diagnosis and as reported currently.

**Results:** Individuals reported a poorer overall current sleep health, with poorer ratings across the six dimensions of sleep health (sleep regularity,

satisfaction, alertness, timing, efficiency, and duration) compared to their ratings as recalled before COVID-19 infection. Greater severity of symptoms during COVID-19 infection was the strongest predictor of poor current sleep health ( $p < .001$ ), independent of demographics, presence of a pre-existing condition, and time since infection. Poor current sleep health was associated with poorer current quality of life ( $p < .001$ ).

**Conclusions:** Poor sleep health is evident in individuals with a history of COVID-19, particularly those with more severe symptoms at the time of their COVID-19 infection, and is associated with a poorer quality of life. Clinicians and researchers should assess sleep health in COVID-19 survivors and investigate long-term associations with their mental and physical health, as well as potential benefits of improving sleep in this population. **Acknowledgements:** Daniela Ramos-Usuga was supported by a predoctoral fellowship from the Basque Government (PRE\_2019\_1\_0164). Dr Stella Iacovides is supported by NRF Thuthuka funding from the National Research Foundation of SA, and also NRF Incentive Funding for Rated Researchers Programme. We thank all the COVID long haulers who participated in this study for their time, and colleagues that help distributing the survey, especially Cristian Logatt.

## EFFICACY OF A NOVEL ITERATIVE DEVICE AND MATERIAL

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### Efficacy of a Novel Iterative Device and Material

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**Introduction:** Launching a new device design or use of a new material with optimistic expectations should always be undertaken with caution and an ounce of skepticism. When this novel device and material was first described in an IRB Abstract derivative report at the AASM, it was under the umbrella of a patient and provider preference survey. In April 2020, the broader availability post FDA clearance is providing strong early indications of excellent efficacy.

**Methods:** An analysis of data from four treatment centers using this novel device and material was undertaken. Patients were to be included if they had a diagnosis of mild, moderate, or severe OSA confirmed by a physician, and an AHI score  $>5$  and a follow up study resulting in treatment success or failure. Results would be grouped as Complete Success = AHI  $<5$ , Clinical Success = 50% reduction and  $<10$ . All patients were to be treated with the Novel ProSomnus EVO Iterative advancement device.

**Results:** 55 total consecutive patients were treated at four centers for dental sleep medicine. 37 male and 18 female patients with an average age of 53.3 ranging from 30 to 78 with pre and post data were included and treated with a ProSomnus EVO. The initial AHIs ranged from 6.0 to 116.0 with an average of AHI pretreatment of 26.4 (15 mild, 23 moderate and 17 severe). Follow up testing for this group revealed an average overall reduction in AHI of 75%, from 26.4 to 6.6. Overall, 62% resolved to below an AHI of 5 (100% of mild, 65% of moderate and 24% of severe patients). Similarly, 85% resolved to below an AHI of 10 and a 50% reduction (100% of mild, 96% of moderate and 59% of severe patients)

**Conclusions:** This novel interactive device and material combination appear, after early analysis, appear to yield significantly better results than previous data has demonstrated. The literature suggests that legacy oral appliance efficacies range from 50%-62% and other AADSM poster/abstracts have reported similar precision milled, control cure PMMA appliances in the 74% - 76% range. These results suggest a need for further investigation of exceptional efficacy for this device design and material.

**Support:** No support was provided for this abstract

## ENHANCED SLEEP FROM USING A THERMOREGULATED PILLOW: REAL-LIFE DATA FROM MOONA DEVICE

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**Introduction:** Body and ambient temperature have a significant influence on sleep. This real-life study aims to evaluate the effects of temperature regulation on sleep quality using a thermoregulated pillow.

**Materials and Methods:** The Moona device controls the temperature of a pillow pad from 64°F to 95°F and has sensors to monitor sleep states throughout the night. A total of 620 Moona users with more than 7 uses of the device and who completed the initial questionnaire (18 profile questions) participated in this study from October 2019 to July 2021. Whether users feel hot at night and how often has been assessed on that questionnaire, and users who feel hot during the night daily or several times a week composed the “frequent hot sleepers” group. Sleep quality was measured on a scale of 1 to 5 before the first use of Moona and after each night of use.

The proprietary algorithm that detects sleep/wake states per 30-sec epochs has been used to calculate the time spent asleep across the 11 first uses for each Moona user. A total of 869 users have been included in this analysis from October 2019 to May 2021.

A survey has been proposed to Moona users in June and July 2021. A total of 103 answers have been collected including 16 patients who reported having been diagnosed with insomnia. Improvement of their insomnia since first use of Moona has been assessed by a 5-point scale (‘much better’, ‘somewhat better’, ‘about the same’, ‘somewhat worse’, ‘much worse’). An improvement of the condition has been determined if the patient answered ‘much better’ or ‘somewhat better’.

Statistical analyses have been performed on Python 3.7. Mean comparisons have been accessed by student t-test with a significance level at  $p < 0.05$ .

**Results:** The sleep quality reported by the user significantly increased with the use of the Moona device (without use: 2.6/5, average over the last seven uses: 3.7/5, t-test,  $p < 0.001$ ). This sleep quality increased linearly over the first ten uses of the device, from 3.4/5 to 3.7/5 ( $R^2 = 0.87$ ). Although frequent hot sleepers have a significantly lower initial sleep quality than users who aren't hot sleepers (2.5/5 vs. 3.2/5, t-test,  $p < 0.001$ ), the difference between these two groups disappeared with the use of the Moona (3.8/5 vs. 3.7/5, t-test,  $p > 0.05$ ). Users have had a significant gain of 23 minutes of sleep, from 391 minutes on the first night using Moona to 414 minutes on the eleventh (t-test,  $p < 0.001$ ). Finally, the use of Moona active cooling pillow pad has been shown to aid those suffering from insomnia: 15 out of 16 insomniacs reported an improvement since using Moona.

**Conclusions:** The present study findings showed that an active thermoregulated pillow like Moona enhanced sleep quality, increased total sleep time and improved reported insomnia symptoms.

**Acknowledgements:** We acknowledge all users that have contributed to this study.

## ENHANCING SLOW WAVE ACTIVITY DURING SLEEP FACILITATES MOTOR PERFORMANCE DURING A FATIGUING TASK THE NEXT MORNING

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**Introduction:** Slow waves (SWs) during sleep are proposed to be central in

restoring brain function. Yet, little is known about whether sleep modulates performance fatigability as assessed by a repetitive finger tapping task at maximal rate. Performing this task for 30s is characterized by gradual slowing of the tapping rate. Supraspinal mechanisms have been shown to play an essential role in evoking this decrease in performance but whether such mechanisms benefit from restorative functions of sleep remains to be tested. Here we investigated if SWs functionally influence motor performance and resistance against fatigability, by applying auditory stimulation known to enhance SWs and established the effect on overnight changes in finger tapping performance.

**Material and Methods:** 18 healthy, middle-aged (30-57 years of age) male participants underwent three nights in the sleep lab where one of three auditory stimulation (stim) modalities were applied in a counter-balanced, cross-over design (no stim, low volume stim, high volume stim). For the results of this abstract, only the no stim and high volume stim nights were analysed. Our finger tapping task consisted of 30 seconds of alternating finger presses by the index and middle finger of the dominant hand. Finger tapping was tested in the evening before and the morning after each sleep period. Motor fatigability was quantified as a difference ( $p < .05$ ) in mean intertap interval (ITI) between the first and last 5 seconds of tapping using linear mixed effect models. All values are cited as mean  $\pm$  SE.

**Results:** Motor fatigability occurred in both evening and morning tapping sessions but was significantly reduced ( $-18 \pm 5\%$ ) in the morning session ( $p < .05$ ). Finger tapping was slightly asymmetric with transitions from index to middle finger taps being significantly longer (ITI:  $128 \pm 6$  ms) than vice versa (ITI:  $108 \pm 7$  ms,  $p < .01$ ). A significantly greater overnight reduction in mean ITI for the index to middle finger transition was observed in auditory stimulation (ITI:  $-7 \pm 3$  ms) compared to no stimulation (ITI:  $-3 \pm 2$  ms,  $p < .05$ ).

**Conclusions:** These findings suggest that SW activity might modulate motor performance during a fatiguing task. This effect was most pronounced for the slowest finger, where there may be more room for motor performance improvement. Further analyses will explore how auditory SW stimulation affects sleep physiology and performance relevant aspects in the motor or cognitive domain.

**Acknowledgements:** This work was conducted as part of the SleepLoop Flagship of Hochschulmedizin Zürich and funded by the Swiss National Science Foundation (PZ00P3\_179795 to CL).

## ERENUMAB IMPACT ON SLEEP ASSESSED WITH QUESTIONNAIRES AND HOME-POLYSOMNOGRAPHY IN PATIENTS WITH MIGRAINE: THE ERESO STUDY

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**Introduction:** Increasing evidence suggests that sleep and migraine share a bidirectional relationship. Patients with migraine frequently report poor sleep quality and excessive daytime sleepiness. In turn, sleep disruption can be a trigger of migraine attacks, which often benefit of sufficient restful sleep. Few previous studies used questionnaires to assess sleep changes in patients treated with migraine-preventive medications. More extensive polysomnography-based studies for this purpose were not available. The main objective of our study is to investigate possible sleep changes in patients with migraine treated with erenumab, a new monoclonal antibody towards calcitonin gene-related peptide receptor (CGRP-R).

**Materials and Methods:** This observational, prospective, open-label pilot study was conducted at the Clinical Neurology Unit Headache Center of Udine University Hospital between 2020 and 2021. Patients started treatment with erenumab for migraine prevention. All patients completed a series of questionnaires collected via face-to-face interviews at baseline, after three and 12 months of therapy. We evaluated subjective sleep quality and daytime sleepiness using the Pittsburgh Sleep Quality Index (PSQI) and the Epworth Sleepiness Scale (ESS), respectively. At each time of assessment, a home-polysomnography (home-PSG) was performed with a self-applicable device (Sleep Profiler™, Advanced Brain Monitoring, Carlsbad, California, USA). Migraine-related disability was also tested with

Migraine Impact and Disability Assessment Scale and the Headache Impact Test, 6th edition. Erenumab efficacy and safety in migraine prophylaxis were also assessed using headache diaries.

**Results:** Twenty-nine patients completed three months of follow-up, whereas 15 patients completed 12 months. We found a weak improvement in daytime somnolence after three months of treatment, with stronger results after 12 months (median ESS score from 6.0 to 4.0,  $p = 0.015$ ); a significant improvement in subjective sleep quality (median PSQI total score from 7 to 5;  $p = 0.001$ ) was also observed. Home-PSG showed a significant increase in objective sleep efficiency, both after three (from 88.1 to 91.0,  $p = 0.006$ ) and 12 months (from 87.1 to 91.0,  $p = 0.006$ ) of treatment. This outcome was related to the improvement of some parameters, particularly the decrease in median wake time, wake after sleep onset and awakening index. In addition, our data confirmed erenumab effectiveness and safety in migraine prevention.

**Conclusions:** Our study demonstrated an improvement in both subjective and objective sleep quality in patients treated with a migraine-preventive therapy. Erenumab, in particular, does not cross the blood-brain barrier, thus a direct action on sleep central pathways is not expected and observed sleep changes could be due to migraine improvement itself. At least in part, migraine and sleep share common anatomic structures, neural pathways and signaling neurotransmitters. Neuropeptides like CGRP and pituitary adenylate cyclase-activating polypeptide (PACAP) are important migraine triggers. PACAP also plays a role in the hypothalamus for sleep homeostasis. In animal models, it seems to act on sleep-wake cycle pathway, clock genes expression and melatonin synthesis. However, little is known about CGRP circadian variability or indirect central effects due to peripheral modulation of CGRP with erenumab. Future studies are needed to better understand the mutual influence between migraine and sleep disorders.

#### ESTIMATED SLEEP-WAKE PATTERNS OBTAINED FROM A LARGE U.S. SAMPLE BY HOME-BASED UNDER-MATRESS MONITORING DEVICES

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**Introduction:** Irregular sleep-wake schedules, characterized by high day-to-day variability in sleep duration or timing, were recently associated with cardiovascular disease and unfavorable metabolic profiles, such as increased blood pressure and insulin resistance. Shift work has also been associated with poor health outcomes including increased risk of diabetes, obesity, hypertension and cancer. However, the prevalence of irregular sleep-wake schedules in a large population has not been studied. This study aims to characterize sleep-wake schedules in a large U.S. sample.

**Materials and Methods:** Descriptive analysis was performed on collected de-identified data from 12507 users (46.9% female, mean age  $48.5 \pm 13.4$  years) of a commercially available home sleep monitoring device (Sleep-tracker-AI Monitor, Fullpower Technologies, California, USA). The device passively monitors sleep using piezo-electric sensors that register the forces exerted through the mattress. Only users with at least 300 days of recordings between January 2019 and December 2019 were included in this analysis. More recent data were excluded to avoid effects of the pandemic. In order to understand sleep-wake schedules and regularity of sleep, Total Sleep Time (TST) standard deviation (SD) and bedtime (BT) SD were included as parameters. Users were divided into six different age groups and weekly summaries of sleep parameters per subject were obtained. Statistical analyses were performed using Python (Python Software Foundation, version 3.8.3).

**Results:** 4,175,260 recorded nights were included in the analyses. In minutes, overall estimated TST SD across subjects' mean was 66.1 (18.7\*) and BT SD was 55.6 (20.5\*). Importantly, for TST SD over the week, across subjects only 25.0% (10.9%) of the variance is explained by the difference between weekends and weekdays, and for BT SD this value is only 26.7% (11.3%\*); substantial variation remains even when considering only weekdays. Population was arbitrarily divided in 6 groups by age: Group 1 (20-30), 2 (30-40), 3 (40-50), 4 (50-60), 5 (60-70), and 6 (70-80). The estimated TST SD in age groups 1, 2, 3, 4, 5, 6 were as follows: 70.7 (20.0\*),

67.2 (18.0\*), 66.8 (18.5\*), 66.1 (18.4\*), 63.4 (18.2\*), and 60.5 (18.9\*) minutes. The estimated BT SD in each age group were: 62.1 (21.1\*), 57.4 (19.4\*), 57.0 (20.2\*), 55.7 (20.0\*), 51.6 (20.3\*), and 46.7 (20.8\*) minutes. When divided categorically into 2 groups of regular or irregular sleep schedules ( $\leq 60$  mins TST SD and  $>60$  mins TST SD respectively) we found the following: 67%, 61%, 60%, 58%, 53%, and 47% of Group 1, 2, 3, 4, 5 and 6 had an irregular sleep-wake schedule, and 58.4% overall.

**Conclusions:** Irregular sleep duration and timing were common over all age categories in this population, indicating that sleep habits might be a common and treatable risk factor of cardiovascular disease. Interestingly, this follows a clear age-dependent trend, with older age corresponding to more regular sleep-wake schedules. This provides a possible and important target for health policy. Furthermore, the ability to estimate sleep parameters in the home environment represents a powerful tool for public health campaigns.

\*Standard deviation of mean sleep parameter SD

#### EVENING SCREEN TIME, SLEEP AND DIURNAL TYPE IN PRESCHOOL AND PRIMARY SCHOOL CHILDREN

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**Introduction:** The screen use seems to be increasing over the last years, and has been associated with more sleep problems. The main goal of the present study was to examine the relationships between evening screen use, diurnal type (morningness-eveningness) and the sleep-wake patterns (e.g., bed and rise times; sleep durations), in pre- and primary school children. Furthermore, it was specifically intended to investigate whether evening screen time would be a significant predictor of sleep variables, when controlling for other potential predictors, namely diurnal type. Additionally, we also compared sleep and psychological symptoms, according to children's school level and diurnal type.

**Materials and Methods:** The final sample encompassed a total of 605 children, being 186 (30.7%) pre-schoolers (4-6 years old; 48.4% girls), and 419 (69.3%) primary schoolers (7-9 years old; 49.5% girls). Diurnal type, sleep patterns, psychological symptoms, and evening screen use, were obtained through tutors'/parents' responses to the Portuguese versions of the Children's ChronoType Questionnaire - Morningness/Eveningness Scale (Werner et al., 2009), the Child Sleep-Waking Questionnaire (Clemente, 1997; Bos et al., 2009), the Strengths and Difficulties Questionnaire (Goodman, 1997), and a set of questions developed to assess evening (i.e., after dinner) time screen use (Gomes et al., 2018) – variables relevant for the present work were evening screen use time/duration, frequency (nights per week), how long before bedtime does the child stop using screens, type of use (passive...active).

**Results:** Most children (89.8% pre-schoolers, 91.5% primary schoolers) displayed evening screen use, with no statistically significant differences between pre and primary schoolers ( $p = .593$ ) or between morning, intermediate and evening children ( $p = .093$ ). The majority (58.5% pre-, 61.7% primary schoolers) use screens all/nearly all nights. Screen evening time averages were  $56 \pm 35$ min (pre-schoolers) and  $61 \pm 33$ min (primary schoolers). At least one hour prior to bedtime, 19.8% of pre- and 16.1% of primary schoolers interrupt screen usage. Psychological symptoms were higher in primary (vs pre-primary) schoolers, and evening-type children. The evening screen use variables (duration, and/or frequency, and/or type of use) were significantly correlated with later sleep-wake schedules variables ( $p < .001$ ), shorter sleep periods ( $p < .001$ ) and lower scores on prosocial behavior ( $p < .001$ ). A more active use was correlated with longer sleep latencies ( $p < .001$ ). Furthermore, in multiple hierarchical regression analyses, the evening screen time was a significant predictor of several sleep variables (bedtime and sleep period on school nights; sleep period, bed and rise times on/prior to free days), after controlling for sex, schooling level, and the children's diurnal type.

**Conclusions:** Research on the evening screen use, in children, as a function of diurnal type seems extremely scarce. Our results show that evening

screen use relates to the children's sleep, regardless of whether they are morning-, intermediate- or evening-types.

**Acknowledgements:** This study was developed as part of larger research project True Times – Morningness-eveningness and time-of-day effects on cognitive performances and emotional states: New lessons from children and adolescents (PTDC/PSI-ESP/32581/2017; CENTRO-01-0145-FEDER-032581), funded by Portugal 2020, Centro 2020, FEDER (UE), and FCT.

## EVOLUTION OF A MOUTH BREATHER WITHOUT TREATMENT

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**Introduction:** The purpose of this study is to cooperate with the whole medical community engaged in the detection and prevention of OSA in infants, by showing how we can help our patients by mere clinical observation –mainly when the patient is a child, for whom we are the architects of his/her health and facial structure.

**Materials and Methods:** Based on pictures taken at different ages, mandibular angle and lower facial height were measured. In the same pictures, the appearance of adenoid facies was found, coincident with symptoms of infant OSA. Considering these images, the aim is to determine the opportunity of having a functional-orthopedic treatment which –as in this case– could have prevented the irreversible facial transformation. Timeline: 60 years.

**Results:** After analyzing the pictures which will be shown in the poster, we have the following **results:**

WHEN SHOULD WE HAVE INTERVENED?

Undoubtedly, as soon as symptoms and signs of respiratory obstruction appear, it is time to act. Let us bear in mind that the sooner we restructure the position of the tongue, we will recover the trophic stimulus that it exerts on the palate and on the floor of the nostrils. Let us remember that the Nitric Oxide secreted in the body by the paranasal sinuses will be essential for the sweep of microorganisms in the upper airway, and if these sinuses are obstructed, we will not have their help during growth.

Let's understand that surgery empties the airway, but does not increase its volume. That is only achieved with the help of an orthopedic treatment.

WHAT KIND OF APPLIANCES CAN YOU USE TO INTERCEPT MOUTH BREATHING?

Any type of equipment that stimulates muscle and bone activity will be useful. There are increasingly more comfortable, more aesthetic appliances for children. If we keep a mandibular forward force for continuous hours or more, the blood vessels of the propellant muscles become smaller, preventing adequate blood flow. By decreasing its gas exchange, Lactic Acid will accumulate. When the device is removed from the mouth, the propellant muscles will become hyper contractible (repeated involuntary contractions) whereby the jaw will move forward, even when the chosen device is not in the mouth all day. To sweep away the lactic acid, muscles increase their blood vessels, reaching them undifferentiated cells that turn into myoblasts, which will form new muscle fibers. This process will maintain stability during growth.

**Conclusions:** It is suggested that a respiratory sleep alteration during childhood impacts on the facial biotype, even after a tonsillectomy, if not treated orthopedically in order to revert and/or modify in due time the muscle and respiratory functions, which would lead to a factor that may cause OSA in adults.

**Acknowledgements:** Dr Liliana Gimenez, Dr Florencia Poletti, Dr Andrea Marti Garcia

## GENDER- SPECIFIC ESTIMATES OF SLEEP PROBLEMS DURING THE COVID- 19 PANDEMIC: SYSTEMATIC REVIEW AND META- ANALYSIS

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**Introduction:** The outbreak of the novel corona virus disease 2019 (COVID-19) changed life styles world wide and subsequently induced individuals' sleep problems. Sleep problems have been demonstrated by

scattered evidence among the current literature on COVID-19; however, little is known regarding the synthesised prevalence of sleep problems (i.e. insomnia symptoms and poor sleep quality) formales and females separately.

**Materials and Methods:** The present systematic review and meta- analysis aimed to answer the important question regarding prevalence of sleep problems during the COVID-19 outbreak period between genders. Using the Preferred Reporting Items for Systematic Review and Meta-Analyses guideline and Newcastle–Ottawa Scalecheck list, relevant studies with satisfactory methodological quality searched for in five academic databases (Scopus, PubMed Central, ProQuest, Web of Science, and EMBASE) were included and analysed

**Results:** The protocol of the project was registered in the International Prospective Register of Systematic Reviews (PROSPERO; identification code CRD42020181644). A total of 54 papers (N=67,722) in the female subgroup and 45 papers (N=45,718) in the male subgroup were pooled in the meta-analysis. The corrected pooled estimated prevalence of sleep problems was 24% (95% confidence interval [CI] 19%–29%) for female participants and 27% (95% CI 24%–30%) for male participants

**Conclusions:** Although in both gender subgroups, patients with COVID-19, health professionals and general populations showed the highest prevalence of sleep problems, it did not reach statistical significance. Based on multivariable meta-regression, both gender groups had higher prevalence of sleep problems during the lockdown period. Therefore, healthcare providers should pay attention to the sleep problems and take appropriate preventive action.

**Acknowledgements:** C-YL was supported in part by a research grant from the Ministry of Science and Technology, Taiwan (MOST109-2327- B-0 0 6 -0 0 5 ) .

## HOW DOES AUSTRIA SLEEP? SLEEPING HABITS AND SLEEP PROBLEMS BEFORE AND DURING CORONA

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In the talk I discuss the sleeping habits and sleep problems before and during the Corona pandemic. An alarming increase in sleep problems from 6-year-old primary school children to adolescents and older adults is shown. Half of the interviewed adult Austrians (N=968) sleep less than 7 hours and only 31% classify themselves as "good sleepers". Changes due to the Corona pandemic and lockdown measures are also found across different cultural groups (Austria/Germany, Brazil, Greece, Cuba, Ukraine) and show, on the one hand, a high level of anxiety due to the pandemic (78% of respondents). In addition, in non-system-relevant jobs we see a consistent later going to bed and an extension of sleep times on working days (13 min daily), which in total lead to a reduced "social jetlag". People in system-relevant jobs also go to bed later and get up later, but show no increase in sleep time on weekdays and even a reduction in sleep time on days off (cf. Florea et al., 2021); overall, they also show a reduction in social jetlag, albeit to a lesser extent.

We find cultural differences only of a general nature in the sense that people in Greece and Ukraine go to bed and get up later than the other cultural groups studied.

Among children and adolescents (N= 2,232), we find 74.8% less physical activity during the Corona pandemic, 44.2% less exposure to daylight and 85% a strong increase in smartphone/tablet use during the pandemic or lock-downs. In addition, a shift of the sleep-wake rhythm to later times (for 94%) & more bedtime, and yet a subjective deterioration in sleep quality is also evident in that data. An alarming number of 33.3–45.3% depending on the age group now even subjectively report sleep problems during the pandemic (cf. Bothe et al., in preparation).

## IMPACT OF COVID-19 PANDEMIC ON SLEEP OF UNDERGRADUATE STUDENTS: A SYSTEMATIC LITERATURE REVIEW

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**Introduction.** COVID-19 has now infected over 187 million globally and continually disrupts society. World universities and colleges have been closed and have shifted to distance learning. This sudden change in living environment aggravates pre-pandemic mental and physical vulnerabilities of undergraduate students, including sleep. This systematic literature review aims to describe the prevalence of sleep problems, circadian rhythm disruption, sleep duration, sleep quality, insomnia symptoms, and psychological factors affecting sleep of undergraduate students from various global regions.

**Methodology.** A systematic search on March 2, 2020 for articles published from January 1 to December 31, 2020 using the search words “COVID-19,” “Coronavirus,” “Pandemic,” “Sleep,” “Mental Health,” and “Students” from PubMed, Scopus, and Cochrane yielded 757 articles. After removing duplicates, and excluding articles not meeting the selection criteria, 26 articles were included. Criteria for selection were: article is originally open-access and in English, participants are undergraduate students and not in the postgraduate level, sleep outcomes were assessed via objective or subjective tools, and participants did not belong to allied health courses.

**Results.** Included works came from the USA (5), Italy (5), Spain (1), China (8), Bangladesh (2), UAE (1), Jordan (1), India (2), and Indonesia (1). All included studies recorded data on sleep after stay-at-home orders. Point prevalence of self-reported sleep problems varied across regions (n=3092, 12.6% in China; n=154, 32.5% in UAE; and n=75, 70.7% in Spain) but was increased when compared to values prior to stay-at-home orders (n=571, 10.1% in China; n=991, 31.4% in UAE; and n=75, 37.3% in Spain). There were also reported disruptions in sleep patterns in student populations from the USA (n=195), Italy (n=103), and India (n=3), delayed sleep times and wake up times in Italian (n=307, n=809) and American students (n=139, n=1222), reduced difference in sleep timing between weekdays and weekends in American students (n=139), irregular sleep and wake up times in Chinese students (n=323489) and UAE students (n=775). Sleep duration was also found to be increased when compared to pre-pandemic levels; and was  $\geq 7$  hrs in the USA (n=139, n=1222), China (n=2485), Bangladesh (n=1979, n=3122), and Indonesia (n=991). On the other hand, sleep quality of students measured via the Pittsburgh Sleep Quality Index varied across regions. Some studies in the USA found that sleep quality did not change (n=1222) but some found a significant worsening (n=107) as in Italian (n=307) and Spanish students (n=75). Furthermore, increased stress, depression, anxiety, discrimination, shame, stigma, negative affect; increased COVID-19 cases, increased digital media use; and living in a rural residence, being unemployed, inaccurate knowledge of COVID-19, and being a college student have been found to negatively influence sleep in the USA (n=1222), China (n=4099, n=995, n=304167), Italy (n=8177, n=307, n=809), Spain (n=75), and Bangladesh (n=3122).

**Conclusion.** Results highlight the impact of stay-at-home orders on the sleep of undergraduate students and reveal opportunities for local and global institutions to intervene with policies and programs to promote the well-being of this group.

**Acknowledgments.** We would like to acknowledge the authors who have provided a copy of their works for this review.

#### IMPACT OF NEIGHBORHOOD AND ENVIRONMENTAL FACTORS ON SLEEP HEALTH AMONG MIDDLE-AGED AND OLDER ADULTS IN THE CANADIAN LONGITUDINAL STUDY ON AGING

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**Introduction:** Emerging evidence emphasizes the importance of neighborhood and environmental factors on sleep patterns. Neighborhood and environmental effects may be opposing in terms of having a health enhancing versus a health threatening effect, therefore it is important to consider a range of factors together to determine the primary factors that influence sleep. Our objective was to explore the neighborhood and environmental correlates of sleep health in a population-based Canadian sample.

**Methods:** We used cross-sectional baseline data from the Canadian Longitudinal Study on Aging (CLSA), a survey of 30,097 community-dwelling adults, aged 45–85. Self-reported sleep measures included sleep duration, sleep dissatisfaction (vs satisfied/neutral), and sleep disturbances (difficulty initiating or maintaining sleep). We used environmental data from the Canadian Urban Environmental Health Research Consortium (CANUE) linked to CLSA data at the postal code level. We explored built and social environment variables (greenness, intersection density, dwelling density, points of interest, material and social deprivation), ambient variables (proximity to roadways, nighttime light, air pollution), and weather and climate (temperature, humidity, pressure, precipitation). We used modified Poisson regression to estimate prevalence ratios (PR) for the associations between neighborhood and environmental variables and sleep dissatisfaction and disturbances, and linear regression for sleep duration. We estimated unadjusted associations, estimates adjusted for all environmental variables, and estimates additionally adjusted for individual-level socio-demographic and clinical variables.

**Results:** In our preliminary findings from our unadjusted analyses, we observed a higher prevalence of sleep dissatisfaction among people residing in the highest quintile of material deprivation relative to the lowest quintile (PR=1.11, 95%CI 1.02, 1.21), as well as sleep disturbances (PR=1.13, 95% CI 1.05, 1.22). Additionally, we observed shorter sleep duration within the highest quintile of material deprivation compared to the lowest (coefficient=-0.13, 95% CI -0.20, -0.06). Higher levels of neighborhood greenness were significantly associated with a lower prevalence of sleep disturbances (PR=0.71, 95% CI 0.56, 0.90) and longer sleep duration (coefficient=0.34, 95% CI 0.10, 0.58). Full adjusted results will be available for presentation at the conference.

**Conclusion:** Our findings provide novel evidence disentangling the relative importance of inter-related and competing environmental exposures on sleep health in a population-based Canadian sample of middle-aged and older adults.

#### IMPACT ON STRESS, MENTAL HEALTH, AND SLEEP QUALITY IN HEALTHCARE PROFESSIONALS DURING THE COVID-19 PANDEMIC: A FOLLOW-UP STUDY IN SPAIN

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**Introduction:** The COVID-19 pandemic has caused a challenging situation worldwide with a major health impact on vulnerable populations and populations with high risk for COVID-19 infection, such as healthcare workers. The purpose of the present study was to assess stress, anxiety, depression and sleep quality on healthcare workers in charge of patients with and without coronavirus in Spain from the first peak to the present time.

**Methods:** Observational study of active healthcare workers aged 25–69 years in charge of patients with and without coronavirus. An on-line questionnaire that included the perceived stress scale, the Goldberg anxiety and depression scale, the pre-sleep arousal scale and the Pittsburgh Sleep Quality Index was completed at the beginning of the COVID-19 pandemic and six months later.

**Results:** Overall 563 questionnaires were included. Of them, 425 were completed from April to July 2020 and 138 from January to October 2021. The mean age was  $43 \pm 9.4$ , 81% were women, and 75% physicians. Moderate-severe stress was reported by 98% of subjects, positive screening for anxiety and depression was identified in 55% and 79% of the study population, and poor sleep quality in 97% of healthcare workers in charge of patients with COVID-19. Anxiety was reported more frequently by females (62% vs. 48%,  $p=0.041$ ) and singles (69% vs. 57%,  $p=0.037$ ). Healthcare workers in charge of patients with COVID-19 compared with those in charge of non-COVID patients showed more anxiety (59% vs. 43%,  $p=0.02$ ) and depression symptoms (68% vs. 82%,  $p=0.01$ ). While regular sunlight exposure reduced the frequency of anxiety and depression, and regular physical activity of depression. Significant changes in sleep latency in healthcare providers on charge of patients with COVID-19 were observed throughout the pandemic, but not in global PSQI score.

**Conclusions:** Stress, mental health disturbance and poor sleep quality are common in Spanish healthcare providers, particularly in those on charge

of COVID's patients. These findings persist throughout the different pandemic waves.

**Acknowledgements:** We thank all the participants in the study. This study was funded by the Spanish Sleep Society.

### IMPROVEMENT OF SLEEP QUALITY SIX MONTHS AFTER TOTAL KNEE ARTHROPLASTY

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**Introduction:** Total knee arthroplasty (TKA) is an accepted, effective treatment to restore function, relieve pain, and improve the quality of life in patients with advanced osteoarthritis. One complication of this major surgery is impaired sleep quality. This study examines the quality of sleep in patients undergoing TKA before and after their operation

**Materials and Methods:** All relevant records were obtained using a systematic search in three online databases: PubMed, Scopus, and Cochrane library. Out of the 177 records retrieved, only eight matched the inclusion criteria. Due to the lack of sufficient data, only four studies entered the meta-analysis. Values reported for sleep quality based on the Pittsburgh Sleep Quality Index (PSQI) were extracted from patient records before and after surgery. A random-effect model was used to analyze the data.

**Results:** The results of the meta-analysis show a significant difference in the improvement of sleep quality after surgery at two time points of 4-6 weeks after surgery (SMD: -0.16; 95% CI: -1.05 to 0.74; P = 0.0) and 3-6 months after surgery (SMD: -0.92; 95% CI: -1.61 to -0.24; P = 0.0).

**Conclusions:** The results show that TKA generally improves the patients' sleep quality. Although some studies reported disrupted sleep quality in periods close to the surgery (especially in the early days after surgery), all studies have reported improved sleep quality in the late postoperative intervals.

### INSOMNIA, SLEEP DISORDERED BREATHING AND CARDIOMETABOLIC RISK FACTORS IN PATIENTS COMPLAINING OF PAIN IN THE OROFACIAL REGION

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**Introduction:** Insomnia and sleep disordered breathing (SDB) are the most common sleep disorders, with a significant impact on health. These two conditions frequently interact potentiating several problems. Cardiovascular and Metabolic disorders (CMD) are often linked to both insomnia and SDB when occurring in isolation. Comorbid Insomnia and Sleep Apnea (COMISA), was showed to increase the risk of CMD in different settings. Persistent pain can also increase on CMD risk either through sympathetic activation or via indirect factors involved in CMD pathogenesis (e.g., anxiety, depression, stress). Such burdens may aggravate pain perception and further negatively impact on general health and well-being. Therefore this study aimed on evaluating Insomnia, Sleep Disordered Breathing and Cardiometabolic Risk Factors (CMRF) and their interactions in Patients seeking care at an orofacial pain clinic.

**Materials and Methods:** Anonymized data of patients, both sexes, with persistent orofacial pain (69,1% women), were extracted from the WISE, a Swiss symptom collection platform, and analyzed. The sample was characterized from a demographic perspective, on the presence of self-reported SDB, on insomnia by applying ISI and on its relation with psychometric variables obtained through validated questionnaires. Prevalence data was estimated for insomnia (ISI>8), SDB (a positive answer for snoring and/or apnea complaints) and COMISA (Insomnia + SDB) both

regarding demographics and BMI, smoking history and drinking history. Psychometric tests for anxiety (GAD-7), depression (PHQ-4 and PHQ-Str) and pain catastrophization (PCS) were applied to assess psychosocial stress factors acting as additional CMRF. A descriptive statistical analysis was used together with analysis of variance and multiple regression models used to determine the associations between the variables under study. The statistical significance was set at  $p \leq 0.05$

**Results:** 1236 patients with orofacial pain complaints were enrolled (age between 10 and 89 years old, 69,1% females). From the global sample, 384 patients (31,1%) reported insomnia, either subclinical (n=184; 40,1%) or clinical (n=200; 43,6%) as defined by an ISI score > 8 and <15 or  $\geq 15$ , respectively. Regarding SDB, 310 patients (25,0%) confirmed snoring or suffering from sleep apnea. Overall, 142 patients (11,5%) had COMISA. BMI of patients with COMISA was higher than those with isolated insomnia ( $p=0,001$ ) but not different from those with isolated SDB ( $p=0,972$ ). Current smoking history was more frequent ( $p=0,007$ ) among patients with COMISA (23,9%) than in patients with isolated conditions (12% for insomnia and 22,0% for SDB). History of drinking was more frequent ( $p=0,007$ ) in SDB (16,1%) and COMISA (14,1%) patients than in insomniacs (7%). Psychometric measures of anxiety, depression, pain catastrophizing, and stress were significantly higher for patients with COMISA compared to patients with isolated conditions, and their differences were clinically relevant between conditions.

**Conclusions:** Patients experiencing orofacial pain and who suffer from OSA or COMISA have additional CMD risks such as increased BMI and increased alcohol consumption compared to those with insomnia alone. Furthermore, COMISA patients scored highest on screening questionnaires for anxiety, depression, pain catastrophizing, and stress, all of which may further potentiate the risk for CMD.

### IS PSEUDO-RBD A SEVERE FORM OF OSA?: FACTORS ASSOCIATED WITH RBD MIMICKING BEHAVIORS IN OSA

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**Introduction:** Pseudo-RBD is defined as movement similar to REM sleep behavior disorder (RBD) along with sleep segments in the REM or non-REM sleep in association with obstructive sleep apnea (OSA). In patients complaining of DEB, it is very difficult to distinguish between RBD and pseudo-RBD. Because these two diseases have different treatment options and prognosis, it is very important to distinguish between the two diseases. Therefore, the authors attempted to identify factors related to pseudo-RBD and to confirm the mechanism of pseudo-RBD by comparing the clinical characteristics of RBD with OSA, pseudo-RBD, and OSA without RBD patient groups with VPSG.

**Materials and Methods:** From May 2017 to December 2020, patients aged 18 years or older who underwent PSG were selected for OSA with an AHI of 5 or higher. Of the total 213 patients, 98 patients were finally enrolled and divided into three groups: idiopathic RBD with OSA, OSA without RBD, and OSA with RBD-mimicking symptoms (pseudo-RBD) according to the diagnostic criteria of 'the International Classification of Sleep Disorders, third edition'. Clinical features such as gender, age, and comorbidities were compared, clinical presentation including questionnaires were compared, and VPSG findings were compared.

**Results:** There was no significant difference in RBD symptoms using RBDQ-KR and other questionnaires in three groups. In the pseudo-RBD group, AHI was higher than in the iRBD with OSA group and the OSA without RBD group ( $p=0.033$ ), whereas the lowest saturation was the lowest ( $p=0.005$ ). And among pseudo-RBD, severe OSA was 60.0% (15/25), moderate OSA and Mild OSA were 20.0% each (5/25). In addition, REM/NREM AHI ratio and supine REM/NREM AHI ratio in mild OSA were significantly higher than those in moderate and severe OSA group ( $p=0.001$ ,  $p=0.001$ ). REM AHI and supine REM/NREM AHI ratio were the highest in pseudo-RBD group (42.80/hr,  $p=0.000$ , 1.77  $p=1.77$ ). In contrast, the iRBD with OSA group had the lowest REM AHI and supine REM/NREM AHI ratio. Total arousal index and REM or NREM arousal index did not show any significant difference in the three groups, but during REM sleep, the respiratory arousal index was the highest in pseudo-RBD at

17.40/hr, followed by the second highest at 15.38/hr in OSA only group ( $p = 0.009$ ). Also, the REM/NREM respiratory arousal index ratio was the highest in the pseudo-RBD group at 1.36 and the second highest at 1.14 in the OSA only group.

**Conclusions:** In iRBD with OSA, modest and severity of AHI were NREM dominant. And in pseudo-RBD, AHI was the highest and lowest oxygen saturation was lowest, so it was consistent with previous studies in that pseudo-RBD is a more severe form of OSA. However, it was a new finding that REM/NREM AHI ratio in supine position and REM/NREM respiratory AI ratio were significantly high in pseudo-RBD, and that it occurred even in mild to moderate OSA. In conclusion, respiratory event-related arousal will contribute to DEB in pseudo-RBD, and even if not severe OSA, the REM/NREM AHI ratio and REM/NREM respiratory arousal index can be considered as important factors and this will eventually trigger DEB.

### LAXATIVE USE IS ASSOCIATED WITH WORSE SLEEP QUALITY AND INSOMNIA SYMPTOMS IN MIDDLE-AGED PATIENTS CROSS-SECTIONALLY ANALYZED IN FIRST NIGHT IN-LABORATORY POLYSOMNOGRAPHY

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**Introduction:** Chronic constipation is a common gastrointestinal disorder resulting in functional impairment and reduced quality of life in the elderly. Recent research has indicated that constipation may also negatively affect sleep quality, based on self-report questionnaires. Additionally, prior literature has demonstrated a relationship between constipation and self-reported insomnia. However, the impact of constipation on objective metrics of sleep quality has remained underexplored. Thus, the objective of our study was to characterize 1) the relationship between laxative use (a surrogate for constipation) and objective sleep metrics, and 2) the relationship between laxative use and self-reported insomnia symptoms in a convenience sample of middle-aged/elderly patients who completed in-laboratory polysomnography.

**Materials and Methods:** We cross-sectionally analyzed first-night diagnostic in-laboratory polysomnography data for 2946 patients over the age of 40 (mean age 60.5 years; 48.3% male). Laxative use and medical comorbidities were obtained through self-reported questionnaires. Patient insomnia symptoms were based on self-report. Associations between laxative use and objective sleep quality were analyzed using multivariable linear regression models. Associations between laxative use and insomnia were assessed using multivariable logistic regression models.

**Results:** After adjusting for age, sex, body mass index, total recording time and relevant comorbidities, laxative users had a 7.1% lower sleep efficiency ( $p < 0.001$ ), 25.5-minute higher wake after sleep onset ( $p < 0.001$ ), and a 29.4-minute lower total sleep time ( $p < 0.001$ ) than patients not using laxatives. Laxative users were found to be at greater odds of reporting insomnia symptoms ( $OR = 1.7, p = 0.024$ ) than patients not using laxatives.

**Conclusions:** Laxative use is associated with impairments in objective sleep quality. Patients using laxatives were also at greater odds of reporting insomnia symptoms.

**Acknowledgements:** Dr. Mark Boulos's research program received support from the Mahaffy Family Research Fund.

### LONGITUDINAL ASSOCIATIONS OF INSUFFICIENT SLEEP DURATION AND INSOMNIA WITH OBESITY FROM ADOLESCENCE TO YOUNG ADULTHOOD IN THE GINIPLUS AND LISA STUDIES

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**Introduction:** Insufficient sleep and insomnia in childhood were reported to increase risk of being overweight/obese in adulthood. However, the causality and direction of the association remain unclear. This study aimed to assess longitudinal associations of insufficient sleep and insomnia and changes over time on overweight/obesity.

**Materials and Methods:** Questionnaire-based information on sleep duration, insomnia and body mass index (BMI) was obtained from two German birth cohorts, GINIplus and LISA. A total of 1665 adolescents (15-year follow-up) with complete data were followed up to young adulthood (20-year follow-up). Insufficient sleep was defined as sleep duration  $< 8$  hours for adolescents and  $< 7$  hours for adults. Each unfavorable sleep behavior (insufficient sleep and insomnia) was categorized into four groups, describing presence/absence at both time-points or at either one time-point. Overweight/obesity was defined as BMI z-score (WHO) above one standard deviation for adolescents and as BMI above 25kg/m<sup>2</sup> for young adults. The associations between unfavorable sleep behaviors and adult overweight/obesity were analysed using logistic regression, adjusted for potential confounders. Interaction of the associations with sex was tested. The role of polygenic risk scores (PRS) for BMI were tested in a subsample with available genotype information ( $n = 774$ ). Furthermore, we tested the change in overweight/obesity over time in relation to insufficient sleep and insomnia in young adulthood.

**Results:** The prevalence of insufficient sleep, insomnia and overweight/obesity among adolescents was 17.7 %, 13.8 %, and 11.4% respectively, and 17.5%, 20.8%, and 16.9% among young adults respectively. Compared with participants who reported sufficient sleep at both time-points, those with insufficient sleep only in young adulthood had an increased risk of young adult overweight/obesity (odds ratio (OR)=2.02, 95%confidence interval (CI)=1.42-2.88), regardless of insufficient or sufficient sleep during adolescence. Compared with participants without insomnia at both periods, participants with insomnia at both time-points had an increased risk of adult overweight/obesity (OR=2.05, 95%CI=1.20-3.47), while no significant finding was observed in those reporting insomnias only at one time-point. There results remained stable when adjusting for BMI during adolescence.

Interaction analysis indicated significantly stronger effects in females than males, with females having unfavourable sleep behaviors at both time-points showing a higher risk of adult overweight/obesity. The PRS for BMI was associated with an increased risk of adult overweight/obesity (OR=1.45, 95%CI=1.18-1.77), but no significant interaction effect with unfavourable sleep behaviors was observed.

In addition, compared with normal BMI at both time-points, overweight/obesity only in young adulthood or at both time-points was associated with young adult insufficient sleep (OR=1.61, 95%CI=1.06-2.45; OR=2.01, 95%CI=1.31-3.07, respectively). Furthermore, only overweight/obesity at both periods was associated with an increased risk of adult insomnia (OR=1.76, 95%CI=1.16-2.67), but not overweight/obesity at only one time-point.

**Conclusions:** Insufficient sleep only presented a cross-sectional association with overweight/obesity, while long-term insomnia in adolescence and young adulthood was associated with young adult overweight/obesity, and vice versa, indicating a bidirectional association. Improving unfavorable sleep behavior might prevent development of overweight/obesity later in life.

**Acknowledgements:** The authors thank all families' participation in the GINIplus and LISA studies and all members of the GINIplus and LISA Study Groups.

### "MY CHILD SLEEPS POORLY, BUT I JUST CAN'T DO IT": PARENTAL BARRIERS TO BEHAVIOURAL SLEEP INTERVENTIONS AND LINKS TO AUTO-VIDEOSOMNOGRAPHY.

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**Introduction:** Paediatric insomnia is believed to affect between 20–30% of infants. Research into interventions for infant sleep have revealed behavioural sleep interventions (BSI) as some of the most efficacious in improving infant sleep quality. Despite this, many parents are deterred from implementing BSIs, up to 30% of families do not benefit, and levels of attrition are high. This study aimed to identify the main barriers of BSI implementation as perceived by parents, as well as possible solutions to reduce the impact of these barriers. We further aimed to compare parents of infants with sleep problems who are willing to implement BSIs compared to those not prepared to use these interventions in their parental self-efficacy, cry tolerance, and endorsement of scientific inquiry. **Materials and Methods:** A total of 775 parents of infants aged 3–18 months with a reported sleep problem completed an online survey, which included items regarding barriers to BSI Implementation, the Maternal Self Efficacy Questionnaire, items regarding parental cry tolerance, and questions related to endorsement of scientific inquiry. Infant sleep was assessed via auto-videosomnography, using Nanit camera monitors for 14 nights.

**Results:** Of the parents who indicated their child had a sleep problem but had not yet implemented BSIs (N=434), difficulty coping with infant crying (39.9%) and guilt (36.4%) were the two most frequently endorsed barriers to trying these interventions. Many parents reported that more education on how to implement the technique (50%), having access to an app to facilitate implementation (35.5%), and more supporting scientific evidence (33.9%) would help them consider trying BSIs.

We then wanted to further compare parents who would not consider sleep training versus parents who would consider trying sleep training. Generalized estimating equations revealed that parents who would consider trying sleep training had infants with significantly shorter night-time sleep (9.36 vs 9.7 hrs,  $p < .001$ ), who woke more frequently (4.9 vs 4.1 awakenings,  $p < .001$ ), and whose parents visited the crib more often throughout the night (3.2 vs 2.5 visits,  $p = .003$ ). Moreover, parents who found infant crying less distressing were more willing to try sleep training ( $p = .032$ ). Groups did not differ on measures of maternal self-efficacy ( $p = .191$ ), or scientific inquiry ( $p = .595$ ).

**Conclusions:** Parents of infants with a sleep problem report that difficulty coping with infant crying and guilt are the two main barriers associated with BSI implementation. Parents reported that more education, the use of an app, and more scientific evidence would help them consider trying BSIs. Unsurprisingly, parents who would consider trying BSIs had poorer objectively measured infant sleep and found infant crying less distressing compared to parents not willing to try BSIs. Contrary to expectations, there were no differences in maternal self-efficacy or endorsement of scientific inquiry between groups who would/would not consider trying BSIs. Future research should consider whether the solutions endorsed by parents in this study help to overcome the barriers experienced associated with sleep training.

**Acknowledgements:** I would like to acknowledge the team at Nanit for assisting with data collection for this study.

#### NATURALISTIC STUDY OF ENVIRONMENTAL FACTORS IMPACTING SLEEP QUALITY IN YOUNG ADULT COLLEGE STUDENTS

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**Introduction:** Sleep quality is compromised in young adult college students. Research studies have identified cognitive decline in terms of grades, initiative in the classroom, participation in courses, reduced sustained study times have been noted. In addition to these factors, the everyday experiences of the college student, such as exposure to noise and natural light levels may affect their sleep.

**Materials and Methods:** Sleep log, Self-report measures of sleep quality, Mood level, Morningness versus Eveningness scale, random sampling using phone app of light and sound. Light and sound meter data from common campus sites will be presented.

**Results:** Sleep log data indicate variable sleep patterns and sleep efficiency scores ranging from 67–99%. The app data collected by participants of noise

and light indicated noise levels of 33db, on average for daytime recordings and 71db, on average for nighttime recordings with considerable variability. Overall, students in the residential community had higher levels than commuter students.

**Conclusions:** Young adult college students have compromised sleep quality secondary to their choices in schedule rather than sleep. It is possible that a portion of the young adult college students' sleep quality is distorted by influence of light and noise factors. A controlled student to examine this further is planned.

**Acknowledgements:**

#### NEW PERSPECTIVE IN DRUG INDUCED SLEEP ENDOSCOPY

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The design of the 5VsEs machine was conceived to solve some of the method issues, including endoscopic pattern classification methods, drug infusion techniques, interoperator interpretive variability, and lack of standardization of the same procedure. etc. reported in the literature.

With the 5VsEs prototype, the operator can continuously evaluate the kinetic and pharmacodynamic profiles of the drugs and all the decision parameters during the procedure and during the re-evaluation in the post-analysis and research, which are indispensable for a correct evaluation in the post-analysis of the endoscopic pattern together with the BIS data and the polygraph results. All in a single monitor.

The 5VsEs project solves the technical problems that prevent the complete recording of the DISE procedure because it homogenizes the response latencies of the instruments used during DISE (video-endoscopy, polygraphy, Bispectral index, TCI pump, others according to the set up): this has allowed to create a single monitor that the operator uses during the execution of the procedure and makes possible an integral multi-parametric storage indispensable for post-analysis and research.

The operator using this new technical solution immediately notices an ergonomics and comfort not found in any known setting. This storage mode, recalling the black box in aeronautics, has repercussions of great interest since it facilitates forensic protection, comparability of data during multicenter studies, facilitates any research concerning the world of endoscopy in induced sleep. It also benefits teaching, telemedicine and teleconsultation.

The following medical devices are part of the 5VsEs prototype: a flexible endoscope, a compatible camera, an American Academy of Sleep Medicine AASM-compliant home sleep apnea testing device, an oximeter, a BIS system, a TCI pump, and a medium latency auditory evoked potential (MLAEP) system.

The first application of the potential for post-analysis with 5VsEs was a study analyzing the response of the MLAEPi vs. the BIS in order to analyze the mid-latency auditory evoked potential index (MLAEPi), compared to the standard bispectral index (BIS), as a method to assess the level of sedation in drug-induced sleep endoscopy (DISE).

In this controlled clinical study on a sample of 99 patients with obstructive sleep apnea (OSA) or snoring, we compared the MLAEPi with the BIS after propofol infusion during the standard DISE technique in order to define the MLAEPi values within the observation window of the procedure. The DISE procedure was divided into eight phases, and we collected both MLAEPi and BIS data values from the same patient at each phase.

The standards and design of this study confirmed that an index derived from MLAEPs is a useful alternative to BIS in DISE with propofol.

The most important finding from this study was a more rapid response of the MLAEP than the BIS. This was most evident as the procedure approached the observation window phase, and it made the DISE procedure more reliable in diagnosis because it avoids the diagnostic error of labeling the event shown on the monitor as obstructive apnea when it might be an undesirable central apnea induced by propofol.

## NIGHT-SHIFT WORK, BREAST CANCER INCIDENCE AND ALL-CAUSE MORTALITY

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**Introduction:** Night-shift work exposure is proposed to link to a wide range of health issues, especially carcinogenesis and lethality. However, the epidemiological associations among night-shift work exposure, breast cancer incidence and all-cause mortality remain inconclusive.

**Materials and Methods:** We performed an updated systematic review and meta-analysis to confirm the potential associations among night-shift work exposure, breast cancer incidence and all-cause mortality.

**Results:** A total of 31 prospective cohort studies, containing 9.3 million participants, 31244 incident breast cancer cases, 12728 cancer-related deaths, 7882 cardiovascular end points and 30807 all-cause mortalities were included. In sum, the summary RR of incident breast cancer for an increase of night-shift work was 1.029 (95% CI 1.003-1.055). Compared with standard day worker, female night-shift workers had a statistically significantly increased RR (1.086, 95%CI 1.032-1.142) for breast cancer incidence in subgroup of >10 years. Moreover, a positive association was revealed in subgroup studies of rotating night-shift work (RR =1.053, 95% CI 1.018-1.090). Besides, significant increased risk of cardiovascular mortality was demonstrated in night-shift work group (RR =1.031; 95% CI 1.006-1.057).

**Conclusions:** Our systematic review and meta-analysis provides strong evidences to support the positive associations among night-shift work exposure, breast cancer incidence and cardiovascular mortality. Overall, night-shift work exposure significantly increased the risk of breast cancer morbidity by: 2.9% for total, 8.6% for subgroup of more than 10 years and 5.3% for rotating night-shift work. In addition, night-shift work increases the risk of cardiovascular mortality by 3.1%.

**Acknowledgements:** This work was supported by funds from the China Postdoctoral Science Foundation (2017M610570) and Training Project Funding Plan of Youth Innovative Talents of Fujian Provincial Maternity and Children's Hospital (YCXB 18-01).

## NIGHT-TO-NIGHT VARIABILITY OF SLEEP QUALITY USING ODDS RATIO PRODUCT: AN ASSESSMENT OF 14-31 NIGHTS OF IN-HOME POLYSOMNOGRAPHY

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**Introduction:** There is a paucity of research on sleep quality using objective polysomnographic data measured in an in-home environment under real-world conditions. In the present study, we assessed objective sleep quality using Odds Ratio Product (ORP) to understand the variability of sleep quality within and between individuals across multiple nights.

**Materials and Methods:** 18 participants (age 40.2±10.5; 9 females) recorded their sleep with in-home PSG over 14 to 31 nights. Sleep quality was measured using ORP (derived from frontal EEG channels) across the duration of the recording (ORP<sub>TRT</sub>). The ORP data were analyzed to assess both between- and within-subject variation to determine the night-to-night variability of sleep quality. Subjective sleep quality was assessed at baseline using the Pittsburgh Sleep Quality Index (PSQI) and was correlated with ORP<sub>TRT</sub>. Subjects tracked their activities (e.g., exercise, substances, light exposure) daily.

**Results:** There was an average of 20.1 (±3.5 SD) PSG nights recorded across 24.3 (± 2.9) days. At baseline, participants had an average PSQI Global Score of 5.3 ± 2.5. Six (33%) participants had PSQI scores >5, which reflected poor sleep quality. Over the duration of the study, participants had an average ORP<sub>TRT</sub> of 1.20 (±0.32). Participants also had a range in variability in sleep depth and quality between nights of 0.68 (±0.44). The between-subjects variation of average ORP<sub>TRT</sub> was large (1.83) and the

within-subjects variation of average ORP<sub>TRT</sub> was small (0.036). Poorer PSQI global scores were associated with higher variability in ORP<sub>TRT</sub> such that greater variability in ORP<sub>TRT</sub> across nights was associated with worse subjective sleep quality ( $r = 0.47, p = 0.05$ ).

**Conclusions:** These results highlight the utility of ORP in capturing differences between subjects in sleep quality across 20 nights. While there were large differences between subjects, the variability across nights within subjects was small. Individuals who did have high variability across nights were more likely to report poorer subjective sleep quality at baseline. Further research could focus on what specific daily activities and lifestyle factors contribute significantly to variation in sleep quality across nights.

## NOCTURNAL PARENTAL INVOLVEMENT IN INFANT SLEEP IS ASSOCIATED WITH WORSE PARENTAL SLEEP, BUT ONLY AMONG FATHERS.

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**Introduction:** Excessive parental involvement in infant sleep has been shown to have detrimental effects on infant sleep health, leading to longer sleep latency, more and longer nocturnal awakenings and shorter sleep duration. However, less is known about the associations between parental involvement in infant sleep and parental sleep health. While sleep is expected to be temporarily and partially disrupted in the postnatal period, it still serves an essential role in several physical and mental health domains for the parent and has been shown to significantly affect the parent-child relationship. Thus, we investigated the associations between parent nocturnal interventions in infant sleep and parental sleep duration and subjective quality, accounting for infant's age, infant nocturnal sleep duration and number of awakenings, and parental perceived stress. We also investigated whether these associations differed in mothers and fathers.

**Materials and Methods:** Ethical approval was obtained by the New York State Psychiatric Institute and Advarra Institutional Review Boards. The cohort was comprised of N=576 infants (age 9.1±1.8 months, 49.6% male) who were recruited among the customer base of the Nanit baby monitor. Information on infant nocturnal sleep duration, number of awakenings and parent interventions were captured via Nanit videosomnography (average nights recorded 11.9±2.2), while information on infants age, parental sleep (Pittsburgh Sleep Quality Index) and stress (Perceived Stress Scale) were collected via questionnaires on REDCap (75.8% mothers, 23.6% fathers).

**Results:** Parental nocturnal sleep duration was 6.9±1.0h, parental sleep quality was 11% very good, 65% fairly good, 18% fairly/very bad. The average number of parent nocturnal interventions was 1.4±1.9 and parental perceived stress was 14.6±6.3. Infant nocturnal sleep duration was 10.2±1.2h and number night awakenings was 3.1±1.4.

More parental nocturnal interventions, higher parental perceived stress and shorter infant nocturnal sleep duration were associated with shorter parental sleep duration (parent nocturnal interventions  $\beta = -0.07 \pm 0.03, p = 0.01$ ; infant nocturnal sleep duration  $\beta = 0.20 \pm 0.04, p < 0.001$ ; perceived stress  $\beta = -0.02 \pm 0.007, p < 0.001$ ), and poorer parental sleep quality (parent nocturnal interventions  $\beta = -0.15 \pm 0.07, p = 0.02$ ; infant nocturnal sleep duration  $\beta = -0.20 \pm 0.09, p = 0.02$ , perceived stress  $\beta = 0.11 \pm 0.02, p < 0.001$ ).

When stratified by caregiver type, we found that there were no differences in parental sleep duration and quality, infants' age, infant nocturnal sleep duration, night awakenings and number of parent nocturnal interventions between mothers and fathers, but reported levels of perceived stress differed (mothers 15.04±6.3; fathers 13.47±6.3,  $p = 0.02$ ). For mothers, shorter infant nocturnal sleep duration and higher perceived stress were associated with shorter sleep duration ( $\beta = 0.23 \pm 0.05, p < 0.001$ ;  $\beta = -0.03 \pm 0.008, p < 0.001$  respectively) and worse sleep quality ( $\beta = -0.23 \pm 0.05, p < 0.001$ ;  $\beta = -0.03 \pm 0.008, p < 0.001$  respectively). On the other hand, for fathers more parental nocturnal interventions were associated with shorter sleep duration ( $\beta = -0.09 \pm 0.04, p = 0.05$ ) and worse quality ( $\beta = -0.09 \pm 0.04, p = 0.05$ ).

**Conclusions:** Our results indicate that the number of parental nocturnal interventions affects parental sleep duration and quality. Stratified analyses by caregiver type, highlighted that maternal sleep is affected by perceived stress and infant nocturnal sleep duration, while paternal sleep is affected by parent nocturnal interventions. These results warrant further investigation into the potential detrimental effects of excessive parental involvement in infant sleep on parental sleep and overall health.

#### ORIENTING CAUSAL RELATIONSHIPS BETWEEN SLEEP AND ADIPOSITY TRAITS USING MENDELIAN RANDOMISATION

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**Introduction:** Poor sleep and obesity are problems that permeate throughout much of the UK population. Previous studies have found increased odds of obesity in relation to an evening-preference chronotype, occurrence of insomnia symptoms, and both short (<6h) and long (>9h) sleep duration. Many studies have also found that individuals involved in night shift work are more likely to become overweight or obese. However, it is difficult to determine direction of effects in many of these studies.

This study aims to use Mendelian randomisation (MR) to explore the causal direction of effect between sleep and adiposity traits. MR is an approach that utilizes genetic variants associated with potentially modifiable risk factors as instruments to estimate causal effects on outcomes.

**Materials and Methods:** We obtained genetic variants strongly ( $p < 5 \times 10^{-8}$ ) associated with sleep traits (chronotype, insomnia, sleep duration, napping during the day, daytime sleepiness, and ease of getting up in the morning) and adiposity traits (hip circumference (HC), waist circumference (WC), body fat percentage (BFP), body mass index (BMI), childhood body size (CBS), and waist-to-hip ratio (WHR)) from published genome-wide association studies (GWAS). Two-sample bidirectional MR was performed to investigate causal relationships between traits.

**Results:** When looking at adiposity effects on sleep traits, we found increased morning-preference per SD increase in BMI [beta=0.035, 95% CI=-0.062,0.008], and an increase in ease of getting up per SD increase in both WC [0.028, 0.001,0.055] and BMI [0.024, 0.007,0.040]. Insomnia was increased per SD increase in BMI [0.039, 0.023,0.055]. We observed increased daytime sleepiness per SD increase in WC [0.033, 0.017,0.048], BMI [0.026, 0.015,0.037], CBS [0.005, 0.001,0.009] and HC [0.019, 0.006,0.033]. We found a decrease in napping per SD increase in CBS [-0.007, -0.013, -0.001] but increased napping per SD increase in HC [0.023, 0.003,0.043], WC [0.053, 0.030,0.075], BFP [0.032, 0.012,0.053] and BMI [0.039, 0.024,0.054]. Sleep duration decreased per SD increase in HC [-0.043, -0.067, -0.020], WC [-0.049, -0.049, -0.021], BMI [-0.044, -0.062, -0.026] and CBS [-0.012, -0.020, -0.004].

For sleep trait effects on adiposity, a reciprocal positive relationship was found for insomnia on BMI, daytime sleepiness on HC, and napping on HC, WC, BFP and BMI. We also found an increase in CBS per SD increase in morning-preference [0.089, 0.140,0.038], and an increase in HC [0.332, 0.162,0.502], WC [0.407, 0.257,0.557], and BFP [0.364, 0.235,0.493] per SD increase in insomnia symptoms. We also found an increase in WHR per SD increase in napping [0.190, 0.038,0.342].

**Conclusions:** Using an MR approach, we investigated the bi-directional relationships between a series of sleep and adiposity-related traits. We found evidence for causal effects, primarily in the direction of adiposity acting on sleep, rather than vice versa. However, there was evidence that insomnia may have a greater causal effect on adiposity, and reciprocal effects were observed particularly between daytime sleepiness and adiposity measures. Unpicking the direction of causality between sleep traits and adiposity is important when developing interventions to improve sleep and lower risk of obesity.

**Acknowledgements:** This research was conducted using the UK Biobank resource (www.ukbiobank.ac.uk) and funded by the Above and Beyond Charity.

#### PHENOTYPIC AND GENETIC CORRELATION BETWEEN SLEEP, BEHAVIOR, AND MACROSCALE CORTICAL GREY MATTER

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**Introduction:** Humans need about seven to nine hours of sleep per night. Sleep habits are heritable, associated with brain function and structure, and intrinsically related to well-being, mental, and physical health. However, the biological basis of the interplay of sleep and physical and mental health is incompletely understood.

**Materials and Methods:** We combined neuroimaging and behavioral genetic approaches in two independent large-scale datasets (HCP (n = 1106), age range: 22–37 and eNKI (n = 783), age range: 12–85) and tested phenotypical association and (co-) heritability of various indices of sleep quality and phenotypical and heritable relationships of sleep quality with brain thickness, physical (i.e. BMI) and mental-health (e.g. depressive symptoms) markers. For our phenotypic analysis, we used Spearman's correlation test, while controlling for age, sex, age × sex interaction, age<sup>2</sup>, age<sup>2</sup> × sex interaction. Analysis of heritability and genetic correlation were performed in the twin-based HCP sample with maximum likelihood variance-decomposition methods. Heritability (h<sup>2</sup>) is the total additive genetic variance and genetic correlations were estimated using bivariate polygenic analysis. We performed partial least squares (PLS) analysis, in order to identify latent relationships between the factors. PLS is a multivariate data-driven approach, enabling simultaneous linking of behavioral measures to brain structure.

**Results:** Our findings demonstrated that sleep, mental, and physical health have a shared neurobiological basis in grey matter anatomy; and that these relationships are driven by shared genetic factors. Though local associations between sleep and cortical thickness were inconsistent across samples, we identified two robust latent components, highlighting the multivariate interdigitating of sleep, intelligence, BMI, depression, and macroscale cortical structure.

**Conclusions:** Our findings highlight the key relation between intelligence, mental and physical health and sleep profile in healthy subjects, which is reflected by shared neurobiological signatures. Though we could establish phenotypic and genetic correlations between sleep duration and local cortical thickness in two independent samples, findings were inconsistent. Our observations provide a system-level perspective on the interrelation of sleep, mental, and physical conditions, anchored in grey-matter neuroanatomy.

**Acknowledgements:** We would like to thank the various contributors to the open access databases that our data was downloaded from, specifically HCP and eNKI data.

#### POOR FALSE SLEEP FEEDBACK DOES NOT AFFECT PRE-SLEEP COGNITIVE AROUSAL OR SUBJECTIVE SLEEP CONTINUITY IN HEALTHY SLEEPERS: A PILOT STUDY

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**Introduction:** Wearable devices are commonly used to monitor sleep. Modern wearable devices calculate a numerical metric of sleep quality

(sleep feedback), which are intended to allow users to monitor and, potentially, improve their sleep. However, the monitoring of device-derived sleep feedback is likely to negatively affect pre-sleep cognitive arousal, and subjective sleep, however, to date, no studies have examined this. The aim of this pilot study was to examine if the presentation of poor false sleep feedback, which participants were told was a sleep metric derived from the measurement of their habitual subjective sleep (sleep diaries) could negatively affect pre-sleep arousal and subjective sleep continuity. It was expected that poor sleep feedback would: 1) increase pre-sleep cognitive arousal, and 2) negatively affect subjective sleep continuity (total sleep time and sleep efficiency), relative to good sleep feedback.

**Materials and Methods:** Healthy good sleepers ( $n = 54$ ) participated. The study was delivered online, and on Day 0, after providing informed consent, participants were randomly allocated to receive either good sleep feedback ( $n = 25$ ) or poor sleep feedback ( $n = 24$ ).

Pre-sleep cognitive and somatic arousal was measured immediately prior to sleep using the Pre-Sleep Arousal Scale (Nicassio et al., 1985). Subjective sleep continuity was measured using Consensus Sleep Diaries (CSD-M; Carney et al., 2012). Measures of subjective sleep continuity (total sleep time (TST), time in bed (TIB), sleep efficiency (SE%), the number of awakenings (NWA) and wake after sleep onset (WASO)) were derived from the CSD-M. Participants completed the PSAS on Night 0, Night 7 and Night 14. The CSD-M was completed daily (Days 1–7, and Days 8–14).

Participants in the good sleep feedback condition were shown a message, in green text, stating “Congratulations! Based on your data, your sleep score is 92/100. Well done!” alongside an icon of a smiling face. Participants in the poor sleep feedback condition were shown a message, in red text, stating “Sorry! Based on your data, your sleep score is: 22/100”, alongside an icon of an unhappy face.

PSAS somatic and cognitive subscores were compared between good and poor feedback groups using a 2 (group)  $\times$  3 (time point: Night 0, Night 7, Night 14) mixed analysis of variance (ANOVA). CSD-M sleep continuity values (TST, TIB, SE%, SOL, NWA) and WASO were compared between groups using 2 (group)  $\times$  2 (time) mixed ANOVAs.

**Results:** Good and poor sleep feedback groups did not show significant differences in pre-sleep cognitive or somatic arousal between Night 0, Night 8 and Night 15 ( $p$ -values  $> .05$ ), or sleep continuity between Days 1–7 and Days 8–14 (all  $p$ -values (adjusted)  $> .008$ ).

**Conclusions:** Contrary to expectations, poor sleep feedback did not affect pre-sleep cognitive arousal or any sleep continuity variable (including TST or SE%) relative to good sleep feedback. These results indicate that occasionally monitoring poor sleep feedback is unlikely to disrupt cognitive arousal or subjective sleep, in healthy sleepers.

**Acknowledgements:** N/A

#### POOR SLEEP QUALITY MAY CONTRIBUTE TO DYSFUNCTIONAL ILLNESS PERCEPTION, PHYSICAL AND EMOTIONAL DISTRESS IN HOSPITALIZED PATIENTS: RESULTS OF A NATIONAL SURVEY OF THE ITALIAN SOCIETY OF CONSULTATION-LIAISON PSYCHIATRY

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**Introduction:** Distress associated with physical illness is a well-known risk factor for adverse illness course in general hospitals. Understanding the factors contributing to it should be a priority and among them dysfunctional illness perception may contribute to it. Since poor sleep quality is recognized as major risk factor for health problems the aim of this study was to study the association among sleep quality, illness perception and levels of distress during hospitalization. The present study was promoted by the Italian Society of Consultation-liaison psychiatry (SIPC), which is a psychiatric subspecialty addressing the psychological care of medically ill patients as well as the relationship between medical and psychiatric disorders and organized the first national survey on the potential role of poor sleep quality in patients hospitalized in general

hospital.

**Materials and Methods:** From January 2018 to December 2020 the current study included a consecutive series of individuals who were hospitalized in medical and surgical wards of different hospitals located throughout the Italian national territory and required an assessment for psychological/psychopathological conditions usually referred to consultation-liaison Psychiatry. A consecutive series of 409 individuals who were hospitalized in medical and surgical wards of different hospitals located throughout the Italian national territory and required an assessment for psychopathological conditions, were included in this cross-sectional study. Sleep quality was assessed with Pittsburgh Sleep Quality Index (PSQI), Emotional and physical distress with the Edmonton Symptom Assessment System (ESAS) Illness Perception with the Brief Illness Perception Questionnaire (BIPQ). Differences between groups, correlations and mediations analyses were computed.

**Results:** The current study has shown that poor sleep quality was frequent in hospitalized patients in Italy, interesting more than the 70% of evaluated patients. Importantly, poor sleep quality in hospitalized patients was related to dysfunctional illness perception and to emotional and physical distress in these patients. Poor sleep quality directly predicted dysfunctional illness perception and emotional/physical distress. Results of the mediation analyses showed that PSQI directly predicted ESAS and BIPQ, but PSQI has also shown a mediated effect on ESAS with BIPQ as a mediator. The relationship between PSQI and ESAS-Total was mediated by BIPQ-Total. The standardized regression coefficient between poor sleep quality (PSQI) and dysfunctional illness beliefs (BIPQ) was statistically significant, as was the standardized regression coefficient between dysfunctional illness beliefs and Physical and emotional distress (ESAS-Total). The indirect effect of PSQI on ESAS-Total was found to be statistically significant (Effect=0.24; 95% CI=0.17 – 0.88).

**Conclusions:** Poor sleep quality may interest more than 70% of hospitalized patients and may favor dysfunctional illness perception and emotional/psychical distress. *Poor sleep quality may favor dysfunctional illness perception and emotional/psychical distress in hospitalized patients and assessing and treating sleep problems in hospitalized patients should be included in the routine of hospitalized patients. Treating sleep disturbance in this context should be useful to provide additional strategies to improve medical/surgical illness recovery.*

**Acknowledgements:** Italian society of consultation-liaison psychiatry

#### PREVALENCE OF SLEEP PROBLEMS AND ITS IMPACT ON ANXIETY, DEPRESSION AND QUALITY OF LIFE IN KOREAN FIRE FIGHTERS

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**Introduction:** Professional fire fighter is a strenuous and unique occupation due to the high levels of stress and risk involved as well as the low control nature of the job. Anxiety and depression are prevalent in the professional fire fighters' population and constitute a dominant area of investigation. Limited attention have been given to impact of sleep problems on the anxiety, depression and quality of life in fire fighters. The aim of this study is to evaluate prevalence of sleep problems and its impact on anxiety, depression and quality of life in Korean fire fighters.

**Materials and Methods:** Using simple sampling method in a cross-section study in Jeonbuk province of Korea, sleep problems, anxiety, depression and quality of life of 1669 professional fire fighters were measured with Patients Health Questionnaire-9 (PHQ-9), Generalized Anxiety Disorder 7 item (GAD-7) and brief version of World Health Organization Quality of Life assessment scale (WHOQoL-Brief). Sleep problem was measured with 3 item of PHQ-9, the definition of sleep problems group was not able to initiate sleep or maintaining sleep. We measured cross-sectional Odds ratios for sleep problems group on depression and anxiety by logistic

regression analysis.

**Results:** The prevalence of sleep problem of Korean fire fighters was 51.2%. Korean fire fighters with sleep problems showed not only more anxiety ( $p < 0.001$ ) and depression ( $p < 0.001$ ) but also lower quality of life ( $p < 0.001$ ). The sleep problems group was more likely to suffer from depression (OR=47.537, 95% CI: 33.669–64.323) and anxiety (OR=9.822, 95% CI: 7.529–12.813). The severity of sleep problems in Korean fire fighters was positive correlated with depression and anxiety.

**Conclusions:** These results show that higher prevalence of sleep problems in Korean fire fighters and Korean fire fighters with sleep problems have more depression and anxiety, and less quality of life than fire fighters without sleep problems. Sleep problems are important risk factor on the depression and anxiety in Korean fire fighters. Early detect of sleep problems of fire fighters will be needed to manage of depression and anxiety.

### PROSPECTIVE ASSOCIATION BETWEEN SLEEP-WAKE PATTERNS IN ADOLESCENCE AND BEHAVIOR CHARACTERISTICS IN YOUNG ADULTHOOD

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**Introduction:** The relation between sleep-wake patterns (SWP) and socio-emotional regulation has been widely studied in the adult population, in particular, sleep alterations with externalizing, aggressive and hyperactive problems, and mood disorder diseases. However, there are scarce longitudinal studies in adolescence. The goal of this research was to assess the association between SWP in adolescence and behavior characteristics in early adulthood.

**Methods:** Participants were part of a cohort follow-up study since infancy. At 16 y actigraphic recordings were performed uninterruptedly for one week. Weekday SWP were analyzed for the (a) daytime period: wake-up time, naps number and duration, and total wake amount, and (b) nighttime period: sleep-onset, wake episodes number and duration, and total sleep amount. At 21 y participants the self-report CBCL questionnaire was completed at the laboratory, and the T- score norm-based on age and gender from 12 syndrome scales and social and life-style questions was analyzed. T-test and GLM analyses were conducted.

**Results:** One hundred and sixty-nine participants (50,8% female and 20,9 ± 0,4 y) completed both data. Eight of the 12 syndrome scales (withdrawn, aggressive, rule breaking, intrusive, strengths, crit label, internalizing and externalizing problems) showed significant correlations with sleep-onset and wake-up times, and questions regarding friends and job. Positive correlations were apparent between wake-up time (late time) and withdrawn ( $p < 0,02$ ), aggressive ( $p < 0,05$ ), rule breaking ( $p < 0,01$ ), externalization problems ( $p < 0,01$ ) and mean adaptation ( $p < 0,02$ ); in turn, negative correlations were evident with having friends and job. Regarding sleep-onset time (late time) showed positive correlations with withdrawn ( $p < 0,05$ ), aggressive ( $p < 0,001$ ), externalizing problems ( $p < 0,01$ ) and mean adaptation ( $p < 0,05$ ), whereas negative correlations with having friends. After controlling for covariates, sleep-onset time was significantly associated with aggressive ( $p < 0,001$ ), withdrawn ( $p < 0,04$ ), and externalizing symptoms ( $p < 0,01$ ) problems. Finally, early wake-up time was associated with having friends and job ( $p < 0,01$ ).

**Conclusion:** Our results show that SWP in adolescence relate to behavior characteristics in early adulthood. In particular, late sleep-onset time in adolescence is prospectively associated with negative behaviors.

**Support:** NIH HD33487 grant

### RACIAL/ETHNIC DIFFERENCES IN TYPES OF SOCIAL SUPPORT AND SLEEP HEALTH IN THE UNITED STATES

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**Introduction:** Social support (SS) is associated with better health, and may

enhance resilience to stress - a determinant of sleep disparities. However, the specific types of SS that benefit sleep are unclear, and whether these associations vary by race/ethnicity are unknown.

**Materials and Methods:** Using National Health Interview Survey data (2007–2008), we assessed cross-sectional associations between types of SS (number of friends, financial, marital, and emotional support) and self-reported short sleep duration (<7 hours) overall and within race/ethnicity groups (Black, Hispanic and White men and women). After adjustment of covariates, we estimated PRs (95% CI) using logistic regression (marginal standardization) and sleep in minutes (95% CI) using linear regression accounting for survey design and weights.

**Results:** Among 3,711 participants, mean age was 57 years; 37% slept <7 hours; 21% Black, 26% Hispanic and 53% White. Black adults had the highest prevalence of short sleep (55%). Overall, participants with financial support and married individuals had a lower prevalence of short sleep, 23% (0.68, 0.88) and 17% (0.72, 0.95), than those without financial support and unmarried, respectively. Participants with all four types of SS had a 49% lower prevalence of short sleep compared to those without SS. Among Hispanic adults, >5 friends and financial support were associated with sleeping 18.5 (7.7, 29.2) and 14.2 (5.3, 23.1) minutes longer, respectively. Among White adults, marital support was associated with sleeping 16.2 (7.1, 25.3) minutes longer, and the association was most pronounced among women. Emotional support was associated with longer sleep duration (38 minutes) among Black men only, not women.

**Conclusions:** Overall, friends, financial, marital support and multiple types of SS were associated with healthy sleep duration. The association of SS and sleep varied by the type of support and race-sex. Targeting specific types of SS may help to improve sleep duration among those most-at-risk.

**Acknowledgements:** This work was funded in part by the National Institutes of Health, National Heart, Lung, and Blood Institute K01HL138211.

### REALIZED WORKING HOURS AND SLEEP AMONG HOSPITAL PHYSICIANS

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**Introduction:** Providing 24/7 health care services requires physicians to work on-call duties in addition to regular working time. Previous survey studies have linked physicians' long working hours to negative outcomes, such as sleep problems and accidents. However, no previous studies have used register-data on physicians' working hours to study well-being outcomes. We investigated the association of hospital physicians' working hour characteristics with sleep using survey and register data.

**Methods:** The participants were hospital physicians (n=728, mean age 43.4 years, 62% females) from four hospital districts participating in the Finnish Public Sector study (FPS). The FPS survey data from 2015 was combined to realized working hour data from employers' registers and working hour characteristics from the 91 days prior to the survey. The associations of working hour characteristics with survey responses on sleep duration, sleep sufficiency and sleep problems (the Jenkins Sleep Scale) were analyzed with logistic and multinomial regression analysis adjusted for age, gender, marital status, number of children, overall stressfulness of the life situation, control over working hours and hospital district.

**Results:** One fourth (26%) of the physicians had a short (≤6.5h) habitual sleep duration. Frequent night work was associated with short sleep duration (>6 shifts/91 days, OR 1.87 95%CI 1.23–2.83) compared to physicians without night on-call duties. Insufficient sleep was reported by approximately one third (32%) of the physicians. Several working hour characteristics were associated with insufficient sleep; long weekly working hours (>48h, OR 1.78 95%CI 1.15–2.76), frequent on-call shifts (>12 shifts/91 days, OR 2.00 95%CI 1.08–3.72), night work (>6 shifts/91 days, OR 1.60 95%CI 1.09–2.37) and short shift intervals (≤11h, >12 shifts/91 days, OR 1.65 95%CI 1.01–2.69). Even though nearly half (47%) of the physicians reported at least one sleep problem, the associations between working hour characteristics and sleep problems were rare. Frequent night work increased odds for difficulties in initiating sleep (OR 2.43 95%CI 1.04–5.59). Weekend work and on-call work at home were not associated

with the studied sleep outcomes.

**Conclusions:** These results indicate that especially the frequency of night work and on-call shifts as well as long weekly working hours should be limited when promoting hospital physicians sufficient sleep.

**Acknowledgements:** This study was funded by the Finnish Work Environment Fund (180 022).

## RECAPTURING A POSTERIOR OPEN BITE USING A PRECISION MILLED MORNING OCCLUSAL GUIDE

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### Recapturing a Posterior Open Bite Using a Precision Milled Morning Occlusal Guide

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**Introduction:** Posterior open bite is often mentioned in the literature as a common and unavoidable side effect of oral appliance therapy. Reducing the therapeutic dose using smaller precision devices (less advancement) and providing the patient with a morning maximum intercuspal position (MIP) re-alignment device (Morning Occlusal Guide) manufacturing of and daily wear of a precision MOG can help patients prevent development of a posterior open bite. MIP posterior contact is often evaluated and recorded using articulating paper and having the patient bite together. If the bite does change, the paper would pull out with little or no resistance. If this condition does occur upon loss of or non-use of their MOG, we can use the archival digital records to recreate the MIP position and re-make a MOG at the original bite relationship. This patient had moved from Dr. Rosenfeldt's care in Fargo, ND to the Detroit, MI area and was referred to Dr. Murphy for evaluation of a posterior open bite due to a lost MOG and 4 months' time passing.

**Methods:** The patient was examined and did demonstrate a unilateral posterior open bite. Two new MOGs were ordered from the digital case archives at ProSomnus of the original delivered EVO appliance and MOG, instructions for use were reviewed and the device was delivered to the patient. The patient was also given instructions for exercises according to the AADSM side effect of OAT document.

**Results:** The patient presented 10 days after delivery and wearing the new MOG and doing the exercises. Posterior occlusion had been re-established as demonstrated with resistance of the articulation paper upon closing together in MIP. The patient reported no discomfort and was happy to have his teeth feel normal again.

**Conclusions:** Digital archives and the ability to remake a MOG in the same MIP can be an important step in recapturing bite changes in oral appliance therapy.

**Support:** No financial support was provided for the treatment of this case. Sheats, R, et al "Management of Side Effects of Oral Appliance Therapy for Sleep-Disordered Breathing" *JDSM* 2017;(4): 111-125  
Cohen-Levy J, "Forces created by mandibular advancement devices in OSAS patients: a pilot study during sleep". *Sleep Breath.* 2013;17(2):781-789.

## SHORT SLEEP DURATION IS ASSOCIATED WITH SUICIDAL IDEATION DURING THE COVID-19 OUTBREAK IN MEDICAL STUDENTS: A LONGITUDINAL COHORT STUDY

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**Introduction:** The 2019 coronavirus disease (COVID-19) has disrupted millions of lives and commerce. Increased rates of suicide have been reported during this era. Short sleep duration is associated with increased risk for suicide in the general population. In this study, we aimed to examine the association between pre-COVID-19 short sleep duration and suicidal ideation (SI) during the COVID-19 outbreak in medical students.

**Materials and Methods:** Shantou College Students Sleep Cohort (STCSSC) is a study designed to investigate sleep problems (ie, poor sleep quality, insomnia symptoms, and excessive daytime sleepiness) as risk factors for depression, anxiety, and poor academic performance. At baseline of this study, a voluntary response sample of Shantou University students were selected to complete a series of online questionnaires related to sleep and mood through Questionnaire Star program in the early May and late October of 2019. Among the included 426 freshmen and sophomores, 334 (response rate was 78%) were followed-up during the first wave of COVID-19 pandemic between February to March of 2020. Short sleep duration was defined based on self-reported habitual sleep duration < 7 hours/night. Sleep quality was assessed by Pittsburgh Sleep Quality Index. SI was defined based on a question form the Beck Depression Inventory "do you have any thoughts of killing yourself". Multiple logistic regression was used to examine the association between baseline short sleep duration and SI during the COVID-19 outbreak after adjusting for age, gender, BMI, the severity of depressive and anxiety symptoms and sleep quality.

**Results:** Among the 334 students included, 50.03% reported habitual short sleep duration at pre-COVID period and 5.70% reported SI during the COVID-19 outbreak. After controlling for potential confounders, short sleep duration at pre-COVID-19 period was significantly associated with SI (OR 5.32 [95% CI 1.34-21.14]) during the COVID-19 outbreak.

**Conclusions:** Our findings show that self-reported short sleep duration is a risk factor for SI during the COVID-19 outbreak in medical students, suggesting the importance of sufficient sleep in medical students.

**Acknowledgements:** NA

## SLEEP AND CIRCADIAN REST-ACTIVITY PATTERN OF CRITICAL COVID-19 SURVIVORS IN THE LONG-TERM: A 6-MONTH FOLLOW-UP STUDY

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**Introduction:** A great percentage of critical COVID-19 survivors report sleep alterations after hospital discharge. The determination of predictive factors for such outcomes is extremely relevant for the personalized management of the patients. Given that sleep fragmentation and circadian disruption are commonly observed among acute respiratory distress syndrome (ARDS) survivors and often potentiated by the intensive care unit (ICU) environment, we hypothesized that a great percentage of critical COVID-19 survivors would present sleep and circadian alterations that would be predicted by the duration of hospitalization and ICU stay. Considering this, we aimed to characterize the sleep and the circadian rest-activity pattern of critical COVID-19 survivors six months after hospital discharge and to determine the baseline predictive factors for the adverse outcomes in this regard.

**Materials and Methods:** Observational, prospective study from March 2020, to March 2021. We recruited 106 consecutive patients with a confirmed diagnosis of SARS-CoV-2 who developed ARDS and were admitted to the ICU. Only those who attended the medical visit six months after hospital discharge were included in the analyses. The main evaluations included the Pittsburgh sleep quality index (PSQI) and seven days of actigraphy.

**Results:** The cohort was composed of 106 patients, mostly males (64.2%) with a median [p25;p75] age of 62.0 [55.0;67.8] years. According to the PSQI, 50.9% of the patients presented a compromised sleep quality, which was confirmed by the objective analysis through actigraphy. The circadian rest-activity pattern presented substantial variability among the patients especially in relation to the fragmentation of the rhythm. Body mass index (BMI) could predict sleep (effect size [SD]: 0.221 [0.096]) and circadian-related (0.353 [0.127]) outcomes at the 6-month follow-up. The fragmentation of the rhythm was also predicted by the time spent at the hospital (0.345 [0.121]), at the ICU (0.321 [0.121]), and by the use of

invasive mechanical ventilation (IMV) (0.508 [0.240]). Furthermore, poor sleep quality was associated with other sequelae such as depression ( $r = 0.58$ ) and anxiety ( $r = 0.49$ ).

**Conclusions:** Our findings demonstrate a remarkable prevalence of sleep and circadian alterations in COVID-19 survivors who developed ARDS and were admitted to the ICU. In this context, baseline characteristics such as BMI, time spent at the ICU, and IMV could be useful in predicting adverse outcomes. Altogether, our findings highlight the importance of considering sleep and circadian health of critical patients in the long-term.

**Acknowledgments:** This study was supported by CIBERESUCICOVID (COV20/00110) and UNESPA.

## SLEEP AND MENTAL HEALTH IN CHILEAN YOUNG ADULTS

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**Introduction:** Sleep and mental health are intrinsically related. Evidence showed that poor sleep contributes to the onset and maintenance of mental health alterations, regardless of their severity. Most studies, however, are linked to insomnia, depression or anxiety. This study aimed to assess the relation of sleep quality and daytime sleepiness with behavioral and emotional problems in young adults.

**Methods:** Participants were part of a cohort follow-up study since infancy. The following questionnaires were applied face-to-face by trained health personnel at INTA: Pittsburgh sleep quality index (PSQI), Epworth sleepiness scale (ESS), and Adult self-report scale (ASR). The global scores of PSQI and ESS were categorized: (a) PSQI: <5 good sleep quality and  $\geq 5$  poor sleep quality, and (b) ESS: <10 lower amount of daytime sleepiness and  $\geq 10$  excessive amount of daytime sleepiness. The ASR comprised eight syndrome scales (anxious/depressed, withdrawn, somatic complaints, thought problems, attention problems, aggressive behavior, rule-breaking behavior, and intrusive) and six Diagnostic and statistical manual of mental disorders (DSM)-oriented scales (depressive, anxiety, somatic, avoidant personality, antisocial personality problems, and attention deficit/hyperactivity [ADH: inattention and hyperactivity/impulsivity subscales] problems). For ASR, we used T-scores norm-based on age and gender. General linear models were conducted and the interaction with sex was assessed using Stata/SE 13.1.

**Results:** Ninety-four participants (46.8% female and  $21.4 \pm 0.3$  y) were assessed: 62.8% had poor sleep quality and 29.8% excessive daytime sleepiness. Participants with poor sleep quality showed higher scores in withdrawn (59.0 vs 54.4,  $p < 0.001$ ), somatic complaints (60.2 vs 55.3,  $p < 0.001$ ), attention (58.9 vs 54.2,  $p < 0.001$ ), aggressive behavior (55.3 vs 52.8,  $p < 0.01$ ), depressive (59.6 vs 53.6,  $p < 0.001$ ), anxiety (59.8 vs 56.8,  $p < 0.05$ ), avoidant personality (59.8 vs 54.1,  $p < 0.001$ ), and ADH problems (59.0 vs 54.0,  $p < 0.001$ ) compared to participants with good sleep quality. Those with excessive daytime sleepiness presented higher scores in attention (59.5 vs 56.2,  $p < 0.05$ ), intrusive (56.6 vs 53.2,  $p < 0.01$ ), and ADH problems (59.8 vs 56.1,  $p < 0.01$ ) relative to those with lower daytime sleepiness. Further, females with excessive daytime sleepiness showed increased scores in intrusive than females with less daytime sleepiness (59.5 vs 55.8,  $p < 0.01$ ), which was also the case in ADH problems compared to females (61.3 vs 54.9,  $p < 0.001$ ) and males (61.3 vs 57.0,  $p < 0.05$ ) with less daytime sleepiness. Males with higher daytime sleepiness presented greater scores in intrusive with respect to males (60.0 vs 56.3,  $p < 0.01$ ) and females (60.0 vs 55.8,  $p < 0.05$ ) with lower daytime sleepiness.

**Conclusion:** Our results show a relation between sleep quality and daytime sleepiness with emotional and behavioral characteristics in a group of Chilean young adults. Participants with poor sleep quality or greater daytime sleepiness presented higher score in scales of withdrawn, somatic complaints, attention, intrusive, aggressive behavior, and depressive, anxiety, avoidant personality, and ADH problems.

**Support:** NIH HD33487 grant.

## SLEEP AS PROTECTIVE FACTOR OF CHILDREN'S EXECUTIVE FUNCTIONS: A STUDY DURING COVID CONFINEMENT

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**Introduction:** The abruptly enforced COVID-19 confinement affects sleep and mental health of adults, adolescents and children. Already young children experience worsened sleep quality during confinement, yet potential consequences thereof concerning their maturation of Executive Functions (EFs) remain unexplored. Longitudinal research demonstrates that sleep behavior predicts later behavioral and cognitive development. Accordingly, we propose young children's sleep quality as protective umbrella, preventing negative developmental outcomes from influences of contextual stress. Through the lens of the confinement being an observational-experimental intervention, we tested whether worsening of young children's sleep is tied to EFs outcomes 6 months downstream confinement. We hypothesized that acutely increased night awakenings and prolonged sleep latency relate to lower later EFs scores.

**Materials and Methods:** First, we assessed sleep behavior during the acute confinement phase (April 2020) with an online survey (Children's Sleep Habits Questionnaire) and analyzed the following 4 core sleep behaviors: bedtimes, sleep latency, nighttime sleep duration, and number of nighttime awakenings. A retrospective sleep assessment referred to the time before confinement (pre-CONFINEMENT), and an assessment referred to the time of survey completion (during-CONFINEMENT). A second survey assessed EFs 6 months later (November 2020, FOLLOW-UP) parent-completed Behavior-Rating-Inventory-of-Executive-Function®-Preschool-Version, (BRIEF-P). This standard behavior-rating scale quantifies EFs for ages 24–71 months. Data on 412 preschool children were collected, and complete data were available for analysis for a total of 45 children aged 36–72 months ( $53.3 \pm 4.4$  months; 27 females). Wilcoxon signed-rank tests were used to quantify differences in sleep behavior from pre- to during-CONFINEMENT. We applied linear mixed models with the difference in the 4 sleep behaviors, age, and sex as fixed factors and subject-ID as a random effect accounting for inter-individual differences. For each standard EFs subscale (Inhibit, Shifting, Emotional-Control, Working-Memory, Planning/Organizing), index (*Inhibitory Self-control, Flexibility, and Emergent Metacognition*) and the Global-Composite-Score, the best fitting model was identified separately (backward selection, Akaike Information Criterion).

**Results:** We demonstrate that young children's sleep acutely changed during confinement (more regular bedtimes  $p = 0.003$ ; shorter sleep latency  $p = 0.002$ ). Further, sleep quality and EFs at FOLLOW-UP were associated, including that acutely increased nocturnal awakenings predicted lower inhibitory self-control indices at FOLLOW-UP ( $p = 0.021$ ). Also, acutely increased nocturnal awakenings predicted lower subscales Inhibit and Emotional-Control downstream ( $p = 0.036$ ;  $p = 0.032$ ). Finally, associations were specific to the confinement-induced sleep-change, as demonstrated by the lack of prediction of EFs outcomes through sleep behaviors at pre-CONFINEMENT.

**Conclusions:** These findings highlight mid-term (i.e., 6 months downstream) behavioral consequences of confinement in young children, related to their acute changes in sleep. These findings transfer the concept formerly evidenced in animals to humans, that inducing poor sleep during developmental periods affects later brain function, thereby supporting the protective sleep-umbrella model.

**Acknowledgements:** Funding from the Swiss National Science Foundation (PCEFP1-181279), the University of Zurich: Forschungskredit FK-18-047, Faculty of Medicine, Research in Science and the Humanities (STWF-17-008).

## SLEEP CHARACTERISTICS OF IRANIAN PEOPLE AND THEIR EFFECTS ON DAYTIME FUNCTIONING: A POPULATION-BASED STUDY

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**Introduction:** Sleep characteristics vary between populations. Detrimental sleep habits have cognitive consequences leading to daytime functioning debilitation. Until now no study has been done to investigate sleep characteristics in Iran thoroughly. In this study, we aimed to evaluate Iranians' sleep characteristics and their association with daytime functioning.

**Materials and Methods:** We conducted a population-based study from January 2017 to May 2019 on people between 30 and 65 who lived in 11 provinces of Iran. We randomly selected the participants using a multi-stage random stratified clustered sampling method. We obtained the participants' demographic and anthropometric characteristics and details of bedtime, sleep duration, sleep onset, and sleep impact on daytime functioning. The data were analyzed using student's t-test and One-Way ANOVA test.

**Results:** In total, 1830 people with a mean age of 40.83 years participated in the study. The gender distribution of the participants was even, and 70.98% of them were married. After adjusting for age and sex, the following three factors had a significant impact on daytime functioning: bedtime, sleep onset latency, and sleep duration. (OR=1.12, P<0.038, OR=1.01, P<0.011, and OR=0.99, P=0.01, respectively). We also found that longer sleep onset latency (P=0.004) and shorter sleep durations (P=0.029) significantly interfere with daytime functioning.

**Conclusions:** Iranians' sleep characteristics, especially their sleep duration and sleep onset latency, are associated with their daytime function. Interventions on people's sleep hygiene are warranted to promote healthier sleep behaviors among Iranians, considering the high impact of current sleep characteristics on their daily lives.

**Acknowledgements:** The authors would like to acknowledge our data collection supervisors, Zahra Beigom Seyedaghamiri from Tehran University of Medical Sciences, Zahra Karami from Shahid Beheshti University of Medical Sciences, and Samaneh Akhavan Malayeri from Iran University of Medical Sciences and all who helped us for the data collection of this study. Somayeh Ghodrati Ansarabadi, Parvin Sheibani, Ghazal Dibaei, and Mohammad Reza Mansouri are also acknowledged for their nice contribution in this study.

Our special thanks go to Dr. Mike Mutschelknaus, International Sleep Research Training Program (IS RTP) program coordinator, World Sleep Society, for his edits on this manuscript.

#### SLEEP DEPRIVATION, IMMUNE SUPPRESSION, SARS-COV-2 INFECTION AND SLEEP DISTURBANCES: THE DEATH-AND-DISABILITY LOOP

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**Introduction:** The conservation of sleep across all animal species suggest that sleep serves a vital function. Major sleep deprivation may induce failure of host defense, major risk for metabolic syndrome and immune suppression. We discuss the link between sleep deprivation, circadian misalignment and immune response against viruses with special regards to SARS-CoV-2 infection. The relationship among sleep disorders and viruses may be bi-directional. Virus diseases present with a variety of symptoms, depending on the organ and system that is infected, but many of these conditions are accompanied by sleep disturbances, fatigue, and fever. Viral infection is linked to anxiety, bad sleep quality and depressive symptoms in patients and caregivers. Poor sleep is associated with metabolism abnormalities, obesity and a higher incidence of cardiovascular

sequelae, leading to an unfavorable clinical progression. This chain of bad events represents the death-and-disability loop for SARS-CoV-2 infected people.

**Materials and Methods:** We performed a retrospective review of 199 patients admitted to our COVID-19 semi-intensive care respiratory unit (SARS-CoV-2 infection confirmed by molecular testing) from October 2020 to March 2021. We collected anamnestic records about previous sleep disturbances and mood disorders before viral infection, data about quality of sleep, anxiety, depression and inflammatory markers during hospitalization and after discharge, and their outcome in terms of morbidity and mortality.

**Results:** We identified a subgroup of SARS-CoV-2 patients with worst mood and sleep quality. In this group, blood chemistry showed 83.3% elevated LDH, 70% high ferritin, 75% high troponin, 91.7% high neutrophils/leukocyte rate, elevated CRP in 100%, high D-Dimer test (81.8%). The mean P/F of this group at our unit admission was 132. Their mortality rised up to 83.3% (p<0.001).

**Conclusions:** These findings are consistent with the possible mechanism of hyperinflammatory form associated with critical illness. Sleep disturbances in this subgroup of patients were related to higher mortality and morbidity, leading to disability for the surviving sample. It is mandatory to investigate sleep health in SARS-CoV-2 infected patients.

#### SLEEP DISORDERS AMONG COMMERCIAL AIRLINE PILOTS: A CROSS-SECTIONAL STUDY

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**Introduction:** Over the next 20 years, international market expansion will necessitate the production of new commercial airplanes and the recruitment of additional crew members and technicians. Research has proven that fatigue and lack of sleep are risk factors for impaired cognitive performance and human error. Pilots frequently report fatigue to their employers, which may be related to sleep disturbance. Airline pilots, in particular, often experience circadian desynchronization and other types of sleep disorders. Shift workers have been observed to be at higher risk of fatigue that affects their performance and alertness. In Saudi Arabia, sleep disorders among airline pilots are understudied and underreported. The primary objective of this study was to screen for and determine the risk of sleep disorders, fatigue, and depression among pilots.

**Materials and Methods:** A cross-sectional epidemiological study with national commercial pilots was conducted from March 2019 to March 2020 using validated questionnaires to screen for the risk of sleep disorders, fatigue, and depression.

**Results:** In total, 344 pilots participated in the study. Half the sample was at risk for insomnia and fatigue. Older and more experienced pilots were less likely to suffer impaired sleep quality, insomnia, sleepiness, fatigue, and depression (p <0.001). In total, 59 (17.2%) pilots were at high risk for sleep apnea.

**Conclusions:** The current study found that pilots were at risk of developing sleep disorders. A more robust and objective assessment is warranted for screening.

**Acknowledgements:** This project was funded by the Deanship of Scientific Research (DSR) at King Abdulaziz University, Jeddah, under grant no. (RG-2-140-40). The authors, therefore, acknowledge with thanks the technical and financial support from the DSR.

The research group would like to acknowledge Mrs. Walaa Abuzahra, Research Coordinator, Sleep Medicine and Research Center (SMRC), and the sleep technicians at SMRC for their useful contributions and dedication to this research.

## SLEEP HEALTH AND HEALTH-RELATED QUALITY OF LIFE AMONG OLDER ADULTS LIVING WITH HIV

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**Introduction:** Human immunodeficiency virus (HIV) has become a chronic disease with a near-normal life-expectancy. The number of people living with HIV (PLWH) older than 55 years of age is expected to reach 38% of the HIV population by 2045. One important goal of HIV care is well-being and health-related quality of life (HRQL), especially for older PLWH. Sleep disturbance is one of the most prevalent symptoms and significantly impacts HRQL. The purpose of this study was to examine the relationships between sleep problems and HRQL for older PLWH.

**Materials and Methods:** This was a descriptive, cross-sectional study. We recruited participants who self-reported as HIV-positive through HIV/AIDS support organizations in the United States between January and October 2021. They completed surveys which assessed (i) HRQL using the Medical Outcomes Study Short Form Health Survey, (ii) sleep quality using the Pittsburgh Sleep Quality Index (PSQI), (iii) daytime sleepiness using the Epworth Sleepiness Scale, (iv) fatigue using the Lee Fatigue Scale, (v) HIV-related symptoms using the HIV symptom index, and (vi) psychological symptoms using the Hospital Anxiety and Depression Scale. Upon the completion of surveys, they wore an accelerometer (ActiGraph GT9X Link) on the wrist for seven consecutive days. The accelerometer measured objective sleep parameters, including sleep efficiency (SE), wake after sleep onset (WASO), total sleep time, number and minutes of awakenings. We performed multiple regression to examine the relationships between sleep problems and HRQL in older PLWH.

**Results:** A total of 54 adults aged 50 and older living with HIV (24% women and mean age 60 years) completed the surveys. They have lived with HIV for an average of 27 years, and 56% reported having been diagnosed with AIDS at least once. Sleep disturbance, fatigue, and pain were the most prevalent symptoms. The PSQI Global score was 9.43 ( $\pm$  4.50), which is greater than cut-off 5 for poor sleeper. 47 of them (87.0%) had sufficient accelerometer data. The overall sleep duration was 5.2  $\pm$  1.3 hours per day. Their average SE was 89.6% with WASO 31.0 minutes. They awoke 12.9 times for 2.6 minutes on average. HIV-related symptom burden was the only significant predictor of HRQL ( $\beta$  = -1.02,  $p$  < 0.001), but not individual sleep parameters.

**Conclusions:** HIV-related symptom burden seems to be the strongest factor associated with HRQL in elderly PLWH. Strategies that reduce prevalent symptoms (such as sleep disturbance, fatigue, and pain) in older adults living with HIV are important. Further studies are needed to evaluate HRQL by enhancing self-management of multiple symptoms in this growing population.

**Acknowledgements:** This project is partly funded by the Rhode Island Foundation Medical Research Grant.

## SLEEP IN ADULTS WITH PHENYLKETONURIA

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**Introduction:** Sleep problems have been reported in adult patients with Phenylketonuria (PKU). Despite this, few studies have explored the frequency of sleep disturbances in this population. The aim of the study is to analyse the prevalence of sleep disorders in a clinical cohort of PKU adult patients.

**Materials and Methods:** 74 PKU patients undergoing dietary treatment [29M (39.1%)-45F (60.8%), aged 17-52; mean 29.8 years; SD $\pm$ 9.15] and taking part in the follow up-PKU programs at Pediatric Unit-Metabolic Disease Center at San Paolo University Hospital (Milan) were consecutively recruited through a survey between 8<sup>th</sup> August and 25<sup>th</sup> November 2020. All participants have been assessed through the following self-

administered questionnaires: 'Pittsburgh Sleep Quality Index (PSQI)', 'Sleep Condition Indicator' (SCI) and 'Beck Depression Inventory –II' (BDI-II). We then reviewed the clinical history and the metabolic profile (dietary treatment, Phe blood levels during the last year) of each patient.

**Results:** 29/74 patients (39.1%) [20 females (68.9%), 9 males (31.03%); mean age 31.5 years, SD  $\pm$ 8.02] reported significant scores of Low Quality of Sleep on Pittsburgh Sleep Quality Index Questionnaire. 6/29 patients (20.6%) presented depressive symptoms (BDI-II scores  $\geq$ 17). Since the altered sleep quality might be linked to the concurrent mood disorder, we therefore excluded those patients from the analysis. None of the subjects reached the clinical cut off in the 'Sleep Condition Indicator' (SCI). Metabolic Data were collected for 17/29 patients of the sample with sleep disturbances on PSQI questionnaire (58.6%): 11 (64.7%) PKU patients presented with a good metabolic control (last year index of dietary control (IDC) < 600 mmol/L) and 6 PKU patients (35.2%) presented poor metabolic control (last year IDC  $\geq$  600 mmol/L).

**Conclusions:** Our findings supports the assertion that sleep disturbances can affect adult people suffering from Phenylketonuria. Further studies are needed in order to understand how metabolic control may relate to the development of Sleep Disorders, both in adult and younger population.

**Acknowledgements:** Epilepsy Center - Sleep Medicine Center, Childhood and Adolescence Neuropsychiatry Unit, ASST SS. Paolo e Carlo, San Paolo Hospital (Milan); Department of Health Sciences, University of Milan, Italy. Metabolic Center, Pediatric Unit, ASST SS. Paolo e Carlo, San Paolo Hospital (Milan); Pediatrics Department, University of Milan, Italy.

## SLEEP QUALITY AFTER EXTREME MUSCLE FATIGUE WITH ACTIVE AND PLACEBO TRANSCUTANEOUS NERVE STIMULATION

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**Introduction:** The present study was designed to investigate the effects of transcutaneous electrical nerve stimulation (TENS) applied immediately after strenuous exercising and its effect on REM sleep/sleep quality and delayed muscle soreness.

**Materials and Methods:-** Twenty-one participants were submitted to three different testings consisting of an exercise-induced fatigue protocol to the quadriceps muscle by an isokinetic knee extension machine. This exercise was followed by one of the three different treatments: no TENS, inactive TENS, or active TENS. A wash-out period was done between testings. Outcomes were REM sleep before, during, and after the exercise were recorded. Perceived muscle pain and fatigue were also recorded.

**Results:** REM sleep percentage (how much REM sleep in total sleep) decreases from the baseline for both active-placebo and placebo-active sequences, probably due to the fatigue from the exercise. On average, 23.3% REM sleep is observed for the baseline, 19.7% REM sleep is observed for the active TENS group, and 18.5% REM sleep is observed for the placebo group. In both sequences, the REM sleep percentage is higher for the active TENS group compared to the placebo group.

**Conclusions:** Active TENS after engaging in strenuous exercise protocol demonstrated better REM sleep vs the placebo. Increased REM sleep is important for recovery and to return to activity.

**Acknowledgments:** Drs. Degani and Kang. I would also like to thank the two DPT students Josh Sparks and Hannah Stefanek.

## SLEEP QUALITY AND PROBLEMS AMONG CHILDREN IN US FOSTER CARE

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**Introduction:** Sleep plays an essential role in all aspects of development but is commonly undermined by adverse early experiences. Children in foster care face a range of risk factors that increase the likelihood of poor sleep, yet research, practice and policy have largely neglected sleep health

in this population. We therefore surveyed foster caregivers from across the U.S. about the sleep of children in their care. We also examined correlates of sleep quality and problems in these children.

**Materials and Methods:**  $N=485$  foster caregivers from 46 U.S. states completed an online survey including questions about the sleep quality and problems of one child in their care (range 4–11 years;  $M$  age=6.4;  $SD=2.2$ ). Children's average length of stay in the current home was 16.5 months ( $SD=16.3$ ). Caregivers were mostly married (72%) White (90%) females (97%).

**Results:** On average, children required more than 45 minutes to fall asleep at night and spent more than 30 minutes awake during the night. The most common sleep-related problems reported were moving to another's bed during the night (86.8%), nightmares (51.2%), sleep terrors (34%), and bedwetting (31.6%). Number of previous foster placements was positively associated with report of nightmares ( $r = .11, p < .05$ ), night terrors ( $r = .17, p < .01$ ), and sleep walking ( $r = .18, p < .01$ ). Duration of the current foster placement was negatively related with current sleep quality ( $r = -.19, p < .001$ ) and positively associated with daytime sleepiness ( $r = .13, p < .05$ ) and several types of sleep problems. Number of minor children in home (range 1–6), whether the child had their own room, caregiver age and the amount of time the caregiver was a licensed foster parent were not associated with any child sleep variable.

**Conclusions:** In a large national survey focused on sleep, foster caregivers reported a wide range of sleep problems among the children in their care. In addition to high rates of various sleep-related problems, findings suggest that, irrespective of various caregiver and environmental factors, sleep is adversely affected by number of foster care placements. Further, even after children have been in a stable placement for an extended period, their sleep does not necessarily improve. Given that poor sleep is associated with negative mental and physical health outcomes, it is imperative to better understand the role of poor sleep health among foster care children and to develop evidence-based sleep interventions for this vulnerable population.

**Acknowledgements:** Jinu Kim<sup>1</sup>, Candice A. Alfano<sup>1</sup>, Madeline Valentine<sup>2</sup>, Josefina Muñoz Nogales<sup>2</sup>, Priscilla Rigos<sup>3</sup>, Josephine S. Kim<sup>3</sup>, Carol H. Ripple<sup>4</sup>, Eleanor L. McGlinchey<sup>3</sup>, Amy R. Wolfson<sup>2</sup>

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## SLEEP QUALITY IN COVID-19 PATIENTS AND ITS ASSOCIATION WITH SEVERITY OF COVID

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**Introduction:** Bad sleep quality is associated with dysregulated immune response; therefore an individual is prone to develop various viral infections. Aim of the study is to assess quality of sleep in COVID 19 patients and its association with severity of disease.

**Materials and Methods:** Prospective questionnaire based study. One hundred and twenty three subjects with microbiologically confirmed COVID 19 were administered Pittsburgh Sleep Quality Index (PSQI) questionnaire. Disease severity was assessed with HRCT thorax. Demographic data and co morbidities were noted. Correlation between quality of sleep parameters and disease severity determined.

**Results:** Analysed data of 123 subjects. Mean age was  $51.69 \pm 13.17$  years. Male: Female ratio was 2.1:1. Co-morbidities were found in 41%; among which Diabetes mellitus, Hypertension, combined DM and HTN, CAD, Hypothyroidism and Airway diseases were 39%, 37%, 22%, 23%, 14% and 10% respectively. Out of 118 patients with HRCT, based on CT Severity Index, subjects with mild, moderate and severe disease were 46% (54), 37% (44) and 17% (20) respectively. Based on global PSQI, 51% (62) had bad quality of

sleep. Good or bad quality of sleep doesn't have association with age and gender. Bad subjective sleep quality were reported in 21% subjects and it's not related to disease severity grades. Insomnia (Sleep latency of >30min) reported in 22% of the subjects and it's correlated with severe COVID disease (P value: 0.095; <0.10). Sleep duration of less than 7 hours were noted in 43% of the subjects and not correlated with severity grades. Poor habitual Sleep efficiency noted in 16% of subjects. Sleep disturbances were noted in 83% of subjects and its not correlated with severity grades. Use of medications for sleep were noted in 23% of subjects. Day time dysfunction noted in 45% of the patients. Among subjects with good quality sleep and bad quality sleep, 10% and 23% were having severe disease respectively. Out of twenty subjects with severe disease 70% had bad sleep quality (global PSQI) and less than 7hours sleep duration.

**Conclusions:** In this study we observed severe COVID is associated with bad quality sleep and reduced sleep duration. Also sleep quality (global PSQI) in COVID 19 subjects compared to general Indian population reported in other studies is significantly bad. Global PSQI can be used as screening instrument to predict severity of COVID 19. Validation of global PSQI as a screening instrument for development of severe COVID 19 is recommended.

**Acknowledgements:** Dean, Government Medical College, Nagpur, Faculties, Residents and Nursing Staff, COVID Hospital, GMCH Nagpur.

## SLEEP QUALITY OF PARENTS AND CHILDREN DURING THE COVID-19 PANDEMIC – A SOUTH-BRAZILIAN SAMPLE

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**Introduction:** In March 2020, the WHO (World Health Organization) declared the outbreak of the disease caused by the new coronavirus, called COVID-19, as a pandemic. With this, the Brazilian government decreed on March 18, 2020, the total closure of non-essential activities. Furthermore, during this period, children and adolescents were challenged by changes that included remote classes and altered routine habits that could affect sleep habits.

**Materials and Methods:** Aligned case-control study, study 1 was through an online questionnaire, made available to parents and children between April and July 2020, the longest quarantine period in Brazil. The sleep of parents and adolescents was characterized using the Pittsburgh Sleep Quality Index and the Epworth Sleepiness Scale. For children ages 0-3, parents completed the Brief Infant Sleep Questionnaire, for children ages 4-12, the Children's Sleep Disorder Scale. Parents also subjectively reported their perception of sleep habits during social distancing. Study 2 started from April 5th to July 30th, 2021, using the same questionnaires as in Study 1. Both in Study 1 and 2, the georeferencing method was used to identify which macro-regions of Rio Grande do Sul / Brazil obtained worse sleep quality. Study 2 integrates the performance of actigraphy, which, for logistical reasons, elected residents of Porto Alegre / Rio Grande do Sul to participate.

**Results:** In study 1, 5,007 responses were obtained throughout Brazil, 788 with children under 18 years of age. Of the 788 parent respondents, 577 resided in Rio Grande do Sul. We chose to analyze the data from Rio Grande do Sul, as there is greater homogeneity between the containment of the spread of COVID-19 than in other regions of Brazil. Thus, the results revealed that of the 577 parents, 69.8% had sleep disorders, 58.6% in children aged 0 to 3 years, 31.9% in the range from 4 to 12 years (with a predominance of sleep disorders. Sleep initiation or maintenance) and 56.6% in adolescents. Gender (female) and children with sleep disorders were significant predictors of a sleep problem in parents ( $p < 0.005$ ). The subjective perception of concerns revealed related to emotional concerns such as anxiety and fear in adults and due to changes in the routine of children and adolescents. Regarding georeferencing in study 1, in Rio Grande do Sul, 1,729 responses (69.7%) were from the Metropolitan Region of Porto Alegre, of these 1,155 cases (66.8%) had poor sleep quality and sleep disorders according to score Global PSQI  $\geq 5$ . Currently, the data are being organized for the analysis of Study 2, it obtained 1,559 responses from Brazil, of which 830 resided in Rio Grande do Sul and of these 135 parents responded to the two studies and to the actigraphy collections, carried out in the time 23 collections.

**Conclusions:** Our data showed an increase in the rate of sleep problems among families in quarantine, demonstrating the importance of addressing this issue with the population to establish comprehensive care.

**Acknowledgements:** This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível superior – Brazil (CAPES).

### SLEEP REACTIVITY IS ASSOCIATED WITH INCREASED AROUSAL DURING AMBULATORY POLYSOMNOGRAPHY IN HEALTHY ADULTS

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**Introduction:** Stress-related sleep reactivity is a risk marker for the development of insomnia. Studies have indicated that good sleepers with high sleep reactivity are more prone to the development of insomnia, suggesting a critical role of sleep reactivity in the pathogenicity of insomnia. However, there is a lack of data on the association between sleep reactivity and sleep macrostructure in healthy individuals, especially on whether the association of sleep changes is independent to that of cognitive arousal, dysfunctional sleep belief and perceived stress level.

**Materials and Methods:** Forty-one healthy adults (mean: 29.29y, SD: 4.63; 65.9% female) were recruited. All participants underwent Structural Clinical Interview for DSM disorder-5 and Diagnostic Interview for Sleep Patterns and Sleep Disorders to rule out any psychiatric and sleep disorder respectively. Participants underwent one-night home ambulatory polysomnography (PSG) with the Nox-A1 ambulatory PSG monitoring system (Nox Medical, Inc., Reykjavik, Iceland). They also completed a set of self-reported questionnaires including Perceived Stress Scale (PSS), Insomnia Severity Index (ISI), Pittsburgh Sleep Quality Index (PSQI), pre-sleep arousal questionnaire (PSAS), Ford Insomnia Response to Stress Test (FIRST) and Dysfunctional Beliefs and Attitudes about Sleep Scale (DBAS). PSG data was scored according to the scoring manual of the American Academy of Sleep Medicine (AASM). Independent T test, Pearson correlation analysis and General linear regression analyses were applied in statistical analysis.

**Results:** The degree of sleep reactivity as reflected by the FIRST score was positively correlated with cognitive arousal ( $r=0.40$ ,  $p=0.010$ ), somatic arousal ( $r=0.37$ ,  $p=0.017$ ), poor sleep quality ( $r=0.34$ ,  $p=0.030$ ), and nocturnal arousal index in total sleep ( $r=0.37$ ,  $p=0.017$ ), NREM ( $r=0.33$ ,  $p=0.037$ ) and REM sleep ( $r=0.33$ ,  $p=0.034$ ). Participants were further classified into two groups according to the median split of sleep reactivity scores [low reactive sleepers (FIRST <19,  $n=19$ ), and high reactive sleepers (FIRST ≥19,  $n=22$ )]. Those with high sleep reactivity had higher perceived stress level, greater insomnia severity, poorer self-perceived sleep quality and more pre-sleep cognitive arousal. They also tended to show significantly higher index of nocturnal arousal as assessed by PSG, when compared with the low sleep reactivity group. The general linear regression analyses indicated that higher sleep reactivity was positively associated with increased total arousal index (B:0.26, 95%CI [0.05–0.47],  $p=0.018$ ) and particularly NREM arousal index (B: 0.29, 95%CI [0.03–0.56],  $p=0.030$ ), after adjusted for age, sex, perceived stress, cognitive arousal and dysfunctional sleep belief, suggesting links between sleep reactivity and nocturnal arousal regardless of different levels of perceived daily stress.

**Conclusions:** Higher sleep reactivity was associated with sleep macrostructure alteration with increased arousal intensity even after controlling for self-perceived stress level in healthy subjects. PSG arousal index may be

a potential EEG biomarker for the risk of insomnia in vulnerable individuals. Targeting sleep reactivity in the intervention might be a potential approach to prevent the future onset of insomnia.

**Acknowledgements:** This study was supported by grant from the Collaborative Research Fund of Hong Kong, China (RGC Ref No. C7069-19GF).

### SLEEP-WAKE PATTERNS AND INSOMNIA SYMPTOMS ON THE FIRST COVID-19 PANDEMIC WAVE IN PORTUGAL

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**Introduction:** This research focused on the impact of the COVID-19 pandemic on the sleep of the Portuguese population, first wave. We aimed to inspect the sleep schedules, durations, quality, insomnia symptoms, and related variables, after the first lock-down.

**Materials and Methods:** During June and July 2020, out of 1174 who participated in the survey, a final sample of 1079 participants from both sexes (874 women and 205 men), 18 ≤ years old ≤ 86 (45.7 ± 16.05 years old, equivalent in both sexes), not shift workers, from all regions of the country in an approximately proportional manner, answered on-line questions regarding sociodemographic-information, basic health, family/domestic and pandemic circumstances; sleep schedules, durations, and difficulties (currently/during the pandemic context, and retrospectively/before the pandemic); together with the Insomnia Severity Index (ISI), and the Basic Scale on Insomnia Symptoms and Quality of Sleep (BaSIQS). From the large sample, a subsample ( $n=410$ ) was also extracted and compared with an equivalent subsample (in terms of region, educational level, and occupation status) selected from a larger one collected before the pandemics in 2017 (cf. Mendes et al., 2018). Statistical analyses were performed using IBM-SPSS.

**Results:** Comparing the current pandemic sleep patterns with those retrospectively reported by the 1079 participants for the pre-pandemic, mean sleep-wake schedules shifted significantly to later hours during the week, decreasing the social jet lag and the restriction-extension pattern. Comparing 2017 and 2020 subsamples, time in bed on weeknights increased significantly during the pandemic. Clinically relevant insomnia symptoms (as suggested by an ISI score > 14) achieved a prevalence of 18.3% in 2020. Although a significant portion of people reports poorer sleep, there were also sleep improvements: 45.7% of the participants considered their sleep was poorer now, 37.8% consider they were sleeping as usual, and 14.6% declared that now they were sleeping better. Examining the 37.8% declaring that their sleep remained unchanged, this group subdivides into 13.1% that declared a sleep problem currently or in the past, and 24.7% that declared not having any current/previous sleep problem.

**Conclusions:** The subjective impact of the COVID-19 pandemic on sleep seems variable: although a significant portion of people reports poorer sleep, there are also sleep improvements. As a possible explanation, when people work and study from home, they have greater flexibility in defining their routine and sleep-wake schedules: On the one hand, they can follow their natural biological rhythm, which can be a protective factor for sleep; on the other hand, it can be a risk factor for the aggravation or development of insomnia, as it allows to adopt counterproductive behaviors like more time in bed without sleep.

**Acknowledgments:** The present investigation was carried out as part of a collaboration between the Portuguese Sleep Association (APS), which supported data collection costs, and the Center for Research in Neuropsychology and Cognitive-Behavioral Intervention (CINEICC), UC. This study was approved and disseminated by the Portuguese College of Psychologists.

## STUDY ON THE SLEEP QUALITY AND BRAIN FUNCTIONAL STATE OF FOCAL EPILEPSY

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**Introduction:** To evaluate the sleep quality, emotion and fatigue state of patients with focal epilepsy by subjective scale, polysomnography and the brain functional state quantitative monitoring, and to explore the influencing factors of sleep quality in patients with epilepsy.

**Materials and Methods:** 102 focal epilepsy patients were selected according to clinical symptom and 24-hour EEG from the outpatient department of neurology from August 2019 to January 2021 in the First Hospital of Jilin University, 102 sex- and age-matched healthy controls were recruited for this study. Pittsburgh sleep quality index (PSQI) was used to evaluate the sleep quality of patients. Hospital Anxiety/Depression Scale (HAD) was used to evaluate the anxiety and depression. Fatigue Severity Scale (FSS) was used to evaluate the fatigue degree. 12 epilepsy patients completed polysomnography monitoring. All participants underwent the brain functional state quantitative monitoring.

### Results:

1. PSQI total score of epilepsy patients were higher than those in control group ( $P < 0.05$ ). PSQI total score was negatively correlated with sleep index ( $r = -0.321$ ,  $P = 0.001$ ).
2. The linear regression analysis of PSQI correlation showed that age, seizure frequency, seizure in sleep, anxiety, depression, and fatigue were related to the influencing factors for the sleep quality of epilepsy patients. Among them, fatigue, age, seizure in sleep, and seizure frequency were independent influencing factors for the sleep quality of epilepsy patients.
3. Wake after sleep onset (WASO) was positively correlated with brain inertia ( $r = 0.720$ ,  $P = 0.008$ ). The oxygen desaturation index was positively correlated with respiratory index in sleep ( $r = 0.892$ ,  $P < 0.001$ ); The oxygen desaturation index was positively correlated with hypoxia index ( $r = 0.727$ ,  $P = 0.007$ ); The lowest oxygen saturation in sleep was negatively correlated with respiratory index in sleep ( $r = -0.824$ ,  $P = 0.001$ ).
4. Brain inertia, brain fatigue, respiratory index in sleep, hypoxia index and anxiety tendency in epilepsy patients were higher than those in control group ( $P < 0.05$ ).
5. Epilepsy patients with  $HAD(A) \geq 11$  had higher anxiety tendency than those with  $HAD(A) < 11$  ( $P < 0.05$ ).
6. FSS total score was positively correlated with brain fatigue ( $r = 0.387$ ,  $P < 0.001$ ).
7. The linear regression analysis of FSS correlation showed that age, seizure frequency, anxiety, depression and sleep quality are related to the influencing factors of fatigue in epilepsy patients. Among them, anxiety, sleep quality and age are the independent influencing factors of fatigue in patients with epilepsy.
8. Epilepsy patients with more extensive interictal discharges had significantly higher excitation density than those with more limited interictal discharges ( $P < 0.05$ ).

### Conclusions:

1. Sleep quality decreased in epilepsy patients. PSQI total score was negatively correlated with sleep index. Seizure in sleep, seizure frequency, age and fatigue degree and were the independent influencing factors of sleep quality in patients with epilepsy.
2. Wake after sleep onset (WASO), the oxygen desaturation index and the lowest oxygen saturation in sleep were respectively correlated with brain inertia, respiratory index in sleep and hypoxia index.
3. Anxiety tendency and brain fatigue in epilepsy patients increased. Epilepsy patients with anxiety had higher anxiety tendency than control group. FSS total score was positively correlated with brain fatigue.

### Acknowledgements:

## THE ASSOCIATION BETWEEN MATTRESS SIZE AND OBJECTIVELY MEASURED SLEEP IN 8,214 USERS WITH BED PARTNERS

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**Introduction:** To date, limited empirical work has been conducted on the association between mattress sizes and objectively measured sleep in the naturalistic environment. Advancements in consumer sleep technologies allow for large-scale measurement of ambulatory objectively measured sleep in the naturalistic environment. In this big data analysis, we examined the association between mattress size and objective sleep metrics for those who share a bed with a partner.

**Materials and Methods:** We examined sleep data from a PSG-validated radio frequency hardware device and accompanying app which uses a non-contact radio frequency sensor to objectively estimate sleep-related metrics. The dataset included 865,348 nights from 8,214 sleepers (mean age  $51.1 \pm 13.8$  years, 57.7% male). Sleep data were captured nightly from 2018-01-01 until 2021-05-01. Mattress details were captured using a mobile application that paired with the aforementioned hardware device. Mattress sizes were based on standardized North American dimensions including: California king (183 x 213.5 cm), King (193 x 203.5 cm), Queen (152 x 203.5 cm), and Full (134.5 x 190.5). We used a linear regression model to compare sleep-related metrics and mattress sizes, controlling for age, gender, BMI, and mattress age.

**Results:** For those with bed partners, sleeping on a queen size mattress as compared to those on a full size or smaller mattress was associated with a 4.9 mins increase in total sleep time (TST,  $p < 0.05$ ). Relative to sleeping on a full size mattress, sleeping on a king size mattress or California king was associated with a 13.3 min increase in TST, a 4.3 min increase in REM sleep, and a 2.0 min increase in deep sleep (all  $p < 0.001$ ). When compared to a queen size mattress, sleeping on a king or California king mattress was associated with an additional 8.4 min of TST, 4.1 mins of deep sleep, 2.3 mins of REM Sleep (all  $p < 0.001$ ), and a 1.1% increase in sleep efficiency ( $p < 0.001$ ). No significant differences in sleep onset latency or number of awakenings were observed.

**Conclusions:** The present analysis showed that larger mattress sizes were generally associated with longer total sleep time and modest increases in sleep efficiency. We also observed slight changes to sleep architecture including increases in deep sleep and REM sleep. These findings highlight the potential importance of mattress size for sleep quality. However, additional research is needed to disentangle the likely complex relationship between mattresses and sleep by further examining mattress composition, environmental sleep disruptors, partner sleep quality, and potentially confounding socioeconomic factors.

## THE ASSOCIATION BETWEEN SLEEP-SMARTPHONE HYGIENE, PSYCHOLOGICAL WELL-BEING, AND SLEEP QUALITY AS REVEALED BY OBJECTIVE AND SUBJECTIVE MEASURES

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**Introduction:** The continuous use of smartphones all hours of the day and night is a feature of modern life. Smartphones' numerous applications have made them an integral part of the individual's functioning to the point of merging the individual with the device. This study focuses on the association between smartphone use in the sleeping environment, sleep quality, and psychological well-being. The study had two aims: first, to examine the association between sleep-smartphone hygiene and sleep quality among students and the mediation effect of psychological well-being (anxiety and FOMO); and second, to examine the differences between subjective and objective measures of sleep-smartphone hygiene as predictors of sleep quality and psychological well-being: anxiety, depression, and FOMO.

**Materials and Method:** In the first stage of the study, a total of 467 Israeli college students filled out five questionnaires: Sleep-Smartphone Hygiene Questionnaire (SSHQ), Fear of Missing Out Scale (FoMOS), Trait Anxiety Inventory (STAI-T), Pittsburgh Sleep Quality Index (PSQI), and a demographic questionnaire. In the second stage, 40 college students out of the total sample measured their smartphone-sleep hygiene via an application installed on their smartphone device (QualityTime by Mobidays Inc.) This application monitored their smartphone detailing the type and time of application used. Each student also kept a sleep diary and filled out

five questionnaires: Sleep–Smartphone Hygiene Questionnaire (SSHQ), Fear of Missing Out Scale (FoMOs), Trait Anxiety Inventory (STAI-T), Pittsburgh Sleep Quality Index (PSQI), and Beck Depression Inventory (BDI-II).

**Results:** The analysis revealed positive correlations between sleep–smartphone hygiene, trait anxiety, FOMO, and sleep quality. In addition, trait anxiety was found to be a moderating variable in the association between sleep–smartphone hygiene and sleep quality. Objective measures showed that 40% of the participants actually woke up during the night and checked their smartphone. However, subjective measures showed that they overestimated this behavior. More frequent nighttime checking of one's smartphone, as recorded by objective measures, was associated with lower sleep quality and psychological well-being.

**Conclusion:** This study demonstrated the association between smartphone use in the sleeping environment, sleep quality, and psychological well-being and the differences between objective and subjective measures of smartphone use at night. An understanding of this association among students is beneficial to those seeking effective practices to cope with the impairment of sleep quality. Certain education programs encourage removing phones from bedroom- but their recommendations for behavioral change would not necessarily improve sleep. This study therefore emphasizes that recommendations should also address aspects of psychological well-being.

#### THE CARDIOVASCULAR, METABOLIC, FETAL AND NEONATAL EFFECTS OF CPAP USE IN PREGNANT WOMEN: A SYSTEMATIC REVIEW

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**Introduction:** Continuous positive airway pressure (CPAP) is the standard treatment for obstructive sleep apnea (OSA), but its outcomes for the pregnant are still undefined. This study aims to review current CPAP intervention during pregnancy, discuss published trials, and propose relevant issues that have yet to be addressed satisfactorily about the cardiovascular, metabolic, fetal, and neonatal effects of CPAP treatment during gestation.

**Materials and Methods:** Two authors independently conducted a systematic review until March 28th, 2021 on PubMed, BVS, and Cochrane Library, using PRISMA guidelines, and risk of bias using NIH guidance. Discrepancies were reconciled by a third reviewer.

**Results:** Of 59 identified citations, eight original trials have submitted a total of 90 pregnant women to polysomnography and CPAP therapy. Concerning CPAP usage time, none of the selected studies specified meantime use per night. Four of them (50%) registered the outcomes after CPAP therapy for one night, while three studies (37.5%) underwent CPAP treatment for at least one month, and another trial (12.5%) for at least two weeks. None of the studies reported CPAP adverse effects in pregnant women or neonatal participants.

Four studies performed in samples with hypertension or preeclampsia presented blood pressure (BP) decrease or maintained the antihypertensive drug dose in the CPAP group. After CPAP utilization, one trial registered cardiac output and stroke volume increase with heart rate and peripheral vascular resistance decrease, which were correlated with birth weight increment. Others documented a higher Apgar in the CPAP group and more fetal movements during CPAP use. There was a reduction in serum uric acid and tumor necrosis factor-alpha in the CPAP groups whose blood pressure decreased. However, two weeks of CPAP use in women with gestational diabetes and OSA did not improve glucose levels but raised the insulin secretion in those adherents to CPAP.

**Conclusions:** CPAP is a safe treatment with long-term benefits for OSA patients, showing a strong correlation with improvement in cardiovascular functions, BP, diabetes, inflammatory markers, subjective sleep quality, quality of life, and mortality. Although physiological changes in pregnancy contribute as risk factors for OSA's development due to lower respiratory function, upper airway edema, and elevated estrogen, the prevalence and comorbidities related to OSA in the pregnant are still a growing area of

study. Despite its undeniable relevance, there were only eight clinical trials about CPAP treatment in the pregnant population and its effects on maternal comorbidities, subjective aspects (sleep quality, daytime sleepiness), fetal, and neonatal outcomes. Despite these positive results without adverse effects, randomized controlled trials with standardized follow-up in larger populations are required to determine CPAP therapy recommendations in pregnancy.

**Acknowledgments:** In memory of Christian Guilleminault for his outstanding role in the field of Sleep Medicine.

#### THE EFFECTS OF BRIGHT LIGHT THERAPY ON SLEEP AMONG YOUNG ADULTS WITH NON-CLINICAL SLEEP PROBLEMS: A PILOT-STUDY

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**Introduction:** Sleep deficiency is a major public health issue affecting daily life and health. Sleep problems and poor sleep quality are usually due to a disruption in the body's circadian rhythms (CRs). Bright light therapy (BLT) has been found to be effective in realigning the CRs in diverse populations but the effectiveness of BLT among healthy young individuals has not been evaluated. Therefore, the aim was to examine the effects of BLT intervention on sleep problems and sleep quality in a sample of young adults.

**Materials and Methods:** A 3-weeks BLT intervention, using light emitting glasses for 30 minutes each morning, was conducted among 40 undergraduate students at Reykjavik University. The participating students, formerly assessed with sleep problems, were randomly assigned to either a control group with non-circadian stimulating light glasses or an intervention group with circadian stimulating light glasses. At baseline and follow-up, sleep problems were measured with the Bergen Insomnia Scale and sleep quality was measured with the Pittsburgh Sleep Quality Index. A 2-x-3 factorial design was applied to test the effectiveness of the BLT.

**Results:** The results showed that the main effect for time was significant for both sleep problems ( $p < 0.001$ ) and sleep quality ( $p < 0.001$ ) and the interaction between group and time was significant for both sleep problems ( $p = 0.005$ ) and sleep quality ( $p = 0.042$ ).

**Conclusions:** The findings indicate that a short, or a 3-weeks, BLT intervention can improve sleep among young adults reporting mild sleep problems. The results indicate that the circadian stimulating light glasses were effective in decreasing sleep problems and increasing subjective sleep quality. This has important public health relevance as this low-burden BLT intervention can easily be disseminated among young adults with non-clinical sleep problems.

**Acknowledgements:** This study was funded by the Icelandic Research Fund, grant number 184999-051.

#### THE GAZE OF SLEEP LOSS: ACUTE EFFECTS OF SLEEP LOSS ON FACIAL PERCEPTION

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**Introduction:** Sleep loss affects the socio-emotional state of an individual, e.g., by increasing negative mood and social avoidance behavior. However, it is unclear if gaze patterns and social perception of different facial expressions are altered by sleep deprivation. Here, we used eye-tracking technology to investigate if acute sleep loss affects gaze patterns and social perception of happy, angry, fearful, and neutral faces.

**Materials and Methods:** Forty-five young adults (20 women) were examined according to a crossover design, including one night with total sleep deprivation and one night with an 8-hour sleep opportunity. After each night, gaze patterns of happy, angry, fearful, and neutral faces were assessed by eye-tracking. The main outcome was time spent on the eyes, as they represent the most potent cue for conveying emotions. Participants also evaluated the attractiveness, trustworthiness, and healthiness of each face.

**Results:** Following sleep loss, participants spent less time exploring faces compared to sleep ( $p < 0.0001$ ). Relative to the total time participants spent on the face, we found that less time was allocated to the eyes when

presented with happy, neutral, and fearful faces after sleep loss ( $p < 0.05$ ). However, the relative time allocated to the eyes of angry faces did not differ between the conditions ( $p = 0.688$ ). Finally, faces were overall perceived as less trustworthy and attractive following sleep loss ( $p < 0.05$ ). **Conclusions:** Acute sleep loss alters gaze patterns when presented with different facial expressions. The finding that the eyes of angry faces maintain the attention of the sleep-deprived observer and that the faces are seen as overall more negative may have adverse implications for emotional well-being.

**Acknowledgements:** The authors want to thank all participants that contributed to this study and the students who helped with the data collection.

### THE IMPACT OF SLEEP DISTURBANCE ON PHYSICAL HEALTH IN A SEVERE ASTHMATIC PEDIATRIC POPULATION

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**Introduction:** Children with severe asthma experience significant daytime symptoms that may impact academic performance resulting in lowered quality of life, increased hospitalizations, and even death. Regular physical activity (PA) participation is an important part of their management yet children with asthma continue to display significantly greater inactivity levels compared to their counterparts without asthma. Understanding the reason for low PA engagement and promoting positive PA behaviors is a modifiable risk factor that will ultimately improve asthma control, decrease symptoms, and improve quality of life across the life-span. Addressing these gaps in the literature will provide pertinent clinical knowledge that may optimize clinical outcomes in pediatric severe asthma populations. Thus, the aim of this study is to evaluate the frequency and intensity of PA, sleep quality and disturbance, sleep duration, and daytime sleepiness in children with severe asthma compared to healthy controls.

**Materials and Methods:** This was a prospective study consisting of two age-sex matched groups: a severe asthma group and a healthy control group. Subjects were given the ActiGraph wGT3X-BT device to be worn simultaneously for 7 consecutive days and nights using a 24 hour-a-day protocol. This device objectively measures wake/sleep cycles to provide continuous, high-resolution sleep quality and PA measures during the period that the device is worn, using age-specific validated cut-off points. The validated Epworth Sleepiness Scale (ESS) was used as a self-reported measure of daytime sleepiness and the Child Sleep Habits Questionnaire (CSHQ) as a self-reported measure of sleep quality and disturbances.

**Results:** A total of 68 children were recruited: 34 children with severe asthma and 34 age-sex matched healthy controls. The mean ( $\pm$ SD) age of those with severe asthma and healthy controls was  $8.5 \pm 1.2$  and  $8.5 \pm 0.8$  years, respectively. There were 22/34 (64.7%) male participants in both groups. The mean ( $\pm$ SD) BMI of the severe asthma and control groups were  $16.8 \pm 3.1$  and  $16.6 \pm 3.6$  kg/m<sup>2</sup>, respectively. No significant differences were found in total ESS daytime sleepiness scores ( $p = 0.11$ ), total CSHQ sleep disturbance scores ( $p = 0.08$ ), sleep efficiency ( $p = 0.22$ ), sleep duration ( $p = 0.56$ ), time spent in weekly light PA ( $p = 0.38$ ), and time spent in weekly moderate-to-vigorous PA ( $p = 0.52$ ) between groups over a 7-day period. However, children with severe asthma were more sedentary compared to controls ( $482.8 \pm 59.3$  minutes vs.  $442.1 \pm 66.5$  minutes;  $p = 0.051$ ) over the same 7 day period.

**Conclusions:** Although children with severe asthma maintained physical activity levels similar to controls, they also had more sedentary behaviours. Further, there were no changes in sleep duration or quality between the groups. Further research in larger sample sizes is needed to better understand the impact of PA participation in children with severe asthma. Moreover, practicing positive PA behaviours represents a safe and non-invasive strategy for the clinical management of severe asthma, resulting in improved asthma care and patient outcomes.

**Acknowledgements:** This research was supported by funds from the Canadian Urban Environmental Health Research Consortium (CANUE).

### THE INTERPLAY BETWEEN PERSONALITY TRAITS, HYPERAROUSAL, AND SLEEP DISTURBANCES IN HEALTHY ADULTS

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**Introduction:** The mechanisms underlying sleep disturbances may be related to complex interactions between biological and psychosocial factors. Although previous literature has suggested that personality traits and psychophysiological hyperarousal are implicated in sleep disturbances, the interplay among these factors remained unclear. This study examined the relationship between NEO-Five personality traits and a variety of sleep-related characteristics (i.e. sleep quality, insomnia severity, pre-sleep arousal) and explore the potential mediating effect of pre-sleep arousal on the relationship between personality traits and insomnia.

**Methods:** A total of 120 adults (mean $\pm$ SD:  $29.39 \pm 4.52$ , 71% Female) aged from 25 to 45 years old free of any psychiatric disorder or sleep disorder as ascertained by structured clinical interviews were recruited from the community. All the participants completed the measures of personality traits (NEO Five-Factor Inventory), sleep-related features (Pittsburgh Sleep Quality Index for sleep quality, Insomnia Severity Index for insomnia severity), and cognitive and behavioral pre-sleep arousal as measured by the Pre-Sleep Arousal Scale.

**Results:** Linear regression analyses showed that neuroticism was significantly associated with poorer sleep quality ( $\beta = 0.45$ ,  $p < .01$ ), more severe insomnia ( $\beta = 0.47$ ,  $p < .01$ ), and a higher level of pre-sleep cognitive arousal ( $\beta = 0.59$ ,  $p < .01$ ). A higher degree of openness was associated with pre-sleep cognitive arousal ( $\beta = 0.21$ ,  $p < .05$ ) while extraversion was found to be negatively associated with sleep quality ( $\beta = -0.23$ ,  $p < .05$ ) and insomnia severity ( $\beta = -0.29$ ,  $p < .01$ ). Mediation analysis revealed that the association between neuroticism and insomnia severity was partially mediated by cognitive arousal before sleep ( $\beta = 0.07$ ,  $p < .01$ ).

**Discussion:** The findings showed the associations of NEO-Five personality traits with sleep quality, insomnia symptoms, and pre-sleep somatic and cognitive arousal among these healthy adults who were free of any sleep or psychiatric problems. In addition, the present study extended the existing literature by showing the interplay between personality traits, which are considered as a predisposing factor, and pre-sleep arousal, which is considered a perpetuating factor, on insomnia. Future longitudinal and interventional studies with objective measures are needed to further explore the mechanism underlying these associations.

**Acknowledgment:** This study is supported by a grant from the Collaborative Research Fund of Hong Kong, China (RGC Ref No. C7069-19GF).

### THE INTERPLAY BETWEEN SLEEP QUALITY AND ADOLESCENTS' PSYCHOSOCIAL DEVELOPMENT: A SYSTEMATIC REVIEW AND META-ANALYSIS OF LONGITUDINAL STUDIES

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**Introduction:** Adolescence is defined as the period of a gradual transition between childhood and adulthood, with conceptually distinct physical changes marking puberty and maturation. Sleep is a critical aspect for overall well-being and healthy development across physical, behavioral, cognitive, academic, and psychosocial domains. This can pave the way to a

new frontier for adolescent research, in which the dynamic interplay between sleep and multiple psychosocial aspects of adolescents' life can explain long-term developmental outcomes. Thus, systematizing and assessing longitudinal research on this topic is required to understand both changes of sleep during adolescence and its complex over time relationship with psychosocial development.

**Material and methods:** The first aim of this systematic review and meta-analysis is to identify all studies that evaluated longitudinally sleep quality, with standardized objective and/or subjective measures, in adolescence. The second aim is to evaluate the longitudinal interplay between sleep quality and psychosocial development in adolescents (particularly considering the domains of social experiences in multiple ecological contexts; identity processes and well-being outcomes). This work could lead to a better understanding of both changes in sleep quality during adolescence and its bidirectional link to psychosocial development.

Pubmed; Psychinfo, PsycArticles, Medline, Web of Science, Scopus; ProQuest Dissertations and Theses; ERIC; GreyNet databases were systematically searched without publication period restriction until 23th of September 2021. Eligible studies had to: include adolescents from the general population aged between 10/11 to 18/19 years old; use a longitudinal design; report sleep quality-related outcomes as measured by objective and/or subjective standardized measures for at least two time-points. The corresponding author worked in pairs with another team member and independently screened at first the titles and abstracts and then the full text against the eligibility criteria.

**Results:** A total of 362 full-texts were screened and a final number of 250 studies were included. The inter-rater agreement between the first and other authors of the team that worked in pairs for the selection process was substantial. Of these studies, 163 evaluated the longitudinally sleep quality of adolescents over time and its connection to physical health; psychological and social wellbeing. 81 studies evaluated longitudinally the interplay between sleep quality and different ecological contexts and identity development of adolescents. Finally, 6 studies evaluated the change over time of sleep quality outcomes and its relationship with wellbeing, context and identity in adolescents before and after the pandemic due to the Covid-19 outbreak.

**Conclusion:** Because of the broad scope of this project, the data can be used to examine a large variety of research questions. From this large selection of literature, different systematic reviews on different specific topics will be obtained. Particularly, our work will focus at first on systematically assessing the development and change over time of the sleep quality during the adolescence period. Furthermore, different works on the longitudinal interplay between sleep quality and physical health, different contexts and identity development will be systematically evaluated and presented.

**Acknowledgements:** This work was conducted within the ERC-Consolidator project IDENTITIES (Grant Agreement n. 101002163).

#### THE INTERRELATIONSHIP OF INSOMNIA SYMPTOMS, PHYSICAL ACTIVITY AND SEDENTARY BEHAVIOUR ON SYMPTOMS OF DEPRESSION AND ANXIETY BEFORE AND DURING THE COVID-19 PANDEMIC LOCKDOWN

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**Introduction:** Many studies from diverse global contexts have reported poor sleep quality and sleep irregularity, changes in lifestyle behaviours, and heightened depression and anxiety during hard lockdowns imposed as a result of the COVID-19 pandemic. However, the way in which these variables interact with each other and their relative importance to each other, remains unknown.

**Materials and Methods:** We conducted an online survey in 1048 South African adults (median age: 27y; 767 women; 473 students) to investigate how insomnia symptoms, sleep regularity, exercise intensity/frequency and sitting/screen-use (sedentary screen-use) interact to predict symptoms of depression and anxiety before and during hard lockdown.

**Results:** Results of our structural equation models, controlling for student status and self-identified gender, showed that irrespective of lockdown symptoms of insomnia were the strongest predictors of depressive and anxiety-related symptoms. Similarly, irrespective of lockdown high levels of sedentary behaviour, including sitting, were associated with these mental health difficulties. Furthermore, the greater the sedentary behavior, the poorer the sleep quality, which in turn was associated with poor mental health outcomes. Interestingly, during lockdown the extent to which individuals engaged in physical activity had a significant impact on symptoms of depression and anxiety via symptoms of insomnia. Individuals who exercised moderately or vigorously tended to have fewer insomnia symptoms and subsequently reported fewer depressive and anxiety-related symptoms.

**Conclusions:** Overall, the results highlight the importance of healthy sleep for mental health, especially during periods of stress and upheaval. We also identify important behaviours that influence insomnia, which can be modified to ensure healthy sleep and subsequent mental health.

**Acknowledgements:** National Research Foundation (NRF) Competitive Support for Unrated Researchers (CSUR) grant 116229

#### THE QUALITY OF NIGHT SLEEP AFFECTS THE PSYCHICS, COGNITIVE PERFORMANCE AND CARDIOVASCULAR SYSTEM OF SURGEONS

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**Introduction:** Sleep quality is extremely important to restore human resources, to assimilate the information received during the day and to prepare to the new day activity. The purpose was to reveal the effects of sleep quality on the psychics, cognitive performance parameters and cardiovascular system activity in surgeons.

**Materials and Methods:** Forty five surgeons aged 24–62 years old (mean age  $\pm$  SD: 40,4 $\pm$ 10,6 yrs) were observed individually using questionnaire, computer based cognitive performance tests, measures of blood pressure and heart rate at the first hours of their working shifts. The quality of night sleep on the eve of the working shift was self-assessed by 5-anchor Likert scale. Data were analyzed using Pearson correlation at  $p < 0,05$ .

**Results:** The quality of night sleep of surgeons varied from 2 to 5 (3,69 $\pm$ 0,92). The asymmetry of blood pressure in the upper extremities ( $>10$  Hg mm) was found in he each second surgeon. The quality of night sleep positively correlated to self-assessment of workability ( $r=0,31$ ), negatively correlated to self-assessment of cognitive fatigue ( $r=-0,30$ ), communicability fatigue ( $r=-0,34$ ), strain ( $r=-0,37$ ), feeling of being upset ( $r=-0,30$ ), nervous ( $r=-0,40$ ), excited ( $r=-0,30$ ), worrying about possible failures ( $r=-0,34$ ). When running the Landolt rings cancellation test, the quality of night sleep positively correlated to productivity ( $r=0,33$ ), velocity ( $r=0,35$ ) and general number of the information processed ( $r=0,31$ ), and negatively correlated to the number of missed rings ( $r=-0,33$ ) and general number of mistakes ( $r=-0,32$ ). When running the simple situation recognition test under time pressure regime, the quality of night sleep positively correlated to the general number of the tasks processed ( $r=0,37$ ), number of correct decisions ( $r=0,36$ ) and velocity of working ( $r=0,33$ ). When running the complicated situation recognition test under time pressure regime, the quality of night sleep negatively correlated to the ratio of the number of incorrect to the number of missed tasks ( $r=-$

0,36), evidencing the improvement of the style of working under time pressure - to prefer to skip a task than solve it somehow. When running the Silhouette Illusion test, the quality of night sleep negatively correlated to the number of uncontrolled changes in the direction of rotation of the silhouette ( $r=-0,31$ ). No correlation to short-term memory or switching of attention was found. Also, the quality of night sleep negatively correlated to the peripheral vascular resistance ( $r=-0,40$ ) and asymmetry in diastolic blood pressure in the upper extremities ( $r=-0,56$ ).

**Conclusions:** Good quality of night sleep on the eve of a working day improves the workability, quantity and quality of both the attention concentration and simple information processing under time pressure, while under processing of the complicated information the style of surgeon work becomes more reliable. The improvement in night sleep quality was accompanied also with the improvement in CVS functioning. So, special efforts are needed to improve the night sleep quality of surgeons to support their workability and CVS health.

**Acknowledgements:** We appreciate the financial support from National Academy of Medical Sciences of Ukraine for this study and also hospital management and surgeons for their assistance and participation in the research.

### THERAPEUTIC OPTIONS AND CHALLENGES OF OBSTRUCTIVE SLEEP APNEA

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**Introduction:** Obstructive sleep apnea (OSA) is a major challenge for physicians and healthcare systems throughout the world, especially due to the high prevalence and impact on daily life. Nocturnal positive airway pressure is currently the mainstay of treatment.

**Materials and Methods:** The authors present two case reports of OSA treated with auto-CPAP, that developed hypercapnic respiratory failure.

**Results:** Case 1: A 70-year-old man, with previous history of severe OSA (AHI 46 events/h), obesity (BMI 34 kg/m<sup>2</sup>), diabetes and hypertension. The patient presented in our medical consultation with normalized sleep and improved OSA-health outcomes, with 96% of auto-CPAP adherence ( $\geq 4$ h per night on 70% of the nights) and residual AHI of 1,8 events/h. He also presented hypercapnic respiratory failure (pCO<sub>2</sub> 51 mmHg) and daytime sleepiness. He reduced BMI (31 kg/m<sup>2</sup>) and had normal pulmonary function tests. He underwent BPAP titration, with normocapnia (pCO<sub>2</sub> 44 mmHg) and excellent adherence after a month of treatment.

Case 2: A 71-year-old woman, with previous history of moderate OSA (AHI 31 events/h) and overweight (BMI 27 kg/m<sup>2</sup>), recently diagnosed with bipolar disorder and cerebrovascular accident, developed hypercapnic respiratory failure (pCO<sub>2</sub> 48 mmHg). The patient presented 88% of auto-CPAP adherence ( $\geq 4$ h per night on 70% of the nights) and residual AHI of 7,4 events/h. She changed to BPAP device with normocapnia (pCO<sub>2</sub> 44 mmHg) after a month of treatment.

**Conclusions:** Although many different diseases cause respiratory failure, a variety of pharmacologic, structural and metabolic disorders of the CNS are characterized by suppression of the neural drive breathe, resulting in hypoventilation and hypercapnia. Characterization of different causes or phenotypes of OSA has provided new pathways for target therapy.

**Acknowledgements:** N/A

### THE RELATIONSHIP BETWEEN ECOLOGICAL CONTEXTS OF ADOLESCENTS AND SLEEP QUALITY

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**Introduction:** Adolescence is a period of gradual transition that is characterized by critical physical, neural and psychological changes. In recent years, increased attention has been devoted to the study of how adolescents' social experiences are intertwined with their health. In this context, sleep quality has been considered a key indicator of health. However, a comprehensive understanding of how adolescents multiple social experiences are related to their sleep quality is still missing. In line with this, the

goal of this study is to examine the interplay between adolescents' social experiences in their main socialization contexts (i.e., family, peers, school) and their sleep quality considering both subjective and objective indicators of it.

**Material and methods:** For the purpose of this study, participants will be about 2000 adolescents involved in the ERC-Consolidator project IDENTITIES (Grant Agreement n. 101002163). Half of them will be aged 14-year-old and 16-year-old, attending respectively the first and the third year of secondary high school. The study will be conducted in the North-East of Italy, in the region Emilia-Romagna. Data will be collected in January 2022 as a part of a broader longitudinal project. Measures regarding adolescents' experiences in main socialization contexts will be collected by means of standardized questionnaires. Data on sleep quality will be collected through subjective measures (i.e., Mini Sleep Questionnaire, Natale et al., 2014) and objective measures (i.e., actigraphy).

**Results:** Data analyses will be conducted using statistical software SPSS and Mplus. Specifically, a within structural equation modelling framework (SEM) multiple regression analyses will be used to test the reciprocal associations between different main socialization contexts (i.e., family, peers, school) and sleep quality (both objectively and subjectively measured). Results will be discussed in light of theoretical and practical implications.

**Acknowledgements:** This work was conducted within the ERC-Consolidator project IDENTITIES (Grant Agreement n. 101002163).

### THE RELATIONSHIP BETWEEN SLEEP AND MULTIMORBIDITY IN COMMUNITY DWELLING POPULATIONS: A GLOBAL PERSPECTIVE

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**Introduction:** Previous research has suggested relationships between poor sleep and risk of multimorbidity, which is defined as the presence of two or more chronic conditions co-occurring in the same individual. The current systematic review seeks to investigate the relationship between sleep quality and duration and multimorbidity in community-dwelling populations. Examining the health impact of sleep hygiene may help support better treatment outcomes of multimorbidity, identify appropriate target groups, and increase public health awareness of sleep as a modifiable risk factor for the prevention of chronic disease.

**Materials and Methods:** A comprehensive search of the PubMed, Embase and CINAHL databases was used to identify studies published between January 1990 to June 2021. Studies were included if they focused on community-dwelling populations  $\geq 18$  years of age, used an observational design, included a measurement of sleep quality or sleep duration, included a measurement of multimorbidity as the main independent variable, and explored the descriptive or multivariable relationship between sleep and multimorbidity. Two reviewers independently conducted study screening and data extraction, and each reviewer independently conducted bias assessments for each of the included articles.

**Results:** Twenty-four cross-sectional and three prospective cohort studies met the inclusion criteria. Across studies, multimorbidity was generally associated with poorer sleep quality, though the strength of this association varied. This association was present regardless of whether the study investigated multimorbidity in terms of mental health disorders of chronic physical conditions. The relationship was also seen in people with insomnia or with multiple sleep disorders, increasing the risk of simultaneously having or developing other chronic diseases. Definitions of sleep duration and sleep quality variables were inconsistent across studies, and this may have contributed to the mixed evidence in the association between sleep and multimorbidity. Most studies used a cross-sectional design which limited the interpretation of causality or direction of association.

**Conclusions:** Our results corroborate relationships between poor sleep and risk of multimorbidity in adult community-dwelling populations around the world. Future studies using a longitudinal design would help

elucidate the direction of the relationship between sleep and multimorbidity.

**Acknowledgements:** Marisa Tippet, Acting Director, Education Library, Western University

### TOO NOISY, TOO DARK: SLEEP ENVIRONMENT AT THE STROKE UNIT

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**Introduction:** Sleep and circadian disturbances are frequent in stroke patients. Stroke units represent an hostile sleep environment (care controls; noise through snoring and bed alarms, insufficient light during the day/light exposure during night) which may contribute to sleep loss and destabilization of the circadian rhythm. The role of noise and lighting levels in a stroke unit have never been evaluated.

**Materials and Methods:** The noise and lighting levels of all 12 beds of the Stroke Unit of the University Clinic Inselspital Bern were assessed between July and August 2021. Noise measurements (LAeq, LAfmax, LAfmin) were recorded every second for at least one 23h period for every single bed via the XL2 audio and acoustic analyser (NTi Audio, Lichtenstein) and a M4261 microphone close to the patients ear. Lighting (photopic lux, melanopic equivalent daylight illuminance in lux, correlated color temperature CCT) were recorded every minute close to the patients eyes via a spectral light detector (CSS-45, Gigahertz-Optik, Germany).

**Results:** We found that recommended sound pressure levels at night of 30 dB and 35 dB during the day are constantly exceeded at both window and door beds. Door beds were more noisy than window beds (53 ± 2.8 dB vs 51.5 ± 3.2 dB at day and 43.3 ± 3 dB vs 39.5 ± 3.1 dB at night). Suggested daytime illuminance of 250 melanopic equivalent daylight illuminance in lux were hardly ever reached during the day at door beds (total of ~15 minutes) and only reached for a total of 3 hours at window beds. Counterproductive to the circadian system, illuminance was highest in the late evening hours (6pm-10pm) rather than in the morning hours (6am-10am) where it would be desirable and effective in realigning the internal body clock.

**Conclusions:** These data suggest that noise and lighting environment in the stroke unit are unfavorable. Further studies are needed to assess their contribution to sleep and circadian disturbance in acute stroke patients and eventually on stroke outcome.

### TRAJECTORIES OF SLEEP DURATION AND TIMING PRIOR TO DEMENTIA: A 14-YEAR FOLLOW-UP STUDY

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**Introduction:** Sleep disturbances have retained attention by their frequent occurrence in the normal aging process but also by their role in the development of cognitive disorders. Longitudinal studies reported that both short and long sleep duration, excessive daytime sleepiness, and insomnia complaints have been associated with incidence of dementia. However, whether changes in sleep measures prior or close to dementia onset remains unknown. The aim was thus to confirm the relationship between sleep complaints and incidence of dementia and to characterize concurrently quantitative sleep measures trajectories over 14 years before dementia diagnosis.

**Methods:** Nighttime and 24-hour sleep duration, napping, wake-up time, bedtime, excessive daytime sleepiness, and insomnia complaints were

self-reported every two years during a 14 years follow-up in a large community-dwelling elderly cohort (3-City, Montpellier). Incident cases of dementia were systematically diagnosed and validated. Cox models were used to estimate the risk of dementia associated with sleep complaints at baseline (n=1749). Based on a nested case-control study matched by sex, age and educational level (182 cases and 720 controls), sleep trajectories between cases and controls were performed using latent-process mixed models and a backward time scale.

**Results:** Long nighttime (≥9 hours) and 24-hour sleep (≥9 hours) durations, earlier bedtime (≤9 p.m), and severe napper (≥7 naps/week and ≥60 min each time) assessed at baseline were associated with a higher risk of dementia. A faster increase in mean 24-hour sleep duration was observed in cases than controls (mean values [95%CI] were 14 years before diagnosis and at diagnosis: 6.8 [6.6-7.0] and 7.2 [7.0-7.3] for controls; 7.1 [6.7-7.4] and 8.0 [7.7-8.3] for cases). Trajectories between both groups differed up to 12.5 years before diagnosis. The same tendency was found for nighttime sleep duration with a significant difference up to -11.8 years. Trajectories of bedtime decrease with a steeper slope in cases than controls (mean values at -14 years and at year 0 were 22.9 [22.8-23.0] and 22.6 [22.5-22.7] for controls; 22.7 [22.6-22.9] and 22.2 [22.0-22.4] for cases) with a significant case-control difference up to 8.2 years prior to diagnosis. No differences between both groups were found for wake-up time (stable evolution) and napping (increase evolution) trajectories.

**Conclusions:** In prodromal dementia, nighttime and 24-hour sleep duration increased, whereas bedtime was getting earlier. Results suggest that optimal period for the management of sleep health to prevent dementia begins at least 12.5 years before the diagnosis of dementia.

**Acknowledgements:** The Fondation pour la Recherche Médicale funded the preparation and first phase of the study. The Three-City Study is also supported by the Caisse Nationale Maladie des Travailleurs Salariés, Direction Générale de la Santé, MGEN, Institut de la Longévité, Agence Française de Sécurité Sanitaire des Produits de Santé, the Regional Governments of Aquitaine, Bourgogne and Languedoc-Roussillon and, the Fondation de France, the Ministry of Research-Inserm Programme "Cohorts and collection of biological material". The Lille Génomipole received an unconditional grant from Eisai.

### TRENDS OF TELECONSULTATION IN A COMPREHENSIVE SLEEP CLINIC DURING THE COVID-19 PANDEMIC

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**Introduction:** COVID-19 pandemic was associated with new onset or worsening of pre-existing sleep disorders related to lifestyle changes, fear of the disease and apprehension about the future. The access to healthcare was significantly limited by lockdown measures which necessitated alternative technology-based solutions such as Teleconsultation. In this study we aim to describe the trends in healthcare seeking patterns in a free-standing comprehensive sleep clinic in India.

**Materials and Methods:** This is a retrospective study conducted at Nithra Institute of Sleep Sciences, Chennai, India, from March 2020 to June 2021. Patient demographics, diagnosis and mode of consultation were collected. Data was analyzed with a focus on preferred mode of consultation ("in-person" and "Teleconsultations") and the trend during this period.

**Results:** There were a total of 2155 consultations, of which 1766 patients (81.9%) were in-person consultations and 389 (18.1%) were teleconsultations. Of these 389 teleconsultations 133 (34.1%) patients were initial visits (new patients), while the rest 256 (65.8%) were follow up consultations. 844 (47.8%) of those who consulted 'in-person' were new patients while 922 (52.2%) were follow up consultation. The number of teleconsultations were more than in-person consultations only during 2 months (April and July 2020), during the first wave of the pandemic.

We also observed a change in the clinical profile of the patients during the peak waves in the pandemic. Sleep disordered breathing is usually the predominant problem seen in our center, we noticed that insomnia was the presenting diagnosis for most patients during the peak periods of March - August 2020 (61.8%) and April - June 2021 (60%).

**Conclusions:** Our study shows that patients were open to the idea of teleconsultations but 'in-person' consultation was still the preferred

option despite lockdown regulations. Follow-up patients were more open to teleconsultations in comparison with those presenting for initial evaluation. Insomnia was the predominant reason for which patients presented during the peak waves of the pandemic. The change in the diagnostic profile of patients may reflect the effect of the pandemic on sleep (insomnia) and possibly the reduced urgency to get evaluated for sleep related breathing disorders.

#### Acknowledgements:

#### WELL-BEING THERAPY AS ADJUNCTIVE TO SLEEP HYGIENE IMPROVES SLEEP AND WELL-BEING IN ADULTS WITH POOR SLEEP AND DISTRESS DURING THE COVID-19 PANDEMIC: A PILOT RANDOMIZED CONTROLLED STUDY

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**Introduction:** Although research has mainly focused on the association between sleep and emotional distress, the construct of psychological well-being has been shown to increase resistance to stressful life situations and buffer the impact of distress on sleep. However, only few studies have examined the impact of well-being interventions on sleep. The objective of this study was to test the efficacy of a combined well-being and sleep hygiene intervention to improve sleep, psychological distress, and well-being among healthy adults reporting poor sleep quality (Pittsburgh Sleep Quality Index [PSQI] >5) and moderate distress (Perceived Stress Scale [PSS] ≥14) during the Covid-19 pandemic.

**Materials and Methods:** In this pilot randomized controlled trial, 31 participants (81% women; age: 40.2±13.0 y, 48% racial/ethnic minority) were recruited from the community between March and November 2020 and randomized (in 1:1 ratio) to receive a combined well-being and sleep hygiene intervention (WBT+SH) or sleep hygiene alone (SH) for 7 weeks. Both interventions were delivered in 7 one-on-one sessions via Zoom by a trained clinical psychologist. The well-being intervention was adapted from Well-Being Therapy, a short-term psychotherapeutic strategy to achieve balance among different areas of psychological well-being. The sleep hygiene intervention included education, stimulus control, goal setting, self-monitoring, feedback, and problem-solving related to sleep. Data were collected at baseline and immediately post-intervention using questionnaires (PSQI, Insomnia Severity Index, Symptom Questionnaire, PSS, and Psychological Well-Being Scale). A sleep diary was administered daily to collect information on total sleep time (TST), variability in TST, sleep onset latency, wake time after sleep onset (WASO), bedtime, and variability in bedtime. All study procedures were performed remotely, using video conferencing and online surveys. Independent-sample t-tests were used to compare group changes in outcomes assessed by questionnaire; linear mixed effects models assessed changes in sleep diary outcomes.

**Results:** Thirty participants completed the study (WBT+SH=15/16; SH=15/15), with a completion rate of 97%. Compared to SH, the combined intervention led to greater improvements in WASO ( $B=3.6\pm 1.5$ ,  $p=0.017$ ), with a reduction over time of about 40 minutes in the group receiving WBT+SH and no change in the SH group. Greater improvements in personal growth (between-group mean difference -3.0 score [95% CI -5.2, -0.8],  $p=0.01$ ) and purpose in life (between-group mean difference -3.5 score [95% CI -6.1, -0.9],  $p=0.009$ ) were also observed in WBT+SH compared to SH. Anxiety, perceived stress, sleep quality, and insomnia symptoms significantly improved in both groups, with no difference between groups.

**Conclusions:** Our preliminary findings demonstrate the feasibility of the remote implementation of a combined well-being and sleep hygiene intervention in the context of the Covid-19 pandemic. Further, while sleep hygiene may be a valuable option to improve sleep and distress in a non-clinical setting, the addition of a well-being intervention may be a more comprehensive treatment option to improve sleep and well-being for those suffering from combined poor sleep and psychological distress.

#### WHO SLEEPS WELL IN CANADA? SOCIAL DETERMINANTS OF SLEEP HEALTH DISPARITIES AMONG MIDDLE-AGED AND OLDER ADULTS IN THE CANADIAN LONGITUDINAL STUDY ON AGING

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**Introduction:** Disruptions in sleep quality or duration affect over half of the older adult population. Poor sleep health is associated with increased risk of mortality and chronic conditions. Inequities in sleep health likely contribute to disparities in poor health outcomes. Our objective was to identify the social determinants of sleep health among middle-aged and older adults in Canada.

**Methods:** We used cross-sectional baseline data from the Canadian Longitudinal Study on Aging, a survey of 30,097 community-dwelling adults, aged 45–85. Self-reported sleep measures included sleep duration, sleep satisfaction (vs dissatisfied/neutral), and sleep continuity (vs problems initiating or maintaining sleep). We selected social determinants 'a priori' based on literature. We used modified Poisson regression to estimate prevalence ratios for sleep satisfaction and sleep continuity, and linear regression for sleep duration. Using block-wise adjustment, estimates were adjusted for all social determinants and further adjusted for lifestyle and clinical covariates.

**Results:** In analyses adjusted for social determinants, groups with better sleep included older age groups, higher household income, higher education level, and South Asian groups, with a higher prevalence of sleep satisfaction and/or sleep continuity. Female sex was associated with a lower prevalence of both sleep satisfaction and sleep continuity. Unemployment (vs retired) was associated with a lower prevalence of sleep satisfaction. For sleep duration, employed or unemployed (vs retired), Black, East Asian, and other/mixed race groups (vs white) had shorter sleep duration, while older age groups, home owners, sexual minorities, and higher education groups had longer sleep duration. Adjusting for lifestyle and clinical variables, effects for household income, unemployment, and education were attenuated, while all other associations persisted.

**Conclusion:** Our findings highlight sleep health disparities among Canadian middle-aged and older adults across socioeconomic gradients and ethnic/racial minority groups. Poor sleep health in disadvantaged population sub-groups may represent an additional source of health disparities and warrants increased attention as a public health problem in our societies.

#### Hypersomnia

#### A CASE OF SODIUM OXYBATE INDUCED CENTRAL SLEEP APNEA RESOLVED WITH TOPIRAMATE CO-ADMINISTRATION IN A CHILD WITH NARCOLEPSY

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**Introduction:** Sodium Oxybate (SO) is a first line treatment for patients with narcolepsy type 1 (NT1) and 2 (NT2). It is a known central nervous system (CNS) depressant that can cause respiratory depression (RD). In fact, it has a warning stating some trial participants taking recommended doses of SO experienced clinically significant RD, including treatment emergent central sleep apnea (CSA). However, there are no clear guidelines for monitoring the respiratory status nor suggestion on how to respond if clinically significant RD occurs. Most providers withdraw treatment, irrespective of efficacy on control of narcolepsy symptoms. Here we describe a case of resolution of SO-induced CSA with topiramate to reduce respiratory events in a pediatric patient.

**Materials and Methods:** A case report of a 10 year old girl with NT1 who developed severe CSA on twice nightly SO that resolved with co-administration of low dose topiramate

**Results:** A 10 yo girl with history of seizure disorder, well controlled with lamotrigine, and NT1, who has symptoms of excessive daytime sleepiness (EDS), frequent cataplexy, sleep paralysis, sleep related hallucinations, and

disturbed nocturnal sleep (DNS), had a baseline polysomnography (PSG) with an AHI 1.4/hr, only obstructive. Multiple sleep latency test (MSLT) with average sleep latency (SL) of 2 minutes and thirty three seconds with no sleep onset REM periods (SOREMPs). She was diagnosed NT1 based on reduced SL and presence of frequent debilitating cataplexy. She was started on SO. In the first month, parent reported concerns for apneic events during sleep low therapeutic doses. Repeat PSG demonstrated severe CSA with an AHI of 103.9, with pronounced emergence of CSA in a Cheyne-Stokes pattern. Patient and parent refused to consider discontinuation of SO due to significant benefit in NT1 symptoms. Alternatively, seizure medication was intentionally changed to topiramate for combined therapeutic benefit for seizure and central sleep apnea. Repeat PSG following transition to Topamax provided remarkable results with AHI of 1.7/hr.

**Conclusions:** Topiramate is an anti-seizure medication and migraine prophylaxis that also has properties as a carbonic anhydrase inhibitor. Carbonic anhydrase inhibition leads to metabolic acidosis that likely shifts the hypercapnia ventilatory response and lowers the PaCO<sub>2</sub> apnea threshold, which could improve central sleep apneas. Improved guidance on appropriate surveillance for clinically significant RD with treatment of SO is necessary. When SO-induced CSA occurs, topiramate, and potentially other carbonic anhydrase inhibitors, may be beneficial but further study is required.

**Acknowledgements:** none

#### ASSOCIATIONS OF DAYTIME EXECUTIVE FUNCTION AND SLEEP MEASURES IN PEDIATRIC NARCOLEPSY TYPE 1

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**Introduction:** Executive functions (EF) are a set of higher order cognitive functions necessary for organizing, planning and monitoring behavior. EF dysfunctions are frequently reported from narcolepsy populations, both by questionnaires and performance on neuropsychological tests. EF dysfunctions in narcolepsy are considered to be a result of sleepiness, but how/if EF dysfunction is associated with objective sleep abnormalities in narcolepsy has not been reported from pediatric narcolepsy populations, while reports from studies in adult narcolepsy populations are inconsistent.

**Materials and Methods:** Participants were 56 youths aged 7-20 (mean age 14.9, 57.1 % females, 85.7 % Pandemrix (H1N1)-vaccinated), with narcolepsy type 1 (NT1) admitted to our national center of expertise on narcolepsy in Norway. All patients underwent clinical evaluation, answered on questionnaires including Epworth Sleepiness Scale (ESS) and had an overnight polysomnography (PSG) followed by multiple sleep latency test (MSLT) after a medication free period of 14 days. All patients fulfilled the ICSD-3 criteria for NT1 (all except one with unknown status were hypocretin (Hct) deficient and were diagnosed by excessive daytime sleepiness (EDS), cataplexy and a positive MSLT). EFs were measured by parent report of behavior on the Behavior Rating Inventory of Executive Function (BRIEF), yielding scores on eight subscales (Inhibit (INH), Shift (SH), Emotional Control (EC), Initiate (INI), Working Memory (WM), Plan / Organize (PO), Organization of Materials (OM) and Monitor (MON)), two index scales (Behavioral Regulation Index (BRI) and Meta Cognitive Index (MI)), and a sumscore (Global Executive Composite (GEC)). A T score > 65 on subscales, index or sum score are considered to be clinically relevant.

**Results:** Thirty-seven youths (66.1%) had one or more subscale in clinically relevant level, most frequently for WM (in 51.8%), followed by PO (37.5%), INI (35.7 %), and EC (in 33.9%) and SH (in 32.1%). The total score GEC, the index score MCI, and the subscales WM, PO, and INI were not significantly correlated with ESS score, mean sleep latency on MSLT, Sleep Stage Shift Index (SSS-I) awakening index (AI), or sleep efficiency (SE) on the PSG. The subscales INH, SH, EC, OM, and MON and the index score BRI were significantly correlated with ESS total score ( $\rho = 0.348, p=0.009$ ;  $\rho = 0.272, p=0.043$ ;  $\rho = 0.275, p=0.040$ ;  $\rho = 0.379, p=0.004$ ;  $\rho = 0.325, p=0.015$ ;  $\rho = 0.293, p=0.028$  respectively). Only the correlations between INH and OM on the one hand, and ESS on the other, survived

Bonferroni correction.

**Conclusions:** EF dysfunction related to inhibition and organizing as measured by the BRIEF questionnaire was moderately correlated with a subjective measure of sleepiness. No measures of EF dysfunction were correlated with objective measures of sleepiness or sleep fragmentation. Our findings do not lend support to the notion that EF dysfunction in narcolepsy are mainly caused by sleepiness or fragmented sleep.

**Acknowledgements:**

#### AUTONOMIC REFLEX TESTING CONFIRMS AUTONOMIC DISTURBANCES IN A COHORT OF PATIENTS WITH IDIOPATHIC HYPERSOMNIA

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**Introduction:** Symptoms suggestive of autonomic nervous system (ANS) dysfunction have been previously described in patients with idiopathic hypersomnia (IH), however objective ANS reflex testing data have not been reported. We aimed to better quantify symptoms of ANS dysfunction in a cohort of patients with IH through the use of standardized ANS reflex testing.

**Materials and Methods:** Patients diagnosed with IH based on ICSD-3 criteria using overnight video polysomnography and multiple sleep latency testing (MSLT) were consecutively enrolled in our study, regardless of ANS symptoms. All patients underwent ANS reflex testing, including measures of parasympathetic (heart rate variability with deep breathing and Valsalva ratio) and sympathetic adrenergic function (Valsalva blood pressure response and 10-minute head-up tilt at an angle of 70 degrees) with continuous blood pressure and heart rate monitoring. Eleven patients also underwent measures of sympathetic cholinergic function (quantitative sudomotor axon reflex testing). All medications that affect ANS function were held prior to ANS testing, including wake-promoting medications and sodium oxybate.

**Results:** Seventeen patients with IH were enrolled. Seven were long sleepers (>11hrs). Mean sleep onset latency and number of sleep onset REM periods (SOREMs) on MSLT were 6.6 ( $\pm 3.1$ ) mins and 0.2 ( $\pm 0.4$ ), respectively. Mean duration of IH symptoms prior to the date of ANS testing was 4.9 ( $\pm 5.3$ ) yrs. Eighty-two percent (14/17) of patients had abnormal ANS testing. Of these, 65% (11/17) had sympathetic adrenergic impairment, 64% (7/11) had sympathetic cholinergic impairment, and 6% (1/16) had parasympathetic impairment. Forty-seven percent (8/17) of patients were diagnosed with postural tachycardia syndrome (POTS), 45% (5/11) with small fiber neuropathy, 6% (1/17) with inappropriate sinus tachycardia and 6% (1/16) with neurally-mediated syncope. Seventy-six percent (13/17) of patients reported orthostatic intolerance regardless of autonomic diagnosis.

**Conclusions:** ANS dysfunction was common and severe in our cohort of IH patients, and affected all domains of ANS reflex testing, with more prominent impairment in sympathetic domains. POTS was the most common comorbid diagnosis, and most patients reported orthostatic intolerance. There was no association with IH disease duration, though our sample size was limited. Future studies will focus on ANS testing in larger cohorts of IH patients, specifically on shared pathophysiological mechanisms of hypersomnia and ANS dysfunction.

#### CIRCADIAN VARIATION OF MUSCLE ATONIA INDEX IN DIFFERENT LEVEL OF VIGILANCE AS POSSIBLE MARKER OF NARCOLEPSY COMPARED TO OTHER HYPERSOMNIAS: A MSLT BASED RETROSPECTIVE STUDY

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**Introduction:** The diagnosis of narcolepsy is often complex and delayed, requiring extensive diagnostic tests and invasive procedures such as CSF orexin dosage. The complexity of the procedures and the difficult clinical picture may induce substantial diagnostic delays. The aim of our study was to evaluate circadian changes in muscle tone (atonia index) in different levels of vigilance during the multiple sleep latency test in patients with narcolepsy type 1 (NT1) and 2 (NT2) compared with other hypersomnias and evaluate its possible diagnostic value.

**Metodi:** We considered a retrospective cohort of 48 patients with type 1 (NT1) and type 2 (NT2) narcolepsy and 20 controls with other hypersomnias. An evaluation of the muscle atonia index (AI) was carried out in different levels of vigilance in each nap and in the entire test of the groups examined by Hypnolab 1.3 automatic analysis software (Statsoft Italy). The validity of AI in the identification of narcolepsy patients (NT1 and NT2) was evaluated using Receiver Operating Characteristic (ROC) curves.

**Risultati:** Wake AI (WAI) was significantly higher in both the narcolepsy groups (NT1 and NT2  $p < 0.001$ ) compared with the control group. Rem sleep AI (RAI) was lower in N1 than N2 ( $p = 0.03$ ). The analysis of the ROC curves returned high AUC values for WAI (NT1 0.88; Youden index  $> 0.57$  Sensitivity 79.3% Specificity 90%; NT2 0.89 Youden index  $> 0.67$  Sensitivity 87.5% Specificity 95%; NT1 and NT2 0.88 Youden index  $> 0.57$  Sensitivity 82.2% Specificity 90%) in discriminating subjects suffering from different central hypersomnias. RAI showed an AUC value of 0.7 (Youden index  $\leq 0.7$  Sensitivity 50% Specificity 87.5%) differentiating NT1 and NT2.

**Conclusions:** AI in different levels of vigilance seems to be a promising electrophysiological marker of narcolepsy and suggests a vulnerable tendency to dissociative waking/sleep dysregulation absent in other forms of hypersomnia.

#### DISCOVERY OF A NOVEL ORALLY AVAILABLE SELECTIVE OREXIN 2 RECEPTOR AGONIST, E2086, AS A THERAPEUTIC DRUG FOR NARCOLEPSY AND OTHER HYPERSOMNIA DISORDERS

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**Introduction:** Orexin neurons in the hypothalamus are a critical regulator of sleep/wakefulness states, and their loss is associated with narcolepsy type 1 (NT1). In patients with NT1, as characterized by reduced orexin levels in cerebrospinal fluid (CSF), excessive daytime sleepiness and cataplexy are observed, both of which are diagnostic for NT1. Orexins act through two classes of G-protein coupled receptors, the orexin-1 receptor (OX1R) and the orexin-2 receptor (OX2R). Although both OX1Rs and OX2Rs are related to sleep-wake regulation, OX2Rs contribute more to sleep-wake regulation. Greater awake/non-rapid eye movement (NREM) sleep episode fragmentation and reduced duration of wakefulness in hypnograms have been seen for OX2R-knockout and double-receptor knockout mice compared with wild-type (WT) and OX1R-knockout mice. Therefore, an OX2R-selective agonist is expected to act as a wake-promoting drug. Here we report the *in vitro* and *in vivo* profiles of a novel, orally available OX2R-selective agonist, E2086.

**Materials and methods:** Three nonclinical studies were conducted. (1) Lenti-X™ 293 cell lines that constitutively and stably express either human, mouse, or rat OX2R or OX1R were used to assess OX2R or OX1R-agonistic activity via calcium influx assay. To evaluate E2086-mediated arousal effects in (2) WT mice and in (3) orexin-neuron deficient mice (*orexin/ataxin-3* hemizygous mice), EEG/EMG recordings were conducted with E2086 or vehicle treatment during the active phase.

**Results:** E2086 activated human OX2R in the calcium influx assay without considerable species differences or activity on the human OX1R. Oral administration of E2086 promoted wakefulness in both WT mice and orexin-deficient mice. Additionally, in orexin-deficient mice, latency of direct transitions from wake to REM sleep, which is a murine analog of human cataplexy, was also prolonged. These results support the potential for E2086 to improve wakefulness and other orexin deficiency-related

symptoms like cataplexy in patients with orexin network hypofunction, and suggest that E2086 may improve wakefulness in patients with excessive daytime sleepiness across a range of orexin levels.

**Conclusions:** The orally available compound E2086 may have potential as a new treatment option for patients with NT1 and other hypersomnia disorders.

**Acknowledgements:** These studies were conducted by Eisai Co., Ltd.

#### GENDER DIFFERENCES OF SLEEPINESS IN CENTRAL HYPERSOMNOLENCE DISORDERS

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**Introduction:** Narcolepsy is associated with excessive daytime sleepiness (EDS) and an increased BMI. In the healthy population, EDS is associated with overweight. De-activation of the ventromedial prefrontal cortex has been associated with sleepiness and, in women, with overeating. In this study, we examine the association of sleepiness, BMI and uncontrolled eating in a large population of patients with narcolepsy and other disorders of hypersomnolence (CDH).

**Patients and Methods:** Our study population constitutes the European Narcolepsy Network (EU-NN) database and entails data collected from 29 different European sleep centers between 2008 and 2020. We analyzed 1'540 patients at first diagnosis (1'035 with narcolepsy with cataplexy and 505 with other CDH according to the International classification of sleep disorders, 2nd edition). We assessed associations of the dependent variables BMI ( $n = 1'540$ ) and Epworth Sleepiness Scale (ESS,  $n = 1'434$ ) with diagnosis, self-reported uncontrolled eating ( $n = 451$ ), age and gender as independent predictors using generalized linear models (glm).

**Results:** ESS scores and BMI were significantly higher in patients with narcolepsy with cataplexy than in other CDH (glm with predictors *Patient group* and *Gender*,  $p < 0.001$  for all predictors). While BMI was higher in men than in women, women scored higher in the ESS than men, independent of the patient group (Post-hoc two sample t-tests,  $p < 0.01$  for all comparisons). However, BMI and ESS were not correlated on an individual level, even when sub-grouping according to *Patient group* and *Gender* ( $| \text{Pearson } R | < 0.12$  for all sub-groups). BMI and the ESS score rise with a roughly logarithmic dependency on age at diagnosis (glm with predictors *Patient group*,  $\log_2(\text{Age})$ , all predictors  $p < 0.001$ ). Specifically in female patients with other CDH, the ESS score exhibits a marked peak around 30 to 40 years, followed by a steep rise of BMI with around 5 years delay. Self-reported uncontrolled eating was more frequent in narcolepsy with cataplexy than in other CDH (31,4% vs 21,6%, Fisher's Exact Test  $p < 0.05$ ). BMI, but not the ESS score was positively associated with uncontrolled eating (glm with predictors *Patient group*,  $\log_2(\text{Age})$ , *Gender*, *uncontrolled eating*, all predictors  $p < 0.01$ ). In females with other disorders of hypersomnolence, uncontrolled eating was associated with lower sleepiness (median ESS of 15.0 (IQR 12.0, 17.0) in presence of uncontrolled eating vs 18.0 (IQR 16.0, 20.0) in absence of uncontrolled eating, post-hoc two sample t-test  $p < 0.01$ ).

**Conclusions:** In patients with CDH, sleepiness is higher in women than in men. In addition, women with CDH other than narcolepsy show a distinct peak of sleepiness at the age of 30 to 40 years. Potential reasons for these difference may be hormonal or sleep-wake pattern changes associated with childbirth and caring for small children in this life period. Further studies on the biological, physiological and social determinants of EDS are planned in the context of the "Swiss Primary Hypersomnolence and Narcolepsy Cohort study" (SPHYNCNS).

**Acknowledgements:** We thank the EU-NN network for providing the data.

#### RE-DIAGNOSING IDIOPATHIC HYPERSOMNIA TEN YEARS AFTER THE FIRST DIAGNOSIS

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**Introduction:** The diagnosis of idiopathic hypersomnia (IH) is predicated by the absence of other conditions that may better explain excessive sleep or sleepiness. Considering that frequent diseases and treatments may induce sleepiness, we wanted to determine whether our patients met IH diagnostic criteria years after the initial diagnosis.

**Materials and Methods:** The patients diagnosed with IH in our department three and more years ago were contacted, and their clinical status was reevaluated by an interview and Epworth sleepiness scale. Confirmation or rejection of the IH diagnosis was then based on the persisting presence of excessive sleep or sleepiness and simultaneous absence of better explanation by reported conditions, medication schemes, and other illnesses.

**Results:** In total, 38 subjects, 13 males, 25 females, with an average age of 46.9 (SD=14.1), were examined. Eighteen subjects suffered from the IH form with long sleep duration. The interval between the diagnosis and the control was 9.8 (SD 8.5) years. Fourteen subjects (34.1%) did not meet the criteria mentioned above. 4 subjects reported disappearance of sleepiness. The diagnosis of one subject was changed to narcolepsy type 2. Two subjects reported significant RLS in both cases combined with severe polymorbidity. Two patients were recently diagnosed with severe OSA and were not receiving treatment. One subject had bipolar disease and two other significant depression and anxiety. All three were extensively medicated without substantial mood improvement, and discontinuation of the medication just to confirm or reject the IH diagnosis was out of the question. One subject reported chronic respiratory and cardiac failure and dominant tiredness, and another was treated with clonazepam and gabapentin for essential tremor and polyneuropathy.

**Conclusions:** Our findings show that a diagnosis of IH might, after years, lose its original clarity due to the development of various previously absent conditions making diagnosis confirmation hard or even impossible. Moreover, the diagnostic criterion of “the absence of better explanation” is widely open to interpretation and requires extensive examination and clinical skills. We also speculate that conditions and treatment occurring during life may prevent the proper IH diagnosis and treatment in patients who develop the symptoms in late adulthood.

**Acknowledgments:** Supported by Ministry of Health of the Czech Republic, grant nr. NU20-04-00088

## SLEEP ARCHITECTURE IN IDIOPATHIC HYPERSOMNIA

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**Introduction:** Idiopathic hypersomnia (IH) is characterized by excessive daytime sleepiness despite normal or prolonged sleep duration. The pathophysiology of IH remains poorly understood. The study of sleep architecture has the potential to reveal sleep abnormalities and to provide new insights into the pathophysiology of this disorder. However, very few studies have described sleep architecture in IH and most had small sample sizes. This study aims to characterize sleep architecture and verify whether sleep parameters correlate with subjective and objective sleepiness in IH participants compared to healthy controls with a sizable sample.

**Materials and Methods:** 123 IH participants (37.8 ± 10.9 years old; 78 women) and 134 healthy controls (38.7 ± 14.2 years old; 78 women) underwent a full night of in-laboratory polysomnography (maximum 9h of sleep allowed). IH participants were tested with a multiple sleep latency test (MSLT) the next day. They all had a MSLT ≤ 8 minutes, < 2 sleep onset rapid-eye movement (SOREM) period and were diagnosed with IH by a sleep physician. Participants with apnea-hypopnea index ≥ 15 were excluded as well as those with comorbid sleep disorders (e.g., restless legs syndrome, narcolepsy, sleep deprivation). 49.6% of IH participants were

taking antidepressant medication at the time of the PSG recording and analyses were performed with and without them. We used two sample t-tests to compare groups on sleep latency, REM sleep latency, total sleep time, wake time after sleep onset, sleep efficiency, sleep stage time and percentage (N1, N2, N3, REM), microarousal index, apnea-hypopnea index, and periodic leg movement index. We used correlations to test whether sleep parameters were associated with Epworth Sleepiness Scale (ESS) scores and mean MSLT. Group differences were considered significant at  $p < 0.05$ .

**Results:** Compared to controls, IH participants had shorter sleep latency ( $t(255) = -2.1$ ,  $p = 0.04$ ), longer total sleep time ( $t(255) = -11.1$ ,  $p < 0.001$ ), shorter wake after sleep onset ( $t(255) = 5.0$ ,  $p < 0.001$ ) and higher sleep efficiency ( $t(255) = -5.2$ ,  $p < 0.001$ ). IH participants also had more minutes of all sleep stages ( $ps < 0.02$ ), but no group differences were observed for sleep stage proportions. IH participants had higher microarousal ( $t(255) = -2.8$ ,  $p = 0.006$ ), apnea-hypopnea ( $t(255) = -3.6$ ,  $p < 0.001$ ) and periodic leg movement indices ( $t(255) = -4.3$ ,  $p < 0.001$ ). When IH participants using psychoactive medication were removed from analyses, the same group differences were observed, except for minutes of N1 and N3 stages and microarousal index for which there were no between-group differences. IH participants with higher ESS scores had shorter REM latency, less N1 sleep and lower microarousal index ( $p < 0.05$ ). Those with shorter mean MSLT had shorter nighttime sleep latency and longer total sleep time ( $p < 0.05$ ).

**Conclusions:** Our results show that IH participants differ from healthy controls on multiple sleep architecture variables, including higher sleep efficiency. Less fragmented and longer total sleep time correlated with subjective and objective sleepiness. Future studies must investigate finer sleep structures, such as sleep microstructure, to further explore the presence of sleep irregularities in IH participants.

**Acknowledgments:** This research project was made possible by an award from the American Academy of Sleep Medicine Foundation (award: 227-SR-20).

## SLEEP DISTURBANCES IN CRANIOPHARYNGIOMA: A CHALLENGING DIAGNOSIS

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**Introduction:** The hypothalamus plays a crucial role in regulating vital functions and circadian rhythms. Both the tumor involving the hypothalamic area and its treatment can lead to hypothalamic dysfunction, resulting in disturbances in sleep-wake patterns, sleep fragmentation, and increased daytime sleepiness.

We describe two patients with craniopharyngioma who came to our attention due to the occurrence of episodes characterized by psychomotor slowing and afinalistic limb movements, temporal and spatial disorientation, psychomotor agitation, and oneiric stupor like episodes diagnosed as severe sleep disturbances.

**Case reports:** Patient 1 is a 19-year-old male diagnosed with surgically treated craniopharyngioma. Subsequently, episodes of psychomotor slowing, afinalistic movements of the upper limbs diagnosed as seizures in another neurological center appeared; antiepileptic treatment was started without improvement. At the first examination in our center, excessive daytime sleepiness (EDS), fragmented nighttime sleep, episodes characterized by bimanual automatic gestures occurring during drowsy state, hypnagogic hallucinations, and sudden loss of muscle tone while awake were recognized. Actigraphy demonstrated irregular bedtimes, frequent nocturnal activity, and inappropriate daytime rest episodes. The Epworth Sleepiness Scale (ESS) showed subjective EDS (ESS=19). At PSG, hyper-somnolence, severe sleep-related breathing disorder (SRBD), and no interictal and ictal seizure abnormalities were found. A BiPAP NIV was started, and antiepileptic therapy was discontinued. In the following

months, PSG revealed marked improvement in SRBD and 1 SOREMP, and the MSLT a mean SOL of 6 min and 10 sec and 3 SOREMPs. These data allowed the diagnosis of secondary narcolepsy, and treatment with pitolisant was initiated with clinical improvement and reduced daytime sleepiness (ESS=9).

Patient 2 is a 12-year-old male, surgically treated for craniopharyngioma at the age of 4 years, who developed episodes of myoclonic jerks, temporal and spatial disorientation, and psychomotor agitation during the lockdown period for COVID-19 emergency. Surmising paroxysmal epileptic episodes, the patient was hospitalized. The anamnestic data collection revealed a sleep-wake rhythm dysregulation, fragmented nighttime sleep, EDS, oneiric stupor-like episodes during which the patient performed simple automatic gestures mimicking daily-life activity, and severe impairment of alertness. The Long-term video-EEG, including polygraphic measurements, showed destruction of the wake-NREM sleep-REM sleep boundaries, episodes of undetermined state of vigilance, and concurrence of elements typical of different sleep stages. Moreover, a severe SRBD (AHI 19/h) has been observed. The MRI showed a volumetric increase in the post-surgical interpeduncular fossa and right paramedian cysts. Therefore, a multifactorial therapeutic plan including sleep hygiene and slow-release melatonin was started with improvement in nighttime sleep, but EDS persisted. Surgical treatment of cyst fenestration improved sleep-wake rhythm and behavior; BiPAP NIV was initiated with very poor adherence.

**Discussion:** We aim to focus on sleep disorders as a possible complication of tumors involving the hypothalamic region. Our cases highlight that the clinical manifestation of these dysfunctions can be challenging to diagnose and can lead to misdiagnosis and inappropriate treatment that can harm patients' health and the quality of life of patients and their families.

**Conclusion:** These findings support the need to incorporate comprehensive sleep assessment in survivors from childhood brain tumors involving the suprasellar/hypothalamic region.

#### SLEEP INERTIA IN HYPERSOMNIAS OF CENTRAL ORIGIN: IMPORTANCE OF DEPRESSION AND SLEEP ARCHITECTURE

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**Objectives:** Sleep inertia (SI) can be defined as difficulty becoming fully awake after sleep. The Sleep Inertia Questionnaire (SIQ) has been validated to evaluate sleep inertia in mood disorders<sup>1</sup> and it has been very recently utilized also in hypersomnolence disorders<sup>2</sup>. Aim of the study is to assess SI, by means of SIQ, in patients affected by hypersomnias of central origin, including narcolepsy type 1 (NT1), narcolepsy type 2 (NT2) and idiopathic hypersomnia (IH) and to evaluate possible correlations among SI, depression and polysomnographic (PSG) parameters.

**Methods:** Patients with NT1, NT2 and IH, diagnosed in accordance to International Classification of Sleep Disorders-3 criteria were recruited at Sleep Medicine Center of Policlinico Tor Vergata. All patients underwent to nocturnal PSG recording, 5 naps Multi-sleep latency test (MSLT) and to evaluation of daytime somnolence using Epworth Sleepiness Scale (ESS). SIQ and Beck Depression Inventory (BDI-II) were administered. SIQ total score (ranging from 21 to 105) and four SIQ subdomains (physiological, SIQ-P cognitive, SIQ-C, emotional, SIQ-E and responses to SI, SIQ-R) were assessed. Kruskal-Wallis test and Spearman correlation were used for statistical analysis.

**Results:** The analysis included 37 patients (23 females, 14 males, mean age 39.17±15.54 years) with diagnosis of NT1 (n=11), NT2 (n=12), IH (n=14). No difference in terms of age, body mass index, ESS and BDI-II scores was found among NT1, NT2 and IH. Mean SIQ total score was comparable in IH (56.14±20.09), NT1 (53±21.05) and NT2 (55±25.5). Strong positive correlation was observed between SIQ (total score and all SIQ subdomains) and BDI-II (p<0.001). Regarding PSG parameters, SIQ-R negatively strongly correlated with percentage of stage N3 (p<0.01). REM latency showed positive correlations with SIQ total score, SIQ-R and SIQ-E (p<0.05). Total sleep period time and total sleep time showed a weak positive correlation with SIQ-R (p<0.05). Finally, we found a positive correlation between SIQ-

E and ESS (p<0.05).

**Conclusions:** SI assessed by SIQ is a common symptom reported by patients with NT1, NT2 and IH without significant differences among the three forms of hypersomnias. Depression can get worse physiological, cognitive, emotional factors of SIQ as well as responses to SI. Some PSG parameters, mainly the reduction of stage N3, secondly the increase of sleep period time, total sleep time and REM latency seem to be associated with sleep inertia.

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#### SLEEP INERTIA MEASUREMENT WITH THE PSYCHOMOTOR VIGILANCE TASK IN IDIOPATHIC HYPERSOMNIA

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**Introduction:** Sleep inertia is a frequent and disabling symptom in idiopathic hypersomnia (IH), but poorly defined and without objective measures. The study objective was to determine whether the psychomotor vigilance task (PVT) can reliably measure sleep inertia in patients with IH or other sleep disorders (non-IH).

**Materials and Methods:** Sixty-two (51 women, mean age: 27.7±9.2) patients with IH and 140 (71 women, age: 33.3±12.1) with non-IH (narcolepsy=29, non-specified hypersomnolence =47, obstructive sleep apnea =39, insomnia =25) were included. Sleep inertia and sleep drunkenness in the last month (M-sleep inertia) and on PVT day (D-sleep inertia) were assessed with three items of the Idiopathic Hypersomnia Severity Scale (IHSS), in drug-free conditions. The PVT was performed four times (the night before at 7:00 PM as baseline, then at 7:00 AM upon awakening after the polysomnography, at 7:30 AM to assess the duration of sleep inertia, and at 11:00 AM to show its natural decline) and three metrics were used: lapses, mean 1/Reaction Time (RT), slowest 10% 1/RT.

**Results:** Sleep inertia was more frequent in patients with IH than non-IH (56.5% and 43.6% with severe sleep inertia in the past month, including 24% and 12% with sleep drunkenness). The number of lapses increased and slowest 10% 1/RT decreased, particularly at 7:00 AM and 7:30 AM, proportionally with M-sleep inertia severity, but regardless of sleep drunkenness and sleep disorder type. Similar PVT profiles were obtained in function of D-sleep inertia, with the largest increase of the number of lapses at 7:00 AM and 7:30 AM associated with severe sleep inertia and sleep drunkenness.

**Conclusions:** PVT is a reliable and objective measure of sleep inertia that might be useful for its characterization, to understand its physiopathological correlates, especially in IH where this phenomenon is often very pronounced and disabling, and to optimize IH management and follow-up.

**Acknowledgements:** We thank all the participants of the study, and the French Association of Patients with idiopathic hypersomnia.

#### SPHYNCs: LONGTERM MONITORING WITH FITBIT IN PATIENTS WITH NARCOLEPSY AND ITS BORDERLAND

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for Computer Science, University of Bern, Bern, Switzerland; <sup>5</sup> Ohio Sleep Medicine Institute, Dublin, United States

**Background and Aim:** The multicenter Swiss Primary Hypersomnolence and Narcolepsy Cohort Study (SPHYNCS) aims to identify novel biomarkers for narcolepsy and its borderland (NBL). Ambulatory monitoring in narcolepsy and NBL is limited in clinical routine to actigraphy over 1–2 weeks. Fitbit devices have been shown to be able to monitor over several consecutive months sleep, physical activity, and circadian rhythm parameters. This study aims to identify new digital biomarkers of narcolepsy and NBL using a Fitbit device over months.

**Patients and Methods:** Of the 82 subjects so far enrolled in the SPHYNCS study, 50 participants agreed to wear a Fitbit device. The Fitbit Inspire 2 calculates physical activity (calories, steps), vital parameters (heart rate), and sleep parameters (sleep stages, awake counts) with a three-axis accelerometer and an optical sensor embedded in the smartwatch. Data from all participants can be monitored in real-time and downloaded for analysis through the Evita healthcare platform. In this first study, we focused the analyses on the use of the device and the compliance defined as the percentage ratio of weeks the device is used at least six days per week to the number of weeks it is owned and where a subject was defined as "compliant" if their use was greater than 60%, i.e., six days per week for at least 60% of the weeks.

**Results:** The 50 participants (10 males, 40 females) with an average age of 26 years (range 17–44) received the Fitbit. There were 13 patients with narcolepsy, 29 with NBL, and 8 controls. The use of the device was 90% for at least six days per week for one week, 84% for two consecutive weeks, 78% for four successive weeks, and 64% for more than one consecutive month. Overall, the Fitbit compliance was 65% across participants. There was no significant difference in compliance according to gender or age, but there were according to diagnosis (75%: controls; 62% NBL; 38%: narcolepsy).

**Conclusions:** Preliminary results of this ongoing study suggest that the use of a Fitbit device in narcolepsy and NBL for an extended period exhibits significant individual differences. This demonstrates the necessity to monitor adherence frequently and accordingly support patients, for example, with technical help to improve compliance.

**Acknowledgments:** The SPHYNCS study is supported by the Swiss National Fonds (320030\_185362)

## THE BERN SLEEP DATABASE: CLUSTERING OF PATIENTS WITH SLEEP DISORDERS

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**Introduction:** Diagnosing many sleep disorders is a major challenge due to the lack of specific disease markers and frequently co-occurring sleep disorders. For central disorders of hypersomnolence, several unsupervised clustering approaches have been reported. The aim of this study is to characterize and cluster patients constituting the full spectrum of sleep disorders based on the current variables obtained in clinical routine, including values from electrophysiological examinations. Within a first cohort of patients with central hypersomnia, we hypothesized that Narcolepsy Type 1 (NT1) would be well distinct from Narcolepsy Type 2 (NT2) and Idiopathic Hypersomnia (IH), as previous studies have reported. With a second cohort, consisting of patients with the full spectrum of sleep disorders, we hypothesized that distinguishing patient groups would be challenging based on existing clinical variables.

**Patients and Methods:** Our study population constitutes the inpatients from the sleep laboratory of the Inselspital, Bern between 2000 and 2016. We analyzed 1'043 patients at first diagnosis (according to the International classification of sleep disorders, 3rd edition) and 57 variables. To establish our analysis pipeline, we performed unsupervised K-means clustering on a subset of patients (Narcolepsy and IH) and 21 variables (selected based on data quality and literature). We extended the analysis to

the full spectrum of sleep disorders in our study population and a larger set of variables.

**Results:** The clustering on the subset of patients with central hypersomnia revealed four clusters, out of which two clusters contain patients diagnosed with NT1 and two each a mix between NT2 and IH. The distributions are: cluster 1: 98% NT1; cluster 2: 93% NT1; cluster 3: 73% IH and 18% NT2; cluster 4: 50% NT2, 43% IH. Main discriminating features separating clusters 1/2 from clusters 3/4 are cataplexy and mean REM latency. Main discriminating features separating cluster 1 and 2 are hallucination, paralysis and gender. Gender separates cluster 3 and 4, consistently, women are over-represented in IH as compared to NT2 (Fisher's Exact test  $p < 0.01$ ).

The clustering of the full dataset revealed two clusters containing almost exclusively patients with obstructive and central sleep apnea syndromes, one cluster containing a big portion of patients with NT1, while the eight remaining contain patients with varied diagnoses.

**Conclusions:** In the subset of patients with central hypersomnia our clustering algorithm could replicate previous findings that NT1 is well distinct from NT2 and IH, separated by the presence or absence of cataplexy. Our preliminary results in the larger cohort confirm that the current set of disease markers obtained in the clinical routine are not sufficiently discriminative of most sleep disorder diagnoses. Our findings call for future studies, identifying novel disease markers for central disorders of hypersomnolence, such as the "Swiss Primary Hypersomnolence and Narcolepsy Cohort Study" (SPHYNCS).

**Acknowledgments:** Our approach was inspired by Gool et al., submitted ("Unsupervised clustering of central hypersomnolence disorders: data-driven insights in improving future phenotyping and diagnostic criteria"). Supported by: Interfaculty Research Cooperation 'Decoding Sleep: From Neurons to Health & Mind' of the University of Bern.

## Insomnia

### A BENEFIT-RISK ASSESSMENT OF DARIDOREXANT FOR THE TREATMENT OF INSOMNIA USING PATIENT PREFERENCE DATA FROM TWO PHASE 3 TRIALS

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**Introduction:** The efficacy and safety of daridorexant, a dual orexin receptor antagonist investigated for the treatment of insomnia disorder, was demonstrated in two placebo-controlled phase 3 trials. Both pivotal trials included instruments for eliciting treatment preferences of enrolled patients, to interpret the trial findings from their perspective using a patient-centered benefit-risk assessment (pBRA).

**Materials and Methods:** Digital ethnographies and qualitative interviews with patients with insomnia informed the design of a discrete choice experiment (DCE). The DCE was pre-tested in qualitative and quantitative pilot studies before inclusion in the pivotal trials. Within the DCE, patients were asked to make trade-offs between seven outcomes ("time to fall asleep", "total time asleep", "daytime functioning", "likelihood of daytime dizziness/grogginess", "likelihood of abnormal thoughts and behavioural changes", "likelihood of falls in the night", and "treatment withdrawal"). The preference data were analyzed using a mixed logit (MXL) model that accounted for preference heterogeneity. Relative attribute importance (RAI) and maximum acceptable risk (MAR) of abnormal thoughts and behavioral changes were obtained from the MXL. A pBRA combined elicited preferences with collected clinical trial data to predict preferences for daridorexant over placebo. Sensitivity analysis accounted for uncertainty in both clinical outcomes and preferences.

**Results:** Patients valued all seven outcomes ( $p < 0.05$ ), but considered improving daytime functioning (RAI = 33.7%) and avoiding treatment withdrawal (RAI = 27.5%) as most important. Patients were also willing to accept an additional 18.8% risk ( $p < 0.001$ ) of abnormal thoughts and behavioral changes for an improvement in daytime functioning from difficulty functioning to restricted functioning. The pBRA suggested that both daridorexant 50 mg and 25 mg were significantly preferred ( $p < 0.001$ )

over placebo. Furthermore, daridorexant 50 mg was significantly preferred ( $p < 0.001$ ) over 25 mg, even after accounting for uncertainty in clinical outcomes and preferences.

**Conclusions:** All seven outcomes included in the DCE were valued by patients, with improving daytime functioning and avoiding severe treatment withdrawal considered as most important. Daridorexant 50 mg and 25 mg were found to be significantly preferred over placebo, suggesting a positive benefit-risk balance of both doses. Overall, the preference data allowed for an innovative interpretation of the trial data from patients' perspective.

**Acknowledgements:** Funded by Idorsia Pharmaceuticals Ltd. This abstract has been previously presented at the virtual SLEEP meeting, the 35<sup>th</sup> annual meeting of the Associated Professional Sleep Societies held June 10–13, 2021.

#### A COMPARISON OF SLEEP RESTRICTION AND SLEEP COMPRESSION ON OBJECTIVE MEASURES OF SLEEP: A RANDOMIZED CONTROLLED TRIAL

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**Introduction:** Cognitive behavioral therapy is recommended as first line treatment for insomnia. One of the central components is sleep restriction therapy, an intervention also effective as a stand-alone treatment. An alternative to sleep restriction therapy is sleep compression therapy, a similar but still different intervention with a stepwise approach which is believed to yield comparable results.

Research on the effects of sleep restriction therapy on objective sleep is scarce and contradictory, but there is evidence of initial decrease in sleep duration and small improvements in sleep initiation and sleep continuity variables. For sleep compression therapy on the other hand, there is almost complete lack of research on objective sleep parameters. To our knowledge, no direct comparison of the two has been performed. It is thus unknown if the assumption of comparable effects of sleep restriction and sleep compression is correct.

The aim of the present study was to examine if sleep restriction and sleep compression lead to similar changes in objective sleep. Focus of the present study was on changes in sleep duration and sleep architecture.

**Materials and Methods:** A total of 36 adults with insomnia were randomized to either sleep restriction ( $n=19$ ) or sleep compression ( $n=17$ ) therapy. Patients underwent therapist supported online treatment for insomnia during five weeks, followed by five weeks of continued work but without therapist support. Assessments with polysomnography were carried out at baseline, after two weeks, five weeks and ten weeks. Preliminary results were analyzed using general estimating equations.

**Results:** From baseline to week two, the sleep restriction group showed a large decrease of time in bed and total sleep time followed by a partial recovery to week 10. The sleep compression group on the other hand displayed a stepwise reduction of time in bed from baseline to week two, five and ten, which was reflected in a more stepwise reduction of total sleep time. At week two, there was a significant difference between the two treatments.

For sleep onset latency, wake after sleep onset or sleep efficiency, there were no differences at any assessment point between the two treatments. Nor did we find any differences in light sleep (N1) or deep sleep (N3) neither during nor after treatment. Both groups exhibited a decrease of transitions from rapid eye movement-sleep to wakefulness. Also, the sleep compression group showed a decrease of intermediate sleep (N2) from baseline to week five.

**Conclusions:** Sleep restriction therapy and sleep compression therapy are associated with different trajectories of change regarding time in bed and total sleep time. Moreover, both treatments lead to similar changes in sleep initiation and sleep continuity variables as assessed by polysomnography. Neither of the treatments affect light sleep or deep sleep.

The findings indicate that sleep compression therapy could potentially be a valid alternative to sleep restriction therapy, with similar effects on sleep but without the initial sleep deprivation that is associated with sleep restriction therapy.

**Acknowledgements:** We thank the Boethius foundation for funding this project, and South West Psychiatry, Region Stockholm, for supporting the research.

#### AFFECTIVE STATES IN PREDICTING AND MEDIATING COGNITIVE-BEHAVIORAL THERAPY FOR INSOMNIA

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**Introduction:** Cognitive-Behavioral Therapy for Insomnia (CBT-I) is considered the first-choice treatment for Insomnia disorder (ID). ID is characterized by high degree of heterogeneity, that might influence treatment response. Profile of Mood States (POMS), a self-report questionnaire that evaluates distinct and transient mood states, could fulfill this role. The aim of this study is to identify ID patients' subtypes based on POMS and their response to CBT-I in order to tailor the treatment, and possibly identifying the mechanisms through which CBT-I determines an improvement in the symptoms of these patients.

**Materials and Methods:** 448 insomniac patients (59% female, age =  $42.25 \pm 12.96$ ) were evaluated pre and post group-CBT-I. A series of questionnaires that evaluate sleep indices (Insomnia Severity Index, ISI; Sleep Diaries) and patients' affective states (Profile of Mood States, POMS; Beck Depression Inventory, BDI) were administered.

**Results:** CBT-I effectiveness has been proven at ISI total score ( $p < .001$ ), sleep diaries indices ( $p < .001$ ), and all POMS indices ( $p < .001$ ) (except for the "vigor" subscale). We found a significant interaction between CBT-I and baseline POMS total score on ISI ( $p < .001$ ): the effect of CBT-I on ISI was greater in subjects with high baseline POMS total score, rather than in those with low baseline POMS total score. In fact, the percentage of treatment responders (ISI decrease  $\geq 8$ ) was 66.5% in the group with high baseline POMS total score. However, in this group at the end of the treatment the percentage of patients in remission (ISI at the end of treatment  $< 8$ ) was 25%. In addition, we found a significant interaction between ISI improvement (DeltaISI) and changes pre- and post-treatment in POMS total score ( $p < .001$ ) (DeltaPOMS): ISI improvement was greater in subjects with a greater change in POMS total score, rather than in those with reduced DeltaPOMS.

Finally, we found that the prediction role of DeltaPOMS on CBT-I outcome evaluated by DeltaISI was mediated by the change in the BDI score between pre- and post-treatment ( $p < .001$ ) (DeltaBDI): in this regard, most of the changes (66%) in the ISI, due to changes in the POMS total score, were mediated by changes in the BDI score between pre- and post-CBT-I.

**Conclusions:** CBT-I determines an improvement in both sleep indices and affective state indices. The baseline POMS total score seems to have an important role in predicting the therapy outcome. Furthermore, the effectiveness of CBT-I on the severity of insomnia is influenced by the change in the patients' affective states due to the therapy. Moreover, most of the influence of the change in affective states on the therapy outcome seems to be due to a change specifically in depressed mood.

**Acknowledgements:**

#### ALTERATIONS OF SUBCORTICAL BRAIN STRUCTURES IN PARADOXICAL AND PSYCHOPHYSIOLOGICAL INSOMNIA DISORDER

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**Introduction:** Insomnia disorder (ID) is a common illness associated with mood and cognitive impairments. Subtyping ID is an ongoing debate in sleep medicine, but the underlying mechanisms of each subtype is poorly understood. Growing evidence suggests that subcortical brain structures play the key roles in pathophysiology of ID and its subtypes. Here, we aimed to investigate structural alteration of subcortical regions in patients with two common ID subtypes i.e., paradoxical and psychophysiological insomnia.

**Materials and Methods:** Fifty-five patients and 49 healthy controls were recruited for this study and T1-weighted images and subjective and objective sleep parameters (i.e., Pittsburgh Sleep Quality Index and polysomnography) were collected from participants. Subcortical structures including the hippocampus, amygdala, caudate, putamen, globus pallidus, nucleus accumbens, and thalamus were automatically segmented in FSL. Volume and shape (using surface vertices) of each structure were compared between the groups, controlled for covariates, and corrected for multiple comparisons. In addition, correlations of sleep parameters and surface vertices or volumes were calculated.

**Results:** The caudate's volume was smaller in patients than controls. Compared with controls, we found regional shrinkage in the caudate, nucleus accumbens, posterior putamen, hippocampus, thalamus, and amygdala in paradoxical insomnia and shrinkage in the amygdala, caudate, hippocampus, and putamen in psychophysiological insomnia. Interestingly, comparing two patients groups, shape alteration in the caudate, putamen, and nucleus accumbens in paradoxical insomnia and shrinkage in the thalamus, amygdala, and hippocampus in psychophysiological insomnia were observed. Both subjective and objective sleep parameters were associated with these regional shape alterations in patients.

**Conclusions:** Our results support the differential role of subcortical brain structures in pathophysiology of paradoxical and psychophysiological insomnia.

**Acknowledgements:** We are thankful to the participants of the study and the staff of the Sleep Disorders Research Center for their help in recruitment and data collection.

#### A NETWORK ANALYSIS OF INSOMNIA SYMPTOMS IN YOUNG ADULTS

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**Introduction:** Insomnia is highly common in young adults with a prevalence rate up to 38%. It is associated with not only significant personal distress but also a wide array of symptoms affecting both daytime and nighttime functioning in young people. However, little is known about the interplay of these symptoms in the context of insomnia. Network analysis is a novel approach to understand the underlying mechanisms of a health-related issue at the symptom level. The current study aimed to investigate the network structure of insomnia in youths.

**Materials and Methods:** A total of 902 participants (Age: 21.20 ± 2.64, female: 70.29%) were recruited from the community. Participants completed Insomnia Severity Index (ISI) online, which is a 7-item self-reported questionnaire to assess different aspects of insomnia including its nocturnal symptoms (difficulties initiating or maintaining sleep, early morning awakening), severity, and consequences. An ISI score between 8–14 denoted subthreshold insomnia and a cutoff score of 15 was used to determine moderate to severe insomnia. Network analysis was applied to all 7 items using regularized partial correlation network modeling in R. Three centrality indices (i.e., “strength”, “closeness”, and “betweenness”) were used to assess the importance of symptoms in the network.

**Results:** Forty-one percent and 14.3% of the recruited participants were considered to have subclinical insomnia and clinical insomnia, respectively. The network model revealed that distress caused by the sleep difficulties was the most central symptom in youths with the strongest strength, betweenness, and closeness. The network model demonstrated robust accuracy and stability (Node strength: CS (cor=0.70) = 0.75).

Dissatisfaction with sleep was connected to the cluster of nocturnal symptoms (i.e., difficulty initiating sleep, difficulty maintaining sleep, and early morning awakening) and daytime symptoms (noticeability of sleep problems by others, distress caused by the sleep difficulties, and impairment in daytime functioning) of insomnia.

**Conclusions:** This was the first study to characterize the network structure of insomnia symptoms in young adults using the network approach. Distress caused by the sleep difficulties was identified as the core symptom in the network, indicating that future interventions could target worries or distress to address insomnia. Future interventions may also target dissatisfaction with sleep to address both clusters of nocturnal symptoms and daytime symptoms.

**Acknowledgements:** This work was supported by Hong Kong Research Grants Council under the General Research Fund (Ref. 17613820, awarded to SX Li).

#### AN RCT OF AN INTERNET INTERVENTION FOR INSOMNIA TAILORED FOR OLDER ADULTS (SHUTI-OASIS)

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**Introduction:** Insomnia is a significant public health problem impacting older adults with 20–30% of those over 55 years of age meeting diagnostic criteria for chronic insomnia. Cognitive-Behavioral Therapy for Insomnia (CBT-I) is an effective intervention and is considered a first line treatment by the AASM, American College of Physicians, and others. Unfortunately, access is significantly limited by a number of factors, including lack of trained clinicians, geography, and expense. Technology, however, has made treatment much more accessible by bringing CBT-I to anyone with a computer or smartphone and internet access. Concerns remain, though, including whether older adults will be willing and able to use technology-delivered solutions, despite the significant growth in use of the internet by older adults. This study aimed to test whether Older Adults with Insomnia (OAWI) would use and benefit from an internet-based insomnia intervention based on CBT-I (SHUTI: Sleep Health Using the Internet) tailored specifically for older adults (SHUTI OASIS: Older Adult Sufferers of Insomnia and Sleeplessness).

**Methods:** For this study, 311 OAWI (≥55 meeting DSM-V criteria for chronic insomnia) were randomized to one of three conditions: SHUTI-OASIS only, SHUTI-OASIS + Stepped Care (SC), or online Patient Education (PE). Participants were assessed at baseline, post-intervention (week 10), and at 6 and 12 month follow-ups. Measures included the Insomnia Severity Index (ISI) and patient reported online prospective consensus sleep diaries (10 days of diaries within a two week period), and Core completions was used to measure program usage.

**Results:** Only fourteen participants activated the SC protocol (14%), and there were no differences between those participants randomized to SHUTI with or without SC; as such, the two SHUTI groups were collapsed (N=207 vs. PE N=104). The majority of participants were female (68.5%) with an average age of 66.3 (SD=7.2; range from 55 to 95 years of age, and 30% who were 70 or older) and 13.5 years of sleep difficulties. SHUTI participants showed significant reductions (ps<.001) in insomnia severity from baseline (15.9±5.2) to post (10.0±5.2), and follow-ups at 6 months (9.1±5.0), and 12 months (8.9±5.1) compared to those who received PE (baseline: 16.2±4.0, post: 15.1±4.7, 6 months: 14.0±5.4, 12 months: 13.2±4.9, respectively). Similar patterns are found with Wake After Sleep Onset (WASO) and Sleep Onset Latency (SOL) as well as a number of secondary variables, including sleep efficiency and sleep quality. With 85% of SHUTI participants completing all six SHUTI-OASIS cores (63% within the 9 week intervention period), this sample of older adults exhibited greater

utilization than adult users of all ages from previous SHUTi trials.

**Conclusions:** As the first study to utilize a tailored internet intervention specifically for OAWI, these findings provide strong evidence that OAWI both use and obtain significant benefits from an automated, interactive, internet-based self-help program, without needing special assistance. SHUTi-OASIS is a promising intervention for OAWI who might not otherwise have access to empirically validated behavioral treatment for insomnia.

**Acknowledgments:** The study was funded by grant R01AG047885 from the National Institute on Aging, NIH

#### A PROCESS EVALUATION OF A DIGITAL CBT-I PLATFORM IN AN EARLY INTERVENTION IN PSYCHOSIS SERVICE

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**Introduction:** Psychosis has significant impacts upon individuals, family, and society. Early psychosis may be a crucial time for intervention when clinical trajectories are uncertain. Sleep interventions hold promise as a treatment option within psychosis. As such, scalable digital sleep interventions may be of use within this group. Here, we present initial results from a digital trial of a digital cognitive behavioural intervention for insomnia (dCBT-I), within a first episode of psychosis (FEP) service.

**Materials and Methods:** This study was situated within NHS Greater Glasgow & Clyde, in a FEP service. Clients with indications of insomnia were invited to take part in the dCBT-I platform (“SLEEPIO”), and to meet the researcher pre- and post-intervention. Staff, including keyworders, were also invited to take part in pre- and post-intervention interviews about their perceptions of SLEEPIO and barriers and facilitators to sleep interventions. Staff were also invited to take part in a focus group on sleep perceptions, and how sleep interventions could be embedded within the service.

**Results:** While data collection is still ongoing, initial results with thematic framework analysis suggest factors which may help and hinder the rollout of sleep interventions within an NHS FEP service. Pre-intervention, keyworder staff reported an awareness of sleep difficulties and their treatment repertoire. Beliefs about SLEEPIO were reported, alongside those regarding how clients may perceive it, and the role of the service within this. Clients have thus far declined to be interviewed. Interviews with clients, and keyworders post-intervention, as well as staff focus groups, will shed additional light on these factors.

**Conclusions:** Sleep interventions hold promise as a part of the treatment repertoire within FEP. However, within this client group and service there may be particular factors which require a more tailored approach, with peer support a potential solution. Ongoing research hopes to elucidate these factors further.

**Acknowledgements:** We are grateful to staff and clients who have taken part in this study.

#### ASK-THE-EXPERT EDUCATION IN INSOMNIA SIGNIFICANTLY IMPROVES KNOWLEDGE AND COMPETENCE FOR NON-SLEEP EXPERTS

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**Introduction:** Because of the large prevalence of insomnia and the relatively small numbers of sleep experts, it is imperative that primary care physicians (PCPs) and other non-sleep experts most likely to encounter patients with insomnia (such as psychiatrists), know how to diagnose and manage insomnia. However, insomnia continues to be underdiagnosed and undertreated. Addressing this issue is dependent on non-expert clinician awareness of the extent of undiagnosed insomnia, diagnostic criteria and current or emerging management approaches.

**Materials and Methods:** PCPs and psychiatrists participated in a 35-minute ask-the-expert activity on insomnia and completed all pre-and post-questions (Dauvilliers Y et al. *Ask the Expert: Questions About Managing Insomnia From Primary Care*. Available at [www.medscape.org/viewarticle/951928](http://www.medscape.org/viewarticle/951928)). The effects of education on knowledge and competence were assessed using a 3-question, repeated pairs, pre-assessment/post-assessment study design; and one question rated on a Likert-type scale assessed confidence. Differences from pre- to post-assessment were evaluated using the paired samples t-test for all questions combined, and the McNemar’s test for individual questions. P values <.05 are statistically significant. The activity launched May 27, 2021, and data were collected through Sept 1, 2021.

**Results:** A substantial proportion of participants completed both pre- and post-assessment questions: 429/690 (60%) PCPs and 530/738 (72%) psychiatrists. Overall significant improvements were seen for PCPs (50% average pre-assessment correct response rate vs 63% at post-assessment; P<.001; N=429), and psychiatrists (57% average pre-assessment correct response rate vs 67% at post-assessment; P<.001; N=530). Specifically, highly significant improvements were shown in a) knowledge regarding the extent of undiagnosed insomnia; b) knowledge regarding the aspects of insomnia that dual orexin receptor antagonists (DORAs) can address; c) competence in diagnosing insomnia.

After participating in the education, 45% of PCPs and 36% of psychiatrists had measurable improved confidence related to their ability to manage patients with insomnia. As many as 94% of PCPs reported that the education will improve their performance and patient outcomes; similarly, 98% of psychiatrists reported the education will improve their performance, and 94% reported it will improve patient outcomes.

**Conclusions:** This study demonstrates the success of online ask-the-expert roundtable discussion education in familiarizing non-sleep expert clinicians with the extent of undiagnosed insomnia, how to identify it, and the role of newer insomnia therapies. The large increase in confidence observed suggest the education will make a difference in clinical practice. That said, substantial gaps remain across these topics, suggesting a need for continued education in order to truly place the majority of routine insomnia diagnosis and management in the court of the non-sleep expert.

**Acknowledgements:** The related CME activity was supported by an independent educational grant from Idorsia.

#### ASSESSMENTS OF SLEEP IN YOUTH WITH INSOMNIA: A COMPARISON BETWEEN POLYSOMNOGRAPHY, SLEEP DIARY, AND ACTIGRAPHY

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**Introduction:** Previous studies suggested poor correlations between subjective and objective sleep assessments in adults with insomnia. However, there were yet studies to systematically compare sleep diary (SD) and actigraphy with polysomnography (PSG) in youths with insomnia. Although PSG is not routinely used as an assessment tool for insomnia, it could provide valuable data that supplement the assessment of insomnia. This current study aimed to compare SD, actigraphy, and PSG as the assessments of sleep in youth with insomnia and healthy controls.

**Methods:** Ninety participants (age = 20.1±2.2 66% female) with symptoms of insomnia (i.e., complaint(s) of difficulty initiating or maintaining sleep, or early morning awakening at least three times a week in the past three months, with Insomnia Severity Index score > 8), and thirty-six healthy sleepers (age = 19.6±2.21 69% female) were recruited. All participants completed SD and actigraphy monitoring (Actiwatch Spectrum Plus, Philips Respironics) for eight consecutive days, during which one adaptation night followed by one night of PSG were concurrently conducted. Actigraphy data were exported at a low threshold. Total sleep time (TST), sleep efficiency (SE), sleep onset latency (SOL), and Wake after sleep onset (WASO) were extracted from SD, actigraphy, and PSG. Data was analysed using Spearman correlations and mixed repeated ANCOVA followed by

Bonferroni post-hoc comparisons.

**Results:** Weak to moderate correlations between the three measures were found for SOL in the healthy group ( $r=.29$  to  $.50$ , all  $p<.05$ ). In the insomnia group, good concordance was found for SOL between SD and actigraphy ( $r=.56$ ,  $p<.001$ ). In contrast, concordance between PSG and SD ( $r=.30$ ,  $p=.002$ ), and between PSG and actigraphy ( $r=.35$ ,  $p<.001$ ) were lower, where actigraphy ( $24.4\pm 19.6$ ) and SD ( $35.4\pm 27.6$ ) significantly overestimated SOL compared to PSG ( $16.9\pm 17.6$ ). For TST, SD and actigraphy showed acceptable concordance in both healthy ( $r=.64$ ,  $p<.001$ ) and insomnia groups ( $r=.49$ ,  $p<.001$ ), but both measures showed poor concordance with PSG. In particular, TST was underestimated by an average of 58 minutes by actigraphy compared to PSG in the insomnia group. Lastly, the correlations between the three measures for WASO and SE were insignificant in both groups. For the insomnia group, actigraphy ( $78.4\pm 26.6$ ) significantly overestimated WASO when compared with PSG ( $25.7\pm 44.5$ ) and SD ( $9.2\pm 13.8$ ), whilst SE was underestimated by actigraphy compared to PSG and SD.

**Discussion:** Our findings showed that PSG tends to have suboptimal concordance with SD and actigraphy for assessing sleep in individuals with insomnia. Whilst one-night PSG might have the limitation of not capturing night-to-night variability commonly observed in insomnia, the overestimation of WASO and underestimation of SE by actigraphy as compared to PSG raised the concern about the reliability of wake detection by actigraphy. Future research should explore the appropriate sensitivity settings of actigraphy and there is a need to consider concurrent use of multiple measures when assessing sleep in youth with insomnia.

**Acknowledgement:** This work was supported by Hong Kong Research Grants Council under the General Research Fund (Ref.17608918 & 17613820) and Early Career Scheme (Ref.27613017) awarded to SX Li.

#### ASSOCIATION BETWEEN INSOMNIA PHENOTYPES AND SUBCLINICAL MYOCARDIAL INJURY: THE MULTI-ETHNIC STUDY OF ATHEROSCLEROSIS

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**Introduction:** Cardiac troponin T (cTnT) is a biomarker of subclinical myocardial injury that associates with fibrosis on cardiovascular magnetic resonance (CMR) imaging and risk of heart failure (HF) and cardiovascular disease (CVD) death. Insomnia symptoms have been linked to an increased risk of CVD, HF, and overall mortality in some studies, but results have been inconsistent. A potential explanation for these inconsistent findings is that insomnia symptoms often co-occur with other sleep disorders, but few studies have objective data on insomnia phenotypes. We hypothesized that the association between insomnia and subclinical myocardial injury as measured by cTnT concentrations and the incidence of HF, CVD death, and their composite differ across insomnia phenotypes.

**Materials and methods:** We measured cTnT in 2188 participants in the Multi-Ethnic Study of Atherosclerosis (MESA) study (Exam 5) who had completed sleep questionnaires and undergone polysomnography (PSG) and 7-day actigraphy. We defined insomnia symptoms based upon reporting a frequency of  $\geq 5$  nights/week over the past four weeks of at least one of the following: "Did you have trouble falling asleep?", "Did you wake up several times a night?", "Did you have trouble getting back to sleep after you woke up too early?" or "Did you take sleeping pills to help you sleep?". OSA was defined as an AHI  $>15$  events/hour.

**Results:** The mean age of the overall sample was 68.6 years (SD 9.2), of whom 53.6% were male, 37.4% white, 11.7% Chinese, 27.3% African American, and 23.6% Hispanic. 47.8% of the participants had insomnia symptoms, and 43.1% had AHI  $>15$  events/hour. In crude analysis, individuals with symptoms of insomnia had slightly higher median cTnT levels than those without insomnia (8.9 ng/L (Q1, Q3; 6.4, 13.3) ng/L vs. 8.0 ng/L (Q1, Q3; 5.8, 11.5 ng/L,  $p<0.0001$ ). In linear regression models, adjusting for sex,

age, race/ethnicity, and smoking, the insomnia phenotype comorbid insomnia and sleep apnea (COMISA) was associated with higher cTnT ( $\beta$  0.08 (SE 0.03),  $p<0.01$ ). Other insomnia phenotypes, such as insomnia with PSG- sleep duration  $<6$ hrs ( $\beta$  0.02 (SE 0.03)) and fragmented PSG-sleep ( $\beta$  0.03 (SE 0.02)) were not associated with higher cTnT ( $p>0.05$ ) in adjusted analyses. OSA alone was also significantly associated with higher cTnT ( $\beta$  0.09 (SE 0.03),  $p<0.01$ ) in adjusted models.

**Conclusions:** The association between insomnia and subclinical myocardial injury may differ across insomnia phenotypes. OSA and COMISA, but not insomnia symptoms alone, appear to be associated with increased circulating cTnT. Our findings suggest that comorbid OSA may play a significant role in the pathophysiology of the cardiovascular complications of insomnia.

**Acknowledgments:** This research was supported by contracts 75N92020D00001, HHSN268201500003I, N01-HC-95159, 75N92020D00005, N01-HC-95160, 75N92020D00002, N01-HC-95161, 75N92020D00003, N01-HC-95162, 75N92020D00006, N01-HC-95163, 75N92020D00004, N01-HC-95164, 75N92020D00007, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168, N01-HC-95169, HL098433, and R35HL13581 from the National Heart, Lung, and Blood Institute, and by grants UL1-TR-000040, UL1-TR-001079, and UL1-TR-001420 from the National Center for Advancing Translational Sciences (NCATS). The authors thank the other investigators, the staff, and the participants of the MESA study for their contributions.

**Keywords:** Insomnia, subclinical myocardial injury, heart failure, cardiac troponin

#### A SYSTEMATIC REVIEW OF COVID-19 AND INSOMNIA USING THE MATRIX METHOD

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**Introduction:** The US Centers of Disease Control and the National Institutes of Health have reported descriptions of neuropsychological symptoms post COVID-19 infection occurring in the United States. These symptoms include depression, fatigue, "brain fog," and insomnia. The purpose of this systematic review was to ascertain if the prevalence of insomnia among COVID-19 survivors is statistically different from that of persons who have not had COVID-19 disease.

**Materials and Methods:** A systematic review was conducted using the Matrix Method and the Preferred Reporting Items for Systematic Reviews (PRISMA). PubMed and CINHAHL were searched from September 28, 2021, to November 2, 2021. Inclusion criteria were any publications that discussed insomnia and COVID-19 infection. Editorials were included because of the recent occurrence of publishing studies in the editorial section. Insomnia related to pandemic factors, healthy healthcare workers and pandemic socio-economic factors were excluded. The MESH terms for PubMed were "SARS cov2 infection" and "insomnia," "actigraph" and "COVID-19," "polysomnography and COVID-19." The MESH terms used for CINHAHL were "insomnia" and "COVID-19," and "SARS COVID" or "SarsCov2," or "COVID-19" or "coronavirus" or "mcoV" and "sleep disorders."

**Results:** 736 articles were retrieved 319 from PubMed and 419 from CINALH. After applying the inclusion and exclusion criteria as discussed, 715 articles were excluded based on abstract review. 21 articles were included in the full text screen of which ten were in the final review.

**Conclusions:** Most studies used the Insomnia Sleep Index (score $>8$ ), the Pittsburgh Sleep Quality Index (Score 16-21), and custom questionnaires to assess for insomnia. International prevalence of insomnia in patients post COVID-19 infection ranges from 30-60 %. One study reported insomnia symptoms up to 110 days post hospitalization. ICU versus medical surgical unit made no difference in prevalence of persistent COVID insomnia. One study showed statistically significant correlation between sleep and neutrophil/lymphocyte ratio. Polysomnography mean results post COVID-19 infection reported a sleep efficiency of 76, (prevalence 3%), sleep latency of 21 (prevalence 9%), sleep time 345 min., 78% had alpha wave intrusion. Alpha wave intrusion is associated with neuropsychiatric disorders such as anxiety, depression, and insomnia. Furthermore, 25% of COVID patients tested with PSG had Rem Behavior Disorder (RBD), which can be a sign of neurodegenerative disorders. Further randomized, case-control studies are needed to study post COVID-19 insomnia. As well as longitudinal

studies for patients with post COVID-19 RBD.

**Acknowledgements:** None

## A VIRTUAL REALITY MIND-BODY APPROACH TARGETING HYPERAROUSAL IN ADOLESCENTS WITH INSOMNIA: NEW DIRECTIONS FOR TREATMENT

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**Introduction:** Insomnia is common in adolescence, especially in older girls. It tends to be chronic and, if left untreated, negatively affects adolescent health. It is, however, challenging to reach and engage adolescents in treatment. Although the pathophysiology of insomnia is not fully understood, it is considered to be a hyperarousal disorder characterized by elevated levels of physiological and psychological arousal that interfere with the processes of falling asleep and staying asleep. Our group has recently developed an intervention based on a combination of virtual reality (VR), guided meditation, and respiratory relaxation techniques that specifically target autonomic, cognitive, and cortical arousal at bedtime by acting on neurocognitive and autonomic pathways. Here we present preliminary data supporting the mechanism of action of this new digital approach in adolescents.

**Materials and Methods:** Fifty-two high school students (16–20 y; 32 girls) with (N = 18) and without (N = 34) clinically significant DSM-5 insomnia symptomatology participated. Using a repeated-measures, counter-balanced, laboratory design, they were exposed to 20 minutes of immersive, nature-based VR-guided meditation and paced breathing (0.1 Hz) (intervention) or 20 minutes of quiet activities before sleep (control), approximately 30 minutes before their desired bedtime, on two separate evenings. Measures of cognitive, cardiac autonomic nervous system (heart rate (HR) and heart rate variability (HRV) measures) and cortical electroencephalographic (EEG) arousal, and saliva cortisol (reflecting hypothalamic-pituitary-adrenal axis activity) were collected and analyzed during 5-min resting periods before and after, as well as during, the intervention/control conditions.

**Results:** The insomnia group showed significantly lower cardiac vagal activity (reflecting autonomic hyperarousal) compared to healthy sleepers at all time points for both conditions ( $p < 0.05$ ), while no significant group differences were detected for cognitive or cortical arousal levels. During the VR intervention, compared with the pre-intervention resting state, both groups showed increases in vagally mediated HRV, increases in EEG sigma, beta, and gamma powers, and decreases in alpha power ( $p < 0.05$ ), reflecting attentional processing. Pre-to-post resting state analysis revealed that both groups had significant reductions in physiological markers of arousal ( $\downarrow$ HR,  $\downarrow$ salivary cortisol), in response to the intervention compared with the control condition ( $p < 0.05$ ). During the 20-minute intervention session, all participants maintained the targeted slow breathing rate. Participants reported no adverse side effects from the intervention.

**Conclusions:** These preliminary data support the hypothesized mechanisms, i.e., hyperarousal downregulation, for this novel, VR-based mind-body digital strategy for insomnia symptoms. Although further research is needed to evaluate the efficacy, acceptability, and feasibility of this intervention in alleviating clinical insomnia symptoms, this approach may ultimately open a new line of technology-mediated mind-body treatments for adolescent insomnia. The advantages of such solutions lie in the possibility of full control and adaptability, standardization, and self-administration, while targeting the main pathophysiological mechanisms underlying insomnia.

**Acknowledgements:** This study was supported by the National Heart, Lung and Blood Institute (NHLBI) grant R01 HL139652 (to MdZ). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

## CARDIOMETABOLIC STATUS IN HIGH RISK PREGNANT WOMEN WITH COMORBID INSOMNIA AND SLEEP DISORDERED BREATHING: A SURVEY BASED COMPARATIVE STUDY

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**Introduction:** Pregnancy is a particularly vulnerable moment of life where sleep and psychological health often interact. High-risk pregnancy is even a more challenging condition as it potentially threatens the health of the mother her fetus and often require specialized care. Insomnia and Sleep Disordered Breathing (SDB), the most common conditions among the large spectrum of dysfunctional sleep often affect adults in general but may particularly impact the pregnant women. Still, comorbid insomnia and SDB (COMISA) further contribute to a deleterious cycle perpetuating the relationship between some frequent psychosocial stress factors (i.e., anxiety and depression) and negative outcomes in pregnancy like cardio metabolic disorders. As cardiometabolic disorders are the leading cause of morbidity and mortality in women worldwide and the relationship between COMISA was suggested to significantly increase this risk in other populations, it is important to early identify and prevent related outcomes. We aimed to compare the cardiometabolic risk status in high risk pregnant women without sleep disorders, isolated insomnia, isolated SDB and COMISA.

**Materials and Methods:** High risk pregnant women of up to 31<sup>st</sup> week of gestation followed in the Women Hospital of São José dos Campos, São Paulo, Brazil, were asked to fill sleep questionnaires as Insomnia Severity Index (ISI), STOP-BANG questionnaire, Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS) and Morningness-Eveningness Questionnaire (MEQ). Groups were divided in “no sleep disturbances”, isolated insomnia, isolated SDB and COMISA (ISI>8 and positive for SDB as assessed by STOP-BANG questionnaire. Cardiovascular disorder (hypertension - HTA) and associated metabolic disorder (diabetes) were clinically assessed and presented as %frequencies. A p value of <.05 was considered significant.

**Results:** A total of 214 high risk pregnant women with a mean age of 30±6 years old ( $p > .05$ ) were divided according to their sleep related diagnosis in 3 groups: isolated insomnia (n=56; 26.2%), SDB (n=26; 12.2%) and COMISA (n=61; 28.5%). Prevalence of hypertension (42.6%), diabetes (55.7%) or both (19.7%) in COMISA group was significantly higher ( $p < .001$ ) than in insomnia (7.1%; 17.9%; 3.6%) or in SDB (34.5%; 30.8%; 7.7%).

**Conclusions:** Our data suggest that cardiovascular and associated metabolic disorders mostly affect high risk pregnant women presenting with COMISA when compared to those without sleep disturbance or even those with isolated sleep conditions (either insomnia or sleep apnea). These findings should be further confirmed since implementation of measures preventing sleep disorders and also directed to manage comorbid sleep disturbances like COMISA may greatly impact clinical outcomes in this particular population.

## CARDIOVASCULAR AUTONOMIC FUNCTION IN CHRONIC INSOMNIA ASSESSED BY CARDIOVASCULAR REFLEXES

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**Introduction:** Restorative and good quality sleep is crucial for maintenance and regulation of various physiological functions such as neuro-cognitive development, restoration of energy spent during the day, elimination of toxic substances, modulation of the immune system,

cognitive performance, etc [1]. The cardiovascular autonomic nervous system (ANS) appears to be closely linked to sleep and circadian physiology, as demonstrated by the disrupted autonomic control that accompanies sleep loss [2]. The purpose of the study was to evaluate cardiovascular autonomic functions during wakefulness in de novo patients with chronic insomnia (CI) compared to healthy controls (HC).

**Materials and Methods:** De novo patients with CI and HC underwent cardiovascular function tests including head-up tilt test, Valsalva Maneuver, deep breathing, hand grip, and cold face.

**Results:** 18 de novo patients with CI and 13 HC were included. The systolic blood pressure (SBP) values at 10 min head-up tilt test were significantly higher in patients with CI than in controls ( $p < 0.031$ ), while heart rate (HR) values at 10 min head-up tilt test were significantly lower in patients than in controls ( $p < 0.034$ ). In addition, the Delta SBP values (difference between resting supine SBP versus SBP at 10 min head-up tilt test) were significantly higher in patients than in controls. Delta HR values (difference between resting supine HR versus HR at 10 min head-up tilt test) were significantly lower in patients than in controls ( $p < 0.01$ ). Furthermore, at Valsalva Maneuver, the Valsalva Ratio values (VR) were significantly lower in patients with CI compared to controls ( $p < 0.048$ ), although without reaching pathological values.

**Conclusions:** Although these values are not suggestive of hypertension, the data emerged from the head-up tilt test suggest the presence of a systolic pre-hypertension that is known to increase the risk of cardiovascular diseases [3]. The VR is an index of parasympathetic function representing the vagal component of the baroreflex [4]. Since parasympathetic response at Valsalva Maneuver was reduced in our sample, we can speculate that the predisposition to hypertension in CI may be favored by a blunted parasympathetic response to changes in blood pressure. These findings support the hypothesis of autonomic nervous system involvement during wakefulness and consequently an enhanced cardiovascular risk in patients with CI.

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#### CLINICAL FEASIBILITY AND PRELIMINARY EFFECTS OF CBT FOR INSOMNIA AT AN OUTPATIENT PSYCHIATRIC CLINIC

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**Introduction:** A majority of psychiatric patients suffer from insomnia or insomnia-like problems. Besides leading to a decreased quality of life, sleep problems can worsen psychiatric conditions, such as depression and anxiety and can make treatment of various psychiatric conditions less successful. Several international guidelines recommend cognitive behavioural therapy for insomnia (CBT-i) as first line treatment. However, patients in psychiatric care are rarely offered CBT-i, and there is a lack of studies that evaluate the treatment in regular clinical settings. In this pilot study, we aimed to determine the clinical feasibility of a group-based CBT-i intervention in an outpatient clinical setting for patients with affective disorders, anxiety disorders and PTSD. We also aimed to investigate if symptoms of insomnia, depression and anxiety changed after CBT-i treatment.

**Materials and Methods:** The study was conducted at a psychiatric outpatient clinic in Stockholm, Sweden, serving patients with affective disorders, anxiety disorders and PTSD. A total of 18 patients with self-reported sleep problems were enrolled in a six-week long group-based CBT-i intervention. Primary outcome was treatment feasibility in the clinical setting, defined as: enough patients at the clinic should be interested in participating in treatment to be able to give at least one group per semester (eg. a minimum of 8), at least half of included patients should attend the first session, patients should attend at least half of the sessions, drop-out rate should be below 50 percent, and the group leaders should

find the treatment manual credible, easy to use and possible to keep using after the end of the study. Secondary outcomes were changes in symptom severity of insomnia, depression, and anxiety, measured at pre – and post treatment with Insomnia Severity Index (ISI), Patient Health Questionnaire (PHQ-9) and Generalized Anxiety Disorder Scale (GAD-7) respectively.

**Results:** Results showed that treatment was feasible in the clinical setting; there were enough patients interested to participate in treatment to sustain at least one group per semester, 89 percent of included patient attended the first session, mean of attended sessions was 5.1 and drop-out rates was 5.5 percent. The group leaders found the treatment manual credible, efficient, and possible to use at the clinic. Symptoms of insomnia decreased after treatment, as well as symptoms of depression and anxiety.

**Conclusions:** Group-delivered CBT-i is a promising treatment option for sleep problems in psychiatric patients. It is clinically feasible in a psychiatric outpatient setting and results indicate positive effects on symptoms of insomnia, depression and anxiety. Randomized clinical trials are needed to confirm and elaborate on these positive findings.

**Acknowledgements:** Peter Renblad, senior specialist in psychiatry at Psykiatri Sydväst, for encouraging this project and participating as co-therapist.

Veronica Sveréus, head of unit, Psykiatri Sydväst, for giving us time and opportunity to do the study in a clinical setting

Jannis Gatzacis and Ellen Lindgren, psychologist, for acting as therapists in the groups

South West Psychiatry (Psykiatri Sydväst) Stockholm Region for funding and encouragement

#### COGNITIVE BEHAVIORAL THERAPY FOR INSOMNIA IN PATIENTS WITH MENTAL DISORDERS AND COMORBID INSOMNIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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**Introduction:** Almost 70% of patients with mental disorders suffer from sleep difficulties and up to one third fulfil the criteria for insomnia disorder. Even though current guidelines recommend cognitive behavioral therapy for insomnia (CBT-I) as the gold standard for the treatment of insomnia, it is often treated pharmacologically. To date, it is not sufficiently understood how effective CBT-I is in patients with different mental disorders. The aim of this meta-analysis was to quantify the effect of CBT-I on the insomnia severity and on the severity of the comorbid mental disorder in patients who suffer from mental disorders and comorbid insomnia.

**Materials and Methods:** We conducted a systematic literature search on the data bases PubMed, CINHAL (Ebsco) and PsycINFO (Ovid). Eligible studies were identified by screening papers according to predefined inclusion and exclusion criteria. The papers had to be randomized controlled trials reporting original data of the effect of CBT-I on the severity of insomnia and the mental disorders. Self-rating questionnaires were required to measure the outcomes for both insomnia severity and the severity of the mental disorder. Control groups, allowing for a conclusion on the efficacy of the study intervention such as waitlist, placebo or treatment as usual were needed. Furthermore, the diagnosis of insomnia disorder and the mental comorbidity had to be based on the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) or the *International Statistical Classification of Diseases and Related Health Problems* (ICD). A risk of bias rating of individual studies was conducted with the Cochrane Tool.

**Results:** Twenty-two studies fulfilled the inclusion criteria. The comorbidities were depression (8 studies), post-traumatic stress disorder (PTSD, 4 studies), alcohol dependency (3 studies), bipolar disorder (1 study), psychosis (1 study) and mixed comorbidities (5 studies). CBT-I had an

overall large effect (Hedges'  $g$ ) of 0.9 (CI 0.7;1.2) on the insomnia severity immediately after treatment and a large effect of 0.8 (CI 0.4;1.3) at follow-up, which was on average 3 to 6 months after post treatment. Regarding the severity of the mental comorbidity, CBT-I had the following effect sizes: 0.5 (CI 0.1;0.8) for depression, 1.3 (CI 0.6;1.9) for PTSD, 0.9 (CI 0.3;1.4) for alcohol dependency in only one study, 0.3 (CI -0.1;0.7, insignificant) for psychosis/bipolar disorder, and 0.8 (CI 0.1;1.5) for mixed comorbidities. CBT-I had an overall medium effect of 0.5 (CI 0.1;0.8) at follow-up for mental disorders (non-significant for individual disorders).

**Conclusions:** Medium to large effects of CBT-I indicate that it is an effective treatment for patients with mental disorders and comorbid insomnia. Not only insomnia severity, but also the severity of the mental disorders was reduced after treatment. In conclusion, insomnia should be treated with CBT-I as a first-line treatment. However, CBT-I should only be regarded as an add-on to the treatment as usual for the mental disorders. More implementation and dissemination studies are needed to further promote CBT-I in the care of patients with mental disorders and to test for long term effects.

**Acknowledgements:** The project was funded by intramural sources.

### COGNITIVE-BEHAVIORAL THERAPY FOR INSOMNIA REDUCES SLEEP DURATION MISPERCEPTION IN CHRONIC INSOMNIA

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Individuals with chronic insomnia frequently present with sleep state misperception, including an underestimation of their sleep duration (TST). This study aims at characterizing whether the perception of sleep duration might be improved by a psychological intervention (cognitive-behavioral therapy for insomnia; CBTi) in adults with chronic insomnia.

Forty-six adults with chronic primary insomnia ( $52.15 \pm 15.15$  y.o.; 34 females) came to the lab to perform a baseline (T1) sleep assessment including polysomnographic (PSG) recording along with subjective sleep assessments, the Insomnia Severity Index (ISI) and questionnaires assessing psychological state (Pre-Sleep Arousal Scale, PSAS; State-Trait Inventory for Cognitive and Somatic Anxiety, STICSA). They were then randomized to either a 3-month CBTi program (CBT group -  $N=25$ ) or a 3-month wait-list (WL group -  $N=21$ ). They performed another sleep assessment after 3 months (T2) and those in the WL group came back again after completion of the CBTi (T3). Whole night PSG recordings included 17 scalp-EEG sampled at 512 Hz, EOG, EMG (Somnomedics, Germany) and were scored according to the AASM guidelines. We also detected spindles and slow oscillations using automatic detection and analyzed power spectral activity. Sleep misperception score (SSM; subjective minus objective TST in minutes) and sleep perception index (SPI: subjective TST/objective TST) were calculated. Mixed-models ANOVAs with age as covariate were used to assess Group\*Time interaction on sleep misperception measures at T1 and T2. ANCOVAs testing the effect of CBTi ( $N=44$ ) were used on sleep misperception measures before (T1) and after CBTi (pooled T2 for CBT group and T3 for WL group). Pearson correlation were performed to assess whether change in sleep misperception could be associated to change in objective sleep (ie, architecture, brain oscillations, spectral power), insomnia severity (ISI) or psychological state (PSAS, STICSA).

At T2, we found a Group effect ( $F(1,87)=6.52$ ,  $p=0.01$ ) and a trend for a Group\*Time interaction ( $F(1,87)=2.9$ ,  $p=0.09$ ) on SSM showing a better perception of sleep duration after CBTi in the CBT group compared to the WL group. Once pooled together ( $N=44$ ), participants exhibited less misperception of sleep duration ( $F(1,84)=6.94$ ,  $p=0.009$ ) by 40min on

average Post-CBTi compared to Pre-CBTi. Similar results were found for SPI at T2 (interaction:  $F(1,87)=3.7$ ,  $p=0.06$ ) and Post-CBTi ( $F(1,84)=6.35$ ,  $p=0.01$ ).

While change in SSM did not correlate with change in insomnia severity ( $p>0.05$ ), we found that reduction of SSM was correlated with reduction of time spent in light sleep ( $N1\%TSP$  -  $r=-0.59$ ,  $p=0.001$ ) and reduced sleep stage switching ( $r=-0.42$ ,  $p=0.03$ ) in the CBT group but not in the WL group. However, we did not find any association with changes in micro-architecture (i.e., spindle, slow oscillation, relative spectral power) nor with changes in psychological state (all  $p>0.05$ ). We found similar results for SPI score as well as with pooled data post-CBTi.

These findings, using PSG and subjective sleep assessments, show the beneficial effects of CBTi on sleep misperception in chronic insomnia. Moreover, the reduced mismatch between objective and subjective after CBTi might result from improved sleep maintenance and reduction in time spent in light sleep.

### COMPARING FACE-TO-FACE COGNITIVE BEHAVIORAL THERAPY WITH DIGITALIZED COGNITIVE BEHAVIORAL THERAPY FOR INSOMNIA: A NETWORK META-ANALYSIS

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**Introduction:** Clinical guidelines recommend cognitive behavioral therapy for insomnia (CBT-I) as the first-line treatment for insomnia. The provision of CBT-I is limited by the scarce availability and accessibility of trained CBT-I providers. Alternative CBT-I delivery formats, as digitalized CBT-I programs, may enhance the dissemination of CBT-I. Yet, direct evidence comparing the efficacy of alternative CBT-I delivery formats with onsite CBT-I is limited. This study aims to synthesize direct and indirect evidence to compare onsite CBT-I with alternative CBT-I delivery formats in terms of their treatment efficacy on insomnia severity utilizing the framework of a frequentist network meta-analysis.

**Materials and Methods:** We performed a systematic computerized search of the following databases: PsycINFO, PsycARTICLES, MEDLINE, PubMed, CINAHL. These databases were searched from 1987 until March 2020 using terms indicative of insomnia, CBT-I, and CBT-I components. We conducted a literature update in November 2021. Full-text screening, data extraction, and risk of bias rating were conducted by two independent reviewers. A frequentist network meta-analysis was performed using the R-package "netmeta". For the interpretation of the effect sizes, the varying CBT-I delivery formats were compared against wait-list control as a reference.

**Results:** The search yielded 6,452 studies. Preliminary results based on the search until March 2020 yielded 48 studies with 8,343 participants eligible for inclusion. Preliminary analyses in which the varying CBT-I delivery formats were compared against wait-list control groups as a reference indicated the largest effect size for onsite individual therapy (Cohens  $d = -1.24$ ; 95%CI [-1.77, -0.71], followed by onsite group therapy (Cohens  $d = 0.98$ ; 95%CI [-1.42, -0.54]. Guided and unguided internet CBT-I yielded moderate effect sizes with Cohens  $d = -0.67$  (95%CI [-1.18, -0.16]) and Cohens  $d = -0.76$  (95%CI [-1.18, 0.33]) respectively. The results of the full network meta-analysis will be presented at the World Sleep Conference 2022.

**Conclusions:** Preliminary results indicate that the effects of the various CBT-I delivery formats may differ in their magnitude. Individual onsite CBT-I yielded a very large effect size, yet also self-help interventions showed moderate to large effect sizes. Given these findings, different health care models should be considered comprising standalone onsite CBT-I as a first-line choice complemented by self-help interventions, blended care concepts, and stepped care approaches. Thereby, health care resources and patient preferences might guide health care providers to exploit the full potential of CBT-I for lowering the public health burden associated with insomnia. Results may change, as we are currently conducting a literature update.

### CROSS-SPECIES VALIDATION OF INSOMNIA-ASSOCIATED LOCI IDENTIFIED THROUGH VARIANT-TO-GENE MAPPING IMPLICATES *PIGQ* AS A CONSERVED REGULATOR OF SLEEP DURATION

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Insomnia is a complex and prevalent sleep disorder with reports of high heritability. More than 200 genome-wide significant loci have been documented for insomnia, yet the underlying mechanism remains elusive. Many of the genome-wide association study (GWAS)-implicated single nucleotide polymorphisms (SNPs) fall within inter- or intragenic regions and are subsequently mapped to the nearest coding gene. This approach often mischaracterizes the true effector gene that may reside several thousands of nucleotides away. To tackle this complexity, our group has developed a variant-to-gene mapping approach that reveals effector genes linked to relevant GWAS signals. Using ATAC-seq and promoter-focused capture C methods in human induced pluripotent stem cell-derived neural progenitor cells, we identified a subset of candidate insomnia target coding genes with accessible promoter regions that were contacted by insomnia-associated SNPs residing in open chromatin. Target genes with known human orthologs and available *Drosophila* RNAi lines were then subjected to deep phenotyping of sleep traits. This pipeline revealed five genes producing robust sleep phenotypes, two of which increased sleep by more than 30 percent and three which decreased sleep more than 20 percent. To further characterize the contribution of these genes to sleep behavior in a vertebrate system, we used zebrafish since they have a developed nervous system and exhibit diurnal sleep characteristics similar to humans. We employed CRISPR/Cas9 mutagenesis in F0 zebrafish at the single cell stage to produce high-efficiency biallelic knockouts of the target genes. Interestingly, we found that loss of *pigq* significantly increased sleep duration in both *Drosophila*, and zebrafish, revealing a conserved, yet novel regulator of sleep duration. *Pigq* encodes phosphatidylinositol N-acetylglucosaminyl transferase subunit Q, which catalyzes the first step in glycosylphosphatidylinositol anchor biosynthesis. This gene has not been implicated in sleep previously, but it is involved in early infantile epileptic encephalopathy potentially underlying an important link between sleep and epilepsy. Our ongoing studies aim to characterize the contribution of other members of the glycosylphosphatidylinositol anchor biosynthesis pathway to sleep phenotypes both in *Drosophila* and zebrafish and to understand possible combinatorial effects due to disruption of this pathway.

### DIGITAL COGNITIVE BEHAVIORAL THERAPY FOR INSOMNIA PROMOTES RESILIENCE DURING THE CORONAVIRUS DISEASE 19 (COVID-19) PANDEMIC

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**Introduction:** Stressful life events contribute to insomnia, psychosocial functioning, and illness. Though individuals with a history of insomnia may be especially vulnerable during stressful life events, risk may be mitigated by prior intervention. This study evaluated the effect of prior digital cognitive-behavioral therapy for insomnia (dCBT-I) versus sleep education on resilience during the COVID-19 pandemic.

**Materials and Methods:** COVID impact, insomnia, general- and COVID-

related stress, depression, and global health were assessed in April 2020 in adults with a history of insomnia who completed a randomized controlled trial of dCBT-I ( $n = 102$ ) versus sleep education control ( $n = 106$ ) in 2016–2017. Regression analyses were used to evaluate the effect of intervention conditions on subsequent stress and health during the pandemic.

**Results:** Insomnia symptoms were significantly associated with COVID-19 related disruptions, and those previously received dCBT-I reported less insomnia symptoms, less general stress and COVID-related cognitive intrusions, less depression, and better global health than those who received sleep education. Moreover, the odds for resurgent insomnia was 51% lower in the dCBT-I versus control condition. Similarly, odds of moderate to severe depression during COVID-19 was 57% lower in the dCBT-I condition.

**Conclusions:** Those who received dCBT-I had increased resilience during the COVID-19 pandemic in adults with a history of insomnia and ongoing mild to moderate mental health symptoms. These data provide evidence that dCBT-I is a powerful tool to promote mental and physical health during stressors, including the COVID-19 pandemic.

**Acknowledgements:** HLK23138166

### DIGITAL COGNITIVE BEHAVIOURAL THERAPY FOR INSOMNIA (DCBT-I) AND EMOTION REGULATION AS EARLY INTERVENTION FOR EMPLOYEES IN THE WORKPLACE

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Insomnia is a serious public health concern and has been linked to impaired work productivity. Studies show a link between poor sleep and aspects of occupational functioning such as absenteeism, reduced productivity and low work satisfaction. One in every three workers in the UK are affected by sleep problems costing the economy around £36 billion/year due to loss of productivity in the workplace. This results in around 200,000 working days lost every year, and it is estimated that the cost to industry will rise steadily to £44 billion by 2030 if nothing is done about it. Few studies have evaluated the effectiveness of CBT-I in workplaces, and have found improvements in severity of insomnia and quality of sleep, and slight improvements in productivity and presenteeism, but not in absenteeism. While most interventions for insomnia are focused on the treatment of those above clinical thresholds, there is crucial need for early intervention/prevention of insomnia. This has been further exacerbated during the Covid-19 pandemic due to isolation, financial insecurities, loss of loved ones and fear of infection, causing extensive sleep problems as well as stress, anxiety and depressive symptoms. This study will examine the efficacy of a new hybrid dCBT-I for mild to severe insomnia and symptoms of depression and anxiety delivered to employees in the workplace.

This trial tests the efficacy of implementing a hybrid dCBT-I + emotion regulation (ER) in the workplace in a mixed methods evaluation with a two-arm randomised waitlist control (WLC) design. The dCBT-I+ER intervention is 8-weeks long and delivered via self-guided online platform and four videoconferencing therapy sessions. Primary outcomes are the Insomnia Severity Index, the Patient Health Questionnaire and the Generalised Anxiety Disorder. Secondary outcomes are job productivity, job satisfaction, well-being, quality of life, self-reported (sleep diary data) and objective (actigraphy) sleep parameters.

We recruited 163 workers with sleep and emotion regulation problems ranging from subclinical to clinical levels not engaged in treatment at the time of the trial. Due to the study design, analyses for the primary hypotheses will be done when the last enrolled participant provides post-intervention follow-up (1-month) outcome measures. We hypothesise that participants randomly allocated to dCBT-I+ER will demonstrate significantly greater improvements on the primary outcomes compared to WLCs post-intervention. They will also demonstrate significantly greater improvements on objective (actigraphy) and self-reported (sleep diary) sleep parameters. Exploratory analyses will also indicate the impact of the dCBT-I+ER on work productivity, job satisfaction, wellbeing, and quality of life.

Evaluation of an early intervention for workers with mild to severe symptoms of insomnia and emotion regulation difficulties will contribute to the understanding of benefits of early interventions in the workplace, and its impact on mental health and productivity. The mixed methods

evaluation will provide insight into the application of intervention and help us understand people's experiences of the intervention and what helped or hindered its use. This pilot study forms the basis of what could become a larger nationwide service delivery programme of mental health interventions for insomnia in the workplace.

#### DISSECTING INSOMNIA FROM SLEEP DURATION IN RELATION TO CORONARY ARTERY DISEASE: EVIDENCE FROM MULTIVARIABLE-ADJUSTED AND FACTORIAL MENDELIAN RANDOMIZATION ANALYSES

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**Introduction:** Multivariable-adjusted (MVA) and Mendelian Randomization (MR) studies identified insomnia symptoms and short sleep duration as risk factors for coronary artery disease (CAD). As sleep is a multidimensional construct, this study aimed to dissect insomnia symptoms from sleep duration in relation to risk of CAD MVA and MR analyses.

**Materials and Methods:** We stratified European-ancestry participants from UK Biobank (N=417,311) into subgroups based on the presence of self-reported insomnia symptoms (yes/no) and short (<7h), average (7-9h) and long (≥9h) sleep duration for MVA cox-proportional hazard models in a population without CAD history. Similarly-stratified groups were constructed using weighted genetic scores for insomnia symptoms and total sleep duration for factorial MR analyses on CAD.

**Results:** Both insomnia symptoms and short or long sleep duration were associated with higher CAD risk in the MVA analysis. With factorial MR, and compared to participant with lower genetically-influenced risk for insomnia symptoms and genetically-influenced average sleep, the genetically-influenced effects of insomnia symptoms on CAD were similar in groups of genetically-influenced short (OR: 1.15; 95% confidence interval: 1.11-1.19), average (1.09; 1.07-1.12) and long (1.07; 1.00-1.14) sleep duration. Conversely, genetically-influenced short and long sleep duration were not associated with CAD in individuals with low or high genetically-influenced risk for insomnia symptoms. Genetically-influenced insomnia symptoms, and not short or long sleep duration, was associated with higher triglyceride levels in both MVA and MR analyses.

**Conclusions:** Insomnia symptoms, and not sleep duration, drive CAD risk and increased triglyceride levels. Targeting insomnia symptoms is therefore likely to be more effective in preventing CAD than targeting short sleep duration.

**Acknowledgements:** We thank all the participants contributing to the UK Biobank resources. The present UK Biobank project was conducted under project number 56340.

#### DOES ONLINE-DELIVERED COGNITIVE BEHAVIOURAL THERAPY FOR INSOMNIA IMPROVE INSOMNIA SEVERITY IN NURSES WORKING SHIFTS? PROTOCOL FOR A RANDOMISED-CONTROLLED TRIAL

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**Introduction:** In order to provide continuous care for sick and elderly people, shift work is often unavoidable in caring professions such as nurses. However, there is evidence that working in shifts may cause sleeping problems. Depending on the methodological procedures used, studies suggest that approximately 10-30 % of shift workers suffer from shift work sleep disorder that is characterised by insomnia and/or sleepiness related to the shift schedule. Little is known about the treatment options for individuals suffering from this sleep disorder, with light

therapy, sleep hygiene and pharmacotherapy being primarily discussed. Few studies explored the efficacy of face-to-face Cognitive Behavioural Therapy for Insomnia in the context of shift work and reported promising results. Due to irregular working hours, it is particularly challenging for shift workers to attend fixed appointments, so online-delivered treatment could be an attractive alternative to face-to-face treatment. In this context, we developed an online-delivered training "SleepCare" for nurses working shifts that is tested for efficacy in the current study. It is hypothesised that the treatment with SleepCare reduces insomnia severity compared to a waiting-list control condition.

**Materials and Methods:** SleepCare is based on Cognitive Behavioural Therapy for Insomnia and it is adapted to the situation of nurses working shifts. It consists of six modules which participants can complete independently and after which they receive individualised feedback from a clinical psychologist. A total of N = 46 unmedicated nurses who suffer from shift work sleep disorder will be included and randomised to either the active treatment group (SleepCare) or the waiting-list control group. Individuals who suffer from any comorbid sleep or psychiatric disorder or report any serious physical illness that affects sleep, who are undergoing psychotherapy or are on a waiting list for it, will be excluded. The primary outcome variable of the study is the Insomnia Severity Index. In addition, other sleep-related as well as work-related questionnaires, sleep diary data and actigraphy data before and after treatment as well as 6 months after treatment completion (follow-up) will be analysed.

**Results:** Recruitment started in October 2021 at the University Medical Centre Freiburg. It is intended to reach the planned sample size by the end of 2022.

**Conclusions:** This study is one of the first studies examining the effect of an online-delivered treatment based on Cognitive Behavioural Therapy for Insomnia adapted to shift work.

**Acknowledgements:**

#### DURING THE COVID-19 EPIDEMIC, THE RELATIONSHIP BETWEEN INSOMNIA AND MENTAL HEALTH-RELATED FACTORS AMONG THE GENERAL IN GERMANY

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**Objective:** The aim of this study is to evaluate during the COVID-19 pandemic in Germany the relationships between insomnia and mental health-related factors.

**Materials and Methods:** The ICSS questionnaires have been collected from May 1 to September 30, 2021. The ICSS Questionnaire included sociodemographic questions, Patient Health Questionnaire (PHQ), Insomnia Severity Index (ISI), Generalized Anxiety Disorder (GAD), and visual analog scale.

The collected questionnaires entered by Redcap, cleaned and analyzed by using SPSS for Mac version 23.0. Qualitative analyses of the demographic characteristics were performed, and correlation analyses of the variables were calculated.

**Results:** A total of 1103 participants obtained 858 valid questionnaires (22.9% Male). The educational level of most participants was less than bachelors (n = 536, 62.5%), non-smoking (n = 772, 90%), and less stress (557,64.9%). Among the participants, the prevalence of insomnia, anxiety, and depression physical were 19.5%, 4.8%, and 6.6%. Compared to the insomnia group, the ISI score, PHQ-4 score, PHQ-2 score, and GAD-2 score of the non-insomnia group had lower mean scores and medians, while the "Quality of Life" and "Quality of Health" scores of the same group had higher mean scores and medians, all of which were statistically significant (P < 0.05). Pearson correlation analysis showed that there is a positive correlation between the ISI score and the PHQ-2 score (P < 0.001), and the GAD-2 score (P < 0.001) and PHQ-4 score (P < 0.001); however, the ISI score was negatively correlated with the "Quality of Life" score (P < 0.001) and the "Quality of Health" score (P < 0.001).

**Conclusions:** The results show that the insomnia, anxiety, and depression are more than before among German during the COVID-19 epidemic. Anxiety and depression in the insomnia group were more serious than those in the non-insomnia group, and they are interacting with each other.

**Keywords:** questionnaire, insomnia, anxiety, depression, coronavirus  
**EFFECT OF LEMBorexant TREATMENT ON FATIGUE SEVERITY AND SLEEP OUTCOMES IN OLDER ADULTS WITH CLINICALLY SIGNIFICANT FATIGUE AT BASELINE**

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**Introduction:** In addition to chronic sleep onset and/or maintenance difficulties, DSM-5 diagnostic criteria for insomnia disorder include the presence of daytime impairments, such as mood disturbances, decreased energy and/or fatigue. Thus, an effective insomnia treatment should improve sleep and reduce fatigue. Lemborexant (LEM) is a dual orexin receptor antagonist approved in multiple countries including the United States, Canada, Japan, and Australia for the treatment of insomnia in adults. In Phase 3 Study E2006-G000-303 (Study 303; SUNRISE-2; NCT02952820), LEM provided significant benefit vs placebo (PBO) on patient-reported sleep outcomes (daily sleep diaries) and fatigue severity, as assessed by the Fatigue Severity Scale (FSS). In these post hoc analyses, sleep outcomes and fatigue severity were analyzed in subjects aged  $\geq 65$ y who had clinically significant fatigue at baseline (FSS total score [TS]  $\geq 36$ ).

**Materials and Methods:** Study 303 was a 12-month, randomized, double-blind study in subjects with insomnia disorder aged  $\geq 18$ y (n=949). For Treatment Period 1 (first 6 months), subjects received PBO or LEM (5mg [LEM5]; 10mg [LEM10]). During Treatment Period 2 (second 6 months; not reported), PBO subjects were rerandomized to LEM5 or LEM10 while LEM subjects remained on their original doses. Changes from baseline in FSS-TS, subjective sleep onset latency (sSOL), subjective sleep efficiency (sSE) and subjective wake after sleep onset (sWASO) for LEM vs PBO during Treatment Period 1 were analyzed.

**Results:** In this subgroup (PBO, n=41; LEM5, n=44; LEM10, n=49), mean (SD) FSS-TS at baseline was 44.1 (6.8), 46.2 (7.6), and 44.9 (6.3) for PBO, LEM5, and LEM10, respectively. As assessed at 6 months, mean (SD) decreases from baseline (improvement) in FSS-TS were significantly greater with LEM vs PBO (PBO: -8.7 [10.0]; LEM5: -18.3 [12.9],  $P=0.006$ ; LEM10: -17.4 [11.6],  $P=0.003$ ). At baseline, median sSOL (min) was 49.0, 44.1 and 54.3 for PBO, LEM5, and LEM10, respectively. At 6 months, median decreases from baseline in sSOL (min) were significantly greater with LEM5 and numerically greater with LEM10 vs PBO (PBO: -9.0; LEM5: -20.1,  $P=0.0008$ ; LEM10: -19.8). At baseline, mean (SD) sSE was 61.8% (18.1%), 65.2% (14.3%) and 61.0% (14.6%) for PBO, LEM5 and LEM10, respectively. Mean (SD) increases from baseline in sSE were significantly greater with LEM5 and numerically greater with LEM10 vs PBO at 6 months (PBO: 5.8% [10.3%]; LEM5: 17.1% [14.3%],  $P=0.0012$ ; LEM10, 13.1% [14.0%]). Mean sWASO (min) at baseline was 134.9 (82.3), 126.8 (65.1) and 166.4 (91.0) for PBO, LEM5 and LEM10, respectively. At 6 months, mean (SD) decreases from baseline in sWASO (min) were significantly greater with either LEM dose vs PBO (PBO: -9.9 [47.2]; LEM5: -58.3 [79.9],  $P=0.004$ ; LEM10, -50.6 [56.6],  $P=0.03$ ). Rates of treatment-emergent adverse events (TEAEs) were similar across treatment groups (58.5%, 65.9%, 53.1% for PBO, LEM5 and LEM10, respectively). The majority of TEAEs were mild/moderate in severity.

**Conclusion:** Subjects aged  $\geq 65$ y with clinically significant fatigue at baseline had greater improvements in FSS-TS and all sleep parameters with LEM vs PBO at 6 months. Reductions in fatigue severity generally paralleled the time course of the improvements in sleep.

**Acknowledgements:** Supported by Eisai Inc.

**EFFECT OF ONE SHOT COGNITIVE BEHAVIORAL THERAPY ON INSOMNIA AND HEART RATE VARIABILITY IN HEALTH CARE WORKERS DURING COVID- 19 EPIDEMIC**

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**Introduction:**The emergence of sleep disturbances in response to major stressful events including natural disasters (eg, wildfires, earthquakes, floods) or 2019 novel coronavirus (COVID-19) pandemic, has been documented previously. Insomnia is one of the sleep problem in this situations and it may lead to unpleasant consequences which it imposes an additional burden on the person and frontline healthcare providers in health facilities are one of the in danger groups .

Hyperarousal hypothesised to contribute to the development, maintenance and 24-hour systemic sequelae of insomnia and Heart rate variability (HRV) is an objective marker that provides insight into autonomic nervous system dynamics. Insomnia and reduced heart rate variability (HRV) increase the risk of cardiovascular disease and its precursors. It has been concluded a cognitive behavioral framework, such as CBT-I, is a likely treatment candidate for acute insomnia. The aim of the present study was to examine the preliminary efficacy and effectiveness of a one-shot session of cognitive behavioral therapy for insomnia (CBT-I) for frontline healthcare providers with acute insomnia and evaluate autonomic system changes and potential cardiovascular benefits of this treatment in an open trial.

**Materials and Methods:** A randomized controlled clinical trial was conducted from february 2020 to july 2021 about fifty health care worker with insomnia (ISI score >8), at 18 years old and higher were randomly allocated to receive one shot cognitive behavioral therapy or routine care. ISI and HRV were assessed before and one month after the intervention.

**Results:** ISI score decreased in the intervention group (from 13.32 (3.72) to 6.74(4.51),  $p$ value=0.0001), the mean difference in ISI score before and after the intervention was significantly different in two group (-6.5 vs 0.15 ,  $p$ value <0.0001). Mean difference in HF ,LF/HF ratio (-1.16 vs 0.55,  $p$ value,0,001) before and after the intervention was significantly different in two group

**Conclusions:** A single-shot session of CBT-I is effective in managing acute insomnia symptoms in health workers. This treatment of intervention group is associated with HRV changes in the form of reduced LF/HF ratio and increase HF that it raises the parasympathetic activation and increased sympathovagal balance

**Acknowledgements:**

**EFFECT OF THE COVID-19 PANDEMIC WAVES ON QUALITY OF SLEEP IN PATIENTS WITH INSOMNIA**

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**Introduction:** An exponential increase in the number of people who have been reporting sleep disturbances has been noted during the COVID-19 pandemic. Those with prior sleep disorders have also noted worsening of their problems during this period. Changes in lifestyle, fear and uncertainty regarding the Corona Virus disease and also generalized apprehension and anxiety about the future have been reported as causative factors. We postulated that better understanding of preventive and treatment options during the second wave would have positive impact and aimed to assess the quality of sleep in patients with insomnia during this period in comparison to the first wave.

**Materials and Methods:** The study was conducted at Nithra Institute of Sleep Sciences, a free-standing sleep clinic in Chennai, India, during July-August 2021 (after the second wave of the pandemic). Patients who had presented to the clinic with insomnia from March to May 2020, during the first wave of the pandemic, were included in the study. The patients were contacted by a research personnel and the following details were collected - i) subjective quality of sleep during the second wave of the pandemic

compared to the previous wave ii) regularity of taking medicines and iii) the primary factor that affected their sleep quality. Demographic details such as age, gender, marital status and chronicity of insomnia were extracted from the medical records.

**Results:** During the study inclusion period, a total of 114 patients had presented to the clinic with insomnia. Of these, 70 patients (61.4%), who were reachable and willing to provide details were included in the study (48.6% Males / 51.4% Females; Mean age -  $45.0 \pm 14.2$ ). Of the 70 patients, 47 (67.1%) mentioned that their sleep quality was better than the previous wave of the pandemic and the rest 23 (32.9%) mentioned that their insomnia had become worse. The group which reported worsened sleep quality was older ( $p=0.01$ ), was irregular in taking medicines ( $p=0.01$ ) and their duration of insomnia was longer ( $p=0.04$ ) compared to the group that reported better sleep quality. There were no significant differences in gender or marital status between the groups. The factors that were mentioned as affecting the sleep quality were 'Uncertainty in personal and professional life' (34.8%), 'fear of the infection and its outcomes' (26.1%), 'change in schedule and lifestyle' (21.7%) and 'emotions that could not be expressed' (17.4%).

**Conclusions:** Our study shows that, most people reported better sleep quality during the second wave of the pandemic compared to the first. Age, chronicity of the insomnia and irregularity in taking medicines were significantly associated with worsened sleep quality.

**Acknowledgements:**

#### EFFECTS OF DARIDOREXANT AND ZOLPIDEM ON NIGHT WAKEFULNESS IN ADULTS WITH INSOMNIA: EXPLORATORY ANALYSIS FROM A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE 2 TRIAL

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**Introduction:** Insomnia disorder increases wake bout duration throughout the night. Daridorexant reduced wake time after sleep onset (WASO) in a phase 2 dose-finding study. This post-hoc analysis evaluates wake bout duration and progression of daridorexant versus zolpidem or placebo.

**Materials and Methods:** Eligible patients were 18–64years with insomnia disorder (DSM-5 criteria), a self-reported history of time to fall asleep  $\geq 30$ minutes, WASO  $\geq 30$ minutes, and total sleep time  $\leq 6.5$ hours on  $\geq 3$ nights/week. After a single-blind, placebo run-in period, patients were randomized (1:1:1:1:1) to daridorexant (5, 10, 25 or 50mg), zolpidem 10mg or placebo for 30days (D).

The primary efficacy outcome was the change in WASO from baseline to D1 and D2 by PSG. Wake bouts at baseline, D1 and D29 were examined in patients on daridorexant 25 or 50mg, zolpidem or placebo. D1 and D29 assessed the immediate and 1-month effects of daridorexant, respectively. Daridorexant 25 and 50mg were selected having demonstrated efficacy on sleep variables in phase 3 trials.

Wake bout data were analyzed for every patient computing the cumulative wake bout time over 8-hour PSG night in half minute intervals (i.e., 1 epoch).

**Results:** The majority of randomized patients ( $n=359$ ) (mean age 45years) were female (64%). This post-hoc analysis included patients treated with daridorexant 25mg ( $n=60$ ), 50mg ( $n=61$ ), zolpidem 10mg ( $n=60$ ) and placebo ( $n=60$ ).

At baseline, there was no difference in cumulative wake bout average time between treatments. The cumulative wake bout average time progressively increased with zolpidem and placebo versus daridorexant 25 and 50mg at D1 and D29. At D1 and D29, most of the time awake after sleep onset occurred during the last two quarters of the night for all patients.

During the last two quarters of the night, the cumulative average time in wake bouts was similar for placebo and zolpidem on D1, and greater for zolpidem versus placebo on D29, indicating a time spent awake increase compared to the first two quarters of the night. Daridorexant 50mg resulted in consistently lower cumulative wake bout average time versus both zolpidem or placebo during the last two quarters of the night.

Cumulative wake bout average time was similar for daridorexant 50mg and zolpidem during the first two quarters of the night, with statistically significant reductions in the last part of the night.

All treatments increased the short wake bout number and reduced longer wake bouts on D1 and D29 versus baseline. The largest effect was observed for daridorexant 50mg, thus reducing the awakenings number that contributed most to the total time awake. Differences in cumulative wake time between daridorexant, zolpidem and placebo were largely driven by reductions in the duration of longer wake bouts.

**Conclusions:** Daridorexant (25 and 50 mg) consistently reduced wakefulness throughout the night versus placebo, possibly due to the optimized pharmacokinetic profile of daridorexant. Daridorexant decreased the duration of longer wake periods, targeting a key insomnia symptom.

**Acknowledgements:** Funded by Idorsia Pharmaceuticals Ltd. This abstract has been previously presented at the 60<sup>th</sup> ACNP meeting held December 5–8, 2021 in San Juan, Puerto Rico.

#### EFFECTS OF DARIDOREXANT ON SLEEP AND DAYTIME FUNCTIONING IN OLDER PATIENTS WITH INSOMNIA DISORDER

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**Introduction:** Insomnia impacts older adults more than younger adults, and comorbidities more prevalent in older adult populations can add to symptom burden and reduce therapeutic options. Drugs that improve insomnia symptoms with limited safety risks are needed to treat this patient group. We report elderly subgroup analyses from a phase-3 registration trial with daridorexant.

**Materials and Methods:** In this multi-center, double-blind trial (NCT03545191), adult (18–64 years) and elderly ( $\geq 65$  years) patients with insomnia were randomized (1:1:1) to receive oral daridorexant 25 mg, 50 mg or placebo every evening for three months. Month 3 endpoints were: change from baseline in polysomnography-measured wake-after-sleep-onset (WASO) and latency-to-persistent-sleep (LPS) (both primary endpoints), subjective total sleep time (sTST), and daytime functioning (Insomnia Daytime Symptoms and Impacts Questionnaire [IDSIQ] – sleepiness domain; with a lower score indicating improved daytime functioning). Safety endpoints included treatment emergent adverse events (TEAEs), AEs of special interest (AESI); symptoms related to excessive daytime sleepiness or complex sleep behavior, and suicidal ideation/self-injury) and withdrawal effects upon treatment cessation (assessed by the Benzodiazepine Withdrawal Symptom Questionnaire total score and relevant AEs).

**Results:** Of the 930 patients randomized, 364 (39.1%) were  $\geq 65$  years: daridorexant 25 mg ( $n=121$ ), 50 mg ( $n=121$ ) and placebo ( $n=122$ ). In this subgroup, at Month 3, the placebo-corrected least-square mean of change from baseline [95%CL] for daridorexant 25 mg and 50 mg were: WASO -17.0 [-27.0, -7.0] and -19.6 [-29.5, -9.7] min; LPS -7.8 [-15.2, -0.4] and -14.9 [-22.3, -7.5] min; sTST 18.7 [4.1, 33.2] and 30.6 [16.1, 45.2] min; IDSIQ sleepiness domain -0.6 [-2.2, 0.9] and -2.6 [-4.1, -1.0], all respectively.

TEAEs were reported in 32.2%, 35.3%, and 31.1% of patients  $\geq 65$  years in the 25 mg, 50 mg and placebo groups, respectively. Falls ( $n=1, 1, 4$  for 25 mg, 50 mg, placebo, respectively) and dizziness ( $n=4, 1, 1$  for 25 mg, 50 mg, placebo, respectively), both of particular interest in elderly, were least frequent in the 50 mg group. Compared to placebo, somnolence was as frequent for 50 mg daridorexant ( $n=6, 1, 1$  for 25 mg, 50 mg, placebo, respectively) while fatigue was more frequent in both daridorexant groups ( $n=4, 3, 1$  for 25 mg, 50 mg, placebo, respectively); the incidence did not appear dose related. AESI, of mild intensity, were reported in two patients  $\geq 65$  years (one in each daridorexant group). There was no evidence of withdrawal symptoms.

**Conclusions:** Daridorexant is efficacious in the older adults for improvements in sleep and daytime functioning. No safety concerns in this vulnerable population were identified at either dose.

**Acknowledgements:** Funded by Idorsia Pharmaceuticals Ltd. This abstract has been previously presented at the virtual SLEEP meeting, the 35<sup>th</sup>

annual meeting of the Associated Professional Sleep Societies held June 10–13, 2021.

### EFFECTS OF DARIDOREXANT ON TOTAL SLEEP TIME (TST) AND SLEEP STAGE PROPORTIONS IN PATIENTS WITH INSOMNIA DISORDER

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**Introduction:** Daridorexant, a new dual orexin receptor antagonist, improved sleep parameters and daytime functioning in two pivotal Phase 3 trials in patients with insomnia disorder (Trial-1, NCT03545191; Trial-2, NCT03575104). Polysomnography data were collected at multiple time-points from >1,800 patients. We report the effects of daridorexant on total sleep time (TST) and sleep stages from both trials.

**Materials and Methods:** Eligible patients with insomnia (according to DSM-5) were randomized (1:1:1) in Trial-1 (N=930) to daridorexant 25 mg, 50 mg or placebo, and in Trial-2 (N=924) to daridorexant 10 mg, 25 mg or placebo. Oral treatment was administered each night during a 3-month, double-blind, treatment period. Assessment of TST and sleep stages (non-rapid eye movement [NREM, N1, N2, N3, REM] measured by polysomnography in sleep laboratory, was performed on two consecutive nights during single-blind placebo run-in (baseline), and Month 1 and 3 (M1 and M3) of double-blind treatment. Change from baseline in TST and sleep stages were exploratory endpoints in both trials. Data for M3 (mean  $\pm$  standard deviation) are presented as change from baseline.

**Results:** Daridorexant dose-dependently increased TST (min) from baseline to M3 more than placebo in Trial-1 (25 mg: 55 $\pm$ 56; 50 mg: 61 $\pm$ 53; placebo: 40 $\pm$ 56) and Trial-2 (10 mg: 37 $\pm$ 57; 25 mg: 50 $\pm$ 53; placebo, 35 $\pm$ 56).

In both trials, sleep stage proportions were preserved from baseline to M3 with no relevant changes in any group. Baseline time spent in each sleep stage (% of TST) was consistent across groups in both trials (range across treatment groups in both trials: N1: 11–13; N2: 55–57; N3: 11–14; REM: 19–20). In Trial-1 (25mg/50mg/placebo), the change from baseline to M3 in % of TST spent in N1(-0.3 $\pm$ 4.7/-0.2 $\pm$ 5/0.1 $\pm$ 5), N2(2 $\pm$ 8/1 $\pm$ 7/1 $\pm$ 7), N3(-2 $\pm$ 6/-2 $\pm$ 6/-2 $\pm$ 6), and REM (1 $\pm$ 6/1 $\pm$ 5/1 $\pm$ 5) was low and numerically similar across treatments. In Trial-2, change from baseline to M3 in % of TST spent in each sleep stage was consistent with Trial-1, with no effect of dose. Mean changes from baseline (% of TST) for each sleep stage appeared to be independent from increasing TST. Data for 25 mg were consistent between trials.

**Conclusions:** Daridorexant at any dose, and each more than placebo, increased TST in a dose-dependent manner without affecting the proportion of all sleep stages in patients with insomnia disorder.

**Acknowledgements:** Funded by Idorsia Pharmaceuticals Ltd. This abstract has been previously presented at the virtual SLEEP meeting, the 35<sup>th</sup> annual meeting of the Associated Professional Sleep Societies held June 10–13, 2021.

### EFFECTS OF DIGITAL COGNITIVE BEHAVIORAL THERAPY FOR INSOMNIA IN A DIVERSE SAMPLE: RESULTS FROM A RANDOMIZED CONTROLLED TRIAL

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**Introduction:** Cognitive behavioral therapy for insomnia (CBT-I) is the first-line treatment for patients diagnosed with insomnia. However, access to treatment is scarce. Recently, digital health applications (DiGAs) have been integrated into the German health care system to help close the indication-application gap, and are available through prescription since. One of these applications delivers digital CBT-I and has previously shown promising effects in a homogenous study sample. With its current use in

mind, we designed the first pragmatic randomized controlled trial to test the effectiveness of digital CBT-I in a diverse insomnia population.

**Materials and Methods:** Participants aged  $\geq 18$  who met diagnostic criteria for insomnia disorder were randomized (1:1) to an 8-weeks digital CBT-I (somnio, mementor DE GmbH) or they were set on a waitlist control (access to digital CBT-I 8 weeks post-randomization). In contrast to typical effectiveness trials, individuals with comorbid mental disorders, physical illness, shift workers, and patients in parallel treatment were included; only patients with regular excessive alcohol/drug consumption, acute suicidality, acute psychotic states, and epilepsy were excluded. The primary outcome was insomnia severity (as assessed with the Insomnia Severity Index ISI) at 8-weeks post-randomization. A one-way ANCOVA with baseline ISI as a covariate was fitted to determine group differences. This trial was registered in the German Clinical Trials Register (DRKS00024477).

**Results:** Of the N = 238 patients (n = 161 female, 67.6%), age range 19 to 81 years (M = 43.73, SD = 13.90) who were randomized to digital CBT-I (n = 118), to waitlist-control (n = 120). Two hundred and seventeen patients (91%) completed the post-treatment assessment. In line with the intention-to-treat principle, missing values were replaced according to the LOCF method (last observed carried forwards). At 8-weeks post-randomization, between-group comparisons revealed significant differences on the ISI,  $F(1,235) = 141.97, p < .001$ , in favor of the digital CBT-I group (9.58 $\pm$ 5.81 vs. 16.03 $\pm$ 4.02). While nearly two-thirds of the patients in the digital CBT-I group showed clinically significant improvements of at least two standard deviations on the ISI (RCI < -1.96, 64%), while only 6% of the patients in the control group showed such decrease,  $\chi^2(1) = 87.79, p < .001$ .

**Conclusions:** The results of our study show that digital CBT-I reduces insomnia symptoms in a diverse study sample in Germany. Our results underscore the potential of digital health applications and their suitability within regular care.

**Acknowledgments:** We thank Bea Bringenberg, Maischa von Reth, Maja Völker, and Lianne Elisa Zeevaert for their tremendous support in collecting the reported data.

### EFFICACY OF DIGITAL CBT-I SMARTPHONE APPLICATIONS: A SYSTEMATIC REVIEW OF THE CURRENT LITERATURE.

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**Introduction:** In the absence of effective and safe habitual and pharmacological options, cognitive behavioral therapy for treatment of insomnia (CBT-I) remains the only first line evidence based option. Multiple studies have compared CBT-I with strong hypnotic agents such as benzodiazepine and have found CBT-I to be just as effective. More importantly, the effects of CBT-I are more durable than medications with almost no adverse effects. Hence CBT-I is recommended as a first line treatment option for insomnia. Despite the fact that CBT-I is an effective treatment option for insomnia, access to this intervention remains very limited. Digital CBT-I hopes to address the problem of scale in delivering one-on-one cognitive behavioral therapy. There are now multiple mobile applications available both on Apple Store and Google Play which claim to deliver evidence based cognitive behavioral therapy for insomnia. These applications largely come at a cost and patients have to pay to access their services. The goal of this study is to review the validation studies and examine the effectiveness of smartphone applications in delivering CBT-I.

**Materials and Methods:** Our methods were informed by similar review studies which focused on digital applications. The initial search of applications was performed within Google Play and Apple iTunes platforms which house more than 90% of mobile applications. Next, we developed an inclusion and exclusion criteria which mainly filtered out applications which are not focused on cognitive behavioral therapy for insomnia. We considered studies published in peer-reviewed journals. We used the PICOS approach to assess study eligibility. The methodological quality was assessed using a combination of metrics from the original Jadad Scale and Cochrane assessment of bias tool.

**Results:** Of the 9 validation studies that we initially found, 6 met our

inclusion criteria. 3 were excluded as they did not solely use CBT-I techniques in their applications. All 6 applications reported significant improvement in important sleep quality metrics such as sleep onset latency and total sleep time. 4 studies also reported on a subjective improvement in quality of sleep. 2 studies looked at populations with comorbidities including cannabis use disorder and epilepsy. Both studied again found improvement in sleep quality in those specific populations. There were concerning patterns of bias found amongst the reviewed studies. 3/6 investigators had direct relationships with companies which designed and marketed the applications.

**Conclusions:** DCBT-I offers an exciting opportunity for developers to tackle the issue of accessibility to CBT-I. There are only a limited number of studies which have examined the effectiveness of the applications on the market. There remains serious concerns about the risk of bias and the quality of validation studies which claim to confirm the effectiveness of these applications.

#### EFFICACY OF LONG-TERM TREATMENT WITH DARIDOREXANT IN PATIENTS WITH INSOMNIA DISORDER ON SLEEP AND DAYTIME FUNCTIONING: A POST-HOC ANALYSIS

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**Introduction:** Daridorexant, a dual orexin receptor antagonist recently approved for use in the US, improved night and daytime symptoms of insomnia disorder in two parallel, phase 3, randomized, 12-week studies and maintained these improvements in a subsequent 40-week extension study [1]. The largest effect in the 12-week studies was seen with daridorexant 50 mg. A post-hoc analysis of the extension study was conducted to further explore the long-term efficacy of daridorexant 50 mg, compared with placebo and daridorexant 25 mg.

**Materials and Methods:** This post-hoc analysis includes 392 patients ( $\geq 18$  years) with insomnia disorder who were randomised (1:1:1) to daridorexant 50 mg, 25 mg or placebo and completed 12-weeks of double-blind treatment (NCT03545191) and subsequently entered the extension study (NCT03679884). In the double-blind extension study, patients originally randomized to daridorexant (50 mg [n=137], 25 mg [n=132]) remained on their respective treatments while patients originally randomized to placebo were re-randomized 1:1 to daridorexant 25 mg (n=66) or placebo (n=57). The treatment period of the extension study was 40-weeks (totaling 12 months of cumulative treatment overall). Exploratory efficacy endpoints were change from baseline over time in subjective total sleep time (sTST) and daytime functioning. The latter was assessed using the Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ). The IDSIQ comprises total score, and three domains of sleepiness, alert/cognition and mood domain scores, with lower scores indicating improved daytime functioning.

**Results:** For patients who participated in the 12-week trial and continued into the extension study, changes in sTST from baseline (baseline of the confirmatory 12-week study) were increased and were consistently larger with 50 mg versus 25 mg and placebo throughout the extension study. Mean ( $\pm$ SD) increase in sTST from baseline to end of the extension study (Month 12) was 75.6 minutes ( $\pm 69.90$ ) in the daridorexant 50 mg group compared with 65.5 minutes ( $\pm 66.61$ ) for daridorexant 25 mg, and 52.8 minutes ( $\pm 75.90$ ) for placebo.

For IDSIQ total score and domain scores, reductions were also consistently larger with 50 mg throughout the 12-month treatment period, with no clear distinction between daridorexant 25 mg and placebo. For IDSIQ total score (range 0–140), mean ( $\pm$ SD) reduction from baseline to Month 12 were  $-27.3 (\pm 25.48)$  for daridorexant 50 mg compared with  $-17.3 (25.79)$  for daridorexant 25 mg and  $-22.1 (25.88)$  for placebo. IDSIQ sleepiness, alert/cognition, and mood domain scores also improved over time and favored daridorexant 50 mg.

**Conclusions:** This post-hoc analysis provides additional evidence for the long-term maintenance over 12 months of the favourable treatment effect of daridorexant 50 mg on both nighttime symptoms and daytime functioning, based on an increase in sTST and improvement in IDSIQ scores, in patients with insomnia disorder.

**Acknowledgements:** Idorsia Pharmaceuticals.

**Reference:** 1. Kunz D, et al. Long-term safety and efficacy of daridorexant in patients with insomnia disorder. Oral presentation, WORLD SLEEP 2022.

#### EVALUATING THE RISKS OF WITHDRAWAL SYMPTOMS AND REBOUND INSOMNIA UPON DISCONTINUATION OF DARIDOREXANT IN PATIENTS WITH INSOMNIA DISORDER

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**Introduction:** Abrupt discontinuation of sleep medications in patients with insomnia often causes withdrawal symptoms and rebound insomnia. In a Phase 3 program evaluating efficacy and safety of daridorexant on sleep and daytime functioning in patients with insomnia during three months of treatment, the risks of withdrawal symptoms and rebound insomnia were evaluated at treatment cessation.

**Materials and Methods:** In two randomized, double-blind, 3-month trials, adult (18–64 years) and elderly ( $\geq 65$  years) patients with insomnia were assigned (1:1:1) to receive oral daridorexant 25 mg, 50 mg or placebo (Trial-1, NCT03545191) or 10 mg, 25 mg or placebo (Trial-2, NCT03575104) every evening. Each trial included a 7-day, single-blind, placebo run-out period following double-blind treatment to evaluate withdrawal symptoms and rebound insomnia. Withdrawal effects were assessed by the change in Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ) total score, from last assessment on double-blind treatment to end of placebo run-out, and occurrence of relevant adverse events (AEs). Rebound insomnia was assessed objectively by change in wake-after-sleep-onset (WASO) and latency-to-persistent sleep (LPS) from baseline to first night of placebo run-out, and by subjective total-sleep-time (sTST) from baseline to end of run-out (mean of 7-days). Analyses included all patients who received  $\geq 1$  dose of placebo run-out treatment (Trial-1: N=852; Trial-2: N=851).

**Results:** No increase in mean BWSQ score from last assessment on double-blind treatment to end of placebo run-out was reported (Trial-1: 25 mg,  $-0.6 \pm 2.3$ ; 50 mg,  $-0.6 \pm 2.3$ ; placebo,  $-0.7 \pm 2.3$ ; Trial-2: 10 mg,  $-0.5 \pm 2.6$ ; 25 mg,  $-0.4 \pm 1.9$ ; placebo,  $-0.4 \pm 1.4$ ). No patients had a BWSQ score  $> 20$  at end of run-out. No AEs suggestive of withdrawal symptoms were reported. Mean WASO and LPS values (min) decreased from baseline to placebo run-out (WASO Trial-1: 25 mg,  $-8.6 \pm 55.5$ ; 50 mg,  $-2.5 \pm 52.4$ ; placebo,  $-20.4 \pm 45.8$ ; Trial-2: 10 mg,  $-11.6 \pm 58.3$ ; 25 mg,  $-5.1 \pm 57.9$ ; placebo,  $-26.2 \pm 53.5$ ; LPS Trial-1: 25 mg,  $-17.2 \pm 56.7$ ; 50 mg,  $-15.0 \pm 55.8$ ; placebo,  $-27.8 \pm 47.2$ ; Trial-2: 10 mg,  $-17.3 \pm 67.2$ ; 25 mg,  $-10.3 \pm 67.3$ ; placebo,  $-18.3 \pm 63.8$ ) while sTST values (min) increased (Trial-1: 25 mg,  $43.3 \pm 53.8$ ; 50 mg,  $42.9 \pm 59.6$ ; placebo,  $42.3 \pm 52.7$ ; Trial-2: 10 mg,  $43.3 \pm 52.9$ ; 25 mg,  $46.8 \pm 55.4$ ; placebo,  $42.3 \pm 53.8$ ) indicating absence of rebound effects.

**Conclusions:** Treatment with daridorexant for up to three months was not associated with any evidence of drug withdrawal or rebound insomnia upon abrupt discontinuation, indicating no safety concerns for patients should treatment be stopped.

**Acknowledgements:** Funded by Idorsia Pharmaceuticals Ltd. This abstract has been previously presented at the virtual SLEEP meeting, the 35<sup>th</sup> annual meeting of the Associated Professional Sleep Societies held June 10–13, 2021.

#### EVALUATION OF DOSE TRANSITION FROM ZOLPIDEM TO LEMBorexant IN FEMALES AND MALES WITH INSOMNIA: POST HOC ANALYSES FROM AN OPEN-LABEL STUDY

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**Introduction:** Pre-specified dosing paradigms for transitioning patients with insomnia from zolpidem (ZOL) immediate- (IR) or extended-release (ER) to lemborexant (LEM; 5mg[LEM5] or 10mg[LEM10]) were evaluated in the open-label study E2006-A001-312 (Study 312; NCT04009577). Post hoc analyses of the subsets of female (F) and male (M) subjects were conducted to evaluate the success of transitioning from ZOL to LEM by sex.

**Materials and Methods:** Study 312 enrolled adults ( $\geq 18$ y) with insomnia who used ZOL-IR/-ER intermittently (3–4 nights/week) or frequently ( $\geq 5$  nights/week). Subjects continued ZOL during a 3-week Pretreatment Phase, followed by 2-week Treatment (Titration) Phase, 12-week Extension (Maintenance) Phase, and 4-week Follow-up. Titration cohort assignments were based on subjects' initial ZOL usage frequency. Cohort-1 began Titration with LEM5 and comprised intermittent ZOL users and subjects who used ZOL intermittently and frequently for 1 week each during the last 2 weeks of screening. Cohort-2 included frequent ZOL users randomized 1:1 to LEM5 (Cohort-2A) or LEM10 (Cohort-2B). Any subject transitioning successfully to LEM during Titration could choose to enter Extension. Subjects could change LEM dose during Titration (only once) and Extension. The primary endpoint was the proportion of subjects at the end of Titration who transitioned successfully to LEM. Treatment-emergent adverse events (TEAEs) were assessed based on LEM dose at the time of the TEAE.

**Results:** Of 53 (35F/18M) total subjects (Cohort-1, n=10 [7F/3M]; Cohort-2, n=43 [28F/15M]), 43 (81.1%; [29F/14M]) transitioned successfully to LEM following Titration. All 43 (100.0%) elected to enter Extension, during which 41/43 (29F/12M) received treatment. Of these, 38/41 (92.7%; 27F/11M) completed Extension. Overall, 29/35 (82.9%) F and 14/18 (77.8%) M subjects successfully transitioned to LEM. In Cohort-1, 7F/3M began Titration with LEM5 and 7F/2M transitioned to LEM (5F/0M ended Titration on LEM5 and 2F/2M on LEM10). In Cohort-2A, 14F/7M began Titration with LEM5; 12F/5M transitioned to LEM (6F/2M ended on LEM5; 6F/3M on LEM10). In Cohort-2B, 14F/8M began Titration with LEM10; 10F/7M transitioned to LEM (3F/0M ended Titration on LEM5 and 7F/7M on LEM10). Median time to first dose change based on modal dose (most frequent dose during Titration/Extension combined) groups was 14.5d (14.5d, F; 18.0d, M) for the LEM5 modal dose group and 36.0d (17.0d, F; not calculable, M) for the LEM10 group. At completion of Extension, 12/27F (44.4%) were receiving LEM5; 15/27F (55.5%) were receiving LEM10; in M proportions were 2/11M (18.2%) and 9/11M (81.8%) receiving LEM5 and LEM10, respectively. TEAEs were mostly mild/moderate in severity. Across Titration and Extension, TEAEs occurred more commonly with LEM10 than LEM5. The most common TEAEs were somnolence (n=4 [3F/1M]) and abnormal dreams (n=4 [3F/1M]).

**Conclusion:** Most subjects were able to successfully transition to LEM, regardless of ZOL usage history. These results provide evidence that both F and M patients with insomnia can directly transition from ZOL to LEM. The proportions of F and M subjects who successfully transitioned to LEM were comparable across treatment cohorts. LEM was generally well tolerated with a safety profile consistent with that observed in Phase 3 clinical development.

**Acknowledgements:** Supported by Eisai Inc.

## EVALUATION OF LONG-TERM PERCEPTION OF MEDICATION EFFECTIVENESS: RESULTS FROM SUBJECTS RECEIVING LEMBorexant FOR UP TO 12 MONTHS

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**Introduction:** The Patient Global Impression—Insomnia version (PGI-I) is a self-report instrument used to evaluate patients' perceptions of the effects of their insomnia medication on their sleep relative to their sleep before the start of treatment. The PGI-I questionnaire includes 3 items related to the effects of medication (helped/worsened sleep; decreased/increased time to fall asleep; and increased/decreased total sleep; the choices for response include: 1=positive, 2=neutral, 3=negative) and 1 item related to perceived appropriateness of study medication strength (the choices for response include: 1=too strong, 2=just right, 3=too weak). In Study

E2006-G000-303 (Study 303; SUNRISE-2; NCT02952820), the percentages of subjects who reported a positive impact of lemborexant (LEM) was significantly greater compared with placebo (PBO) at 1, 3, and 6mo for the PGI-I items related to the effects of medication. LEM is a dual orexin receptor antagonist approved in multiple countries, including the United States, Japan, Canada and Australia for the treatment of insomnia in adults. We present here the PGI-I results at 9 and 12mo for subjects that received continuous treatment with LEM for up to 12mo.

**Materials and Methods:** Study 303 was a 12mo, randomized, double-blind, PBO-controlled (during the first 6mo [Period 1]), phase 3 study. Subjects were age  $\geq 18$  years with a diagnosis of insomnia disorder. During Period 1, subjects received PBO (n=318) or LEM (5mg, [LEM5], n=316; 10mg, [LEM10], n=315). During Period 2 (second 6mo), LEM subjects continued their assigned dose while PBO subjects were rerandomized to LEM5 or LEM10 (data for PBO subjects rerandomized to LEM in Period 2 reported separately). All subjects (LEM and PBO) were administered the PGI-I at 1, 3 and 6mo (previously presented). PGI-I was also administered at 9 and 12mo, and only subjects who had received LEM during Period 1 are summarized here.

**Results:** At 9 and 12mo, the majority of LEM5 (9mo: n=241; 12mo: n=205) and LEM10 (9mo, n=211; 12mo, n=192) subjects reported that their study medication “helped” sleep at night (9mo: LEM5=73.4%; LEM10=76.3%; 12mo: LEM5=74.6%; LEM10=77.6%), reduced time to fall asleep (9mo: LEM5=79.3%, LEM10=78.2%; 12mo: LEM5=76.6%, LEM10=80.2%), and increased total sleep time (9mo: LEM5=62.2%, LEM10=73.0%; 12mo: LEM5=62.4%; LEM10=65.1%). Also, at both 9 and 12mo the majority of subjects in the LEM5 and LEM10 groups responded that their perception of the appropriateness of the strength of their treatment was “just right” (9mo: LEM5=60.6%, LEM10=62.1%; 12mo: LEM5=63.4%; LEM10=60.4%), which were higher percentages than reported “just right” at 1, 3 and 6mo (1mo: LEM5=43.7%, LEM10=43.4%; 3mo: LEM5=49.8%, LEM10=51.5%; 6mo: LEM5=55.6%; LEM10=53.4%). LEM was generally well tolerated. The majority of events were mild or moderate in severity.

**Conclusion:** The majority of subjects receiving LEM5 or LEM10 reported a positive medication effect at both 9 and 12mo. These results are similar to positive effects for LEM achieved at earlier time points during the first 6mo of treatment in Study 303 and suggest that for the majority of subjects, a positive perception of their insomnia medication is sustained for up to 12mo.

**Acknowledgements:** Supported by Eisai Inc.

## EXPERIENCE WITH THE USE OF A DIGITAL SLEEP DIARY IN PERSONS WITH SYMPTOMS OF INSOMNIA AND PATIENTS WITH CHRONIC INSOMNIA AND SLEEP APNEA (COMISA)

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**Introduction:** Chronic insomnia is the most common sleep disorder in the general population. The most effective treatment is cognitive behavioural treatment for insomnia (CBTi). A sleep diary where the patient reports their sleep observations is a core element of CBTi. Traditionally, sleep diaries have been completed on paper, and standardized feedback has been based on manual calculations. The digital sleep diary in the CAPABLE platform is based on the “Consensus Sleep Diary” with standardized feedback based on the formulas proposed by Reed and co-workers. The “Consensus Sleep Diary” is a standardized sleep diary for people with insomnia.

The aim is to elicit user experiences with the digital sleep diary among community-dwelling persons with symptoms of insomnia and patients with COMISA.

**Materials and Methods:** The study has a mixed-method design. The material consists of semi-structured, individual interviews in 11 community-dwelling persons and 9 patients with COMISA participating in the Akershus Sleep Apnea epidemiological- and clinical cohort respectively. The collected data was transcribed and thematically analysed. Quantitative data is based on reports from the digital sleep diary, specifically number of

entries and average sleep efficiency for each participant. The quantitative material will be analysed with descriptive statistics.

**Results:** The digital sleep diary provided the participants with insomnia a better overview of their sleep and increased awareness of the factors that could affect their sleep quality. The data distinguish between clinical utility of a digital sleep diary, and the significance of opportunities with the digital sleep diary for overview and visualization of observations over time. Further, the results indicate that these digital features add value to the self-reporting for the participants and support clinical practice. However, the participants sensemaking of their observations recorded in the digital sleep diary seems to be important for their experienced benefit from the diary.

**Conclusions:** The digital sleep diary in the CAPABLE platform was perceived as useful in general among people with insomnia symptoms and patients with COMISA. Active use of self-reported data can contribute to improve adherence of CBTi, greater understanding of the participants sleep disorders and facilitate new ways to collaborate between patients and health personnel. The digital sleep diary has the potential to deliver CBTi and expand people with insomnia capabilities to efficiently handling their sleep disorder.

**Acknowledgements:** I would like to express my gratitude to Harald Hrubos-Strøm and Anne Moen for their contribution to the analysis and the abstract, to Way Bong for the collaboration on the analysis, and to Norsk E-helse who is developing CAPABLE.

### FATAL FAMILIAL INSOMNIA: A CASE REPORT

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**Introduction:** Fatal familial insomnia (FFI) is a rare fatal autosomal dominant neurodegenerative prion disease caused by a mutation of the prion protein (PRNP) gene, which is characterized by a severe sleep disorder, dysautonomia, motor signs and abnormal behaviour, and structural damages in the thalamus and cortex are mostly responsible for clinical manifestations of FFI.

**Objective:** Describe the clinical and polysomnographic findings of a patient from Andalusia with a family background of FFI.

**Case report:** We reported a 69-year-old woman with a family background of FFI; her mother had a similar presentation and died at age 73 and was also suspected to be affected. The mutation was confirmed in 2 of her brothers, one nephew and one son. She had chronic clinical insomnia from 1 year ago, treated with Lorazepam, Zolpidem and Agomelatine, but she did not present other sleep disorders (RLS, parasomnias, movement disorders). Neurological and medical examinations were normal. She was followed up for anxiety by the psychiatrist.

The polysomnography showed a reduction in total sleep efficiency (76%) and total sleep time (381 minutes), with normal proportion in sleep stage (N1: 2%, N2: 49%, N3: 20%, REM 29%), longer sleep latency (85 minutes) and REM sleep latency (102 minutes). Arousal index was 55/h, periodic leg movement index (PLM) was 67.2/h, and apnea/hypopnea index was 3.5/h. We observed no dysfunctional transition between sleep stages. The electroencephalogram (EEG) showed an occipital alpha rhythm at 10Hz with preserved reactivity. Typical sleep elements spindles and K complexes were adequately represented in morphology and location, and no periodic sharp-wave complexes or other EEG abnormalities were noted. The diagnosis was confirmed with genetic testing, which showed (P.M129V) NM\_000311.4:c.532G>A;p.(D178N), in the position 129 has the variant methionine and valine.

**Discussion:** FFI is caused by degeneration of medial thalamo-limbic structures. This disease is a rare medical entity, and there are few published cases. In the presented clinical case, insomnia is the first typical clinical manifestation of FFI, but periodic legs movement syndrome is not usual and could indicate a dopaminergic dysfunction. Combined PSG findings and genetic testing are crucial to making the diagnosis.

### FATIGUE, ADHERENCE TO COGNITIVE-BEHAVIOURAL THERAPY FOR INSOMNIA, AND TREATMENT OUTCOME: DOES DEFINITION MATTER?

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**Introduction:** Adherence to cognitive-behavioural therapy for insomnia (CBT-I) has been inconsistently defined in the literature and may differentially predict insomnia improvement following treatment (Agnew et al., 2021). Similarly, insomnia treatment outcome can be defined objectively (using sleep diaries) and subjectively (using self-report inventories). Fatigue has been found to influence adherence to CBT-I in patients with medical and psychiatric comorbidities (Dyrberg et al., 2021; Koffel et al., 2020; Matthews et al., 2012), and predicts therapist-rated treatment agreement and sleep diary-derived adherence in people with insomnia (Dong et al., 2017). Additionally, change in fatigue is a significant predictor of post-treatment subjective insomnia severity (Marway et al., 2017). In this study, we investigated if fatigue moderates the effect of adherence on insomnia outcomes, using various operationalizations, in a sample of adults with Insomnia Disorder receiving CBT-I. We hypothesized that fatigue moderates the effect of adherence on subjective but not objective insomnia outcome.

**Materials and Methods:** Participants ( $N=156$ ; 70% female;  $M=47.40$  years old,  $SD=14.77$ ) completed the Fatigue Severity Scale (FSS) and the Insomnia Severity Index (ISI) at baseline (BL) and post-treatment (PT). They received four sessions of CBT-I and completed daily sleep diaries for the duration of treatment. We defined adherence as follows: 1) difference mean time in bed (TIB) and prescribed TIB during treatment; 2) change in risetime variability from pre- to post-treatment; 3) and average therapist-rated adherence (0-100%) over the four sessions. Objective insomnia outcome was defined as change in total wake time (TWT) from BL to PT. Subjective insomnia outcome was defined as change in ISI score from BL to PT. Regression models included adherence, baseline FSS score, and their interaction. All predictors were mean-centered.

**Results:** All three definitions of adherence (TIB adherence, risetime adherence, or therapist-rated) did not significantly predict ISI change ( $ps>.05$ ). FSS score did not moderate the relationships between adherence and ISI change ( $ps>.05$ ). Risetime adherence ( $p=.928$ ) and therapist-rated adherence ( $p=.666$ ) similarly did not predict TWT change. TIB adherence significantly predicted TWT change ( $B=-.520$ ,  $p<.001$ ) and interacted with fatigue ( $B=.023$ ,  $p<.001$ ),  $R^2=.14$ ,  $F(3,141)=7.41$ ,  $p<.001$ . Increases in TIB adherence were associated with greater changes in TWT in those with high fatigue (+1 SD;  $B=.793$ ,  $p<.001$ ) compared to low fatigue (-1 SD;  $B=-.236$ ,  $p<.001$ ).

**Conclusions:** Contrary to hypotheses, fatigue, adherence, and their interactions did not predict subjective insomnia outcome. Considering previous research that therapist-rated and behavioural adherence predict insomnia symptom reduction (Dong et al., 2017), the lack of significant predictors of ISI change is surprising and raises the question of what is reflected in ISI scores. Only TIB, but not risetime or therapist-rated adherence, predicted objective insomnia outcome, and this was moderated by fatigue. Adherence to TIB restrictions—a critical component of CBT-I—was associated with significantly larger changes in TWT at post-treatment among those with high versus low fatigue at baseline. Positive effects of TIB restriction, including increasing sleep drive and promotion of behavioural activation during out-of-bed hours, may be of particular import for highly fatigued individuals with Insomnia Disorder.

**Acknowledgements:** Canadian Institutes of Health Research (#130395 and #143551)

### FINDINGS FROM AN OPEN-LABEL STUDY OF NEXT-DOSE TRANSITION FROM ZOLPIDEM TO LEMBOREXANT IN OLDER ADULTS WITH INSOMNIA

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**Introduction:** Some commonly prescribed insomnia medications, including the GABA-ergic agonist zolpidem (ZOL) are associated with

safety considerations in older adults. Lemborexant (LEM) is a dual orexin receptor antagonist approved in multiple countries, including the United States, Japan, Canada and Australia for the treatment of adults with insomnia. Study E2006-A001-312 (Study 312; NCT04009577) assessed prespecified dosing methods for directly transitioning from ZOL (immediate [IR] or extended release [ER]) to LEM (5mg [LEM5] or 10mg [LEM10]). Here, we report the findings from post hoc analyses that examined outcomes among subjects  $\geq 60$  years of age in Study 312.

**Materials and Methods:** Study 312 included a 3-week Screening Period during which subjects continued on ZOL, a 2-week Titration Period (TITR), a 12-week Extension Period (EXT), and a 4-week Follow-up Period. Subjects were adults (age  $\geq 18$  years) with insomnia and were intermittent (INT; 3–4 nights/week) or frequent (FREQ;  $\geq 5$  nights/week) users of ZOL-IR or ZOL-ER. The most common reason for wanting to transition was sleep maintenance difficulties. Cohort-1 comprised subjects with two weeks of INT ZOL or 1 week each of INT and FREQ ZOL use during the last 2 weeks of the Screening period. Subjects in Cohort-1 initiated TITR with LEM5. Cohort-2 comprised subjects who were FREQ ZOL users during the Screening Period. Subjects in Cohort-2 were randomized 1:1 to LEM5 (Cohort-2A) or LEM10 (Cohort-2B). Subjects who successfully transitioned to LEM had the option to enter EXT. Subjects could change LEM dose once during TITR and multiple times during EXT. The proportion of subjects who transitioned successfully to LEM at the completion of TITR was the primary endpoint. Treatment-emergent adverse events (TEAEs) were assessed.

**Results:** Of 53 subjects (Full Analysis Set), 30 (56.6%) were  $\geq 60$  years of age (Cohort-1,  $n=6$ ; Cohort-2,  $n=24$ ). In this subgroup of older adults, 23/30 (76.7%) subjects transitioned successfully to LEM after TITR. In Cohort-1: 5/6 (83.3%) subjects transitioned successfully with 3 subjects ending TITR on LEM5 and 2 on LEM10. In Cohort-2A: 7/8 (87.5%) subjects transitioned successfully with 3 subjects ending TITR on LEM5 and 4 on LEM10. In Cohort-2B: 11/16 (68.8%) subjects transitioned successfully with 1 subject ending TITR on LEM5 and 10 on LEM10. During TITR, 7 subjects discontinued; 6 discontinued due to TEAEs. All 23 subjects who transitioned successfully to LEM chose to continue in EXT, and 22/30 (73.3%) subjects completed the study. Across TITR and EXT, TEAEs occurred more frequently with LEM10 than LEM5, and all were mild or moderate in severity. Abnormal dreams ( $n=4$ ) and somnolence ( $n=2$ ) were the most commonly reported TEAEs.

**Conclusion:** Most (76.7%) of the older subjects from Study 312 successfully transitioned directly from INT or FREQ ZOL-IR or ZOL-ER use to LEM. LEM was generally well tolerated with a safety profile consistent with previously reported Phase 3 clinical studies. These results were generally consistent with those observed in the Full Analysis Set and suggest that older patients with insomnia, who have previously used ZOL could be offered an alternative treatment for insomnia.

**Acknowledgements:** Supported by Eisai Inc.

#### GROUP COGNITIVE BEHAVIORAL THERAPY FOR INSOMNIA: AN EXCELLENT ALTERNATIVE TREATMENT IN PUBLIC HEALTHCARE SYSTEM.

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**Introduction:** Cognitive behavioral therapy for insomnia (CBT-I) is highly recommended as first line treatment for chronic insomnia due to produce sustained benefits without the risk for tolerance or adverse effects associated with pharmacologic treatment.

Considering the high prevalence of insomnia and the overcrowding for medical consultation, Group CBT-I is considered as an alternative treatment in our public healthcare system.

To determine the efficacy of Group CBT-I in adults with chronic insomnia, a comparison of the Insomnia Severity Index (ISI) was made before and after the end of the therapy.

**Materials and Methods:** Single-size, observational study from March 2018 to December 2021 were performed. 92 participants with chronic insomnia started a 3 month therapy for insomnia.

Sleep diaries were used to determine sleep onset latency, total sleep time and sleep efficiency, and treatment effects were assessed by comparison ISI before and after therapy.

Descriptive statistical analysis was performed using frequency distributions for qualitative variables and mean and standard deviation for quantitative variables. The comparison of means had used Student's t test for repeated measures and the relationship of qualitative variables was analyzed with Chi-square.

**Results:** 72 patients meet the inclusion criteria: 45.8 % were men with mean age of  $51.8 \pm 10.1$  years and a Body-mass index  $25.1 \pm 4.5$  Kg/m<sup>2</sup>.

Group CBT-I produced a statistically significant ( $p < 0.05$ ) reduction on ISI from  $17 \pm 3.7$  to  $14 \pm 4.1$ ; and an improvement in sleep efficiency (from  $64.6 \pm 25.2\%$  to  $81.2 \pm 11.7\%$ ) and in total sleep time ( $4.7 \pm 1.3$  to  $5.6 \pm 1.0$  hours),  $p < 0.05$ .

Furthermore, there was an increase in the % of patients with subjective sleep latency of less than 30 min, from 45.2 % at the beginning of therapy to 69.1 % at the end of therapy.

**Conclusions:** In our patient sample, this review demonstrated as in other published works, a clinically meaningful effect of Group CBT-I, which represents an excellent alternative in our public healthcare system. Future research is needed to investigate the long term effect of Group CBT-I.

**Acknowledgements:** We would hereby like to express our gratitude to the staff of the sleep unit and the psychiatry service of the Araba University Hospital.

#### GROUP COGNITIVE BEHAVIOURAL THERAPY FOR INSOMNIA ON-LINE IN THE TIME OF COVID-19

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**Introduction:** Cognitive behavioral therapy (CBT-I) is considered the first line of treatment for chronic insomnia. Group CBT-I has proven to be an effective therapeutic option in clinical practice. However, the COVID-19 pandemic made in-person meetings impossible, temporarily suspending group therapy. The multiple video call through Zoom® was the alternative to continue with this practice. But, is cognitive behavioral therapy for insomnia effective non-face-to-face? The aim was to assess the efficacy of online group CBT-I in our sleep unit.

**Materials and methods:** Prospective cohort study where patients who received online group CBT-I with Zoom® were included and compared with data collected from participants in face-to-face group therapy at Araba University Hospital from March 2018 to December 2021.

Anthropometric data, subjective total sleep time (TST), subjective sleep latency, subjective sleep efficiency (SE), as well as the insomnia severity index (ISI) were studied both at baseline and at the end of therapy.

Descriptive statistical analysis was performed using frequency distributions for qualitative variables and mean and standard deviation for quantitative variables. For the comparison of means had been used Student's t test for repeated measures and the relationship of qualitative variables was analyzed with Chi-square.

**Results:** Seventy-two patients were included, 44 on-line and 28 face-to-face. The mean age of the patients was 51.8 (SD=10.1) years, with a range of 20–71 years, 45.8% were men, and the mean body mass index was 25.1 (SD=4.5) Kg/m<sup>2</sup>. No statistically significant differences were found between the characteristics of the samples, with the mean age in the online group being 51.4 years (SD=10.1) and in the face-to-face group 52.4 years (SD=10.3). The percentage of men was 50 % and 39.2 % and BMI of 24.6 (SD=6.1) and 24.9 (SD=4.1) respectively.

A significant reduction ( $p < 0.001$ ) in ISI was observed after group CBT-I, showing no significant differences ( $p=0.68$ ) between on-line ( $18.3$  (SD=3.9) to  $14.5$  (SD=4.3) and face-to-face ( $17.5$  (SD=3.3) to  $13.3$  (SD=3.7)). In addition, there was an increase in subjective SE from 66.6% (SD=28.7) to 81.0% (SD=11.7) in the online group and from 59.4% (SD=12.4) to 81.5% (SD=12.2) in the face-to-face group ( $p < 0.001$ ) and increase in subjective TST from 4.9 hours (SD=1.4) to 5.7 hours (SD=1.0) in the online group and from 4.5 hours (SD=1.0) to 5.4 hours (SD=1.0) in the face-to-face group

( $p < 0.001$ ).

Furthermore, there was an increase in the % of patients with subjective sleep latency of less than 30 min, from 34.1% (online) and 14.3% (face-to-face) at the beginning of therapy to 65.9% and 32.1% respectively at the end of therapy.

**Conclusions:** In our experience, the results of group CBT-I have a clear positive impact on the clinical improvement of the patient, both face-to-face and on-line. The group CBT-I on line is the first choice in times of pandemic and a good alternative for patients with difficulties in attending on-site therapy.

**Acknowledgements:** We would hereby like to express our gratitude to the staff of the sleep unit and the psychiatry service of the Araba University Hospital.

## HEART RATE VARIABILITY IN NON-RAPID EYE MOVEMENT SLEEP STAGE 2 INDICATES INSOMNIA AND IS RELATED TO SUBJECTIVE DAYTIME PERFORMANCE

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**Introduction:** Insomnia disorder is characterized by subjectively perceived poor sleep and impaired daytime performance. However, objective findings of deficits in sleep continuity and cognitive functioning are often mild. The aim of this study was to examine whether objective markers of autonomous hyperarousal, specifically sleep stage related heart rate variability (HRV), would indicate insomnia more reliably than objective sleep continuity measures; and further, if such biomarkers would correlate with poor cognitive daytime performance.

**Materials and Methods:** Polysomnographic measures of 41 insomniacs (age:  $37.9 \pm 12.7$  years, 56.1% females) were compared to a control group of 27 normal sleepers. Frequency domain measures of HRV (very low (VLF), low (LF) and high frequency (HF) power) were extracted from artefact-free 5-min ECG segments of non-rapid eye movement sleep stage 2 (NREM-S2). Daytime performance was assessed by subjective ratings with insomnia severity index (ISI; items "interference" and "noticeability") and objective testing of alertness (TAP: Testbatterie zur Aufmerksamkeitsüberprüfung). **Results:** HRV measures in NREM-S2 distinguished between insomnia and normal sleep, with increased NREM-S2-VLF%-power ( $p = .012$ ,  $g = .702$ ) and decreased NREM-S2-HF%-power ( $p = .041$ ,  $g = -.564$ ) in insomnia. HRV findings in NREM-S2 sleep differed over the course of the night, with the largest contrast between insomnia and control group in NREM-S2-HF %-power in the first available NREM-S2-sleep segment ( $p = .019$ ) and NREM-S2-VLF%-power in the last available NREM-S2-sleep segment ( $p = .006$ ). Concerning objective sleep continuity parameters the two groups only differed by increased "sleep onset latency" (SOL) in insomniacs ( $p = .033$ ). Concerning sleep architecture, insomnia was characterized by trend by decreased REM-sleep percentage ( $p = .055$ ). However, there was no difference concerning NREM-S1- ( $p = .524$ ), NREM-S2- ( $p = .302$ ) or slow wave sleep percentage ( $p = .965$ ). Furthermore, insomniacs presented with both, higher perceived impairment of daytime performance (ISI item "noticeability",  $p < .001$ ,  $g = .80$ ) and increased objective reaction time ( $p = .084$ ,  $g = .435$ ). Moreover, the above-mentioned NREM-S2-HRV-findings in insomnia correlated with both, poor subjective daytime performance ("noticeability"; VLF%-power:  $r = .334$ ,  $p = .013$  and HF%-power:  $r = -.316$ ,  $p = .019$ , resp.) and prolonged objective reaction time (VLF%-power:  $r = .471$ ,  $p < .001$  and HF%-power:  $r = -.348$ ,  $p = .008$ , resp.).

**Conclusions:** HRV in NREM-S2 sleep discriminates insomnia patients from healthy controls with moderate effect sizes, especially NREM-S2-HF %-power in the first and NREM-S2-VLF%-power in the last third of the night. The pattern of the results in NREM-S2 sleep suggests lower vagal activity in insomnia, which relates to the subjective complaints of

hyperarousal and non-restoring sleep. We conclude that HRV analysis in NREM-S2 delivers more sensitive markers for insomnia than common sleep EEG variables and confirms previous evidence that insomnia is a disorder of hyperarousal. Moreover HRV-markers relate more closely to the subjective and objective complaints of non-restoring sleep and poor daytime functioning than sleep continuity measures.

**Acknowledgements:** No conflicts of interest.

## IMPACT OF LEMBOREXANT VERSUS PLACEBO AND ZOLPIDEM ON REM SLEEP DURATION BY QUARTER-OF-THE-NIGHT INTERVALS IN OLDER ADULTS WITH INSOMNIA DISORDER

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**Introduction:** Lemborexant (LEM) is a dual orexin receptor antagonist approved in multiple countries, including the United States, Japan, Canada and Australia for the treatment of adults with insomnia. The effects of LEM on sleep architecture in adults  $\geq 55$  years with insomnia disorder were assessed in Study E2006-G000-304 (Study 304; SUNRISE-1; NCT02783729). These post hoc analyses examined the acute effect of LEM on REM pressure, as assessed by changes from baseline in REM latency and in REM sleep duration in 2-hour quarter-of-the-night (QoN) intervals.

**Materials and Methods:** Study 304 was a 1 month, randomized, double-blind, placebo (PBO)- and active-controlled (zolpidem tartrate extended-release 6.25mg [ZOL]) study of LEM (5mg, LEM5; 10mg, LEM10). Subjects received PBO ( $n=208$ ), ZOL ( $n=263$ ), LEM5 ( $n=266$ ), or LEM10 ( $n=269$ ). Paired polysomnographic assessments were conducted at baseline, the first 2 (N1/2), and the last 2 (N29/30) nights of treatment; mean values from the paired assessments are reported.

**Results:** Baseline REM latency (minutes) was similar across treatments (98.4-101.4). On N1/2, significant mean (SD) decreases from baseline in REM latency were observed for LEM5 ( $-42.6$  [53.9]) and LEM10 ( $-49.6$  [52.9]) vs PBO ( $-6.9$  [54.5]) and vs ZOL (0.2 [54.2]) (all  $P < 0.0001$ ). On N29/30, REM latency was also significantly decreased from baseline with LEM5 ( $-30.7$  [55.7]) and LEM10 ( $-37.7$  [56.2]) vs PBO ( $-7.7$  [62.3]) and vs ZOL ( $-4.0$  [56.4]) (all  $P < 0.0001$ ). No difference was observed for ZOL vs PBO at either N1/2 or N29/30.

Within each QoN, baseline REM sleep duration (minutes) was similar across treatments. On N1/2, mean REM (minutes) across quarters ranged from 16.5-23.8 for LEM5, 19.7-26.1 for LEM10, 10.3-21.6 for PBO, and 8.5-22.8 for ZOL. On N29/30, mean REM values were 14.4-22.4 for LEM5, 16.9-24.1 for LEM10, 9.2-21.5 for PBO, and 8.3-22.3 for ZOL.

In each QoN during N1/2, REM sleep duration (minutes) significantly increased from baseline with LEM10 vs PBO (all  $P < 0.0001$ ) and vs ZOL (all  $P < 0.001$ ). With LEM5 during N1/2, REM sleep significantly increased from baseline vs PBO during Q1, Q3, and Q4 (all  $P < 0.05$ ) and vs ZOL in Q1 and Q2 (both  $P < 0.01$ ). With ZOL, REM was significantly decreased vs PBO during Q1 ( $P < 0.05$ ) and significantly increased vs PBO during Q3 ( $P < 0.05$ ).

On N29/30, REM sleep (minutes) significantly increased from baseline with LEM10 vs PBO in each QoN (all  $P < 0.05$ ) and vs ZOL in Q1, Q3, and Q4 (all  $P < 0.05$ ). With LEM5, REM sleep significantly increased from baseline vs PBO and vs ZOL in Q1 (both  $P < 0.0001$ ). No significant differences were observed for ZOL vs PBO in any QoN on N29/30. In each QoN, the increases in REM sleep were significantly greater on N1/2 than N29/30 with LEM5 (all  $P < 0.05$ ) and LEM10 (all  $P < 0.0001$ ).

**Conclusion:** LEM, but not ZOL, acutely increases REM pressure as evidenced by REM latency and REM duration per QoN. In each QoN, increases in REM sleep were greater with LEM5 and LEM10 than with ZOL or PBO. Decreases in REM latency and increases in REM sleep per QoN with LEM were greater during N1/2 than N29/30.

**Acknowledgements:** Supported by Eisai Inc.

## IN-DEPTH CHARACTERIZATION OF SLEEP PATTERNS AMONG PEOPLE WITH INSOMNIA DURING THE PANDEMIC OF COVID-19

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**Introduction:** The effects of the COVID-19 pandemic on sleep duration and insomnia have been well studied in different studies. However, there is no study available on the characteristics of insomnia during the pandemic. This study aimed to evaluate the characteristics of insomnia experienced by the general Iranian population during the COVID-19 pandemic.

**Materials and Methods:** A cross-sectional community-based study was designed. We designed an online questionnaire and sent it to Iranian people via available social platforms. The questionnaire contained questions on the socio-demographic characteristics of the participants. We used Fear of COVID-19 scale (FCV-19), Insomnia Severity Index (ISI), Patient Health Questionnaire-2 (PHQ-2), and Generalized Anxiety Disorder Scale-2 (GAD-2) for detailed characterization of insomnia and its symptoms.

**Results:** In total, 675 people with insomnia with the mean age of 40.28 years (SD=11.15) participated in our study. Prevalence of difficulty initiating sleep (DIS), difficulty maintaining sleep (DMS), and early morning awakening (EMA) were 91.4%, 86.7%, and 77%, respectively. DIS, DMS, and EMA were more common in people with depression and anxiety. FCV-19 score was higher in those with more severe types of DIS, DMS, and EMA ( $P<0.001$ ). FCV-19 was a risk factor for all patterns of insomnia (OR=1.19, 1.12, 1.02 for DIS, DMS, and EMA, respectively).

**Conclusions:** Fear of COVID-19 is a major contributing factor to insomnia patterns. Investigation of COVID-19 fear in people with insomnia and the addition of attributed relieving or management strategies to conventional management of insomnia are reasonable approaches to improve the sleep condition of people in the pandemic.

#### INSOMNIA AND ITS ASSOCIATION WITH ABSENTEEISM: A CROSS-SECTIONAL STUDY AMONG IRANIAN NURSING TEAM

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**Introduction:** Given the potential impact of insomnia on nurses' performance, it is assumed that insomnia is associated with their absence from work. The present study aimed to determine the insomnia status and its association with absenteeism among a selective group of Iranian healthcare providers.

**Materials and Methods:** This cross-sectional study was conducted on 304 healthcare providers working at Imam-Khomeini hospital complex in Tehran. The study population were assessed by insomnia severity index for characterization of insomnia symptoms. The data of absenteeism was collected from the employees' attendance system of hospital's nursing and staff department. The multivariable linear regression model used for predicting determinants of insomnia and absenteeism in nursing team.

**Results:** Different degrees of insomnia was found in 79.9% of the study population, which 57.2% suffered from mild insomnia, 21.4% from moderate insomnia, and 1.3% from severe insomnia. The prevalence of insomnia was significantly higher in persons who were absent from their workplace frequently, or left because of illness. The mean days for total absenteeism in healthcare workers with moderate to severe insomnia was significantly higher than others with mild and no insomnia. In multivariate analysis, having night shifts and the severity of insomnia could predict absenteeism in studied population.

**Conclusions:** A majority of healthcare workers suffer from insomnia that may lead to their work absenteeism and decreased performance. Proper administrative and individuals for management of sleep problems is required to avoid long hours of absenteeism among nursing team

**Acknowledgements:** A majority of healthcare workers suffer from insomnia that may lead to their work absenteeism and decreased performance. Proper administrative and individuals for management of sleep

problems is required to avoid long hours of absenteeism among nursing team

#### INSOMNIA AND NIGHTMARE PROFILES DURING THE COVID-19 PANDEMIC IN PORTUGAL: CHARACTERIZATION AND ASSOCIATED FACTORS

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**Objective/Background:** To describe and characterize insomnia symptoms and nightmare profiles in Portugal during the first six weeks of a national lockdown due to COVID-19.

**Patients/Methods:** An open cohort study was conducted to collect information of the general population during the first wave of SARS-CoV-2/COVID-19 pandemic in Portugal. We analyzed data from 5011 participants ( $\geq 16$  years) who answered a weekly questionnaire about their well-being. Two questions about the frequency of insomnia and nightmares about COVID-19 were consecutively applied during six weeks (March-May 2020). Latent class analysis was conducted and different insomnia and nightmare profiles were identified. Associations between individual characteristics and both profiles were estimated using odds ratios (ORs) and 95% confidence intervals (CI).

**Results:** Five insomnia (No insomnia, Stable-mild, Decreasing-moderate, Stable-severe, Increasing-severe) and three nightmares profiles (Stable-mild, Stable-moderate, Stable-severe) were identified, respectively. After adjustment, being female, perceiving their income as insufficient and feelings of fear towards COVID-19 were associated with higher odds of insomnia (Women: aOR=6.98 95%CI:4.18-11.64; Insufficient income: aOR=7.47 95%CI:3.54-15.75; Often presenting fear of being infected with SARS-CoV-2 infection: aOR=8.96 95%CI:6.25-12.85), and nightmares (Women: a OR=2.60 95%CI:1.74-3.86; Insufficient income: aOR=2.39 95% CI:1.17-4.91; Often/almost always presenting fear of being infected with SARS-CoV-2 infection : aOR=6.62 95%CI:5.01-8.74). Having a diagnosis of SARS-CoV-2 virus infection was associated with worse patterns of nightmares about the pandemic

**Conclusions:** Social and psychological individual factors are important characteristics to consider in the development of therapeutic strategies to support people with sleep problems during COVID-19 pandemic.

#### INSOMNIA PATIENT-DERIVED IPSC NEURONS WITH POTENTIAL FOR DISEASE MODELING

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**Introduction:** About 10% of the world population suffers from chronic insomnia and to date there are no disease models to investigate the neuropathophysiology of this disorder. The artificial generation of neuronal populations *in vitro* from patient-derived cells could in principle recapitulate this complex disorder within the human physiological environment to identify disease mechanisms. Our aim is to generate an *in vitro* human neuronal model to explore neurons-glia interplay in sleep regulation and decipher how they control biological clocks during sleep deprivation.

**Materials and Methods:** Samples were collected from fresh urine samples to isolate renal epithelial cells which were converted into induced Pluripotent Stem Cells (iPSCs) by nucleofection of integration-free reprogramming episomal vectors. iPSCs were then differentiated into specific neurons by a culture-driven protocol and characterized regarding

their morphology and functionality.

**Results:** Here, we show step-by-step generation of an innovative human model, with the morphology and functionality characterization, including calcium imaging of neurons.

**Conclusion:** The data obtained shows evidence that non-invasive/cost-effective methods can provide an innovative platform to study the insomnia pathophysiology. Insomnia's cell model will provide a new platform to study the mechanisms underlying sleep deprivation and to explore clinically translatable therapeutics with patentable potential.

**Acknowledgements:** European Regional Development Fund (ERDF), through the Centro 2020 Regional Operational Programme, under the project CENTRO-01-0145-FEDER-000012 (HealthyAging 2020); through Operational Programme for Competitiveness and Internationalization (COMPETE 2020) and Portuguese national funds via Fundação para a Ciência e a Tecnologia (FCT), under the projects POCI-01-0145-FEDER-029002 (noOSAnoAGEING, PTDC/MEC-MCI/29002/2017), UIDB/04539/2020 and UIDP/04539/2020; and 2020.04499.BD.

### INSOMNIA SEVERITY IS ASSOCIATED WITH INCREASED ALPHA AND THETA POWER DURING NON-RAPID EYE MOVEMENT SLEEP

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**Introduction:** Pathophysiological models of insomnia identify hyperarousal as a core feature. Emerging studies have shown that individuals with insomnia exhibit increased high-frequency electroencephalographic (EEG) activity during non-rapid eye movement (NREM) sleep. Recent data also suggest that localized sleep dysregulation, characterized by elevated theta and alpha activity, was observed in insomnia patients relative to controls. However, the association between the severity of insomnia symptoms and topographic distribution of theta and alpha activity remains largely unknown. The present study aimed to characterize sleep pathophysiology in middle-aged and older adults with insomnia by examining associations between insomnia severity and frontal EEG spectral power density profiles during NREM sleep.

**Materials and Methods:** Participants were 26 cognitively unimpaired middle-aged and older adults (61.0±5.4 years [range: 50–70 years]; 69.2% female) with evidence suggestive of insomnia, i.e., a score ≥8 on the Insomnia Severity Index (ISI). The sample was free of history of significant neurological conditions or depressive symptomatology (mean score on the Geriatric Depression Scale=1.0±1.6). Participants underwent one night of polysomnography assessment with 256-channel high density EEG. Spectral analyses using Fast Fourier Transform was performed on artifact-free epochs, leveraging the multitaper method to generate estimates of absolute spectral power within NREM sleep for different frequency bands (delta: 0.5–4.5 Hz, theta: 4.5–7.5 Hz, alpha: 7.5–11 Hz, slow sigma: 11–13 Hz, fast sigma: 13–16 Hz, beta: 16–28Hz, and gamma: 28–40Hz) for each individual electrode. Pearson's correlations were conducted at each electrode across topography to examine associations between insomnia severity (i.e., log-transformed ISI scores) and spectral power. The Threshold-Free Cluster Enhancement (TFCE) procedure was used to correct

for multiple comparisons across topography. Absolute spectral power from resulting clusters of electrodes showing significant TFCE-corrected associations were averaged. Multiple linear regression models, adjusting for age and sex, were used to examine the associations between insomnia severity and NREM spectral power across frequencies.

**Results:** We found significant TFCE-corrected positive associations between log-transformed ISI and absolute frontal theta (40 electrodes,  $b=0.440$ ,  $p=0.031$ ) and frontal alpha (37 electrodes,  $b=0.450$ ,  $p=0.022$ ) power after adjusting for age and sex. Across topography, increased log-transformed ISI scores were associated with greater absolute theta ( $b=0.463$ ,  $p=0.018$ ) and alpha ( $b=0.448$ ,  $p=0.027$ ) power over fronto-temporal derivations following TFCE correction and adjustment for age and sex. No significant associations were detected for other frequency bands following TFCE correction.

**Conclusions:** Amongst middle-aged and older individuals with insomnia, perceived severity of insomnia problems was associated with elevations in theta and alpha power, particularly over frontotemporal derivations, during NREM sleep. Such altered EEG profiles in low frequency bands are consistent with the conceptualization of local sleep/wake dysregulation in insomnia. Research is warranted to further investigate the functional implications of these findings in insomnia and in the aging brain.

**Acknowledgements:** R56 AG052698, P50 AG033514, F31 AG048732, K01 AG068353

### INSOMNIA SUBTYPES

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**Introduction:** Insomnia disorder (ID) is a heterogeneous disorder whose diagnosis is based on subjective symptoms. The etiology is unknown and there has surely not a single cause. Until now, there is no effective and long-term treatment for many patients with ID. For this reason, it is essential to identify new clinical and biological markers that allow new individualized and more effective therapeutic modalities.

Attempts to classify ID based on different sleep characteristics have not allowed to define valid subgroups, except for the objective sleep duration (1). However, this classification requires polysomnography, which is not usually performed in patients with ID. Another classification has recently been proposed, based on characteristics not related to sleep, or not exclusively (2) using the Insomnia Type Questionnaire (ITQ), which divides insomniacs into 5 subtypes.

The goal of our study is to replicate the ITQ study done using an Online platform (*Netherlands Sleep registry*) (2), in ID patients treated in Spanish specialized sleep clinics.

**Methods:**

**Design:** Multicenter prospective study (7 centers, Spain). Approved by the Research Ethics Committee of the Balearic Islands (CEI-IB IB4280-20PI)

**Subjects:** Patients with insomnia disorder referred to sleep medicine centers.

**Inclusion criteria:** Men and women > 18 years, meeting DSM-5 diagnostic criteria for ID. At the time of evaluation, Patients must have an Insomnia Severity Index (ISI) > 10 and agree to participate in the study by signing the IC.

**Exclusion criteria:** Alcohol consumption (> 20 g / day in women and 30 g / day in men); substance abuse: cocaine, heroin, and other drugs of abuse. Comorbid medical or psychiatric illnesses that may interfere with the study.

**Assessment instruments:** Structured clinical interview and self-administered questionnaires: Pittsburgh Sleep Quality Scale, Munich Chronotype, STAI to assess anxiety trait and state, IDS 30-SR to assess symptoms of depression and the ITQ.

All data were entered in an interactive common database (Redcap)

**Results:** The analysis of the first 78 cases among all centres: 67,12% women

and 32.88% men, mean age 53 years (+/- 2.2), show the following percentages: 29.5 % type 1 very distressed; 16.7 % type 2 sensitive to reward moderately distressed; 51.3 % type 3 moderately distressed insensitive to reward; 2.4 % type 4 little distressed very reactive; 0% type 5 little distressed little reactive. To all participating patients we offer an inform showing them to which subtype they belong

**Conclusions:** The percentages of types found in the clinical setting is different from those obtained in the Banken et al study: type 1 (29.5% vs 19%); type 2 (16.7% versus 31%); type 3 (51.3% vs. 15%); type 4 (2.4% Vs 20%) and type 5 (0% Vs 15%)

It is premature to draw conclusions with only 78 cases. We are continuing with the recruitment and analysis of data.

**Acknowledgements:** To T. Blanken and E. Van Sommeren

1.Vgontzas, A et al.(2010) Insomnia with Short Sleep Duration and Mortality. *Sleep*, 33 (9) 1159–1164

2. Blanken, T. F. et al (2019). Insomnia disorder subtypes derived from life history and traits of affect and personality. *The Lancet Psychiatry*, 6(2), 151-163.

### INSOMNIA SYMPTOMS AND CARE-GIVING VS. COMPETITION MENTALITIES: PRELIMINARY FINDINGS

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**Introduction:** Many factors are known to be involved in Insomnia (e.g. hyperactivation and rumination). Recently, selfcompassion has been proposed as a protective factor against sleep difficulties. However, the potential association between care-giving mentality (selfcompassion) and competition mentality (self-criticism, shame and submissive behaviours) and Insomnia/sleep quality is not clear. This study aimed to explore, in a non-clinical sample, the role of selfcompassion, selfcriticism, shame and submissive behaviours on Insomnia and sleep quality.

**Materials and Methods:** 201 participants (68% F), 18-78 years old (37.47±15.68), from the community, completed an online questionnaire (ongoing) evaluating: presence/gravity of insomnia symptoms (ISI); insomnia symptoms and sleep quality (BaSIQS); selfcompassion (SCS); forms of self-attacking and self-reassuring (FSCSR), external shame (OAS) and submissive behaviours (SBS). Cronbach's alpha values on all scales showed good internal consistency (0.77≤α<0.93). Scale correlations were assessed through Pearson correlation coefficient (r) and its non-parametric equivalent (rs). Effect sizes were considered using Cohen's conventions for Small (0.1<r<0.29), Medium (0.3<r<0.49), and Large (≥0.5) effects for correlation coefficients. ISI scores (ISI>14) were used to detect participants with probable clinical insomnia.

**Results:** Participants with ISI>14 scored significantly higher on both ISI ( $t_{(63.724)}=19.70, p<0.01$ ) and BaSIQS ( $t_{(199)}=11.71, p<0.01$ ), meaning poorer sleep. A negative medium correlation was found between selfcompassion (SCS) and ISI ( $r=-0.38, p<0.01$ ) and BaSIQS ( $r=-0.30, p<0.01$ ) scores, showing fewer insomnia symptoms and better sleep quality with higher selfcompassion scores. SCS scales were all negatively correlated with ISI scores, with low to medium association sizes. Thus, more self-kindness ( $r=-0.28, p<0.01$ ), common humanity ( $r=-0.16, p<0.05$ ) and mindfulness ( $r=-0.29, p<0.01$ ) are associated with lower ISI scores, and less self-Judgment ( $r=-0.35, p<0.01$ ), isolation ( $r=-0.32, p<0.01$ ) and over-identification ( $r=-0.31, p<0.01$ ) (as higher scores indicate higher selfcompassion) correlate with lower ISI scores. Regarding FSCSR, Inadequate Self and Hated Self (competitive mentality) were both positively correlated with ISI scores, with medium effect associations ( $r=0.34, p<0.01$  and  $r_s=0.37, p<0.01$ , respectively). Reassure Self (care-giving mentality) was negatively correlated with sleep disturbance ( $r=-0.35, p<0.01$ ). Both external shame (OAS) ( $r=0.38, p<0.01$ ) and submissive behaviours (SBS) ( $r=0.31, p<0.01$ ) presented medium size positive associations with ISI, revealing a correlation between higher external shame and submissive behaviours with insomnia symptoms. When accounting only for participants with ISI>14,

only OAS ( $r=0.39, p<0.05$ ) and SBS ( $r=0.36, p<0.05$ ) showed to be associated with symptom severity. However, when analysing insomnia symptoms and sleep quality through BaSIQS, large negative associations were found with both SCS ( $r=-0.57, p<0.01$ ) and Reassure Self ( $r=-0.58, p<0.01$ ).

**Conclusions:** The adoption of attitudes of selfcompassion and self-reassurance is associated with fewer sleep disturbances in terms of insomnia symptoms and sleep quality, whereas self-criticism, as its opposite, as well as shame and submissive behaviours, are associated to more insomnia symptoms. These findings give preliminary support to the idea that competitive mentality may be associated with Insomnia and that fostering a care-giving mentality might protect against sleep disturbances.

**Acknowledgements:** This work is part of an ongoing Ph.D. research supported by the Portuguese Foundation for Science and Technology (FCT) through a PhD scholarship awarded to the first author [SFRH/BD/147556/2019].

### INSOMNIA SYMPTOMS ARE ASSOCIATED WITH IMPAIRED RESILIENCE IN BIPOLAR DISORDER: POTENTIAL LINKS WITH EARLY LIFE STRESSORS AND CONSEQUENCES ON MOOD FEATURES AND SUICIDAL RISK

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**Introduction:** Bipolar disorders (BDs) are among the most prevalent and the most likely to be recurrent, chronic and disabling psychiatric conditions leading to global burdens of disease in terms of disability, morbidity, premature mortality, and to a significant suicidal risk. The understanding of the mechanisms involved in the development and maintenance of BDs should thus be considered as a priority to identify potential early markers that could help in improving treatment strategies. Within this framework insomnia might be such a potentially modifiable early marker in BDs. In particular, insomnia likely plays a triggering role in the onset and maintenance of BD to emotional hyper-reactivity or impulsivity, and to increased suicidality. Insomnia might play a key role in BDs by potentially dysregulating the systems involved in mood and emotion regulation, including stress and inflammatory systems. Resilience is a modifiable stress-risk dimension evolving process that determines an individual's capacity to adapt successfully to stressful events. Low resilience has been related to a dysregulation in emotions and stress response involved in psychopathological process of mental disorders including bipolar disorders and increased suicidal risk in particular psychiatric population. Although sleep processes and insomnia may affect resilience, to date no studies have examined the association between insomnia symptoms and levels of resilience in BDs.

Among the factors, affecting resilience in BDs early life stressors may play a role. Interestingly, early life stressors have been demonstrated to alter sleep regulation leading to life-long/late-life insomnia and, via sleep alterations, contributing to the clinical pictures of BD during adulthood. In any case, little is known about the associations among resilience, insomnia symptoms, exposure to early life stressors, and the clinical manifestations of BDs.

**Methods.** A sample of 188 adult participants with BD of type I or II were assessed during depressed phase using the Structural Clinical Interview for DSM-5 (SCID-5), the Beck Depression Inventory-II (BDI-II), the Young Mania Rating Scale (YMRS), the Early Trauma Inventory Self Report-Short Form (ETISR-SF), Resilience Scale for Adults (RSA), the Insomnia Severity Index (ISI) and the Scale for Suicide Ideation (SSI). Participants with or without clinically significant insomnia were compared and we carried out correlations, regression and mediation analyses.

**Results.** Participants with insomnia showed a greater severity of depressive symptoms as well as of suicidal risk, early life stressors and lower level of resilience. Insomnia symptoms mediated the association between early

life stress and low resilience and between low resilience in planning future and depressive symptoms ( $Z=2.17$ ,  $p=0.029$ ) and between early life stressors, low resilience and suicidal risk ( $Z=3.05$ ,  $p=0.0002$ )

**Conclusions:** Insomnia may be related to the severity of BDs, to higher early life stressors and lower level of resilience. Assessing and targeting insomnia symptoms may potentially promote resilience in BDs in response to early life stressful events. These results should be interpreted in light of several limitations including the cross-sectional design affecting causal interpretations.

**Acknowledgements:**

#### INTERACTIONS BETWEEN INSOMNIA AND PSYCHOSOCIAL STRESS IN PATIENTS SEEKING CARE AT AN OROFACIAL PAIN CENTER: PRELIMINARY FINDINGS

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**Introduction:** Insomnia, the most common sleep disorder, is highly prevalent and causes clinically significant functional distress or impairment, both at physical and psychological levels. Orofacial pain (OFP) includes the pain arising from the regions above the neck, in front of the ears and below the orbitomeatal line, the oral cavity itself and is associated to temporomandibular disorders. Few studies have been evaluating the relationship between OFP and insomnia but failed to address the triad OFP, insomnia and associated psychosocial factors which was the purpose of the present study.

**Material and Methods:** Anonymized data of 184 adult patients seeking care at an orofacial pain center, both sexes (71.2% women), aged  $45.8 \pm 16.4$  years were extracted from the self-screening WISE platform. Significant medical or psychiatric conditions, substance abuse, shift working, or drug treatments that may cause insomnia were exclusion criteria. Prevalence data for insomnia (ISI), stratified by severity grade, and psychometric measures (DCQ, GAD-7, IPQ, PCS, PHQ-4, PHQ-9, IEQ and PHQstr) assessing dysmorphic concern, anxiety, illness perception, injustice experience, pain-related catastrophizing and disability, depression, and distress were performed. The correlation of psychometric scores with insomnia grades having gender, age, and employment status as putative confounders was analysed.

**Results:** Globally, patients had a normal weight or were pre-obese, being most of them light smokers and active workers. From the recruited patients, 34.8% reported insomnia symptoms, with 16.3% of them reaching moderate to severe insomnia which are clinically relevant. Pain intensities, psychosocial burden, and sleep disturbances were higher in women than men. Severe depression, anxiety, and distress were the most frequent symptoms (18.5–23.9%), while stress and dysmorphic concern were the least. The results of correlation analysis of the psychometric measures and insomnia scores were as follows: DCQ, GAD-7, IPQ, PCS, PHQ-4, and PHQ-9 had moderate and strong associations ( $>0.300$ ) with ISI scores of all respondents and women (unlike the male group). The IEQ scores were strongly correlated with ISI scores between 8 and 21 ( $-0.608 - 0.626$ ). The association between PHQstr and ISI scores was only found in patients unable to work. Patients aged between 30 and 39 years had the greatest number of statistically significant correlations between the variables, while the seniors ( $>70$  years) had none. The active workers constitute the employment status with the highest number of associations between sleep problems and impaired well-being (anxiety, pain catastrophizing, distress, and depression), followed by the retired ones.

**Conclusion:** Insomnia and psychosocial stressors biunivocal influence each other, with different weights in this particular cohort. Due to the high incidence of clinically relevant insomnia in patients complaining from pain or discomfort in the orofacial region, these patients should always be screened for insomnia, at least, with a self-assessed questionnaire and adequately followed for an optimized management.

#### INTERNET-DELIVERED COGNITIVE-BEHAVIORAL INTERVENTION FOR CANCER SURVIVORS SUFFERING FROM INSOMNIA: THE STUDY PROTOCOL OF A PRAGMATIC SUPERIORITY RANDOMIZED CONTROLLED TRIAL

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**Introduction:** Persistent insomnia is one of the most prevailing and distressing complaints among cancer survivors and has adverse health and functional consequences. Albeit cognitive-behavioral therapy is the gold-standard treatment for chronic insomnia, its access is limited. Internet-delivered interventions may represent a notable opportunity to provide access to survivorship care. We aim to study the effectiveness of a 6-week self-guided internet-based cognitive-behavioral therapy intervention developed to improve insomnia in cancer survivors when compared to a waitlist control group.

**Materials and Methods:** A well-established cognitive-behavioral protocol was tailored to the idiosyncrasies of cancer-related insomnia. A two-arm parallel randomized waitlist-controlled trial will be accomplished to ascertain the effects of an internet intervention designed for cancer survivors immediately post-treatment (primary endpoint) and at 3-, 6- and 12-months follow-ups (secondary endpoints). Main inclusion criteria include having at least mild insomnia symptoms, history of cancer, and the completion of acute treatment at least 1 month prior. Potential participants will complete an online screening and consent process. Insomnia severity, measured via the Insomnia Severity Index (ISI), will be the primary outcome. Secondary outcomes will include cancer-related fatigue, quality of life, sleep quality and efficiency, anxiety, depression, sleep-related cognitions, and perceived cognitive functioning. The present study was approved by the Deontology Committee for Research of the Faculty of Psychology and Education Sciences. The clinical trial is registered at ClinicalTrials.gov (NCT04898855) and any changes to the protocol will be described in that registry.

**Results:** Our primary hypothesis is that, compared to the control group, the intervention group will show improved insomnia severity by the end of treatment. Our secondary hypotheses are that, compared to the control group, the intervention group: 1) will show reduced symptoms of fatigue, anxiety, depression, cognitive impairment by the end of treatment; 2) will show improved sleep efficiency, quality of life and sleep quality by the end of treatment; 3) will maintain improvements at follow-ups. The results of this study will be reported in accordance with CONSORT e-health guidelines.

**Conclusions:** This study will inform on the effectiveness of a e-mental health program in improving insomnia and insomnia-related outcomes in cancer survivors when compared to a waitlist control group. We anticipate the program will prove to be effective in the intervention outcomes and an accessible tool to deliver the gold start treatment for chronic insomnia to cancer survivors.

**Acknowledgements:** This work is part of an ongoing Ph.D. research supported by the Portuguese Foundation for Science and Technology (FCT) through a PhD scholarship (grant number 2020.05728.BD).

#### IS POST-ISCHEMIC STROKE INSOMNIA RELATED TO A NEGATIVE FUNCTIONAL AND COGNITIVE OUTCOME?

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**Introduction:** Our study examined the association between sleep disorders, other than obstructive sleep apnea, and cognitive as well as

functional outcomes in a cohort of ischemic stroke patients and aimed at determining which features were associated with the development of post-stroke sleep disturbances in these patients and how these sleep disturbances might affect stroke prognosis.

**Materials and Methods:** One hundred and fifty-seven ischemic stroke patients were evaluated during their hospitalization in the inpatient Stroke Unit and re-assessed two years afterwards, at a follow up appointment. Data regarding clinical variables, vascular risk factors, sleep disturbances developed after stroke (diagnosed in accordance with the third edition of the International Classification of Sleep Disorders), use of psychotropic drugs, further sleep studies, and specific measures of cognitive function, severity of stroke and functional evaluation were collected.

**Results:** Twenty eight point seven per cent of patients who developed post stroke insomnia presented worse functional and cognitive performance as well as a higher degree of neurological severity deficits on follow up, when compared with patients without sleep disturbances. Male gender ( $\chi^2(1)=7.556$ ,  $p = 0.006$ ) and previous major vascular events ( $\chi^2(1)=6.540$ ,  $p = 0.013$ ) were significantly associated with development of sleep disturbances after ischemic stroke. There were no significant differences between development of insomnia in patients suffering from anterior circulation stroke when compared with those who had suffered a stroke in the posterior circulation ( $\chi^2(1)=0.738$ ,  $p = 0.390$ ).

**Conclusion:** Sleep disruption itself, and insomnia in particular, may have a negative influence on neurological recovery from ischemic stroke, and it seems to associate with worse functional and cognitive outcome of these patients. Screening and appropriate management of post-stroke sleep disorders should become a part of the therapeutic strategy to optimize outcomes and decrease morbidity and mortality of this potentially devastating disease.

**Keywords:** Sleep disturbances, Insomnia, Ischemic Stroke, Functional Outcome, Cognitive outcome.

**Acknowledgements:** The authors would like to thank the participation of patients and all the professionals engaged in the assistance of patients of the Stroke Unit of Centro Hospitalar Trás-os-Montes E Alto Douro and that made possible the data collection and the realization of this study.

#### LACK OF STRUCTURAL BRAIN ALTERATION ASSOCIATED WITH INSOMNIA: FINDINGS FROM THE ENIGMA-SLEEP WORKING GROUP

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**Introduction:** Despite numerous studies focusing on neurobiological substrates associated with insomnia, its neurobiological mechanism is poorly understood. Previous structural MRI studies revealed grey matter changes in insomnia, but the results of such individual studies and even

the findings of previous neuroimaging meta-analysis on insomnia are divergent and often conflicting. The possible reasons for this uncertainty include heterogeneity of clinical study populations, small sample sizes, and differences in methodology and statistical analysis. In the present study, we performed a meta-analysis of structural MRI in 1085 subjects with insomnia symptoms from three international cohorts to measure cortical and subcortical brain changes between subjects with and without insomnia symptoms. Furthermore, to investigate the effect of insomnia on the brain structure, we assessed the possibility of an insomnia brain score, which, similar to other scores such as brain age, quantifies subtle, but widespread deviations in regional brain structures.

**Materials and Methods:** To identify structural changes associated with insomnia using the ENIGMA-Sleep framework, we collected case-control data gathered by the Kermanshah University of Medical Sciences (KUMS), Iran (N=100, 59.8% female, mean age of 42.1±11.5), and University Medicine Freiburg, Germany (N=72, 62.5% female, mean age of 39.3±12.1), as well as population-based data from the Study of Health in Pomerania, Germany (SHIP-Trend, N=913, 48.2% females, mean age of 52.27±13.6) to investigate insomnia-related changes in cortical and subcortical brain structures using T1-weighted MRI scans. MRI-segmentation was performed with FreeSurfer (version 7.2) using the Desikan-Kiliany-atlas for cortical structures (68 regions of interest) and the ASEG-atlas for subcortical structures (34 regions of interest). Within each cohort, we used ordinary least-square linear regression to investigate the relationship between the individual cortical grey matter thicknesses and subcortical grey matter volumes and the presence of insomnia symptoms and then performed meta-analysis across three cohorts based on the first-level results using a fixed-effect approach. For the KUMS and Freiburg datasets, insomnia symptoms were defined using ICD-3 and DSM-5 criteria respectively, while in SHIP-Trend subjects were classified using the insomnia-severity index with a threshold of 15. For the insomnia brain score, weighted logistic ridge regression was performed on the Freiburg sample, to train a model based on the cortical and subcortical segmentation measurements, which optimally separated individuals with insomnia from individuals without. The score was validated using the KUMS and SHIP-Trend sample, where the model was used to predict the log-odds of the subject having insomnia given the individual specific brain atrophy pattern, i.e. quantifying the individual's insomnia related brain atrophy.

**Results:** After adjusting for multiple testing, we observed no significant associations between insomnia symptoms and local subcortical grey-matter volumes or cortical thickness neither in the individual cohorts nor in the meta-analysis across three samples.

**Conclusions:** The current study found no brain morphology difference between subjects with and without insomnia. However, given the high impact of insomnia on quality of life and health-related costs, further longitudinal studies using objective sleep measurements in combination with structural and functional neuroimaging methods are warranted.

#### LEMBorexant VERSUS Zolpidem: AN ASSESSMENT OF WAKE BOUTS IN ADULTS WITH INSOMNIA

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**Introduction:** Dual orexin receptor antagonists (DORAs), including lemborexant (LEM), are thought to promote sleep by inhibiting orexin-mediated wakefulness. In Study 304 (SUNRISE-1; NCT02783729; ≥55 years with insomnia), LEM significantly improved sleep efficiency and wake after sleep onset (WASO) versus placebo (PBO) and zolpidem tartrate extended-release 6.25mg (ZOL). The precise effects of LEM on WASO dynamics were examined by evaluating the effect of LEM on frequency and duration of wake bouts.

**Materials and Methods:** Study 304 was a 1 month, randomized, double-blind, PBO (n=208)- and active-controlled (ZOL; n=263) study of LEM 5mg (LEM5; n=266) and LEM 10mg (LEM10; n=269). Polysomnographic data from Night (NT) 2 and NT31 of treatment were analyzed to determine the number and total duration of all wake bouts (any duration), short (≤2 minutes) and long (>2 minutes) wake bouts. P-values are based on

differences in least squares mean changes from baseline, in the number and total duration of all, short, and long wake bouts among treatment groups.

**Results:** Wake bouts of any duration were more frequent in LEM-treated subjects during NT2, (LEM5, 35.1; LEM10, 37.8) versus PBO (32.7) or ZOL (31.5), and during NT31: 37.9, 40.3, 31.7, and 31.0, respectively. LEM-treated subjects spent fewer total minutes in wake bouts during NT2 (LEM5, 62.2; LEM10, 55.2) versus PBO (93.0) or ZOL (72.7) and during NT31: 66.4, 67.3, 92.4, and 79.7, respectively.

LEM-treated subjects had more short wake bouts during NT2 (LEM5, 30.4; LEM10, 33.4) versus PBO (26.9) or ZOL (26.3) and during NT31: 32.8, 34.7, 26.1, and 25.9, respectively. LEM5- and LEM10-treated subjects spent significantly more minutes in short wake bouts than PBO- or ZOL-treated subjects during NT2 (LEM5, 22.0 [ $P < 0.05$  vs PBO and ZOL]; PBO, 20.1; and ZOL, 19.5; LEM10, 24.5 [ $P < 0.0001$  vs PBO and ZOL]). Findings were similar during NT31 (LEM5, 23.9; LEM10, 25.7 [both  $P < 0.0001$  vs PBO and ZOL]; PBO, 19.4; and ZOL, 19.3). ZOL was not significant versus PBO for total time spent in short wake bouts at either NT2 or NT31.

LEM-treated subjects had fewer long wake bouts (LEM5, 4.7; LEM10, 4.4) versus PBO (5.9) or ZOL (5.2) during NT2 but were similar during NT31: 5.1, 5.6, 5.5, and 5.2, respectively. LEM5- and LEM10-treated subjects spent significantly fewer minutes in long wake bouts than PBO- or ZOL-treated subjects during NT2 (LEM5, 40.3; LEM10, 30.8 [both  $P < 0.0001$  vs PBO and ZOL]; PBO, 73.0; and ZOL, 53.2). Findings were similar during NT31: LEM5, 42.5; LEM10, 41.6 (both  $P < 0.0001$  vs PBO and ZOL); PBO, 73.0; and ZOL, 60.4. ZOL was significant versus PBO at NT2 and NT31 (both  $P < 0.001$ ).

**Conclusion:** Relative to PBO and ZOL, WASO decreased with LEM, mediated by a decrease in the number and time spent in long wake bouts, and an increase in the number and time spent in short wake bouts. These findings are consistent with the effects of the DORA, suvorexant on WASO (Svetnik V, et al. SLEEP. 2018;41(1)) and reflect differences between hypnotics with different mechanisms of action.

**Acknowledgements:** Supported by Eisai Inc.

## LEVERAGING MACHINE LEARNING TO IDENTIFY THE NEURAL CORRELATES OF INSOMNIA WITH AND WITHOUT SLEEP STATE MISPERCEPTION

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**Introduction:** Polysomnography (PSG) is not recommended as a diagnostic tool in insomnia. However, this consensual approach might be tempered in the light of two ongoing transformations in sleep research: big data and machine learning.

**Method:** We analyzed the PSG of 347 patients with chronic insomnia, including 59 with Sleep State Misperception (SSM) and 288 without (INS). 89 good sleepers (GS) were used as controls. PSGs were compared regarding: (1) macroscopic indexes derived from the hypnogram, (2) mesoscopic indexes extracted from the electroencephalographic (EEG) spectrum, (3) sleep microstructure (slow waves, spindles). We used supervised algorithms to differentiate patients from GS.

**Results:** Macroscopic features illustrate the insomnia conundrum, with SSM patients displaying similar sleep metrics as GS, whereas INS patients show a deteriorated sleep. However, both SSM and INS patients showed marked differences in EEG spectral components (meso) compared to GS, with reduced power in the delta band and increased power in the theta/alpha, sigma and beta bands. INS and SSM patients showed decreased spectral slope in NREM. INS and SSM patients also differed from GS in sleep micro-structure with fewer and slower slow waves and more and faster sleep spindles. Importantly, SSM and INS patients were almost indistinguishable at the meso and micro levels. Accordingly, unsupervised classifiers can reliably categorize insomnia patients and GS (Cohen's  $k = 1/4$  0.87) but fail to tease apart SSM and INS patients when restricting classifiers to micro and meso features ( $k = 1/40$  0.04).

**Conclusion:** Analyses of PSG recordings leveraging machine learning can

help moving insomnia diagnosis beyond subjective complaints and shed light on the physiological substrate of insomnia.

## LIGHT THERAPY AS ADD-ON THERAPY TOOL TO COGNITIVE BEHAVIORAL THERAPY FOR INSOMNIA (CBT-I) - A STUDY PROTOCOL

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**Introduction:** Insomnia disorder (ID) is very common, around 10% of the general population meet the diagnostic criteria with the prevalence being 50% higher among women compared to men. ID has a substantial negative impact on daytime functioning, mood and quality of life. Today, it is most commonly treated pharmacologically, although guidelines recommend cognitive behavioral therapy for insomnia (CBT-I) as first-line treatment. Previous meta-analyses found that CBT-I can increase subjective sleep efficiency (SE) by around 10% to 82%. This represents a clinically significant amelioration; however it is still under the  $\geq 85\%$  threshold, which is considered as indicator of good sleep quality by the National Sleep Foundation. Among the ambient factors that affect sleep, daylight is an effective modulator of sleep timing, quality and mood. At the same time, modern societies usually suffer from a relative lack of daylight exposure. Light therapy (LT) with daylight lamps, emitting high proportions of short-wavelength light, has been successfully applied in seasonal affective disorders. Surprisingly, LT is barely examined in the treatment of sleep onset and sleep maintenance disorders. Our primary hypothesis is that CBT-I + LT outperforms CBT-I + Placebo LT in terms of insomnia severity. Our secondary hypothesis is that CBT-I + LT reduces depressive symptoms and daytime sleepiness more and increases the quality of life to a greater extent compared to CBT-I + Placebo LT.

**Materials and Methods:** 46 adult patients diagnosed with ID (DSM-5) will be recruited. Patients will be block randomised either to (i) CBT-I + LT or to (ii) CBT-I + Placebo LT. The CBT-I consists of four weekly sessions à 50 min, the LT and Placebo LT of four sessions a week à 20 min over four weeks. The LT and the Placebo LT are applied at home using daylight lamps by the participants themselves. Illuminance (measured in photopic lux) differs between the conditions. Polysomnographic sleep data will be assessed before and after the treatment period. Cortisol and melatonin samples will be collected during these sleep laboratory stays; dim light melatonin onset and cortisol awakening response will also be examined in the laboratory. Questionnaires regarding insomnia severity, depressive symptoms, daytime sleepiness and quality of life will be used at baseline, post-treatment and three months follow-up. Self-reported changes in sleep will be monitored by a sleep diary starting one week before the treatment period and ending one week afterwards. Daylight exposure and physical activity will be assessed on a daily level. Linear regression analyses and analyses of covariance will be conducted to evaluate treatment effects.

**Results:** Our next step will be to recruit the first patient and to start with the data collection.

**Conclusions:** The aim of the planned study is to investigate LT as add-on therapy tool to CBT-I to enhance treatment outcomes.

## LONG-TERM, NATURALISTIC, NON-CONTACT MEASUREMENT OF SLEEP IN CHRONIC INSOMNIA

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**Introduction:** Individuals with insomnia report poor sleep quality and non-restorative sleep, and often exhibit irregular sleep patterns over days and weeks. In the laboratory, first-night effects and logistical challenges make it difficult to measure these sleep characteristics. In the field, sensitivity to sleep disruption from obtrusive tools confounds sleep measurements in

people with insomnia. Non-contact sleep measurement devices have the potential to address these issues and enable ecologically valid, longitudinal characterization of sleep in individuals with insomnia in their naturalistic setting. Here we use a non-contact device – the SleepScore Max (SleepScore Labs) – to assess the sleep of individuals with chronic insomnia, compared to healthy sleeper controls, in their home setting.

**Materials and Methods:** As part of a larger, ongoing study aiming to enroll 120 participants, 44 individuals with chronic insomnia (ages 19–63, 30 females) and 29 healthy sleeper controls (ages 19–54, 21 females) participated in an at-home sleep monitoring study. Enrollment criteria included age between 18 and 65 and, for the insomnia group, International Classification of Sleep Disorders (Third Edition) criteria for chronic insomnia with no other clinically relevant illnesses. Participants used the non-contact sleep measurement device to record their sleep periods each night over a period of 8 weeks. Participants in the insomnia group were assigned to one of three conditions: passive sleep monitoring only, passive sleep monitoring with online cognitive behavioral therapy for insomnia, or sleep monitoring with feedback and integrated sleep coaching from the SleepScore Max app. Analyses of the present sample of 73 individuals focused on group differences, leaving differentiation by condition until enrollment of the full sample is complete. Sleep measurements were extracted by the SleepScore Max software and analyzed for group differences, collapsed over conditions in the insomnia group. Both means (describing sleep overall) and within-subject standard deviations (quantifying night-to-night variability) were analyzed, using mixed-effects regression controlling for systematic between-subject differences.

**Results:** On average, individuals with chronic insomnia exhibited increased total wake time during time in bed ( $F_{1,72} = 6.29$ ,  $p = 0.014$ ), wakefulness after sleep onset ( $F_{1,72} = 7.53$ ,  $p = 0.008$ ), and decreased sleep efficiency ( $F_{1,72} = 7.34$ ,  $p = 0.008$ ) as compared to healthy sleeper controls. Additionally, those with chronic insomnia demonstrated greater night-to-night variability in total wake time during time in bed ( $F_{1,72} = 93.89$ ,  $p < 0.001$ ), wakefulness after sleep onset ( $F_{1,72} = 135.06$ ,  $p < 0.001$ ), sleep latency ( $F_{1,72} = 324.53$ ,  $p < 0.001$ ), sleep efficiency ( $F_{1,72} = 92.51$ ,  $p < 0.001$ ), and deep sleep amount ( $F_{1,72} = 7.19$ ,  $p = 0.010$ ). No significant differences between groups were found for averages and variability in estimated bedtime, time in bed, total sleep time, number of sleep interruptions, and light and REM sleep amounts.

**Conclusions:** In this group of individuals with chronic insomnia, a non-contact device used to measure sleep naturalistically exposed differences from healthy sleeper controls in multiple insomnia related parameters including several measuring night-to-night variability. Capturing night-to-night variability in the home setting adds a potentially critical dimension to our understanding of poor sleep and provides a more comprehensive, ecologically valid characterization of chronic insomnia as experienced by individuals in daily life.

**Acknowledgements:** Supported by NIH grant KL2TR002317; devices provided by SleepScore Labs.

## LONG-TERM SAFETY AND EFFICACY OF DARIDOREXANT IN PATIENTS WITH INSOMNIA DISORDER

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**Introduction:** Ideal treatment for insomnia disorder should persistently improve night-time sleep and daytime functioning and be safe over the long-term. This study investigated the safety profile and long-term efficacy of daridorexant, a dual orexin receptor antagonist, up to 52 weeks.

**Materials and Methods:** The extension study (NCT03679884) included 804 adult (18–64y) and elderly ( $\geq 65y$ ) patients with insomnia disorder (per DSM-5 criteria) who completed the 12-week double-blind treatment and 7-day placebo run-out in two phase 3 studies (NCT03545191/NCT03575104). Patients originally randomized to daridorexant (10mg [ $n = 142$ ], 25mg [ $n = 270$ ],

50mg [ $n = 137$ ]) remained on their respective treatments; patients randomized to placebo were re-randomized to daridorexant 25mg [ $n = 127$ ] or placebo [ $n = 128$ ]. The extension study treatment period was 40-weeks, followed by a 7-day placebo run-out. Patients/investigators remained blinded to treatment assignments. The primary objective was to assess long-term safety/tolerability. Endpoints included treatment-emergent adverse events (TEAE), AEs of special interest (AESI; symptoms related to excessive daytime sleepiness or complex sleep behaviours, suicidal ideation/self-injury), withdrawal effects upon treatment cessation (Benzodiazepine Withdrawal Symptom Questionnaire, AEs) and rebound (change in subjective total sleep time [sTST] from baseline to run-out). Exploratory efficacy endpoints were change from baseline over time in sTST and daytime functioning (Insomnia Daytimes Symptoms and Impacts Questionnaire [IDSIQ]).

**Results:** Daridorexant was well tolerated at all doses. Overall incidence of TEAEs was similar across groups (35–40%); most were mild/moderate and no dose-dependent pattern observed. The most common TEAE in all groups was nasopharyngitis. The incidence of serious TEAEs was low ( $< 5.5\%$ ). Two non-treatment related deaths (cardiovascular-related) occurred in patients receiving daridorexant (10mg, 25mg). Two non-serious AESIs of somnolence (25mg) and abnormal dreams (50mg) were reported with daridorexant and 1 serious AESI of suicidal ideation with placebo. Accidental overdose was reported in 15 patients receiving daridorexant; all cases were asymptomatic. Somnolence was reported in 7 patients receiving daridorexant; all were non-serious. There was no evidence of withdrawal-related symptoms or rebound after treatment discontinuation.

Improvements in sleep and daytime functioning observed at 3-months were maintained for sTST and IDSIQ domain scores through to Month 12. Improvements were most pronounced with daridorexant 50mg. Mean (SD) increases from baseline in sTST (min) at Month 6, 9 and 12 were 67.7 (68.65), 68.9 (65.89), 75.6 (69.90), respectively for daridorexant 50mg, 58.06 (58.61), 65.1 (58.75), 66.0 (61.09) for daridorexant 25mg, and 50.3 (65.73), 59.0 (62.62), 62.6 (72.42), respectively, for placebo. For IDSIQ total score (range 0–140), mean (SD) reductions (improvements) from baseline at Month 6, 9, and 12 were  $-25.6$  (25.79),  $-24.9$  (25.35),  $-27.3$  (25.48), respectively for daridorexant 50mg,  $-20.3$  (22.55),  $-22.2$  (23.28),  $-22.8$  (26.50) for 25mg and  $-14.7$  (21.72),  $-16.8$  (20.82),  $-19.1$  (24.15), for placebo. Similar improvements were observed for IDSIQ sleepiness, alert/cognition and mood domain scores.

**Conclusions:** In this study, daridorexant, at all doses studied, was safely administered for up to 1 year in patients with insomnia disorder. The efficacy of daridorexant in improving night-time and daytime symptoms of insomnia was sustained for up to 1 year, in particular with 50mg, with no evidence of tolerance or dependency.

**Acknowledgements:** Idorsia Pharmaceuticals.

## MEASURING INSOMNIA AMONG ADOLESCENTS – ANALYSIS OF THE MINIMAL INSOMNIA SYMPTOM SCALE (MISS) WITH THE RASCH MEASUREMENT MODEL

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**Introduction:** The Minimal Insomnia Symptom Scale (MISS) is a three-item screening instrument that has been found to be psychometrically sound and capable of screening for insomnia among adults and older people. This study aimed to test the measurement properties of the MISS together with an additional item focusing on daytime functioning among adolescents using the Rasch measurement model.

**Materials and Methods:** A cross-sectional design were used, and data from adolescents (age 13–17 years,  $n = 3022$ ) was analyzed using the Rasch measurement model.

**Results:** The MISS had good measurement properties. When replacing the original MISS item “not rested by sleep” with the item “daytime disturbance”, the measurement properties slightly improved. We label this new scale the MISS-Revised (MISS-R). The reliability was significantly better for the MISS-R (0.55) compared to the MISS (0.50). The optimal cut-off was

found to be >6 points, both for the MISS and the MISS-R.

**Conclusions:** This study provides general support that both the MISS as well as the MISS-R have good fit to the Rasch model. At this stage, neither the MISS nor the MISS-R can be advocated over the other for use among adolescents, although the MISS-R had slightly better reliability than the MISS. Additional studies are needed to determine the clinically optimal cut-off score for identification of insomnia.

**Acknowledgements:** The authors wish to thank all the adolescents as well as the school administrations, teachers, and school nurses for facilitating data acquisition, and Magnus Lindberg for valuable discussions. Funding was received from the Gyllenstiernska Krapperrup Foundation, the Crafoord Foundation, the Research Platform for Collaboration for Health, Faculty of Health Sciences, Kristianstad University, and Lund University.

#### MEDIATING EFFECT OF SYMPATHETIC ACTIVATION ON THE ASSOCIATION BETWEEN OBJECTIVE SHORT SLEEP DURATION AND INCREASED BLOOD PRESSURE IN PATIENTS WITH CHRONIC INSOMNIA

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**Introduction:** Objective short sleep duration is associated with hypertension in patients with insomnia. However, the underlying mechanisms were not well understood. Sympathetic activation is one of the primary mechanisms in hypertension and chronic insomnia. In this study, we hypothesized that sympathetic activation mediates the association between objective short sleep duration and increased blood pressure in patients with chronic insomnia.

**Materials and Methods:** A total of 85 patients with chronic insomnia age between 18–65 years were included. All included subjects completed an overnight polysomnography recording in the sleep laboratory. The mean heart rate during sleep onset latency was used to assess sympathetic activity. Higher heart rate indicates higher levels of sympathetic activity. Blood pressure was measured twice at before bedtime and right after finishing polysomnography recording in the morning. The mean blood pressure values of these two measures were used for analyzing in this study. The mean arterial pressure is calculated by the formula  $[MAP = DBP + 1/3 * (SBP - DBP)]$ . Pearson correlation analysis was used to examine the correlation between total sleep time, heart rate and MAP. The bootstrap test was used to assess the significance of the mediation effects.

**Results:** Correlation analyses showed that shorter total sleep time as measured by polysomnography was significantly correlated with increased heart rate ( $r = -.318$ ,  $p = .018$ ) and higher MAP ( $r = -.275$ ,  $p = .011$ ). Furthermore, increased heart rate was significantly correlated with increased MAP ( $r = .336$ ,  $p = .013$ ). Mediation analysis showed that the mediating effect size of increased heart rate was 50.74% for the association between objective short sleep duration and increased MAP (95% CI = -2.46, -0.14,  $P = 0.043$ ) after adjusting for age, gender and BMI, which suggested that increased heart rate accounted for 50.47% effect of the association between objective short sleep duration and increased blood pressure in patients with chronic insomnia.

**Conclusions:** Objective short sleep duration is associated with increased blood pressure in patients with chronic insomnia, and this association is mediated by sympathetic activation. It appears that treatments for reducing levels of sympathetic activity (i.e.,  $\beta$ -blockers) in chronic insomnia patients with objective short sleep duration might be helpful to reduce the risk for cardiometabolic diseases.

**Acknowledgements:** NA

#### NETWORK INTERVENTION ANALYSIS: A NOVEL WAY TO UNRAVEL TREATMENT TARGETS AND MECHANISMS OF COGNITIVE BEHAVIORAL THERAPY FOR INSOMNIA

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**Introduction:** While cognitive behavioral therapy (CBT) is the treatment of choice for insomnia, about 20–30% of patients do not clinically respond, and around 60% does not remit. To increase efficacy and optimize treatment, we must better understand how the treatment works. CBT consists of a cognitive and behavioral part, which are theoretically supposed to work via different pathways, but empirical findings on their differential effects remain limited. In a series of studies, we aimed to unravel treatment targets and mechanisms of CBT by using novel Network Intervention Analysis (NIA). First, we identified the sequential and symptom-specific treatment effects of CBT [1]. Second, we disentangled the specific and differential effects of CT and BT [2]. Finally, we investigated mechanisms of change by evaluating the effect of CT and BT on specific process mediators [3].

**Materials and Methods:** We developed NIA to follow the development of treatment-induced changes over time, while distinguishing direct from indirect effects. First, we investigated the symptom-specific treatment effects of CBT by applying NIA to participants receiving either CBT ( $n = 52$ ) or no treatment ( $n = 52$ ). We estimated networks of ISI symptoms prior, during, and after treatment, to identify sequential effects. Second, we aimed to delineate whether the active components of CBT (i.e., CT and BT) have different points of engagement in line with their theoretical underpinnings. We applied NIA to patients receiving either CT ( $n = 72$ ) or BT ( $n = 73$ ) and inspected whether ISI symptoms and sleep efficiency were differentially affected by either treatment. Third, we aimed to replicate findings of this second study in an independent dataset. In addition, we extended the study by evaluating the effect of CT ( $n = 65$ ) and BT ( $n = 63$ ) on process mediators (CT process mediators: worry, unhelpful beliefs, monitoring for sleep-related threat; BT process mediators: sleep-incompatible behaviors, bed- and risetime variability), delineating potential treatment mechanisms.

**Results:** Our research reveals that throughout treatment CBT targets specific sleep complaints, predominantly difficulty maintaining sleep and early morning awakenings. The discovered differential effects of CT and BT were in line with their theoretical underpinnings: CT predominantly targeted daytime complaints whereas BT targeted mainly sleep efficiency. CT and BT also showed differing effects on process mediators: CT targeted cognitive processes such as dysfunctional beliefs whereas BT targeted behavioral processes like rise-time variability.

**Conclusions:** Together, these studies show that CBT targets specific insomnia symptoms throughout treatment, and that the active components of CT and BT have different points of engagement. By elucidating treatment mechanisms and differential treatment effects, the studies provide opportunities to optimize and personalize treatments, based on the specific symptoms that are most pronounced for the individual patient.

#### Acknowledgements:

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#### NETWORK META-ANALYSIS EXAMINING THE EFFICACY OF COMPONENTS OF COGNITIVE BEHAVIORAL THERAPY FOR INSOMNIA

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**Introduction:** Cognitive Behavioral Therapy for Insomnia (CBT-I) is recommended as first-line treatment for insomnia in clinical guidelines. CBT-I

is a multicomponent intervention comprising psychoeducation, relaxation therapy, sleep restriction therapy, stimulus control therapy, and cognitive therapy. The aim of this network meta-analysis is to combine direct and indirect evidence to quantify the efficacy of individual components of CBT-I in regard to insomnia severity, sleep quality, subjective and objective sleep parameters.

**Materials and Methods:** The electronic databases PubMed, MEDLINE, PsycINFO, PsycARTICLES, and CINAHL were searched to identify potential studies for this systematic review and network meta-analysis. These databases were searched from 1987, which is the publication date of DSM-III-R, until November 2021. For the literature search, terms indicative of insomnia (e.g., insomnia, sleep initiation, sleep maintenance) were combined with those of psychological interventions (e.g., CBT, CBT-I, sleep hygiene, psychoeducation, cognitive therapy, cognitive restructuring, cognitive control, paradoxical intention, problem solving, behavioral therapy, stimulus control, sleep restriction, imagery, relaxation).

Effect sizes (Cohen's *d*) were calculated for change from baseline to post-treatment assessment. Network meta-analysis allows the comparison of multiple treatments simultaneously in a single model by combining direct and indirect evidence.

**Results:** 8006 studies were identified, of which 69 fulfilled the inclusion criteria. In total 9568 people with the diagnosis of insomnia were examined in these studies. Here the preliminary result for the outcome parameter insomnia severity is presented. For this parameter 48 studies could be analysed. The results of all analysed outcome parameters will be presented on the World Sleep Conference 2022.

The components cognitive restructuring and sleep restriction therapy showed a significant influence on insomnia severity.

**Conclusions:** Regarding the reduction of insomnia severity, the two components cognitive restructuring and sleep restriction therapy seem to be particularly effective

#### PATIENT EXPERIENCES ASSOCIATED WITH FALLING ASLEEP/SLEEP ONSET WITH ZOLPIDEM VS LEMBOREXANT: RESULTS FROM AN OPEN-LABEL STUDY

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**Introduction:** In clinical practice, patients managing their insomnia with medication may need to change medications for various reasons, including inadequate clinical response or side effects (Schutte-Rodin S, et al. *J Clin Sleep Med*. 2008;4:487–504). When changing between insomnia medications with different mechanisms of action, patients may inquire about how the new medication may compare with their old medication with respect to how it makes them feel while falling asleep (Yang C-M, et al *Consciousness and Cognition*. 2010;19:1084–1092). In open-label Study 312 (E2006-A001-312; NCT04009577), patients with insomnia disorder transitioned directly from zolpidem (ZOL) to lemborexant (LEM; 5 mg [LEM5] or 10 mg [LEM10]). Information on patient experiences associated with falling asleep/sleep onset was collected to explore potential differences in how subjects felt while taking each medication. The purpose of this analysis was to explore patient-reported experiences associated with falling asleep with ZOL or LEM in subjects who were frequent ( $\geq 5$  nights/week) ZOL users.

**Materials and Methods:** Adults with insomnia who used ZOL intermittently (3–4 nights/week) or frequently ( $\geq 5$  nights/week) were enrolled. The study design included a 3-week Screening Period (subjects continued their typical ZOL dosing pattern) and a 2-week Titration Period (TITR). Cohort-2 included frequent ZOL users (randomized 1:1 to LEM5 or LEM10). The Sleep Drug Experience questionnaire designed specifically for this study, asked subjects to identify subjective experiences while taking their sleep drug, and if endorsed, to rate the severity of the experience. The questionnaire was completed at the end of Screening regarding ZOL and at end of TITR regarding LEM.

**Results:** A total of 38 subjects from Cohort-2 completed the questionnaire for ZOL, and 35 subjects completed the questionnaire for LEM. Experiences reported regarding sleep onset endorsed by  $\geq 50\%$  of subjects for both ZOL and LEM, respectively, included: “drowsiness, grogginess, sleepiness”

(76.3% vs 82.9%); “feeling relaxed/calm” (84.2% vs 85.7%); “falling asleep so quickly that you don't remember falling asleep” (68.4% vs 74.3%); “difficulty with remembering details of the night right before falling asleep” (60.5% vs 51.4%); “feeling sedated” (63.2% vs 60.0%); “dreams” (76.3% vs 80.0%); and “feeling peaceful” (65.8% vs 85.7%).

**Conclusions:** These data suggest that the most frequently endorsed subject experiences while falling asleep were generally similar for ZOL and LEM. These results may be helpful in discussions between clinician and patient when discussing transitioning to lemborexant for insomnia.

**Acknowledgements:** Supported by Eisai Inc.

#### PERIOPERATIVE BIOPHILIC VIRTUAL REALITY IMPROVES SLEEP ONE MONTH LATER AFTER DISCHARGE AMONG PATIENTS WITH INSOMNIA DISORDER, A PILOT STUDY

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**Introduction:** Virtual reality (VR) is a promising method to relieve stress and anxiety. Biophilic VR (VR-B) is thought to bring nature and its therapeutic benefits to people who cannot get out to experience it firsthand. Whether VR-B can reduce anxiety level associated with surgical procedures, and ameliorate sleep disorder remain unclear. We assessed the ability of a single VR-B session to improve postoperative sleep quality and explored if anxiety and depression influenced these outcomes in patients following laparoscopy.

**Materials and Methods:** 23 patients with chronic sleep disorder received one VR-B session during hospitalization. Prior to the session, patients completed MMSE, SAS, SDS, and the Pittsburgh Sleep Quality Index (PSQI) questionnaires. The primary outcome consisted of changes of PSQI and doses of hypnotics following VR-B (immediately, and one week after discharge). Secondary outcomes included changes in anxiety /depression level and cognition status.

**Results:** VR-B use was associated with a decrease in sleep onset latency and the overall mean score of PSQI immediately and one month after discharge. Reductions in hypnotic doses were observed up to one month following VR-B. VR-B was also associated with a reduction in anxiety only immediately after application. While patients with higher depression level, they did not show larger depression reductions following VR-B compared to those with lower depression level.

**Conclusions:** VR-B intervention perioperatively may be beneficial in improving sleep quality for patients with the sleep disorders. This study informs the design of a larger, randomized, controlled study assessing VR-B for sleep management.

**Acknowledgments:** The authors extend special acknowledgment to Dr. Gui Yu for his help. The mentioning of commercial products does not imply endorsement. This study is supported by the Medical Health Science and Technology Project of Zhejiang Provincial Health Commission (2021KY318); Special Fund for Science and Technology of Ningbo Science and Technology Council (2020F027); Ningbo 2025 science and technology innovation major project (2019B10035). The funders did not take part in any of the trial design, data collection or analysis, or submission for publication.

#### PHARMACOKINETICS, SAFETY, AND TOLERABILITY OF LEMBOREXANT IN HEALTHY CHINESE SUBJECTS

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**Introduction:** Lemborexant (LEM) is a dual orexin receptor antagonist approved in multiple countries for the treatment of adults with insomnia

and is being developed for the treatment of insomnia in China. This study investigated pharmacokinetics, safety, and tolerability of LEM in healthy Chinese subjects.

**Materials and Methods:** Study 014 (E2006-J086-014; NCT04555733) was a phase 1, single center, open-label, single and multiple oral dose study. Subjects enrolled into one of 3 cohorts. Cohort-1 (n=8; LEM 5mg [LEM5]) and Cohort-3 (n=8; LEM 25mg [LEM25]) received a single dose in the morning of Day 1. Cohort-2 (n=10; LEM 10mg [LEM10]) received a single dose in the morning of Day 1, followed by a 2-week washout, then daily LEM10 in the evening for 2 weeks. Plasma concentrations of LEM and its pharmacologically active, but clinically inactive (poor brain penetration), metabolites, M4, M9, and M10, were quantified from plasma collected predose and up to 240h postdose by validated liquid chromatography with tandem mass spectrometry. For Cohort-2, predose and postdose samples were collected during the multiple dosing period and up to 324h after the final dose. Adverse events (AE) and serious AEs were recorded.

**Results:** LEM maximum concentration ( $C_{max}$  mean [SD], ng/mL: LEM5, 29.8 [12.8]; LEM10, 56.2 [16.9]; LEM25, 116 [46.8]) and area under the curve from time zero to infinity ( $AUC_{0-inf}$  mean [SD], ng·h/mL: LEM5, 163 [46.0]; LEM10, 329 [97.7]; LEM25, 976 [257]) increased dose-proportionally across LEM dose levels following single doses on Day 1. Geometric mean terminal elimination half-life for LEM, M4, M9 and M10 ranged from 35–47, 20–43, 19–44, and 30–45 hours, respectively, after single and multiple doses. Mean total clearance and apparent volume of distribution at terminal phase were consistent (not dose-dependent) across LEM doses. Metabolite to parent ratio for  $AUC_{0-inf}$  (%) was detected in the following decreasing order after single dose administration: M10 (61–64%) > M4 (30–33%) > M9 (20–21%). In Cohort-2, steady-state was reached at Day 12 after multiple daily dosing. The accumulation ratio for LEM  $C_{max}$  and  $AUC_{0-24h}$  was 1.59 and 2.09, respectively; ratios were similar for the M4 (1.39, 1.74) and M9 (1.34, 1.73) metabolites, but higher for M10 (2.54, 3.00).

All subjects in Cohorts-1 and -3, and 9/10 subjects in Cohort-2 completed the treatment regimen. The number of subjects with  $\geq 1$  treatment-emergent AE (TEAE) was comparable across cohorts (Cohort-1 6/8 [75.0%]; Cohort-2 5/10 [50.0%]; Cohort-3 5/8 [62.5%]). Most TEAEs were mild and consistent with the known safety profile of LEM.

**Conclusion:** In healthy Chinese subjects, LEM and metabolite exposure increased in a dose-proportional manner with single-dose administration, and steady-state level was reached at Day 12 after multiple daily dosing. Data from this study are consistent with those from a study of LEM in Japanese and White subjects and with the pharmacokinetic analyses of race in the LEM clinical development program; all indicated no important exposure differences based on race. LEM was well tolerated following single doses up to 25mg and following multiple daily doses of 10mg.

**Acknowledgements:** Supported by Eisai Co., Ltd.

## PREDICTORS OF INSOMNIA AMONG ADOLESCENTS A LONGITUDINAL STUDY

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**Introduction:** Insufficient sleep is a public health problem that can impact children's' and adolescents' mental and physical health. This longitudinal study aimed to investigate whether sleep habits, sleep duration and family financial situation among school-aged girls and boys (age 6–10 years) can predict insomnia among female and male adolescents (age 14–16 years).

**Materials and Methods:** School-aged children (n = 522, 49.8% girls) in southern Sweden answered a questionnaire at baseline (age 9.4, SD 1.28 years) and at follow-up (age 14.3, SD 0.69). The survey consisted of questions about tiredness in school, problems waking up, sleep duration, sex, family financial situation and questions from the Minimal Insomnia Symptom Scale - Revised (MISS-R). Multivariate binary logistic regression analyses were used to examine whether tiredness at school, problems waking up, short sleep duration, gender, and family financial situation at baseline predicted insomnia at follow-up.

**Results:** Poor family financial situation (OR: 3.3) and short sleep duration

(<10 hours, OR: 2.3) among girls at baseline was associated with insomnia at follow-up. Problems waking up among boys at baseline was associated with insomnia at follow-up (OR: 3.6).

**Conclusions:** Short sleep duration, problems waking up and poor family financial situation in childhood are linked with adolescent insomnia. However, these associations differ between girls and boys, and therefore need to be further investigated to understand adolescent insomnia.

**Acknowledgements:** The authors wish to thank all the adolescents as well as the school administrations, teachers, and school nurses for facilitating data acquisition. Funding was received from the Gyllenstiernska Krapperup Foundation, the Crafoord Foundation, the Research Platform for Collaboration for Health, Faculty of Health Sciences, Kristianstad University, and Lund University.

## PRESCRIPTION DIGITAL THERAPEUTIC FOR PATIENTS WITH INSOMNIA (SLEEP-I): A PROTOCOL FOR A PRAGMATIC RANDOMIZED CONTROLLED TRIAL

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**Introduction:** Cognitive behavioral therapy for insomnia (CBT-I) is effective at treating chronic insomnia, yet in-person CBT-I can be challenging to access. Prior studies have used technology to bridge barriers but have been unable to assess the impact of the digital therapeutic on patient experience in real-world clinical settings, including on outcomes related to patient satisfaction, clinical efficacy, and healthcare utilization. Among patients with insomnia, our aim is to determine the impact of a Prescription Digital Therapeutic (PDT) for chronic insomnia (PEAR-003b, FDA-authorized as Somryst) on these patient-reported outcomes (PROs), as well as healthcare utilization.

**Materials and Methods:** We are conducting a pragmatically designed, prospective, multi-center randomized controlled trial leveraging Hugo, a unique patient-centered health data-aggregating platform for data collection and patient follow-up. A total of 100 participants with insomnia from two U.S. health centers will be enrolled in Hugo, provided with a linked Fitbit (Inspire 2) to track activity, and then randomized 1:1 to receive (or not) the PEAR-003b PDT for mobile-delivered CBT-I. The primary outcome is a change in the insomnia index scale (ISI) score from baseline to 9-weeks post-randomization. Secondary outcomes include healthcare utilization, health utility scores, and clinical outcomes; change in sleep outcomes; and a change in individual PROs including depressive symptoms, daytime sleepiness, health status, stress, and anxiety. For those allocated to the PEAR-003b PDT, we will also assess engagement with the PDT.

**Results:** Although the trial is ongoing and results are not yet available, study results will ultimately advance our understanding of: (1) how novel ways of collecting and aggregating clinical and PROs data can support informed clinical decision-making; (2) digital therapeutic engagement and its relationship to clinical outcomes; and (3) evaluation of data from linked devices by providing novel information on a PDT used for chronic insomnia, connected with the Hugo platform. The outcome of this research will provide crucial data to inform the latest thinking about how data from both digital therapeutics and EHR systems can be utilized to evaluate real-world patient-centered clinical and utilization outcomes. These data will be used to demonstrate the value of implementing technology within healthcare systems, supporting the broad uptake of similar technology platforms. In addition, they will inform reimbursement discussions with payers to support coverage of and broad access to effective digital therapeutics. For this audience, interim baseline data will be shared, as well as

lessons thus far learned from integration of multiple technological devices in a single RCT.

**Conclusions:** This trial will provide important data to patients, clinicians, and policymakers about the impact of the PDT device delivering CBT-I on patient-reported outcomes, clinical outcomes, and healthcare utilization.

**Acknowledgements:** This work was supported by the Medical Device Innovation Consortium (MDIC) on behalf of the National Evaluation System for health Technology (NEST) Coordinating Center (6292-2019-R2TC-B18), initiative funded by the U.S. Food and Drug Administration (FDA).

### PROLONGED-RELEASE MELATONIN FOR INSOMNIA IN CHILDREN WITH AUTISM SPECTRUM DISORDER

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**Introduction:** pediatric insomnia is a sleep problem, with a prevalence of 3% to 12% in the general pediatric population and 44% to 83% in children with autism spectrum disorder (ASD). In particular, sleep maintenance insomnia in the form of repeated awakenings or early awakenings in children with ASD, is one of the sleep disturbances that mostly affect the quality of life of patients and their families and which most aggravates the daytime autistic symptoms. The main objective was to describe the efficacy of prolonged-release melatonin minitablets (PedPRM) (Slenyto®) for the treatment of insomnia in children with ASD.

**Material and methods:** Prospective descriptive study on the efficacy of PedPRM after at least 6 months of use measured by anamnesis (total sleep time, sleep latency and awakenings) as well as with objective scales (Paediatric Sleep Disturbance Scale (SDSC, pathological >70) and Paediatric Daytime Sleepiness Scale (PDSS, pathological >16).

**Results:** 23 children and adolescents (13 boys, mean age 11 years [4-18]) were studied after twenty-four weeks of PedPRM treatment with a mean dose of 6 mg/day (range 2-10 mg). Before PedPRM treatment mean total sleep time was 8.4 hours [5-10]; sleep latency was 41.2 minutes [10-120]; and the number of nighttime awakenings was 3.6 awakenings/night [1-10]; mean total SDSC score was 75.04 [44-100] and for onset and maintenance disturbance (SDSC subscale) was 80.82 [57-100], both considered pathological; mean PDSS score was 14.6 [23-8]. Six months from the start of treatment with PedPRM participants slept on average 47.83 minutes longer at night. Sleep latency was reduced on average by 23.53 minutes. The number of awakenings decreased on average by 2.36 awakenings/night, in all patients the number of nocturnal awakenings decreased by more than 50%. The mean total SDSC score was 61.6 [80-42], onset and maintenance disturbance (SDSC subscale) was 63.05 [41-95] both lower than 70 and thus no longer a sleep disturbance pathology. The mean PDSS score was 10.36 [6-19]. No adverse effects were recorded except for one patient who withdrew treatment due to irritability, and no problems with ingestion of the formulation were reported. To sum up, we can say that Slenyto met the treatment objectives by reducing sleep latency by 30 min, reducing the number of awakenings, and increasing total sleep time according to the National Sleep Foundation.

**Conclusion:** PedPRM appears to be a safe and effective alternative for the treatment of maintenance insomnia in children with ASD.

### PSYCHOLOGICAL AND BIOLOGICAL RISK FACTORS FOR INSOMNIA AND DEPRESSED MOOD AMONG HOSPITAL NURSES WORKING IN SHIFTS

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**Introduction:** There is a vast body of knowledge about the associations between insomnia and depression in the working population; however, studies have yet to examine psychobiological risk factors for developing insomnia and depressed mood concomitantly in high-functioning, shift-working nurses. The theoretical framework for this study is based on the Behavioral Model for Insomnia<sup>1</sup> and the Analytical Rumination Hypothesis

for Mood and Depression<sup>2</sup>. The latter model is novel in that it conceptualizes rumination and depressed mood as adaptive behavioral features in the context of stressful situations. This study examines the contribution of common biological and psychological risk factors in the development of insomnia and depressed mood and aims to develop a novel psychobiological conceptual model to describe their co-occurrence among hospital nurses working in shifts

**Materials and Methods:** In this cross-sectional design, we recruited female hospital nurses, shift and day workers, and assessed them for insomnia, depressed mood, stress, analytical rumination and chronotype by validated self-administered questionnaires delivered online. Using structural equation modeling (SEM), we assessed common pathways between psychological and biological factors affecting insomnia and depressed mood.

**Results:** Four hundred and forty-eight nurses filled out the electronic questionnaires. The age (mean ± standard deviation) of shift nurses (n=358) was 40±9.67 years, compared to 47±7.81 years of day-work nurses (n = 90) working mornings only (p=.003). Shift nurses compared to day-work nurses were found to have higher rates of insomnia and depressed mood (70.1% vs. 52.2% and 45.8% vs. 30%, respectively). Shift nurses reported higher levels of insomnia (p <.001), depressed mood (p=.001), stress (p=.033), and a tendency to an evening chronotype (p<.001) compared to day-work nurses. No group differences were found for analytical rumination level. A positive linear relationship was found between insomnia and depressed mood in both shift nurses (r=.527, p<.001) and day-work nurses (r=.534, p <.001). SEM showed that shift work contributed directly to insomnia but indirectly to depressed mood. Chronotype and stress mediated the associations between shift work and both insomnia and depressed mood. Analytical rumination, stress, and evening chronotype were directly associated with insomnia and depressed mood.

The overall model showed a good fit between the empirical and theoretical model proposed in the study [ $\chi^2$  (4)=.16, p=.060, CFI=.99, RMSEA=.053].

**Conclusions:** Understanding factors underlying insomnia and depressed mood among shift-working nurses, who are particularly vulnerable to develop these disorders, is a first step towards developing interventions aimed at improving nurses' health and quality of life, which in turn improves the quality of care provided to patients. This study provides the groundwork in creating a theoretical psychobiological model to examine these phenomena in hospital nurses.

<sup>1</sup> Spielman et al., (1987). *The Psychiatric Clinics of North America*. 10(4):541-53.

<sup>2</sup> Andrews & Thomson (2009). *Psychological Review*. 116(3):620-54

### PSYCHOLOGICAL CHARACTERISTICS OF COMMUNITY PEOPLE WITH INSOMNIA FOCUSED ON : ATTENTION DEFICIT HYPERACTIVITY SYMPTOMS, DEPRESSION, ANXIETY AND MOOD DISORDER

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**Introduction:** Insomnia is known as the cause and aggravation of various mental symptoms. In this study, we aimed to find out the psychological characteristics according to insomnia in the community sample.

**Materials and Methods:** This study was conducted with 800 adults, and 756 of them were included for the data analysis. Demographic factors were investigated. Psychosocial factors were evaluated using the Adult ADHD Self-Report Scale (ASRS), Wender-Utah Rating Scale (WURS), Patient Health Questionnaire-9 (PHQ-9), Generalized Anxiety Disorder-7(GAD-7), Korean version of Mood Disorder Questionnaire (MDQ-K) and Insomnia Severity Index(ISI). According to the ISI score, it was divided into 3 groups: mild [0-7, (a)], moderate [8-14, (b)], and severe [15-28, (c)]. Independent t-test, one-way ANOVA and logistic regression analysis were used to compare differences among groups.

**Results:** In comparison of the insomnia group to the non-insomnia group,

there were significant differences in the ASRS ( $t=-6.175$ ,  $p<0.001$ ), WURS ( $t=-6.087$ ,  $p<0.01$ ), GAD-7 ( $t=-7.583$ ,  $p<0.001$ ), PHQ-9 ( $t=-10.388$ ,  $p<0.001$ ), and MDQ ( $t=-6.254$ ,  $p<0.01$ ). Psychological characteristics differed significantly in ASRS ( $F=22.517$ ,  $p<0.001$ , in comparison of the insomnia-positive group to the insomnia-negative group, the OR was 4.088 in the PHQ-9 positive group (95% CI: 2.02-8.28) and 2.286 in the MDQ positive group (95% CI: 1.38-2.86).

**Conclusions:** Insomnia was associated with a variety of mental symptoms, and the psychological symptoms were shown to be severe according to the severity of insomnia. Therefore, adequate intervention is needed to improve the symptoms of insomnia.

**Acknowledgements:**

#### PUBLIC HEALTH IMPACT OF POOR SLEEP ON COVID-19, INFLUENZA AND UPPER RESPIRATORY INFECTIONS

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**Introduction:** Poor sleep is associated with an increased risk of infections and all-cause mortality and acute sleep loss and disruption have been linked with inflammation and poorer immune control. Previous studies, however, have been unable to evidence causality between the chronic effects of poor sleep and respiratory infection risk. In light of the ongoing COVID-19 pandemic and future disease outbreaks, understanding the risk factors for these infections is of great importance.

**Aim:** Our goal was to understand if chronic poor sleep could be identified as a causal risk factor for respiratory infections including influenza, upper respiratory infections and COVID-19.

**Methods:** We used population cohorts from the UK Biobank (N=230,000), and FinnGen (327,000) with ICD10-based electronic health record and questionnaire based information on self-reported short sleep and insomnia, diagnosis of insomnia and diagnosis of respiratory infections at primary care and hospitals. We computed logistic regression to assess association between poor sleep and infections, disease free survival hazard ratios, and used data from genetic studies of insomnia, COVID-19 and infections in Mendelian randomization analyses to assess the causal direction of association.

**Results:** Utilizing 20 years of registry data and follow-up, we saw that Insomnia diagnosis associated with increased risk for infections in FinnGen and in UK Biobank (FinnGen influenza HR = 5.32 [4.09, 6.92],  $P = 1.02e-35$ , UK Biobank influenza HR = 1.67 [1.52, 1.84],  $P = 3.12e-27$ ). Mendelian randomization suggested that insomnia predisposed to influenza (OR = 1.59,  $P = 6.23e-4$ ), upper respiratory infections (OR = 1.71,  $P = 7.60e-13$ ), COVID-19 infection (OR = 1.08,  $P = 0.037$ ), and severity of respiratory infection measured as COVID-19 hospitalization (OR = 1.47,  $P = 4.96e-5$ ) and death from COVID-19 (OR = 1.64,  $P = 1.02e-3$ ).

**Conclusions:** Our findings indicate that chronic poor sleep is a causal risk factor for contracting respiratory infections, and in addition contributes to the severity of respiratory infections. These findings highlight the role of sleep in maintaining sufficient immune response against pathogens as suggested by earlier work. As the current COVID-19 pandemic has increased the number of people suffering from poor sleep, safe interventions such as sleep management and treating individuals with insomnia could be promoted to reduce infections and save lives.

**Acknowledgements:** We acknowledge the participants of the FinnGen and the UK Biobank studies for making this research possible. We also acknowledge the work of the international COVID-19 Human Genetics Initiative for making their genetic association results publicly available.

#### REAL WORLD EFFICACY OF A MULTICOMPONENT CBTI PROGRAM WITH CHATBOT AND AI

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**Introduction:** Cognitive behavioral therapy is the gold standard treatment for insomnia (CBTi), but access to it remains restrictive. Although digital models have been developed worldwide and proved effective, dropout rates still challenge their scalability, and no solution so far has been validated using artificial intelligence (AI), as a strategy to personalize therapy and improve engagement. We analyze real-world data of a novel multi-component program developed by Vigilantes do Sono (Sleep Watchers), using chatbot and AI.

**Materials and Methods:** A virtual assistant interacts with users daily, for 5-10 minutes during ~7 weeks, asking them to complete tailored diaries and delivering CBTi knowledge pills in ~45 sessions, distributed in seven modules. Behavioral strategies include stimulus control, sleep restriction, sleep hygiene, and light therapy. Relaxation trainings include deep breathing, progressive muscular relaxation, meditation/mindfulness, visualization, and autogenic training. Cognitive techniques include the idea parking lot matrix, paradoxical intention, thought stopping, gratitude diary, and challenging negative thoughts, besides education about sleep and health. The Insomnia Severity Index (ISI) is used before and after sleep restriction cycles. Participants (18+ years) were recruited through social media, organic search, or referred by health-care professionals (HCPs), from January/2020 to November/2021, without face-to-face evaluation. All of them electronically signed an informed consent. Generalized Estimating Equations (GEE) indicated changes in sleep parameters adjusting for gender, age, insomnia duration, medication, and number of diaries.

**Results:** Of 144,903 sleep diaries registered in our database, 81% were included in analysis, from 3,341 individuals (40.2±11.9 years, 76.7% women) who completed seven or more diaries, and had insomnia (ISI>7). Modules 2, 3, 4, 5, 6, and 7 were completed by 1,547, 1,133, 906, 773, 658, and 574 individuals, respectively, reaching the following therapeutic response (ISI reduction >7) or remission (ISI<7) rates at the end of each module: 55%, 58%, 60%, 63%, 65%, and 67%. GEE showed sleep duration increased on average 21.3 (7.5-35.1) minutes from first to second week and 70.0 (50.1-90.0) minutes after week seven, representing a 33% increment in sleep efficiency among women and 24% among men. Stimulus control was the behavioral strategy reported as most used, in 51% of sleep diaries, whereas the gratitude diary was the cognitive technique most used, reported in 53% of the nights. Among individuals who completed the program, 91% said they would recommend it. The program's Net Promoter Score is 95.

**Conclusions:** Chatbot with AI provided CBTi personalization, favoring engagement and effectiveness compared to referenced models worldwide. The findings demonstrate efficacy of the program and reinforce the use of AI in optimizing this new therapeutic modality.

**Acknowledgements:** We would like to thank Taqtile(R) for funding our initiative, as well as our collaborators, Prof. Fatima Cintra, Prof. Maria Laura Pires, Tatiana Vidigal, Daniel Polesel, and Altay de Sousa, for their technical support and methodological advices.

#### RESPIRATORY SAFETY OF LEMBOREXANT IN ADULT AND ELDERLY SUBJECTS WITH MODERATE TO SEVERE OBSTRUCTIVE SLEEP APNEA: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, CROSSOVER STUDY

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**Introduction:** A safety risk of some commonly prescribed sleep-promoting drugs, including benzodiazepines and nonbenzodiazepine receptor agonists, is central respiratory depression. Subjects with coexisting respiratory disease such as obstructive sleep apnea (OSA), and/or the elderly, are particularly at risk. Lemborexant (LEM) is a dual orexin receptor

antagonist (DORA) approved in multiple countries for the treatment of adults with insomnia. In study 102 (E2006-A001-102; NCT03471871), no differences between LEM 10 mg (LEM10) and placebo (PBO) were found on peripheral oxygen saturation (SpO<sub>2</sub>) and the apnea-hypopnea index (AHI) in adult and elderly subjects with mild OSA following a single dose and multiple doses. Study 113 (E2006-A001-113; NCT04647383) is the first to investigate the effect of LEM on respiratory safety in adults and elderly subjects with moderate to severe OSA.

**Materials and Methods:** This was a multicenter, multiple-dose, randomized, double-blind, PBO-controlled, 2-period crossover study in adult (age  $\geq 45$  to  $< 65$ y) and elderly (age  $\geq 65$  to  $\leq 90$ y) subjects with moderate ( $15 \leq \text{AHI} < 30$ ) to severe ( $\text{AHI} \geq 30$ ) OSA. Subjects were randomized to two 8-night treatment periods (separated by a washout  $\geq 14$ d) with either LEM10 or PBO. In-lab polysomnography and transmissive pulse oximetry were performed at screening, on Day 1 (after a single dose) and Day 8 of study drug during both treatment periods. Treatment-emergent adverse events (TEAEs) were recorded throughout the study.

**Results:** Forty-eight subjects were screened; 33 (68.8%) were randomized; of these  $n=13$  had moderate OSA and  $n=20$  had severe OSA. Mean age was 60.6y; 22/33 subjects (66.7%) were age  $\geq 45$  to  $< 65$ y and 11/33 (33.3%) were  $\geq 65$  to  $\leq 90$ y. During total sleep time, mean baseline SpO<sub>2</sub> was 93.5% and mean AHI for moderate OSA and severe OSA groups together ( $n=33$ ) was 44.2. No significant difference was found in AHI (least squares mean [LSM]) after a single dose or multiple doses of LEM10 versus PBO in subjects with moderate (single: LEM10, 31.49; PBO, 32.41,  $P=0.818$ ; multiple: LEM10, 34.66; PBO, 37.16,  $P=0.442$ ) or severe (single: LEM10, 48.22; PBO, 52.69,  $P=0.172$ ; multiple: LEM10, 51.48; PBO, 51.15,  $P=0.902$ ) OSA. LEM10 versus PBO was also not significantly different for SpO<sub>2</sub> (LSM with moderate [single: LEM10, 93.68; PBO, 93.86,  $P=0.696$ ; multiple: LEM10, 93.74; PBO, 93.86%,  $P=0.784$ ] or severe [single: LEM10, 92.57; PBO, 92.65,  $P=0.841$ ; multiple: LEM10, 92.63; PBO, 93.02,  $P=0.283$ ] OSA). Furthermore, no significant difference was found in percentage of total sleep time during which SpO<sub>2</sub> was below the thresholds of  $< 90\%$ ,  $< 85\%$ ,  $< 80\%$  for LEM10 vs PBO following a single dose ( $P=0.694$ ,  $P=0.134$ ,  $P=0.195$ , respectively) or multiple doses ( $P=0.481$ ,  $P=0.711$ ,  $P=0.699$ , respectively) in subjects with moderate or severe OSA.

TEAEs were higher with LEM10 (18.2%) versus PBO (9.1%). One subject did not complete treatment due to an adverse event unrelated to LEM10 (COVID-19). Overall, LEM was well tolerated, and most TEAEs were mild.

**Conclusion:** As objectively measured by AHI and SpO<sub>2</sub> during TST, LEM, a DORA, demonstrated respiratory safety with single and multiple dosing in subjects with moderate and severe OSA, and was well tolerated.

**Acknowledgements:** Supported by Eisai, Inc.

## RETHINKING NAP CULTURE? IMPACT OF DAYTIME SLEEP ON NIGHTTIME SLEEP AND TOTAL SLEEP DURATION IN CHINESE PATIENTS WITH INSOMNIA

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**Introduction:** Napping is often considered beneficial in Chinese culture. Yet from a sleep biology perspective, daytime sleep can interfere with nighttime sleep by reducing homeostatic sleep drive and increasing wakefulness at night. This raises the question of how to make appropriate recommendations regarding napping for Chinese patients with insomnia. In this study, a group of Chinese patients with insomnia who completed Cognitive Behavioral Therapy for Insomnia (CBT-I) were followed intensively to examine the effects of daytime naps on nighttime sleep and total sleep duration.

**Materials and Methods:** Patients with insomnia ( $N=34$ ), as confirmed by clinical evaluation and Insomnia Severity Index score  $> 10$ , completed 4 sessions of weekly group CBT-I conducted in Mandarin via telehealth. Participants completed daily sleep logs including self-reported nighttime sleep duration, sleep onset latency, wake after sleep onset, daytime nap duration, total sleep time across 24 hours, and daily stress levels. Multilevel structural equation modeling was used to examine within-person and between-person effects of daytime napping on nighttime sleep and 24-hour sleep duration.

**Results:** All variables showed remarkable within-person variation, with

ICCs ranging from 0.21 to 0.58, indicating that more than 40% of the variance was within individuals. Multilevel models suggested that daytime napping significantly predicted nighttime sleep. Specifically, after controlling for daily stress levels, longer daytime naps were associated with longer nighttime sleep latency ( $B=0.104$ ,  $SE=0.048$ ,  $p=.030$ ), more wake after sleep onset ( $B=0.063$ ,  $SE=0.034$ ,  $p=.061$ , marginal), lower sleep efficiency ( $B=-0.144$ ,  $SE=0.043$ ,  $p=.001$ ) and shorter sleep duration ( $B=-0.069$ ,  $SE=0.042$ ,  $p=.097$ , marginal) at the within-person level. Napping also had a significant effect on sleep duration at the between-person level, with people who took shorter daytime naps more likely to sleep longer at night compared to those who took longer daytime naps ( $B=-0.445$ ,  $SE=0.196$ ,  $p=.023$ ). However, total sleep time across 24 hours was equivalent in both groups.

**Conclusions:** In this sample of Chinese participants with insomnia who completed CBT-I, daytime napping negatively impacted nighttime sleep, with longer daytime naps associated with poorer nighttime sleep, especially longer time to fall asleep and poorer sleep efficiency. As well, those who took longer naps showed shorter nighttime sleep duration compared to those who did not nap or took shorter naps but showed equivalent sleep duration across 24 hours. These findings provide insight into whether it makes sense to promote “nap culture” in Chinese patients with insomnia. The results suggest that a flexible approach to accommodating nap culture, along with education about the impact of daytime napping on nighttime sleep and total sleep duration, may be more appropriate, as it respects cultural differences as well as individual autonomy.

## SLEEP DISORDERS & FATIGUE IN CANCER – RESULTS OF A MULTICENTRE STUDY

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**Introduction:** Fatigue and sleep disorders, especially Insomnia, are very common in different kinds of cancer, but their prevalence and incidence are not well known. Fatigue and / or disturbed sleep in cancer can be caused by different reasons and usually appears as comorbid disorder to different somatic, psychiatric diagnosis, psychological disturbances and treatment methods.

Despite many advances in psycho-oncological research and care, structured psycho-oncological care through psycho-oncological services (POD) is currently not sufficiently established in the German Comprehensive Cancer Centers (CCC).

The multicentre project should research the psycho-oncological counseling and care in the various cancer centers from an individual as well as structural point of view. The project was a cooperation with all 13 German CCCs.

In the study, the psychosocial stress in the patients was systematically determined, the need and the concerns of the patients for psycho-oncological help was researched for the users as well as the non-users of psycho-oncological support. The various criteria were recorded over four measurement times.

Furthermore, special cancer-specific comorbidities - such as insomnia, fatigue and pain - were also recorded.

**Methods:** All patients with malignant tumor diseases, who were older than 18 years and were being treated in one of the CCCs. Patient access was coordinated by local cooperation partners Berlin, Dresden, Erlangen, Essen, Frankfurt / a. M., Freiburg, Hamburg, Heidelberg, Cologne-Bonn, Nuremberg, Tübingen, Ulm and Würzburg. All cancer patients should gradually receive psycho-oncological counseling and care. All endpoints of the study protocol should be evaluated for T0 to T3 - including Cancer-related Fatigue (CrF) and Insomnia.

The longitudinal multicenter study included 1,511 T1-patients with cancer (58.2 % females – 41.8 % males, mean age: 55.8 years; T3:  $N = 836$ ). CrF was measured by the EORTC-Fatigue. Socio-demographic and clinical data, as well as psychological parameters (Distress Thermometer, PHQ-9, GAD-7, SF-12, SSUK-9, Pain Scale and Insomnia Severity Index (ISI)), were assessed at baseline (T1), even 6 months later (T2) and 12 months later (T3).

**Results:** In our sample, a high prevalence of relevant fatigue symptoms (38.7 %, moderate and severe) and insomnia (insomnia symptoms: 49.4 %, moderate and severe) were found.

ISI > 7; clinical insomnia: 12.8 %, ISI > 14) were found. When fatigue was present at T1, this problem was persistent after one year in 28.4 %. However, significantly more women suffered from fatigue symptoms.

The insomnia problem was persistent after one year in 64 %. However, at T2 significantly more women suffered from insomnia symptoms (53.3% women vs. 39.3% men;  $p = .003$ ).

Fatigue was associated with many clinical and psychological parameters, especially with insomnia ( $r = 0.5$ ); even Insomnia was associated with many clinical and psychological parameters, especially with fatigue ( $r = 0.5$ ).

In all participants, levels of distress, depression, and anxiety decreased from T1 to T2 ( $p$ 's < 0.016).

**Discussion:** Cancer-related Fatigue (CrF) and Insomnia is a common in cancer patients. Although medical and psychological parameters improved during the 12-month course of cancer treatment. The results show that fatigue is highly persistent, especially in women. This indicates that adequate support for those affected is needed.

### SLEEP DISORDERS AND MENTAL HEALTH IN HOSPITAL WORKERS DURING THE COVID-19 PANDEMIC: A CROSS-SECTIONAL MULTICENTER STUDY IN NORTHERN ITALY

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**Introduction:** From the beginning of the COVID-19 pandemic, healthcare workers had to face unprecedented emergency needs associated with an extraordinary amount of psychological distress. In this cross-sectional multicenter study, we investigated sleep disturbances, and the level of anxiety and depression among the healthcare and nonhealthcare staff of three hospitals in Milan (Italy) during the COVID-19 outbreak. Moreover, we explored potential predisposing factors for affective symptoms and poor sleep.

**Materials and Methods:** Between June and July 2020, we administered an online questionnaire to evaluate the presence of sleep disorders (Pittsburgh Sleep Quality Index), insomnia (Sleep Condition Indicator), anxiety (State Trait Anxiety Inventory) and depression (Beck Depression Inventory-II). We used univariate and multivariate analysis to evaluate the association between the personal conditions and sleep and affective disorders.

**Results:** The 964 participants reported high rates of sleep disorders (80.3% - mainly insomnia (30.5%) - anxiety (69.7%) and depression (32.8%). The multivariate analysis showed a strong association of sleep disorders, especially insomnia, with female gender ( $p=0.004$ ), divorced marital status ( $p=0.015$ ), self-isolation ( $p=0.037$ ), and chronic diseases ( $p=0.003$ ). Anxiety was significantly associated with teleworking ( $p=0.001$ ), while depressive symptoms were associated with self-isolation ( $p=0.028$ ), modified work schedules ( $p=0.03$ ) and chronic diseases ( $p=0.027$ ).

**Conclusions:** In hospital workers, the high prevalence of sleep and psychiatric symptoms during the COVID-19 outbreak appears to be determined mainly by modifications of personal or work habits. Teleworking was associated with increased anxiety. An accurate planning of hospital activities and a psychological support are needed to prevent and manage sleep and mental disorders.

### SLEEP DISTURBANCE AND AGGRESSION INCIDENTS IN SECURE MENTAL HEALTH SETTINGS

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**Introduction:** Insomnia symptoms are a prevalent transdiagnostic feature of psychiatric disorders. Within secure (forensic) psychiatric settings, insomnia symptoms have also been associated with the occurrence of aggressive incidents, with disinhibitory fatigue proposed as a causal mechanism. Research on sleep-related patient incidents is limited by small sample sizes, low reliability of incident recording, and the under-representation of women. The present study assessed relationships between sleep disturbance and electronically recorded adverse incidents in a large sample male and female patients in a UK secure psychiatric setting.

**Materials and Methods:** 756 patients (361 female, 395 male) participated. At baseline and follow-up (at least 30 days after baseline) those who: a) responded "Often" or "All of the time" to the ReQoL-20 item "Over the last week, I had problems with my sleep"; and b) consumed hypnotic drugs on at least 3 nights over the same 1-week period, were defined as 'seriously sleep disturbed'. Frequency and severity of adverse incidents (involving aggression, self-harm, or hospital security) was extracted from patient records. Risk was assessed in binary logistic regression models with the occurrence of at least one adverse incident during the 1-week baseline or 30-day follow-up period as dependent. Covariates were: serious sleep disturbance; gender; quintile age-group (18 to 47+); anxiolytic use; neuroleptic use; antidepressant use; and two interaction terms for age or gender by serious sleep disturbance. Prospective associations with adverse incidents among new cases of sleep disturbance (reporting sleep disturbance only at follow-up) and 'good sleepers' (reporting no sleep disturbance at either assessment) were analysed using chi-squared.

**Results:** At baseline, 42% of patients (179 female and 137 male) were categorised as 'seriously sleep disturbed'; 19% of patients were involved in adverse incidents. Sleep disturbance and female gender were independently associated with a significantly elevated risk of adverse incidents in the baseline models ( $X^2 = 10.0$ ,  $df = 1$ ,  $p < 0.01$ , and  $X^2 = 37.9$ ,  $df = 1$ ,  $p < 0.001$ , respectively). In the follow-up models, sleep disturbance and gender significantly interacted to elevate incident risk (OR = 0.23; 95% CI = 0.07-0.83;  $p < 0.0$ ). At follow-up, new cases of sleep disturbance showed the highest level of participation in adverse incidents ( $X^2 = 10.0$ ,  $df = 3$ ,  $p < 0.05$ ), while 'good sleepers' (no sleep disturbance at baseline or follow-up) showed both the lowest participation in, and the lowest impact scores resulting from adverse incidents ( $X^2 = 8.45$ ,  $df = 3$ ,  $p < 0.05$ ).

**Conclusions:** Risk of adverse incidents is significantly increased by disturbed sleep. This risk is amplified in female patients, and, longitudinally, in those patients acquiring new disturbed sleep symptoms. Both the prevention of new sleep disturbance incidents, and the appropriate treatment of existing sleeping problems could help reduce adverse incidents among inpatients in secure psychiatric environments.

### SLEEP QUALITY AND MORTALITY IN COMORBID INSOMNIA AND SLEEP APNEA: A 10-YEAR FOLLOW UP COMPARATIVE STUDY ON THE POLYSOMNOGRAPHIC FEATURES

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**Introduction:** Co-morbid insomnia and sleep apnea (COMISA) is a prevalent disorder, which results in additive impairments to patients' sleep,

cardiometabolic comorbidities and death. Although Insomnia and SDB as isolated conditions have been focus of different clinical studies, there are no reports focusing on their interactive role as in comorbid insomnia and sleep apnea (COMISA) and the differences between them as regard the sleep architecture. The aim of the current study is to assess the burden of sleep disordered breathing and comorbid insomnia among patients suspicious of obstructive sleep apnea and the impact they have on sleep and following them up in a cohort of Egyptian patients.

**Materials and Methods:** We conducted a follow up study among adult patients (18 years or above), referred to the outpatient sleep clinic in the Alexandria main university hospital during the period from 2010 to 2020 (ten years). Patients with structural brain lesion, chronic pulmonary disorder, depression and anxiety were excluded. The data collected were (demographic, clinical, and biochemical). The insomnia was classified based on the DSM 5 criteria and subdivided by the Insomnia Severity Index. Polysomnography was the tool to subclassify the severity of sleep disordered breathing and the data were analyzed based on the AASM 2020. We used frequencies and means for qualitative and quantitative variables as appropriate.

Frequency of cardiometabolic risk factors were assessed for both 3 conditions insomnia, sleep apnea and cardiovascular comorbidities. Follow up for 10 years for the outcome was another objective. The study was ended in 2020 or after the death of the participant.

The subjects of the study were subdivided into a control normal group, patients with isolated sleep apnea, isolated insomnia and the fourth group was COMISA.

**Results:** The study included 391 patients who were on average 52 year old ( $\pm 15$ ), 53.5% were males, 20.2% were smoking, 22.3% had diabetes, 41.2%, were hypertensive, 35.5% with ischemic heart disease and 23.3% had cerebrovascular stroke. 82.9% of patients suffered from both apnea and insomnia while 7.9% complained of either one of them. There was a significant association between sleep disorders with gender, total sleep time in minutes, REM sleep percentages, sleep efficiency, and total arousal index, as well as highest heart rate in REM and lowest oxygen saturation. The mortality rate in the COMISA subgroup was the highest, yet did not reach a statistical significant threshold.

**Conclusion:** In this sample, patients with COMISA revealed the poorest polysomnographic outcomes when compared with isolated conditions. Given the relationship of PSG parameters with cardiometabolic outcomes and morbidity and mortality rates, future studies should look for such relationship in wider samples in order to confirm our findings. Meanwhile, although lacking statistical significance, the suggestive finding on the impact of COMISA in mortality, should benefit of further attention with an improved analysis which will be implemented in the future for this particular cohort.

## SLEEP REACTIVITY AND POOR SLEEP IN ADOLESCENTS: A LONGITUDINAL INVESTIGATION

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**Introduction:** Sleep reactivity, the vulnerability for disturbed sleep when facing stressful experiences, is commonly researched in adults and is a risk factor for insomnia. Sleep disturbances are also a widespread complication in adolescence, which often becomes chronic and causes great daytime impairments. Therefore, this study investigates the cross-sectional and longitudinal associations of sleep reactivity, poor sleep, and daytime complaints in adolescents.

**Materials and Methods:** 66 German adolescents ( $M_{age} = 14.6$  years,  $SD = 1.8$ , 60% female) participated at two measurement points, with about eight months in between, in which they answered the Ford Insomnia Response to Stress Test and a 14-days sleep diary. Cross-lagged structural equation models tested for bivariate associations between sleep reactivity, sleep quality, total sleep time, sleep latency, wake after sleep onset, waking restored, daytime mood, and performance capability.

**Results:** The results indicate a moderate stability for sleep and a high stability for sleep reactivity. Those adolescents with higher sleep reactivity were more likely to have lower sleep quality, poorer mood, and were more likely to perform worse, but not vice versa.

**Conclusions:** These findings suggest that an increased stress-sensitivity of the sleep system goes along with a lower subjective appraisal of one's sleep and more daytime difficulties. Adolescents with high sleep reactivity are therefore a risk group for long-lasting sleep disturbances, which should be targeted in interventions.

## SLEEP SPINDLES CHARACTERISTICS AS A POTENTIAL PREDISPOSING FACTOR IN INSOMNIA

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**Introduction:** Hyperarousal is a core feature of insomnia and is associated with deficient sleep protection mechanisms as reflected by altered sleep spindle profiles. Emerging evidence suggested that elevated sleep reactivity, as assessed by the Ford Insomnia Response to Stress Test (FIRST), is associated with cognitive and physiological indices of hyperarousal, conferring a higher risk for insomnia. To the best of our knowledge, no study has investigated the role of sleep spindle as potential predisposing factor to insomnia incidence. The present study aimed to compare sleep spindles characteristics amongst individuals with insomnia and good sleepers with high or low sleep reactivity.

**Materials and Methods:** Participants were 30 adults ( $M$  26.5 years,  $SD=5.2$ ; 70.1% female) with insomnia (INS;  $n=10$ ) and without insomnia. Based on a median score of 20 on the FIRST, good sleepers were subdivided into those with high (HSR;  $n=10$ ) and low sleep reactivity (LSR;  $n=10$ ). They underwent two consecutive nights of polysomnography (PSG) recordings, including a screening/adaptation night and a stress condition night. Spindle density (number of spindles per minute), duration (more than 0.5 sec), frequency (in Hz), and amplitude (in  $\mu V$ ) were calculated during nonrapid eye movement (NREM) sleep stages N2 and N3 for both nights. One-way ANOVAs were computed to compare group differences on spindle characteristics.

**Results:** While a mean number of spindles of 110.6 ( $SD: 93.7$ ), mean density/minute of 3.0 ( $SD: 1.5$ ) and mean duration of 0.6 sec ( $SD: 0.1$ ) were observed throughout N2 and N3 amongst all three groups, mean spindles' frequency and amplitude were respectively 13.1 ( $SD: .5$ ) and 35.8 ( $SD: 9.9$ ). ANOVAs revealed that frequency ( $F=28.9$ ,  $p<.001$ ) was significantly different between groups; the HSR group showed a lower frequency than both the LSR and INS groups. In addition, we found that amplitude differed significantly between groups ( $F=9.3$ ,  $p<.001$ ). Post-hoc analyses revealed that HSR individuals displayed higher amplitude than LSR, no significant differences were observed between HSR and INS. Surprisingly, the observed significant between-groups differences were similar on both nights.

**Conclusions:** The introduction of a stress protocol during the experimental night did not impact spindle's characteristics. Lower frequency and higher amplitude observed in individuals with high sleep reactivity might be reflective of a lack of consolidation and efficiency of the sleep spindle. Altered sleep protection mechanisms might constitute premorbid biomarker for insomnia vulnerability. Future research is required to expand these preliminary findings.

## STRUCTURAL BRAIN DIFFERENCES IN INDIVIDUALS WITH INSOMNIA COMPARED TO GOOD SLEEPERS FOR VOLUME, THICKNESS, AND SHAPE

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**Introduction:** Structural brain differences in individuals with insomnia are anticipated based on genome-wide analysis. Tissue or cell-type gene sets predict structural alterations in several cortical and subcortical regions including the anterior cingulate, medial frontal gyrus, basal ganglia, hypothalamus, and cerebellar hemispheres. Structural imaging studies have

identified altered volume, thickness, and shape in association with insomnia in numerous areas. However, neuroimaging studies have yielded inconsistent and contradictory findings in terms of location and direction of alterations. This study sought to investigate structural differences in a well-characterized sample of individuals with primary insomnia ( $n = 58$ ) compared to controls ( $n = 67$ ) using high-dimensional surface-based mapping procedures. It was hypothesized the insomnia group would demonstrate altered cortical thickness and localized volume differences in deep brain structures relative to the control group in regions predicted by prior genetic analyses.

**Materials and Methods:** Insomnia diagnosis was established using a structured clinical interview per Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria. Participants completed either a 1.5 Tesla (T) three-dimensional volumetric spoiled gradient recalled echo pulse sequence or a magnetization-prepared rapid acquisition with gradient echo pulse sequence at 3T. The 1.5 and 3T scans were harmonized for scanner effects using ComBat procedures that preserved the biological variation for age, sex, group, depression, and anxiety. Regions of interest (ROIs) were derived from the prior genome-wide analysis described above. We also investigated other brain regions implicated from prior neuroimaging studies including the hippocampus and thalamus. Image processing included the FreeSurfer toolkit and large-deformation diffeomorphic metric mapping. Group (insomnia vs. control) differences in volume, thickness, and shape deformation were determined using repeated-measures analysis of variance (ANOVA), multivariate ANOVA, and vertex-wise contrasts.

**Results:** Compared to controls, the insomnia group demonstrated significantly lower cortical thickness in the anterior cingulate ( $F_{1,123} = 4.82$ ,  $p=0.03$ ). The insomnia group also demonstrated greater cerebellar ( $F_{1,123} = 5.20$ ,  $p=0.02$ ) and posterior hypothalamic ( $F_{1,123} = 4.97$ ,  $p=0.03$ ) volume relative to controls. Finally, insomnia also showed significantly greater inward shape deformation in the head of the right caudate ( $F_{10,114} = 2.12$ ,  $p=0.03$ ) and exaggerated outward deformation of the right hippocampus ( $F_{10,114} = 1.93$ ,  $p=0.05$ ) compared to controls.

**Conclusions:** Results support the presence of insomnia-related structural alterations in regions implicated by tissue and cell-type gene sets associated with those regions. These regions are major hubs of conscious awareness and sensory processing (e.g., ACC), thermoregulation and histaminergic production (i.e., posterior hypothalamus), episodic memory (i.e., hippocampus), and REM and NREM sleep regulation (i.e., caudate), processes likewise implicated in the etiology of insomnia.

**Acknowledgments:** Protocols used in this study were supported by federal grants including the National Heart, Lung, and Blood Institute (HL65112) and National Institute of Mental Health (MH24652, MH61566).

#### SUBTYPING OF INSOMNIA DISORDER ON PREDICTION OF TREATMENT RESPONSE TO E-BASED COGNITIVE BEHAVIORAL THERAPY FOR INSOMNIA IN YOUTH

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**Introduction:** Insomnia disorder in youth is characterized by a high degree of phenotypic heterogeneity, which is related to its comorbidity with mental problems. Subtyping insomnia disorder based on comorbid psychopathology may help to understand differential treatment response so as to maximize treatment effects. Thus, we aimed to identify subgroups of insomnia disorder through data-driven analysis and evaluate the treatment response of different subgroups towards e-based cognitive behavior

therapy for insomnia (e-CBT-I) in youth.

**Materials and Methods:** In this study, Chinese youth (aged 15–25) with diagnosed insomnia disorder were randomly assigned (1:1) to 6-week e-CBT-I or e-based health education (e-HE as control), and assessed at baseline, post-intervention, 6-month and 12-month later. Subgroups of insomnia disorder were discriminated by latent class analysis. In the latent class model, baseline characteristics of participants, including insomnia, depression and anxiety symptoms, suicidality, fatigue, sleep beliefs and chronotype preference, were used to determine the subtype profile with two conditions (e-CBT-I and e-HE) and outcome variable (Insomnia Severity Index score at post-intervention) included as grouping variable and covariate, respectively. This trial was registered in ClinicalTrials.gov (NCT04069247).

**Results:** A total of 559 participants were randomly allocated to e-CBT-I or e-HE group. The latent class analysis was based on the initial sample of 449 participants (e-CBT-I:  $n = 224$ ; e-HE:  $n = 225$ ) who completed assessments at post-intervention. Five insomnia disorder subgroups were identified: 1) moderate insomnia with high level of suicidal ideation comorbid with moderate depression and anxiety, 2) moderate insomnia with moderate depression and anxiety only, 3) severe insomnia with moderate depression and mild anxiety, 4) moderate insomnia with moderate depression and mild anxiety, and 5) moderate insomnia with mild depression and anxiety. In e-CBT-I group, the remission rate for insomnia at post-intervention was significantly lower in subgroup 1 (33%) compared to subgroup 4 (70.1%) and 5 (76.9%). In addition, the remission and response rates in both subgroup 1 and 3 did not differ significantly from e-HE group, whereas the remission rate was higher in subgroup 4 and 5 than controls. Although majority of the youth in subgroup 2 also did not achieve better remission after e-CBT-I intervention, the response rate of this subgroup was significantly higher than controls.

**Conclusions:** The results suggested that insomnia disorder in youth can be categorized into different subgroups by severity of insomnia, depression, anxiety, and suicidality. High level of suicidality comorbid with moderate depression and anxiety as well as severe insomnia comorbid with moderate depression will predict poor response or treatment resistance in youth receiving sleep intervention, such as e-CBT-I. The study highlights the importance of further subtyping insomnia disorder especially on the need for assessments of comorbid depression, anxiety and suicidality. Our data suggests the need for personalizing e-based sleep intervention with add-on modules on mood and suicide management for these subtypes.

**Acknowledgments:** Li Chiu Kong Family Sleep Assessment Unit, Department of Psychiatry, The Chinese University of Hong Kong, Hong Kong SAR and grant from National Natural Science Foundation of China (no. 81761128036) supported this work.

#### TESTING AN INTERNET-DELIVERED INSOMNIA PROGRAM AMONG FAMILY CANCER CAREGIVERS: USE, SATISFACTION, AND PRELIMINARY EFFECTS

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**Introduction:** Family cancer caregivers experience insomnia at about twice the rate of the general population, but have significant barriers to accessing cognitive-behavioral therapy for insomnia (CBT-I). Delivering CBT-I by the Internet may allow more caregivers to access this treatment. This pilot study aimed to examine cancer caregivers' use, satisfaction, and treatment benefits, as well as the association of caregiving context with these metrics, for an evidence-based Internet-delivered CBT-I program, Sleep Healthy Using the Internet (SHUTi).

**Methods:** Family members who provided care to a cancer patient and who endorsed significant sleep disturbance received access to SHUTi for 9 weeks. Program use was tracked as number of intervention 'Cores' completed of 6 total, and satisfaction was measured at post-assessment (Client Satisfaction Questionnaire [CSQ]). At baseline and post-assessment, caregivers reported insomnia symptoms (Insomnia Severity Index [ISI]) and completed 10 sleep diaries (sleep onset latency [SOL], wake after sleep onset [WASO]). Characteristics of the caregiving context – time since diagnosis, relationship to the care recipient, average time spent caregiving per week, and caregiving stress and self-efficacy – were measured at

baseline.

**Results:** Of the 14 enrolled caregivers, 7 have completed the study at the time of abstract submission, 1 withdrew due to the patient's death, and the remaining 6 will complete by the end of 2021. Of study completers, caregivers completed a median of 4 of the 6 total Cores (range= 0-6). Of the 6 participants who completed any SHUTi Cores, 3 reported on the CSQ that most of their sleep needs were met and were generally satisfied with the program, 4 reported that they would use SHUTi again, and all 6 reported they would recommend SHUTi. On open-ended follow-up items, those who were dissatisfied indicated reasons related to the program not addressing caregiving-specific needs. Participants reported a large decline in ISI scores (baseline M(SD)=15.33(7.26); post M(SD)=9(5.14);  $t(5)=3.18$ ,  $p=.02$ ,  $d=1.42$ ), SOL minutes (baseline=28.08(17.95); post=15.44(10.75);  $t(4)=2.57$ ,  $p=.06$ ,  $d=1.29$ ), and WASO minutes (baseline=81.92(49.94); post=74.87(42.28);  $t(4)=2.40$ ,  $p=.07$ ,  $d=1.20$ ). There was an association between number of Cores completed and time spent caregiving per week ( $t(2.56)=3.54$ ,  $p=.05$ ): caregivers providing care for  $\leq 20$  hours/week completed 5-6 Cores on average compared to those caring  $>20$  hours/week completing 2-3 Cores. There were no other associations between change in number of Cores completed, overall CSQ score, or change in ISI scores, SOL, or WASO with caregiving context factors ( $ps>.11$ ). Results will be updated pending final post-assessment data collection.

**Conclusions:** Preliminary data provide the first evidence that an Internet-delivered CBT-I intervention developed for the general population can produce significant sleep improvement among family cancer caregivers. While caregivers generally reported treatment to be usable and satisfactory even without tailoring, caregivers with greater time involvement in care completed less of the intervention, and those who reported had remaining sleep needs unaddressed by the program indicated that caregiving-related tailoring would have been helpful. Further study is underway to understand what caregiver-specific tailoring is needed, and for whom, to optimize the intervention for caregivers.

**Acknowledgements:** U.S. National Center for Advancing Translational Sciences UL1TR003015, KL2TR003016; University of Virginia iTHRIV; ClinicalTrials.org:NCT04661306.

#### THE EFFECT OF DIGITAL COGNITIVE BEHAVIOURAL THERAPY FOR INSOMNIA ON SLEEP AND COGNITION: A RANDOMISED CONTROLLED TRIAL

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**Introduction:** Insomnia is a highly prevalent sleep disorder characterised by persistent problems with sleep initiation and maintenance, accompanied by significant impairment to cognitive functioning. Digital cognitive behavioural therapy for insomnia (dCBTI) has been shown to effectively improve self-reported insomnia severity. However, the effect of dCBTI on objective measures of sleep and cognition has not been systematically investigated. The aim of this randomised controlled trial was to assess objective and subjective measures of sleep and cognition in participants with insomnia before and after undergoing a 10-week period of either dCBTI or no treatment (wait-list (WLC)).

**Materials and Methods:** Thirty-three participants meeting diagnostic criteria for insomnia were randomised to either dCBTI ( $n=15$ ;  $f=14$ ; mean age 54.8 (standard deviation (SD): 8.1)) or WLC ( $n=18$ ;  $f=13$ ; mean age 53.1 (SD: 8.1)). All participants underwent three nights at the sleep laboratory: one sleep disorder screening night, one assessment night prior to the 10-week period (baseline), and one assessment night after the 10-week period (post-assessment). During the treatment period the dCBTI group received dCBTI (Sleepio program), whereas the WLC group received no treatment. Sleep and cognition were assessed using PSG, a word-pair task and self-reported questionnaires. Statistical analysis was performed using an ANCOVA with multiple imputations with the baseline as a covariant.

**Results:** At post-treatment the dCBTI group reported significantly better subjective sleep compared to the WLC group (Sleep Condition Indicator:

mean difference: 4.40 (standard error: 1.41);  $p$ -value=0.002). However, no significant differences in objective sleep (i.e. sleep architecture and sleep continuity) were found between the groups ( $p$ -values ranging from 0.28-0.94). In addition, no changes in cognition were observed (word-pair task;  $p$ -value=0.82).

**Conclusions:** Our findings show that dCBTI led to an improvement in subjective but not objective sleep outcomes in participants with insomnia. Furthermore, no significant changes in cognition were found after dCBTI. These findings are in line with results from face-to-face CBTi reporting that CBTi primarily improves self-reported sleep measures. In a next step we will analyse sleep microstructure and EEG spectral data.

**Acknowledgements:** The research was supported by the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre (BRC) and the Dr Mortimer and Theresa Sackler Foundation. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

#### THE EFFECTS OF COGNITIVE BEHAVIOUR THERAPY FOR INSOMNIA AND CONTINUOUS POSITIVE AIRWAY PRESSURE ON NEUROCOGNITIVE FUNCTIONING IN INDIVIDUALS WITH COMORBID INSOMNIA AND SLEEP APNEA (COMISA)

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**Introduction:** Neurocognitive impairments have been reported in individuals with OSA and insomnia separately, however, the evidence for impairment in comorbid insomnia and OSA (COMISA) is much less abundant and the evidence for the efficacy of treatment in reversing the neurocognitive impairment is inconclusive. We aimed to evaluate the benefits of treatment on neurocognitive performance.

**Methods:** COMISA participants ( $n=45$ ; 51.1% female; mean age=52.07 $\pm$ 13.29) from a 3-arm randomized clinical trial combining CBT and CPAP concurrently or sequentially, completed neurocognitive testing at baseline and before and after treatment. From this, we could deduce the effects of CBT alone, CPAP alone and combined treatment (CBT+CPAP). Bayesian mixed model analyses were conducted to assess the effect of each treatment (CBT-I alone, CPAP alone, CBT-I+CPAP) compared to baseline and the combined treatment option against CPAP alone. Since we compared the treatment combinations to everyone's baseline, all analyses included both within and between comparisons. To control for this, we used a mixed-methods structure and included the variation between individuals as a random effect. Age, gender, race, total sleep time and sleepiness were covariates. Some variables (e.g., reaction time) were reversed so that higher scores indicated better performance.

**Results:** Baseline neurocognitive functioning (working memory, vigilance/attention, verbal memory, associative ability, and executive functioning) was worse compared to normative values reported in the literature. Scores after receiving CBT-I alone were compared to baseline scores. In only 4 of 13 neurocognitive markers CBT-I was superior to baseline, indicating that after CBT-I, individuals had mostly poorer neurocognitive performance compared to baseline. The probability of superiority (ProS, the probability of the superiority of treatment over baseline) varied from 10-70%. Non-superiority of CBT-I compared to baseline (worse performance) was considerable (Cohen's  $d>1$ ) for working memory in particular. When comparing CPAP alone to baseline, 11 of the 13 markers were higher after treatment compared to baseline. ProS varied from 5-99%. Superiority of CPAP was considerable (Cohen's  $d>1$ ) for associative ability, executive functioning, verbal memory (delayed recall) and working memory. Comparing CBT+CPAP to baseline generated almost identical results to the CPAP only comparisons (except that treatment was superior to baseline in 9 of the 13 markers). When comparing CBT+CPAP to CPAP alone,

neurocognitive scores were higher on only 4 of the 13 comparisons; ProS varied from 16–64%. Non-superiority of CBT+CPAP over CPAP alone was considerable (Cohen's  $d > 1$ ) for working memory and associative ability.

**Conclusions:** After receiving CBT-I alone neurocognitive performance is poorer than at baseline. If combined with CPAP, neurocognitive performance is poorer than after CPAP alone. These patterns are particularly pronounced for working memory and associative ability, and may be a result of sleep restriction therapy (a component of CBT-I), which is associated with a temporary reduction in total sleep time. COMISA patients require close monitoring, especially when undergoing CBT-I. These effects may only be temporary (our follow-up were only 60 or 90 days) and thus, need to be replicated over longer periods.

**Acknowledgements:** This study was funded by an NIH supplemental grant to support diversity in health-related research.

### THE EUROPEAN PORTUGUESE VERSION OF THE DYSFUNCTIONAL BELIEFS AND ATTITUDES ABOUT SLEEP SCALE (DBAS-30): EXPLORING ITS RELIABILITY AND DIMENSIONALITY

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**Introduction:** The Dysfunctional Beliefs and Attitudes about Sleep Scale (DBAS) has become a core instrument for assessing sleep-related cognitions.

The 30-item DBAS comprises five well-known dimensions. Although the scale's internal consistency is satisfactory, some dimensions show low internal consistency. Furthermore, studies failed to replicate its original dimensional structure. This study aimed to examine the reliability of the Portuguese version of the DBAS-30 and its original dimensions, and explore the dimensionality of the scale.

**Materials and Methods:** After translation, back-translation and pilot testing, the DBAS-30 was applied to a total of 824 participants (201 with insomnia disorder from a Sleep Medicine Center [SMC] and 623 from the community). Then, two groups were generated - Insomnia Group (IG) and Normal Sleepers Group (NSG). The IG comprised 355 participants (261F, 94M),  $18 \leq \text{age} \leq 85$  years ( $47.90 \pm 13.25$ ) combining 201 patients with insomnia disorder from the SMC (129F, 72 M),  $18 \leq \text{age} \leq 85$  years ( $49.98 \pm 13.36$ ) and 154 individuals from the community (132F, 22M),  $18 \leq \text{age} \leq 73$  years ( $45.19 \pm 12.63$ ) presenting sleep difficulties as evaluated through a "yes-no" question and ISI scores  $\geq 14$ . The NSG comprised 292 participants from the community (237F, 54M)  $18 \leq \text{age} \leq 72$  years ( $39.90 \pm 13.88$ ) without sleep problems ("yes-no" question and ISI < 14). Reliability was estimated by Cronbach's coefficients. Factor structure was assessed in IG by three different techniques: (1) Exploratory Factor Analysis (EFA) with Principal Axis Factoring followed by Direct Oblimin rotation, (2) Principal Component Analysis followed by Promax rotation, using Kaiser's eigenvalues  $> 1$  and Cattell's Scree plot, and (3) EFA with Parallel Analysis followed by Direct Oblimin rotation using a Robust Diagonally Weighted Least Squares (DWLS) technique.

**Results:** Cronbach's alpha was .89 demonstrating good internal consistency. Item exclusion would not increase the scale reliability. Cronbach's alpha was .86 for IG, and it was also .86 for NSG. Regarding the original dimensions of the scale, only the dimension "Consequences" presented satisfactory internal consistency ( $\alpha > 0.70$ ) both for the IG and the NSG.

We found different solutions for the DBAS-30 factor structure, depending on the techniques used. The first analysis failed to reach convergence. The second analysis yielded an 8-factor solution (total explained variance = 57.4%), in which three are somewhat comparable to theoretical original dimensions, while the others did not resemble any dimension. The third analysis using the DWLS technique produced 3 interpretable factors accounting for 46.4% of the total variance. Based on the content of the factors, they were labelled as follows: F1 - "Aging and Hopelessness", F2 - "Sleep Expectations", and F3 - "Consequences and Helplessness". Factors 1 and 3 revealed satisfactory ( $\alpha = 0.74$ ) and good ( $\alpha = 0.86$ ) internal

consistency, while the value for factor 2 was lower ( $\alpha = 0.51$ ).

**Conclusions:** DBAS-30 PT appears to be a reliable tool for clinical practice and research, including non-clinical samples. This study also adds to research by suggesting a new and meaningful dimensionality of the DBAS-30, supported by the most recent factor analysis techniques.

**Acknowledgements:** We are grateful to all participants involved in this study.

### THE FUNCTION OF BEDTIME PROCRASTINATION IN INDIVIDUALS WITH CLINICAL INSOMNIA

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**Introduction:** Bedtime Procrastination (BP) is defined as the behavior of going to bed later than intended, despite the absence of external factors. Bedtime procrastination has been associated with various sleep problems including insomnia. Behavioral principles assert that most problem behaviors are maintained because they fulfill a function. To date, there have been no studies investigating the function of bedtime procrastination in clinical insomnia patients.

**Materials and Methods:** This study was conducted in 80 adults (mean age  $22.26 \pm 2.36$  years, 80.0% females) with clinical insomnia selected based on DSM-5 criteria. Participants who scored 33 or higher on the Bedtime Procrastination Scale (BPS) and scored 15 or higher on the Insomnia Severity Index (ISI) were included in this study. Functional analysis of bedtime procrastination as a problem behavior was conducted with an interviewer. Functional analysis consists of the following: Antecedents(A); Behaviors(B), and Consequences(C). After functional analysis, responses of the participants were classified into 7 categories as following: (1) emotion regulation; (2) compensation; (3) social interaction and feelings of belonging; (4) searching for information; (5) trying to fall asleep; (6) feelings of accomplishment and (7) pleasure. These categories were defined by interviewers discussing the functions of bedtime procrastination of each individual recorded on the recording tape based on previous study. Data was analyzed using descriptive statistics and multiple response analysis.

**Results:** As a result, data from 80 participants were used for analysis, but since duplicate responses were allowed, the total frequency of responses was 140. The sum of the response ratios for each item was 175.0%. Among the total frequency of responses, the most common functions of bedtime procrastination were emotional regulation (49.3%), compensation (14.3%) and trying to fall asleep (10.7%).

**Conclusions:** These findings suggest that individuals with clinical insomnia engage in bedtime procrastination mainly to regulate their emotions and for compensation from the day, but also to try to de-arouse and fall asleep. It is important to consider the functions of bedtime procrastination, a factor that has emerged as an important clinical predictor, when developing interventions for individuals with clinical insomnia.

**Acknowledgements:** This work was supported by the Ministry of Education of the Republic of Korea and the National Research Foundation of Korea (NRF-2018S1A5A8026807)

### THE IMPACT OF ADDING QI-GONG TRAINING TO PHARMACOTHERAPY IN POST COVID INSOMNIA. A PROSPECTIVE STUDY

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**Introduction:** The COVID19 pandemic affected the sleep of a large number of patients who suffer from insomnia, especially in the post covid period. This affects their lives and does not improve easily after applying the recommended guidelines for insomnia management such as sleep hygiene

rules, CBT and short term pharmacotherapy (z-drugs). Several studies came recently to light; talking about the positive effect of Qi-gong exercises on mental health and sleep disorders in particular.

The aim of this study is to evaluate adding Qi-gong training to pharmacotherapy on insomnia during the post covid period in Egyptian COVID-19 patients.

**Materials and Methods:** A simple selection of insomnia cases referred to the sleep clinic at Elhadara University Hospital complaining of insomnia following documented covid-19 infection. Patients less than 18 years were excluded from the study as well as critically ill and hospitalized patients. They were stratified according to the severity of covid infection into having an asymptomatic, mild, moderate or severe. The study included 106 cases and 251 control subjects.

A good sleep history was taken as well as the insomnia severity scale was performed (the arabic validated version) to all cases on the first visit. All cases were on sleep aids mainly the z drugs and all of them performed simple Qi-gong training for two weeks besides sleep medications. Again a post insomnia severity scale was done to all participants.

**Results:** There was a statistically significant difference between cases with covid and the control group as regard the severity at the baseline screening. (\* $P < 0.001$ )

By comparing the pre and post training results there was a statistically significant result both in the insomnia patients with COVID-19 (\* $P < 0.000$ ) and those without COVID-19 (\* $P < 0.000$ ), denoting the positive effect of the Qi-gong training.

The severity of infection affected the severity of insomnia: the milder the infection the less the severity of insomnia.

**Conclusions:** The results showed a significant improvement in both; Post-COVID-19 and non-post-COVID insomnia by 68.18% and 64.2% respectively in response to the Qi-gong training, with no difference between males and females.

**Acknowledgements:** We acknowledge the help of the Sleep lab team at the Hadara university hospital, Faculty of medicine and the team of the department Of Fitness, Gymnastics and Sports at the faculty of Physical Education.

### THE INCIDENCE OF ABNORMAL DREAMS AND NIGHTMARES IN ADULTS WITH INSOMNIA TREATED WITH LEMBorexant: RESULTS FROM TWO PHASE 3 STUDIES

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**Introduction:** Abnormal dreams and nightmares have been reported by patients with insomnia both before and after treatment with hypnotics. Since dual orexin receptor antagonists (DORAs) such as lemborexant (LEM) increase REM sleep, during which dream content is more likely to be recalled, we assessed the frequency of reports of nightmares/abnormal dreams in subjects treated with LEM during two Phase 3 studies. LEM is approved in multiple countries including the United States, Japan, Canada and Australia for the treatment of adults with insomnia.

**Materials and Methods:** Study 303 (SUNRISE-2; NCT02952820) was a 12 month, randomized, double-blind, placebo (PBO)-controlled (first 6 month [Period 1]), phase 3 study that enrolled subjects aged  $\geq 18$  years with insomnia disorder and Insomnia Severity Index (ISI) scores  $\geq 15$ . During Period 1, the safety analysis set (SAS) included: PBO, n=319; LEM 5 mg, (LEM5), n=314; LEM 10 mg (LEM10), n=314. Study 304 (SUNRISE-1; NCT02783729) was a 1 month, randomized, double-blind, PBO- and active-controlled (zolpidem tartrate extended-release 6.25 mg [ZOL-ER]) study of LEM5 and LEM10. The SAS included: PBO, n=209; ZOL-ER, n=263; LEM5, n=266; LEM10, n=268.

**Results:** In Study 303 Period 1, 28/947 subjects (3.0%) reported nightmares (n=12; PBO, n=1; LEM5, n=4; LEM10, n=7) or abnormal dreams (n=17; PBO, n=6; LEM5, n=7; LEM10, n=4) as treatment-emergent adverse events (TEAEs). In Study 304, 12/1006 subjects (1.2%) reported nightmares (n=4; PBO, n=1; ZOL-ER, n=0; LEM5, n=2; LEM10, n=1) or abnormal

dreams (n=8; PBO, n=1; ZOL-ER, n=3; LEM5, n=0; LEM10, n=4). 32/40 subjects (80.0%) reporting these events were female. In the LEM groups, 11/28 subjects (39.3%) reported the TEAE within 3 days of treatment initiation. There were 2 TEAEs of nightmare/abnormal dreams during the PBO run-in prior to randomization.

**Conclusions:** Abnormal dreams/nightmares were not common events in either study. Incidence was slightly higher with LEM10 and higher in females, which was consistent with a greater proportion of females being enrolled in both studies.

**Acknowledgements:** Supported by Eisai Inc.

### THE MEDIATING ROLE OF NEURO-IMMUNE MARKERS IN THE LONG-TERM ASSOCIATION BETWEEN INSOMNIA AND DEPRESSION: AN EIGHT-YEAR FOLLOW-UP

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**Introduction:** Robust meta-analytic evidence of longitudinal epidemiological studies shows that insomnia (i.e., difficulties falling asleep or maintaining sleep, non-restorative sleep) may be associated with future onset of depressive symptoms in short- to medium-term follow-ups. However, there is still a dearth of literature on the long-term association between sleep disturbance and depression, and on the psychobiological processes underlying this association. To address these gaps, this study aimed to investigate the long-term association between insomnia and depressive symptoms in older adults and ascertain whether this association is mediated by neuro-immune markers.

**Materials and Methods:** Data analysis was conducted on 3998 participants aged 50 and above from the English Longitudinal Study of Ageing (ELSA) across three waves of data collection. Conditional process analysis was employed to estimate the association between insomnia symptoms assessed in 2008/9 using the Jenkins sleep scale, and self-reported depressive symptoms assessed in 2016/2017 using the Centre for Epidemiological Studies-Depression (CES-D). Serum levels of high sensitivity C-reactive protein (hs-CRP), white blood cell (WBC) count, and insulin like growth factor-1 (IGF-1) measured in 2012/2013 were considered as mediators. Participants with hs-CRP values  $> 10$  mg/L were excluded from the study since this could reflect current acute infection rather than chronic inflammation. Analyses were adjusted for health-related and psychosocial confounders including cardiovascular disease, age, co-habitation status, alcohol intake, smoking, and baseline depression.

**Results:** Insomnia at baseline significantly predicted depression at eight-year follow-up. hs-CRP and IGF-1 significantly mediated the association between insomnia and depression only in unadjusted analysis. When adjusted for health-related and psychosocial confounders, simple slopes analysis revealed that insomnia predicted higher hs-CRP only in participants with concomitant short sleep duration ( $\leq 6$  hours), as well as lower IGF-1 independent of sleep duration. Also, hs-CRP directly predicted depressive symptoms. WBC count did not significantly correlate with insomnia in preliminary correlation analysis; thus, WBC count was not considered in the mediation model.

**Conclusions:** Whilst insomnia resulted significantly associated with depressive symptoms in a long-term follow-up, present data does not provide robust evidence that increased inflammation may mediate this association. Rather, present findings suggest that difficulties in sleep onset and sleep maintenance may be associated with inflammation and depressive symptoms only when coupled with short sleep duration. The mediation role of further neuro-immune markers should be explored in future longitudinal studies, including interleukin-6 (IL-6), and the brain-derived neurotrophic factor (BDNF).

**Acknowledgement:** ELSA data is available in the UK Data Service. Blood samples were analysed at the Royal Victoria Infirmary laboratory in Newcastle upon Tyne, UK. Detailed information on biological data collection and analysis is reported in Sproston K, Mindell J. Health Survey for England: methodology and documentation, vol. 2. Leeds: The Information Centre; 2004.

## THE ROLE OF COGNITIVE EMOTION REGULATION STRATEGIES IN EXPLAINING INSOMNIA SYMPTOMS IN ADOLESCENCE AND EARLY ADULTHOOD

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**Introduction:** Cognitive emotion regulation (CER) may be defined as the cognitive way of managing emotional information and refers to the mental side of the emotion regulation process. The association between maladaptive CER strategies and psychopathological symptoms is widely documented. However, the link with insomnia has been less thorough, and there is even less evidence about the difference in these relationships between young adults and adolescents. In this regard, neurological changes that occur during adolescence might shape the use of more advanced cognitive and emotional abilities with consistent differences in the use of specific CER strategies. To address these gaps, we present the results of two studies to examine the unique predictive power of each cognitive ER strategy on insomnia in two samples of adolescents and young adults.

**Materials and methods:** A convenience sample of 431 young adults aged 18–28 years (Mage = 20.66, SD = 2.21) was recruited among the Student Community of Sapienza University of Rome. On the other hand, a total of 271 adolescents, aged 13–17 years (Mage = 14.80, SD = 0.59, 55.4% males) were enrolled from two high schools in Rome. The Cognitive Emotion Regulation Questionnaire (CERQ) and the Insomnia Severity Index (ISI) were administered to assess CER strategies and insomnia symptoms. Nine CER strategies were evaluated: putting into perspective, acceptance, positive refocusing, positive reappraisal, refocus on planning, rumination, catastrophizing, self-blame and other-blame.

After a series of assumptions check, two hierarchical linear regression models were implemented to assess the impact of CER on insomnia in both samples. Gender was forced into the equation in the first step as control variables, while the major set of CER entered in the second step.

**Results:** The final model accounted for approximately 15% of the variance of insomnia symptoms among young adults. Specifically, after controlling for the effect of gender, catastrophizing ( $\beta = .130$ ;  $p < .05$ ), self-blame ( $\beta = .181$ ;  $p < .001$ ), and putting into perspective ( $\beta = -.109$ ;  $p < .05$ ) significantly predicted insomnia. On the other hand, the regression model explained approximately 29% of the variance of insomnia in adolescents. After accounting for gender, rumination ( $\beta = .236$ ,  $p < 0.001$ ) and catastrophizing ( $\beta = .195$ ,  $p < 0.01$ ) were significant predictor of insomnia symptoms.

**Conclusions:** These findings corroborate the role of maladaptive CER strategies as potential contributors of sleep quality impairment, as well as the benefit of incorporating emotion regulation training in insomnia intervention programs. We highlight that, differently from what was found in adolescents, adaptive CER strategies (i.e., putting into perspective) may be relevant in preventing adults' insomnia. Results are consistent with research on the refinement of emotion regulation repertoire across the lifespan, suggesting a general trend to increase adaptive CER strategies. Future longitudinal studies are needed to infer the direction of the relationship of the use of emotion regulation strategies with insomnia symptoms and investigate whether the contribution of CER strategies changes depending on age-specific biological, social, or environmental resources.

## THINK POSITIVE: POSITIVE RUMINATION ASSOCIATION WITH BETTER SUBJECTIVE SLEEP IS MEDIATED VIA REDUCED EMOTION SUPPRESSION IN A NON-CLINICAL SAMPLE

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**Introduction:** Affect-focused emotion regulation strategies play a role in subjective sleep quality. One type of affect-focused emotion regulation strategy is rumination, which is also a key sign of insomnia. Rumination was originally defined as perseverative negative thinking about personal worries, their causes and their consequences, both triggered by- and maintaining negative affect. However, recent research has further proposed the concept of 'positive rumination' (PR), which refers to the tendency to respond to positive affective states with repetitive cognitions of positive content and valence.

According to the Cognitive Model of Insomnia, negative rumination (NR) perpetuates insomnia as it is associated with sympathetic nervous system arousal which interferes with sleep. There is evidence, however, that PR is also associated with increased arousal, while protecting against symptoms of anxiety and depression. Thus, in the context of insomnia, there are two equally plausible hypotheses: [a] the tendency for cognitive perseveration on either positive or negative emotionally-arousing cognitions, will be associated with more insomnia symptoms; [b] alternatively, that NR will be associated with more insomnia symptoms whereas PR will be associated with better subjective sleep quality.

The primary aim of the present study was to test these competing hypotheses, in a non-clinical sample, positing that the association between rumination tendencies and insomnia symptoms is mediated by emotion regulation strategies, namely reappraisal or suppression.

**Materials and Methods:** 354 participant (59% women), ages 18–50, responded to online questionnaires regarding their sleep (Pittsburgh Sleep Quality Index, [PSQI]) and Insomnia Severity Index [ISI]), emotion regulation questionnaire (ERQ) that categorizes two strategies: Reappraisal and Suppression, NR (ruminative response scale [RRS]), PR using the positive subscales of the Dampening and Positive Rumination (DPR), general health and demographics.

**Results:** Although young and healthy, 72% scored above 5 on the PSQI. Of respondents who scored above 5, 69% scored below 14 on the ISI scale, classifying their symptoms as subclinical. Additionally, women had higher scores on both ISI and PSQI scales ( $p < .05$ ), thus gender was entered as a background variable. Due to the sample size, all correlations were statistically significant. The ISI had 'very weak' negative correlations with the ERQ Reappraisal subscale and with PR subscales of the DPR ( $R_s < 0.19$ ), had a 'weak' correlation with ERQ Suppression subscale ( $R = .363$ ), and 'moderate' correlations with NR measures (DPR dampening:  $R = .528$ ; RRS:  $R = .596$ ). ISI and PSQI had a 'very strong' correlation ( $R = .840$ ).

To test the primary hypothesis, separate models were tested for NR and PR. Rumination was entered as a predictor, emotion regulation style (Reappraisal/Suppression) was entered as mediators, with ISI as the outcome variable. For NR, there was a significant direct effect NR → ISI ( $\beta = 0.84$ ,  $p < .001$ ) but indirect effects were not significant. For PR, the direct effect was significant PR → ISI ( $\beta = 0.18$ ,  $p = .009$ ), and only the indirect effect of Suppression was significant (PR → suppression → ISI:  $\beta = -0.32$ ,  $p < .001$ ).

**Conclusions:** The results suggest that positive rumination is also associated with insomnia symptoms, where higher positive rumination is linked with reduced insomnia symptoms through reduced active suppression of emotions.

**Acknowledgements:** The author thanks Ms. Lilach Portal

## WHEN PROTOCOL DOES NOT WORK – EFFECTIVE TREATMENT OF INSOMNIA WITH COGNITIVE-BEHAVIORAL THERAPY

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**Introduction:** Cognitive Behavioral Therapy for Insomnia (CBT-I) is the first-line treatment of primary insomnia. Findings indicate that alone or in combination with pharmacotherapy, CBT-I is a highly effective intervention (Jacobs et al. 2004). Still, some patients do not respond to this method. How to address their needs?

A Transdiagnostic Sleep and Circadian Intervention (TranS-C) developed by Allison G. Harvey and Daniel J. Buysse (2018) seems promising in addressing more complex issues. It is based on a more flexible approach. However, it still includes basic elements of the insomnia treatment,

highlighted in the classical therapy protocol. This poster describes an attempt to combine CBT-I and Trans-C ideas in a group therapy for patients responding in a heterogeneous way to the intervention.

**Method:** The poster presents the course of treatment for patients with insomnia. They have been qualified for 8-week cognitive-behavioral group therapy for insomnia (CBT-I). During the therapy two patients were unable to follow the protocol so the treatment had to be modified. The changes introduced were inspired by the TranS-C model. Two TranS-C components were put into practice : Cross-Cutting Module - Behaviour Change and Motivation and Core Modules – Establishing Regular Sleep-Wake Times and Correcting Unhelpful Sleep-Related Beliefs.

**Results:** It has been found that treatment modification in the case of those two patients allowed resolving the deadlock in the therapy. Concentration on generating motivation to change, modification of unhelpful beliefs and establishing regular sleep and activity times enabled introduction of crucial behavioural interventions in the course of treatment.

**Conclusion:** The various nature of sleep problems even in the case of the same diagnosis induces searching for optimized treatment methods. There are new therapeutic proposals – as TranS-C, combining traditional elements with flexibility. Does it mean the new will replace the old? It does not seem so. The poster illustrates that you can derive from a variety of available ideas and follow the general path of the protocol at the same time. However, to not get lost it is advisable to keep the treatment structure and follow the therapeutic aim.

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#### WHITE MATTER MICROSTRUCTURE BEFORE AND AFTER 6 WEEKS OF INSOMNIA INTERVENTIONS

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**Introduction:** Insomnia disorder is a common sleep disorder that poses a high risk factor for developing depressive symptoms. Insomnia interventions such as cognitive behavioural therapy for insomnia (CBT-I) successfully mitigate this risk and reduce insomnia severity. Whether interventions for insomnia alter brain structure is not known. The key components of CBT are training and learning. While intense training and learning can alter white matter microstructural properties, few studies evaluated the effects of CBT and only in other disorders. Using a longitudinal design, this study aimed to determine whether different insomnia interventions affect white matter microstructure in people with insomnia at high risk of developing depression. In addition, we studied the association between pre-intervention white matter microstructure and treatment-elicited improvements in the severity of insomnia and depression symptoms.

**Materials and Methods:** People fulfilling the DSM-5 criteria for Insomnia Disorder (n=117) participated in a randomized-control trial (registered with the Netherlands Trial Register NL7359) comparing 6 weeks of no treatment (NT) with therapist-guided digital CBT-I, or Circadian Rhythm Support (CRS), or their combination (CBT-I+CRS). Diffusion weighted images (3 Tesla) were acquired pre- and post-treatment. Diffusion tensor models were fitted to estimate fractional anisotropy (FA) and mean diffusivity (MD) as measures of white matter microstructure. We performed whole brain analysis using tract-based spatial statistics (TBSS) adapted for longitudinal studies combined with permutation-based testing. Subsequently, we performed region of interest analysis in the 48 white matter tracts of the ICBM-DTI-81 white-matter atlas

**Results:** CBT-I and CBT-I+CRS significantly reduced insomnia severity index scores (respectively  $d = -1.05$ ,  $p < 0.001$ ,  $d = -0.87$ ,  $p = 0.002$ ) and self-rated inventory of depressive symptomology scores (respectively  $d = -0.78$ ,  $p = 0.001$ ,  $d = -1.01$ ,  $p < 0.001$ ) compared to no treatment during the 1-year follow-up. However, TBSS revealed no significant clusters with changes in FA or MD after CBT-I, CRS or CBT-I+CRS compared to the no treatment group. None of the pre-treatment FA or MD measures significantly predicted post-treatment outcome in ISI or IDS-SR. Subsequent ROI analysis revealed significant lower MD within the right superior corona radiata of the CBT-I+CRS group compared to the NT group after the intervention ( $d = -0.148$ ,  $p_{FDR}$ -value = 0.043,  $n = 112$ ). But this did not correlate with changes in ISI ( $R = -0.03$ ,  $p = 0.88$ ) or IDS-SR ( $R = 0.23$ ,  $p = 0.30$ ).

**Conclusions:** In spite of effectively reducing insomnia and depression severity, 6 weeks of insomnia interventions did not significantly alter white matter microstructure in people with insomnia. Only subsequent ROI analysis found lower MD in the right superior corona radiata showed after CBT-I+CRS, but did not correlate with improvement in symptom severity. Compared to previously studied nonclinical learning and training protocols, clinical insomnia interventions are likely too broad to effectively elicit white matter microstructural changes measurable with diffusion MRI.

**Acknowledgements:** This work received funding from the European Research Council ERC-ADG-2014-671084. TB and JL have been supported with an University Research Fellowships by Vrije Universiteit Amsterdam.

#### WORRY, RUMINATION AND INSOMNIA IN PATIENTS WITH CORONARY HEART DISEASE -A CROSS-SECTIONAL STUDY WITH LONG-TERM FOLLOW-UP

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**Introduction:** Insomnia is prevalent and reported in up to 40% among patients with coronary heart disease (CHD). It is associated with anxiety and depression in these patients. Cognitive behaviour therapy for insomnia (CBT-I) is the most effective psychological treatment for insomnia, but generally only 30-40% achieve full remission and in older patients (>60 years) only mild effect on sleep problems are reported. Therefore, there is a need to develop effective psychological interventions of insomnia in CHD patients. Worry and rumination are potential risk factors for maintenance of insomnia, anxiety and depression that may be modified by psychological treatment grounded in the Self-Regulatory Executive Function model. However, the relationships between worry, rumination, anxiety and depression and insomnia are not known. Therefore, we investigated these relationships both cross-sectionally and longitudinally among CHD patients.

**Materials and Methods:** This cross-sectional study consecutively included 1127 patients (median age 62 years, 21% females, acute myocardial infarction was the index event in 79%) in 2014-15, and 686 participated in a follow up study after 4.7 years. Data were gathered from hospital records and self-report questionnaires comprising assessment of insomnia (Bergen Insomnia Scale), worry (Penn State Worry Questionnaire), rumination (Ruminative Responses questionnaire) and anxiety and depression (Hospital Anxiety and Depression Scale). Pearson's r and hierarchical multiple blockwise logistic regression analyses were applied for predicting insomnia at baseline and follow up.

**Results:** Insomnia was reported by 45% at baseline and 38% at follow up. Insomnia correlated moderately with all other psychological factors ( $r$  0.18-0.50, all  $p$ -values  $< 0.001$ ). Worry and rumination scores correlated 0.61 and both variables correlated moderately with insomnia at baseline and follow-up. After adjustments for anxiety and depression, Odds Ratio for insomnia at baseline were 1.27 (95% CI 1.08-1.50) per 10 points increase of worry and 1.60 (95% CI 1.31-1.94) per 10 points increase of rumination, whereas Odds Ratio for insomnia at follow-up were 1.28 (95% CI 1.05-1.55) and 1.38 (95% CI 1.09-1.75) also per 10 points increase of worry and

rumination. Anxiety remained significantly associated with insomnia after adjustments for worry and rumination, but depression was no longer significant.

**Conclusions:** Worry and rumination predicted insomnia both cross-sectionally and prospectively above anxiety and depression. Future studies may test psychological interventions that target these factors in CHD patients with insomnia.

**Acknowledgements:** The project was supported by the University of Oslo and the Research Council of Norway (project no. 271555/F20).

## Memory

### DISRUPTED SLEEP MODERATES THE ASSOCIATION BETWEEN PSYCHOTIC-LIKE EXPERIENCES AND WORKING MEMORY IN YOUNG ADULTS.

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**Introduction:** Psychotic-like Experiences (PLEs) refer to psychotic symptoms in a subclinical population. Individuals with PLEs (e.g., increased bizarre experiences) were found to have cognitive deficits, such as low working memory capacity. Although growing literature has suggested the negative effects of sleep disturbances on cognitive functioning, it remains unclear whether poor sleep would exacerbate cognitive problems in people with PLEs. The current study aimed to examine the moderating effect of sleep on the association between PLEs and working memory in young adults.

**Methods:** A total of 64 university students (age = 19.21 ± 1.5, % female = 76.6) were included in the analyses. Participants were free of any psychiatric disorders as ascertained by Mini International Neuropsychiatric Interview (MINI). They completed the Community Assessment of Psychic Experiences (CAPE) as a measure of PLEs, the Insomnia Severity Index (ISI) and Pittsburgh Sleep Quality Index (PSQI) as measures of self-perceived sleep quality, and 8-day actigraphy sleep monitoring, followed by a laboratory-based assessment using a computerized n-back task and digit span task to measure working memory. Weighted d prime (d'), which considered both hit and false alarm rates, was used to reflect the accuracy, while Response time (RT) was calculated for only correct responses in the n-back task. Sleep onset latency (SOL), wake after sleep onset (WASO), total sleep time (TST), and sleep efficiency (SE) were derived from sleep diary and actigraphy for analyses. Hayes' PROCESS Macro version 4.0 was used to test the moderating effect of sleep on the association between PLEs and working memory performance.

**Results:** Total PLEs were associated with n-back RT at a marginal significance ( $B = -1.60, p = .057$ ). Moderation analyses indicated that most sleep parameters significantly moderated in the association between total PLEs and n-back RT. These included WASO measured by both actigraphy ( $B = -.157, p = .002$ ) and sleep diary ( $B = .669, p = .014$ ), sleep diary measured by SOL ( $B = .416, p = .003$ ), as well as TST ( $B = .040, p = .011$ ) and SE ( $B = .400, p = .005$ ) measured by actigraphy. Self-reported sleep quality (PSQI,  $B = -.556, p = .510$ ) and insomnia symptoms (ISI,  $B = -.177, p = .536$ ) and other parameters from sleep diary and actigraphy did not significantly moderate the association between PLEs and n-back RT. No significant associations were found between PLEs and the performance on digit span task.

**Discussion:** The findings of the present study provided preliminary support for the moderating effect of sleep on the relationship between PLEs and working memory. Future studies should include a larger sample size and utilize a longitudinal design to examine the causality of these associations. The findings also implied the potential need for timely assessing and addressing disrupted sleep in vulnerable young adults, especially those with PLEs.

### INSOMNIA SYMPTOMS AFFECT FALSE MEMORIES PRODUCTION

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**Introduction:** It has been shown that false memories production is increased when memory of word lists is tested after experimental sleep deprivation compared to normal night sleep (Diekelman et al., 2008; Verma & Kashyap, 2019). Instead, the influence of poor sleep quality on false memories formation in populations with impaired sleep has not yet been addressed. In individuals with insomnia, poor sleep is also accompanied by several cognitive impairments involving prefrontal functioning that could affect source-monitoring processes and contribute to false memories production (Balleisio et al., 2018). Therefore, the aim of this study is to compare false memories production between individuals with insomnia symptoms and good sleepers, also addressing their executive functioning and source monitoring ability.

**Materials and Methods:** Thirty-two individuals with insomnia symptoms (IN group; 11M; age:24.4±4.0), screened through the Insomnia Severity Index (ISI, Bastien et al., 2001) and the Pittsburgh Sleep Quality Index (PSQI, Buysse et al., 1989), and 37 good sleepers (GS group; 10M; age:25.3±4.89) were administered the Deese-Roediger-McDermott paradigm (Roediger & McDermott, 1995). Participants completed an immediate free recall test and a recognition test after listening to 16-word lists, each made up of 15 words semantically related to a non-presented critical lure word. On a separate day, participants also underwent a cognitive assessment including the WAIS-IV's working memory subtests (Wechsler, 2008), the Stroop task, and a Source-Monitoring Test (SMT).

**Results:** At the immediate free recall test, the IN group produced a higher number of non-presented critical lures and intrusions (i.e. unstudied words not semantically related to the critical lure) compared to the GS group ( $p = .006$  and  $p = .002$ , respectively), whereas no differences between groups were observed for veridical memories (i.e. correctly recalled studied words). No between-groups differences emerged at recognition testing. Furthermore, the IN group showed a lower working memory index (WMI) than the GS group ( $p = .014$ ). Correlational analysis revealed that: a) the number of veridical memories negatively correlated with reaction times at the Stroop task ( $r = -.29, p = .016$ ) and with the number of correct responses at the SMT ( $r = .31, p = .010$ ); b) the number of lures was negatively associated with WMI ( $r = -.31, p = .009$ ); c) the number of intrusions positively correlated with Stroop reaction times ( $r = .29, p = .016$ ) and negatively with the number of correct responses at the SMT ( $r = -.32, p = .007$ ); d) the number of false recognitions negatively correlated with WMI ( $r = -.44, p < .001$ ). Moreover, both the number of lures and of intrusions showed positive associations with PSQI ( $p = .023, p = .05$ , respectively) and ISI scores ( $p = .037, p = .014$ , respectively).

**Conclusions:** Our data show that poor sleep quality promotes false memories production at immediate free recall but not at recognition testing, suggesting that an impairment of executive functioning in individuals with insomnia symptoms mainly affects more cognitively demanding tasks. Results from our correlational analyses also support the hypothesis that the impact of poor sleep on false memories production is mediated by impairments in executive functioning. Finally, the association of ISI and PSQI scores with false recall suggests that the process of false memories formation is modulated by the degree of sleep impairment.

### INVESTIGATING CHANGES IN COGNITION ASSOCIATED WITH THE USE OF CPAP IN COGNITIVE IMPAIRMENT AND DEMENTIA: A RETROSPECTIVE STUDY

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**Introduction:** Obstructive Sleep Apnea (OSA) manifests as recurrent obstruction of the upper airway during sleep. OSA, prevalent in patients with cognitive impairment, is an independent risk factor for dementia and cognitive decline. Continuous Positive Airway Pressure (CPAP), which administers pressurized air to keep the airway open, can treat OSA. However, it is unclear whether CPAP affects cognition in the cognitively impaired since previous studies have yielded conflicting findings. In addition, past analyses have not controlled for the impact of baseline sleepiness on any changes in cognition with CPAP despite its known influence on cognitive

performance. Furthermore, the MoCA has been underexplored in longitudinal studies in this specific population despite being among the most commonly used cognitive assessments. Thus, our objective was to characterize the impact of CPAP use on cognition in a clinical cohort with OSA and cognitive impairment (due to neurodegenerative and/or vascular etiologies) while controlling for baseline sleepiness.

**Materials and Methods:** We retrospectively analyzed 158 patients with cognitive impairment due to a neurodegenerative and/or vascular etiology and an OSA diagnosis confirmed with in-laboratory polysomnography or home sleep apnea testing (mean age  $69.9 \pm 10.7$ ; 69% male). Baseline Epworth Sleepiness Scores (ESS) and relevant comorbidities were obtained from self-reported questionnaires. Baseline and follow-up Montreal Cognitive Assessment (MoCA), and Mini-Mental Status Examination (MMSE) scores were obtained from clinical and research visits conducted 2–12 months apart where CPAP was prescribed in the intervening period. Adherence was defined as CPAP use  $\geq 4$  hr/night, 7 days/week at follow-up. Associations between CPAP adherence and follow-up cognitive scores were analyzed using multivariable linear mixed-effects models.

**Results:** After adjusting for age, sex, body mass index, ESS, duration of CPAP therapy, relevant comorbidities and the random effect of study cohort, good CPAP adherence (compared to poor CPAP adherence or no use of CPAP) was significantly associated with a 2.6-point increase in follow-up MoCA scores ( $p > 0.001$ ) and a 1.1-point increase in follow-up MMSE scores ( $p = 0.04$ ). Subgroup analyses revealed no significant differences in outcomes between different diagnoses of cognitive impairment.

**Conclusions:** In patients with OSA and cognitive impairment due to a neurodegenerative and/or vascular etiology, cognitive dysfunction may be stabilized or reversed with good adherence to CPAP therapy. The findings of this study will aid in motivating patients to use CPAP and support future randomized controlled trials in this area.

**Acknowledgements:** This work was supported by an Ontario Graduate Scholarship awarded to Yakdehikandage S. Costa and the Innovation Fund of the Alternative Funding Plan from the Academic Health Science Centers of Ontario.

#### OBSTRUCTIVE SLEEP APNEA-RELATED BLOOD OXYGEN DESATURATION IS ASSOCIATED WITH PREFERENTIAL CONSOLIDATION OF NEGATIVE MEMORIES IN OLDER ADULTS

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**Introduction:** Obstructive sleep apnea (OSA) is associated with damage to the hippocampus which is thought to underlie OSA-related cognitive impairment. The hippocampus is implicated in pattern separation—the process of storing highly similar experiences as non-overlapping memory representations. Mnemonic discrimination (a behavioral correlate of pattern separation) is a sensitive marker of hippocampal change in age-related cognitive decline and Alzheimer's disease (AD). Recent work has demonstrated that overnight sleep supports mnemonic discrimination in young adults. Less is known about the impact of sleep, or sleep disorders such as OSA, on mnemonic discrimination in older adults. While OSA has been shown to impact sleep-dependent processing of spatial, motor, and verbal memory, it is unclear whether OSA impacts the consolidation of emotional memories which typically exhibit a sleep benefit. This study aimed to determine whether OSA influences sleep effects on mnemonic discrimination of emotional experiences in older adults.

**Materials and Methods:** Eighteen cognitively-healthy older adults (MMSE  $\geq 27$ ;  $\mu_{\text{age}} = 73.1 \pm 5.3$ ; 10F) were evaluated with overnight polysomnography and the Apnea-Hypopnea Index (AHI), Respiratory Disturbance Index (RDI), Respiratory Arousal Index (RAI), and measures of blood oxygen desaturation (number, duration, and frequency of desaturations  $\geq 4\%$ , desaturation nadir) were derived. Participants completed the

emotional version of the Mnemonic Discrimination Task prior to and following overnight sleep, using positive, negative, and neutral images as stimuli. During memory testing, stimuli were split evenly among images seen during encoding (targets), new images (foils), and images similar to targets (high and low similarity lures). The Lure Discrimination Index (LDI;  $p(\text{'New'|Lure}) - p(\text{'New'|Target})$ ) was derived to assess emotional mnemonic discrimination. Sleep-dependent memory consolidation was measured by calculating overnight change in LDI. AHI and RDI were log-base 10 transformed to meet assumptions of normality.

**Results:** Three-way repeated measures ANOVA (valence, similarity, time) revealed that discrimination of highly similar negative stimuli significantly deteriorated following overnight sleep whereas positive and neutral stimuli were relatively preserved ( $F(2,34) = 3.76$ ,  $p = 0.034$ ). Log-AHI ( $r = 0.642$ ,  $p = 0.004$ ), Log-RDI ( $r = 0.801$ ,  $p < 0.001$ ), and RAI ( $r = 0.814$ ,  $p < 0.001$ ) were positively associated with overnight change in LDI for negative high similarity stimuli. The frequency ( $r = 0.697$ ,  $p = 0.001$ ), duration ( $r = 0.474$ ,  $p = 0.047$ ), and nadir during NREM sleep ( $r = -0.526$ ,  $p = 0.025$ ) of blood oxygen desaturations were all associated with overnight change in LDI for negative high similarity stimuli.

**Conclusions:** These data suggest that while sleep is generally associated with a loss of high-fidelity negative memories in older adults, OSA severity and associated hypoxia may exert the opposite effect to promote greater overnight retention of highly detailed negative experiences. These findings further suggest that blood oxygen desaturations during sleep may facilitate a negative memory bias, potentially increasing risk for mood disorders, such as depression, which may also indirectly increase AD risk. Future work is needed to test these hypotheses.

**Acknowledgements:** This work was supported by NIMH T32MG119049, NIA R01AG053555, NIA K01AG068353, and the American Academy of Sleep Medicine Strategic Award.

#### OBSTRUCTIVE SLEEP APNEA SEVERITY, SIMOA ASSESSED PLASMA A $\beta$ 42/A $\beta$ 40, AND DIAGNOSED CSF BRAIN AMYLOIDOSIS AND TAU PATHOLOGY

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**Introduction:** We examined the association of obstructive sleep apnea (OSA) severity with plasma levels of A $\beta$ 42/A $\beta$ 40, and determined whether the combination of plasma A $\beta$ 42/A $\beta$ 40 and OSA-severity improved diagnosed brain amyloidosis and tau pathology.

**Materials and Methods:** Cross-sectional analysis of baseline data from 120 community-dwelling cognitively normal older-adults, selected from ongoing NYU longitudinal studies on memory, sleep and aging. Of the 120 participants, 70 had baseline CSF-A $\beta$ 42, and CSF-PTau (measured using ELISA), dichotomized using data driven approach to quantify brain amyloidosis (CSF-A $\beta$ 42  $\leq 375$  pg/ml) and tau pathology (CSF-PTau  $\geq 53.7$  pg/ml). OSA-severity was defined using AHI4% ( $\{5 < \text{AHI4\%} \leq 15$  [mild],  $15 < \text{AHI4\%} \leq 30$  [moderate],  $\text{AHI4\%} > 30$  [severe]} vs  $\text{AHI4\%} < 5$  [control]). Levels of plasma A $\beta$ 42/A $\beta$ 40 were assayed using SIMOA technology. Associations of OSA-severity and plasma A $\beta$ 42/A $\beta$ 40 ( $n = 120$ ) were assessed using regression and correlation analyses. Association of OSA severity and plasma A $\beta$ 42/A $\beta$ 40 dependent on CSF-A $\beta$ 42 and CSF-PTau levels ( $n = 70$ ) was assessed using generalized linear models. Receiver operating characteristic (ROC) analyses were performed to evaluate the ability of plasma A $\beta$ 42/A $\beta$ 40 and OSA to diagnose CSF brain amyloidosis and tau pathology ( $n = 70$ ) and were implemented with PROC LOGISTIC. Analyses controlled for age, sex, BMI, education and APOE4.

**Results:** Of the 120 participants, 80 (67%) were women. Mean (SD) age was 69.1 (7.2) years. Mean (SD) AHI was 14.3/hr (16.3). Forty-eight subjects

(40%) had AHI <5, 30 (25%) had AHI: 5 to ≤ 15, 18 had AHI: 15 to ≤30 and 22 had AHI >30. OSA severity was associated with higher levels of plasma Aβ42/Aβ40 ( $r=.20$ ,  $p\text{-value}=.05$ ). OSA\*CSF- Aβ42 and OSA\*CSF-PTau interactions were significant ( $P\text{-value} \leq .001$ ). Among individuals with a negative CSF-Aβ42 status, relative to controls, OSA severity was associated with higher levels of plasma Aβ42/Aβ40 (Mean Difference {d} (SD) 0.009 (0.0032), 95%CI: 0.003, 0.016; d (SD) 0.010 (0.0036) 95%CI: 0.005, 0.019; d (SD) 0.008 (0.0037) 95%CI: 0.004, 0.017.  $P\text{-value} \leq .05$  for mild, moderate and severe OSA respectively). Among individuals with a negative CSF-PTau status, relative to controls, OSA severity was associated with higher levels of plasma Aβ42/Aβ40 (Mean Difference {d} (SD) 0.013 (0.0036), 95%CI: 0.006, 0.020; d (SD) 0.011 (0.001) 95%CI: 0.002, 0.019; d (SD) 0.009 (0.003) 95%CI: 0.004, 0.018.  $P\text{-value} \leq .05$  for mild, moderate and severe OSA respectively). Data was sparse for subjects positive for CSF-Aβ42 and PTau. Plasma Aβ42/Aβ40 had a low correspondence with CSF-amyloid status (receiver operating characteristic area under the curve [AUC] 0.54 (95% CI=0.45 - 0.62) and CSF-PTau (AUC 0.51 (95% CI=0.41 - 0.60). The combination of plasma Aβ42/Aβ40, and OSA severity significantly improved correspondence with CSF-amyloid status (AUC 0.78 (95% CI=0.67 - 0.90) and CSF-PTau status (AUC 0.71 (95% CI=0.61 - 0.84).

**Conclusions:** In cognitively normal older-adults, together with AHI indices, plasma Aβ42/Aβ40 may represent a minimal-invasive reliable and cost-effective blood test that can potentially power large clinical OSA-AD trials.

**Acknowledgements:** Funding: NIH/NIA/NHLBI (K23AG0685324, L30-AG064670, CIRAD P30AG059303 Pilot, NYU ADRC P30AG066512 Dev. Grant, NYU PRIDE R25HL105444 Small Research Project, AASM 231-BS-20, R01HL118624, R21AG049348, R21AG055002, R01AG056031, R01AG022374, R21AG059179, R01AG056682, R01AG056531, K07AG05268503)

## OBSTRUCTIVE SLEEP APNEA SYNDROME AND COGNITIVE DISORDERS IN ADULTS AND THE ELDERLY: A RETROSPECTIVE OBSERVATIONAL STUDY

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**Background:** Untreated moderate and severe Obstructive Sleep Apnea Syndrome (OSAS) predisposes to deficits in attention, memory, executive functions and leads to the onset of depression.

Continuous Positive Airway Pressure (CPAP) Therapy significantly improves these cognitive deficits, showing a reversible cognitive impairment. The functional deficit can be clinically detected with neuropsychological tests, but to demonstrate the related anatomical brain damage is still conflicting. Some studies show how the cognitive deficit does not correspond to a real focal brain damage. Other studies instead have found that OSA patients have brain atrophy mainly in the hippocampus, cerebellum, thalamus, basal ganglia and frontal, temporal and parietal cortex.

**Objectives:** The aim of the study is to verify the relationship between OSAS, depression and cognitive impairment. In addition, the study aims to evaluate the possible correlation of cognitive impairment and anatomical brain damage, observed with Structural Magnetic Resonance Imaging.

**Materials and Methods:** the population of the study consisted of 404 patients with mild, moderate or severe OSAS. All of them underwent medical history, recording of anthropometric parameters, MMSE, GDS and polysomnography. For the purpose of the study, patients were divided into two groups stratified by age, respectively older and younger than 65 years. A subgroup of 71 patients underwent morphological brain-neck MRI for clinical investigation.

**Results:** there is a direct, statistically significant relationship ( $p<0.001$ ) between AHI and GDS score, and between mean nocturnal SpO2 and MMSE score. An inverse correlation ( $p<0.001$ ) exists between AHI and MMSE score. These correlations are confirmed in the geriatric patient, but not in the adult patient. Of all the patients that underwent MRI, 2 (2.8%) had hippocampal damage, 11 patients (15%) had thalamus and/or basal ganglia damage, 2 patients (2.8%) had cerebellum damage. In 13 patients (18.3%) there was damage in the frontotemporal cortex, in 3 patients (4.2%) there was damage in the parieto-occipital lobe.

There was no significant relationship between AHI and brain damage on

MRI. The correlation between mean nocturnal SpO2 values and the presence of focal brain damage was not significant, but a multivariate analysis including age, gender, BMI, and hypertension and diabetes mellitus as covariates, showed that mean nocturnal SpO2 values correlated independently with the presence of fronto-temporal damage. The same multivariate analysis using AHI as an independent variable showed no significant correlations. However, a bias due to the small number of patients cannot be excluded.

**Conclusions:** our study confirms the relationship between OSAS and cognitive decline, as well as between OSAS and depression. The correlations are significant for the elderly patient but not for the adult patient. In agreement with a part of the literature, in our patients cognitive functional impairment correlates with typical anatomical brain damage.

## PHYSIOLOGICAL RESPONSIVENESS TO PHASE-LOCKED AUDITORY STIMULATION DURING SLOW WAVE SLEEP PREDICTS INCREASES IN EPISODIC MEMORY PERFORMANCE IN OLDER ADULTS

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**Introduction:** Previous research suggests that phase-locked acoustic stimulation (PLAS) during slow wave sleep (SWS) is able to boost ongoing oscillatory activity and – as a downstream effect – improve sleep-dependent memory consolidation. Due to an assumed bi-directional link between SWS disturbances and memory decline in aging, older adults might profit most from such interventions.

**Materials and Methods:** 33 healthy participants (age: 59-80 years, M = 69.2; 25 female) were randomly allocated to an intervention or control group. Participants completed one baseline night and three consecutive experimental nights. The intervention group received PLAS during experimental nights and sham stimulation during the baseline night. In the control group sham stimulation was applied during all nights. Participants completed a face-occupation association memory task on each evening and morning as well as one week and three months post-intervention.

**Results:** In the intervention group but not in the control group, PLAS induced a physiological response in form of an entrained slow-wave peak in all three experimental nights compared to the baseline night. A linear regression model showed that within the intervention group the physiological response to PLAS predicted memory performance: the higher the amplitude of the entrained slow wave peak, the better participants' memory performance. This relationship was statistically significant starting on the evening of the second experimental night ( $p_{E2\_evening} = 0.02$ ) and lasting until the three-months follow up ( $p_{E2\_morning} = 0.02$ ,  $p_{E3\_evening} = 0.01$ ,  $p_{E3\_morning} = 0.01$ ,  $p_{FU1} < 0.01$ ,  $p_{FU2} < 0.01$ ). Responsiveness to stimulation did not correlate with age, education, sleep quality, or other cognitive assessments.

**Conclusions:** PLAS is able to entrain slow oscillatory activity in older adults and the degree to which participants physiologically respond to the stimulation predicts increases in overnight memory performance. These results indicate that PLAS could be developed into a non-invasive and inexpensive tool to battle cognitive decline.

**Acknowledgements:** This work is supported by the Synapsis Foundation, the Peter Bockhoff Foundation, the Heidi Seiler Foundation [2018-PI02], and the Interfaculty Research Cooperation 'Decoding sleep' at the University of Bern.

## POST-LEARNING SLEEP AND OVER DAY REACTIVATION THROUGH PRACTICE DO NOT MODULATE MOTOR MEMORY CONSOLIDATION

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**Introduction:** Retrieving information after an initial offline stabilization or consolidation episode reactivates the memory trace, that becomes again

unstable and vulnerable to interference. This reactivated, labile memory trace needs to be reconsolidated and will stabilize in a strengthened or weakened form as a function of the reactivation condition (interference or reinforcement). Regarding motor memory, behavioural studies evidenced performance weakening/strengthening upon reactivation, but the literature remains scarce. The effect of sleep on motor memory consolidation also remains disputed; meta-analyses indicate small-amplitude positive effects, but these are not systematically observed. It is also unclear how subsequent reactivation of motor memories interacts with sleep-related consolidation processes.

**Materials and Methods:** We investigated here the effect of a short behavioural reactivation (Day 2; the day after motor learning) on delayed motor performance (at Day 5) and its interaction with the presence of sleep the night after learning (and before reactivation, i.e., between day 1 and 2) in 80 young (18–30 years) adults. Performance on a Serial Reaction Time Task (SRTT) was assessed in a 2x2 between-subjects design with factors *Sleep* (Regular Sleep vs. Sleep Deprivation on post-learning night) and *Reactivation* (Short Morning Practice vs. No Practice on Day 2), with learning *Efficiency* as a covariate. We hypothesized that morning reactivation (Day 2) will increase delayed offline behavioural gains (Day 5 testing) and will interact with the effects of post-learning sleep on consolidation.

**Results:** In the learning session, reaction times (RT) improved across sequential blocks (1–17, 19–20) but deteriorated at random block 18 ( $p < 0.001$ ), evidencing successful sequential motor learning. Regarding offline gains (i.e., RT comparison between the end of the learning session [Day 1] and final retest [Day 5]), performance improved offline from Day 1 to Day 5 ( $p < 0.001$ ), but the main *Reactivation* effect was marginal ( $p = 0.06$ ), and the main *Sleep* ( $p = 0.32$ ) and *Sleep\*Reactivation* ( $p = 0.46$ ) effects were non-significant. The ANCOVA also revealed a main *Efficiency* covariate effect ( $p = 0.021$ ), evidencing a relationship between learning and offline improvement levels.

**Conclusions:** Our results did not evidence significant reactivation-related effects on delayed performance (but a marginal trend), which might be due to the availability of time and/or sleep on the two days/nights following reactivation and before final testing. Also, although performance improved offline from Day 1 to Day 5, it was not modulated by sleep, indicating mere time-dependent gains, and sleep was not found to interact with reconsolidation effects. Previous studies also failed to induce supplementary gains at the behavioural level upon reactivation, suggesting that reactivation triggers memory strengthening under specific conditions that need to be further investigated. Similarly, other studies failed to disclose post-learning sleep-related effects on performance improvement, which might be due to specific conditions (type of task, material, delays...). Still, this does not detract from the possibility of sleep- or reconsolidation-related covert neurophysiological changes underlying similar behavioural performance levels.

**Acknowledgements:** Study supported by Excellence of Science (EOS) MEMODYN project. WS is Research Fellow at Fonds de la Recherche Scientifique (FNRS).

#### SLEEP IN HEALTHY ELDERLY AND AMNESTIC COGNITIVELY IMPAIRED (CI) PATIENTS DUE TO NEURODEGENERATION

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**Introduction:** Sleep patterns change with aging and in neurodegeneration, but it is still unclear if and how sleep is disrupted in early stages of dementia beyond what is expected by age. Only few studies compared sleep and memory in mild cognitive impairment and mild dementia versus age-matched controls.

**Methods:** We performed overnight sleep polysomnography with high-density (256 channel) electroencephalography, together with breathing

assessment and cognitive testing in amnesic cognitive impaired (CI) patients (Montreal Cognitive Assessment (MoCA) score  $< 26$ ) including patients with amnesic mild cognitive impairment ( $n=11$ ) and mild dementia ( $n=5$ ). Exclusion criteria included history of neuropsychiatric disorders or use of CNS-acting drugs such as hypnotics or SSRIs. Sleep was scored using established guidelines of the American Academy of Sleep Medicine.

**Results:** We found that cognitive profiles were significantly degraded in CI patients ( $n=16$ , age  $70.63 \pm 6.96$ , Mini Mental State Examination (MMSE) =  $24.0 \pm 5.42$ , MoCA =  $19.5 \pm 5.42$ ) compared to aged-matched healthy controls ( $n=14$ , age  $68 \pm 5.14$ , MMSE =  $29.33 \pm 0.87$ ,  $p(\text{MMSE}) = 0.0056$ , MoCA =  $28.0 \pm 1.57$ ,  $p(\text{MoCA}) < 0.00001$ ). The two groups did not differ significantly in other aspects such as age or gender. With respect to sleep, CI showed more wake after sleep onset (WASO); ( $21.5\% \pm 13.9$ ), than controls ( $11.8\% \pm 7.4$ ,  $p=0.026$ ), less Rapid Eye Movement (REM) sleep ( $8.1\% \pm 6.3$  in patients vs.  $15.6\% \pm 5.6$  in controls,  $p=0.0009$ ), and a trend toward lower sleep efficiency ( $74.0\% \pm 18.0$  in patients vs.  $81.0\% \pm 6.8$  in controls,  $p=0.09$ ).

**Conclusion:** These interim results suggest that sleep is already significantly disrupted in early stages of cognitive impairment. We are now analyzing breathing profiles to rule out potential sleep apnea and conducting further analysis to examine the precise changes in slow wave/spindle occurrence, timing, frequency and topography, and their correlation with memory consolidation.

**Funding:** Supported by the European Research Council (ERC-2019-CoG 864353).

#### SLEEP MEASUREMENT HETEROGENEITY IN MILD COGNITIVE IMPAIRMENT AND EARLY DEMENTIA - TOWARDS A CORE OUTCOME SET: A SCOPING REVIEW

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**Introduction:** Sleep abnormalities emerge early in dementia and may accelerate cognitive decline. Accurate sleep measurement in this population may facilitate earlier clinical identification and allow for systematic assessment of sleep intervention efficacy. However, we hypothesise that sleep outcomes are reported heterogeneously inhibiting side-by-side comparison of studies. To inform choice and decisions on developing optimal measures, this scoping review determines how sleep is currently measured and reported in MCI and early dementia.

**Materials & Methods:** The full protocol is published in AMRC Open Research. CINAHL Plus, Embase, Medline, Psycinfo and British Nursing Index databases were searched from inception - 12/03/2021. 10% of returned titles and abstracts and all full-texts were screened by  $\geq 2$  reviewing members. Discrepancies were resolved by team consensus. Principle inclusion criteria for each study included: 1)  $\geq 1$  group of participants diagnosed with dementia or MCI; 2) Majority of group mild severity; 3) Sleep assessment as key objective and outcome measure.

**Results:** 19,569 titles were returned following duplicate removal. 931 full-text articles were reviewed with 183 studies included in the final analysis (observational  $n=153$ ; interventional  $n=28$ ; validation  $n=2$ ). Studies dated from 1982–2021, with only 9 published before 2000. Sleep data was reported on 16,977 unique patients, mean age 73.7 years. Participants had a wide range of often incompletely delineated diagnoses with 'Unspecified' MCI comprising the largest proportion of MCI patients ( $n=4982$ , 61.6% total MCI) with more specific diagnoses uncommon e.g. AD-MCI ( $n=252$ , 3.1% total MCI). Of 8894 participants with early dementia, the majority had a diagnosis of AD ( $n=7563$ , 85%).

Despite technological advances, sleep was measured most commonly by validated questionnaires (participants  $n=12,445$ , studies  $N=127$ ), specifically the Pittsburgh Sleep Quality Index (PSQI) ( $n=5666$ ,  $N=55$ ). Fewer participants have undergone polysomnography (PSG) ( $n=3451$ ,  $N=86$ ) and actigraphy ( $n=3359$ ,  $N=38$ ) with almost no adoption of non-PSG EEG ( $n=53$ ,  $N=2$ ). The proportion of studies utilizing each measurement means has remained broadly similar over time.

Sleep outcomes were reported heterogeneously. 51/135 (37.8%) unique parameters were described only once in the literature. As expected, by study, global questionnaire totals and total sleep time (TST) were most frequent (both  $N=106$ ), followed by sleep efficiency (SE) ( $N=97$ ) and sleep latency ( $N=71$ ). Comparable sleep outcomes between interventional sleep studies were sparse, possible for Total PSQI Score (8/23 studies), SE by actigraphy and PSG ( $N=7/23$ ), Total Epworth Sleepiness Score (ESS) score ( $N=6/23$ ) and TST by actigraphy and PSG ( $N=6/23$ ). These studies reported 55 separate sleep outcome parameters, with 33 (60%) unique to one study. Despite current interest, there was surprising underrepresentation of circadian ( $n=725$  [4.3%],  $N=25$ ) and micro-architectural ( $n=300$  [1.8%],  $N=10$ ) measure of sleep within this cohort.

**Conclusions:** Whilst there is rich diversity of sleep outcome measures reported, this heterogeneity inhibits comparison across studies. Furthermore, sleep is reported in relatively diagnostically undifferentiated cohorts and means of measuring sleep have remained static despite technological advances. Alongside identifying under-researched areas and relative under-characterisation of MCI populations, here we advocate for international consensus on a core set of sleep outcome measures to enable causal inference and direct comparison of therapeutic sleep interventions in this cohort.

## SYSTEMATIC REVIEW AND META-ANALYSES ON THE EFFECTS OF NAPPING ON COGNITION

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**Introduction:** Naps, the short periods of sleep that occur outside a longer main nocturnal sleep period, are gaining traction not only as a countermeasure against the cognitive consequences of short sleep, but also as a tool to enhance learning at school and work by leveraging on sleep's role in memory and learning. As investigations are extended to a wider range of nap characteristics and cognitive domains, a summary of the present landscape is timely to facilitate future studies in this area of sleep and cognitive health.

**Materials and Methods:** We quantitatively summarized the findings of existing studies on the effects of napping on cognition. Of the 60 samples, 52 focused on memory performance. Overall effect sizes for cognition and domains of memory, vigilance, speed of processing and executive function were evaluated. In addition, we examined whether nap effects would vary depending on age group, nap length, nap start time, sleep restriction, and nap habit.

**Results:** We found that naps had a significant benefit for cognition (Cohen's  $d = 0.379$ ,  $CI_{95} = 0.296 - 0.462$ ), effects of which were larger for naps 60 min or longer, when a nap followed sleep restriction, and for habitual nappers compared to non-habitual nappers. Of the cognitive domains examined, the largest effects were seen for vigilance (Cohen's  $d = 0.610$ ,  $CI_{95} = 0.291 - 0.929$ ) followed by memory (Cohen's  $d = 0.393$ ,  $CI_{95} = 0.299 - 0.486$ ) and speed of processing (Cohen's  $d = 0.211$ ,  $CI_{95} = 0.052 - 0.369$ ).

**Conclusions:** In sum, the use of naps to optimize cognitive performance is supported and the results of this meta-analysis should serve as a solid foundation for drafting policies regarding nap implementation in education and work settings.

**Acknowledgements:** This work was supported by the National Medical Research Council Singapore (STAR19may-0001).

## THE EFFECT OF SLEEP AND WAKEFULNESS ON EMOTIONAL MEMORY CONSOLIDATION

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**Introduction:** Although it is widely established that sleep has a beneficial effect on memory consolidation, its influence on emotional memory is currently debated. Furthermore, whether a night of rest occurring several hours after the encoding of new information can facilitate memory

consolidation is still unclear. Studies investigating the role of sleep on the night preceding the encoding, on the following memory performance are also lacking. In the present study, we investigate the role of sleep vs wake on emotional images memory consolidation and subjective emotional reactivity. Moreover, we explored potential associations between sleep parameters both during the night preceding the encoding and the following night.

**Methods:** Forty healthy participants were randomly assigned to the Sleep or Wake Group. Both groups underwent the encoding phase of an emotional images task at 9 AM (Wake Group) or 9 PM (Sleep Group) and three recognition tests (immediate/12hr/24hr-later). Arousal and valence levels were rated for each picture. Sleep parameters were recorded at participants' homes with a wearable device.

**Results:** At the 12hr test, the Sleep Group showed a lower forgetting than Wake Group, although no sleep parameter was associated with the performance. At the 24hr test, performance decreased in the Sleep group, who spent the previous 12hrs awake, but not in the Wake group, who had a period of sleep in the previous 12hrs. Overall, negative images were remembered better than neutral ones. Interestingly, we observed a positive association between memory performance for negative items at the immediate test and the percentage of time spent in REM sleep the night before the encoding.

**Conclusions:** Our study confirms the beneficial role of sleep on emotional memory consolidation, either just after the encoding or 12hrs later. Moreover, although emotional reactivity was not influenced by a single night of sleep, our results showed that negative stimuli are overall better remembered than neutral ones. We also showed that the level of encoding of negative images seems to be associated with REM sleep during the night preceding the learning.

## THE ROLE OF IMMEDIATE RECALL PERFORMANCE IN DELAYED FALSE MEMORY PRODUCTION AFTER SLEEP AND WAKE

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**Introduction:** The effect of a retention period spent asleep on false memories production is the object of a few recent studies which have yielded mixed results. Inconsistencies could be accounted for by methodological issues, such as the absence of immediate recall testing. Here we assess the effect of a retention period spent asleep vs. awake on delayed recall at a modified Deese-Roediger-McDermott task (DRM) in which immediate recall is tested during the learning phase for half of the presented lists.

**Methods:** In a within-subjects design, 18 participants ( $M^{age} = 22.5 \pm 1.9$ , 10F) were orally administered 8 lists of 15 semantically-related words either at 9 AM (Wake condition, WK) or 9 PM (Sleep condition, SL, in which sleep was home-monitored using the Dreem Headband, a portable polysomnographic device). Immediate Free Recall (IFR) was tested after the presentation of each of the 4 selected lists. The order of the lists, as well as their selection for IFR, was balanced between participants. Twelve hours later (9 PM for WK and 9 AM for SL) Delayed Free Recall (DFR) of all the studied material was assessed. On the next day, each participant underwent the other condition (SL or WK), with the same procedure but using a different set of 8 lists.

**Results:** IFR performance did not differ between conditions. At DFR, we found a higher recall of studied items in SL vs. WK, whereas the number of false recalls was similar between conditions. For both variables, DFR performance was strongly influenced by IFR performance. In particular, participants displaying more numerous false recalls at IFR tended to report a higher number of false recalls at DFR as well, but this effect was observed in the Sleep condition only. Also, most words reported at DFR corresponded to those of lists tested during IFR. Correlational analysis revealed a negative correlation between false recall at DFR and sleep efficiency.

**Conclusions:** Our results confirm that night sleep facilitates the consolidation of veridical memories, whereas false memories production seems to depend strongly on the presence of immediate recall testing and on

baseline performance. Further, in line with other literature, findings from our correlational analysis suggest that sleep quality also influences false memories production.

## Movement Disorders

### ASSOCIATION OF BST1 POLYMORPHISM WITH IDIOPATHIC RESTLESS LEGS SYNDROME IN CHINESE POPULATION

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**Introduction:** Parkinson's disease (PD) and restless legs syndrome/Willis-Ekbom disease (RLS/WED) are both common movement disorders. Based on their clinical overlap, association studies of PD and RLS/WED have been conducted for many years.

**Objective:** To investigate whether or not the genetic risk factor of PD was also associated with RLS/WED.

**Materials and Methods:** We included 102 idiopathic RLS/WED patients and 189 matched controls from southeast China. The clinical data included the International Restless Legs Syndrome Study Group Rating Scale, the subtypes of RLS/WED symptoms (painful or other discomfort), the comorbidities, the pregnancy history of female patients, the Hamilton Depression Scale (HAMD), and the Pittsburgh Sleep Quality Index (PSQI) questionnaire. Risk gene analysis between RLS/WED and control groups including 21 SNPs (single nucleotide polymorphisms) was conducted. Genotyping was done by Sanger sequencing.

**Results:** We found that rs4273468 polymorphism of BST1 gene increased the risk of idiopathic RLS/WED patients in southeastern Chinese population ( $P = <0.001$ , OR = 2.85,  $p = 0.019$  after Bonferroni correction). Moreover, the haplotype of G-G (rs4698412-rs4273468) was significantly associated with Chinese RLS/WED patients ( $p = <0.001$ ).

**Conclusions:** BST1 may contribute to the development of RLS/WED. Further studies on larger cohorts are needed to confirm these findings.

**Acknowledgements:** We thank all the participants who contribute to this study.

### DIAGNOSTIC CHALLENGES OF A RARE SUB-TYPE OF A RHYTHMIC MOVEMENT DISORDER IN A 21-MONTH-OLD BOY

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**Introduction:** Rhythmic movement disorder (RMD) consists of repetitive stereotypic movements, such as head banging or body rocking, recurring every second or so and lasting from a few minutes to hours, usually prior to sleep onset. It is likely to start in infancy and have a developmental course with spontaneous resolution in early childhood. It is a distressing condition with the potential to disrupt the sleep of child and family, with several deleterious consequences. No single treatment approach has sufficient high-quality evidence to be recommended. Diagnosis could be difficult delaying a clinical decision with important consequences for the patients and the caregivers.

**Case Report:** A male toddler, with divorced parents, no relevant medical history, and a normal neurodevelopment, presents, since his 11 months, repeated, fast, stereotyped contractions of muscular groups, which led to flexion of both legs in the transition between wakefulness and sleep, sometimes accompanied by cat-like vocalizations. The duration of the movement's varies, but sometimes it takes longer than an hour. According to parents, movements were stopped on command. He underwent to lab tests that revealed only a mild reduction in ferritin levels with normal iron measurement. He was receiving oral iron in the context of a previously diagnosis of Restless Legs Syndrome. It was reported that there was significant difficulty in falling asleep, with multiple awakenings and repetition of movements throughout the night.

A gradual behavioral approach was suggested together with some sleep hygienic measures. Video recordings were requested which, after careful analysis, the diagnosis was considered to be RMD, variant leg-banging.

**Discussion:** The ICSD-III provides a clear description of the diagnostic features of RMD as well as correspondent criteria. According to the diagnostic criterion C, it is required that RMs should have a clinical consequence for the child (sleep interference or significant impairment of daytime functioning). However at this early ages, when other sleep problems concur, these may be less specific. While the American Academy of Sleep Medicine describe polysomnographic scoring criteria, neurophysiological measures have limitations as many children suppress RMs during a single night. Actigraphy can be useful for assessment of total sleep time and sleep efficiency but cannot distinguish periods of RMs from normal movements when a child is awake. Parent report, however, may be unreliable and videosomnography has potential advantages in diagnosis allowing direct visualization. When legs are primarily affected, differential diagnosis with other sleep-related movement disorders in childhood should include benign infant myoclonus, sleep starts, restless leg syndrome, periodic limb movement disorder, hypnagogic foot tremor and alternating leg muscle activation.

**Conclusion:** RMD, in toddlers, when presenting as a rare variant such as leg-banging may turn diagnosis challenging. Video recording, in different nights, should be important for direct visualization of whole body movements and confirm the phase relationship of the movements with sleep, wakefulness, or both. Whether movements are simple or complex and whether epilepsy could be mimicking a movement disorder should also be a standard among differential diagnosis for an accurate characterization and diagnostic assessment.

### MULTIPLE THERAPEUTICAL BLEEDING IN PATIENTS WITH POLYGLOBULIA AND PERIODIC LIMB MOVEMENTS

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**Introduction:** Restless legs syndrome (RLS) and Periodic Limb Movements (PLM) associated with frequent blood donation have been described as a cause of iron deficiency or, conversely, in patients with hemochromatosis. The presence of PLMs in polysomnographic studies is a common finding in patients referred for other sleep disorders and is more frequent in older patients. It is increasingly common in sleep units to evaluate patients with polyglobulia to rule out a sleep-disordered breathing. However, there are no data regarding the presence of PLMs in these patients with polycythemia, nor if there is a relationship with therapeutic bleeding.

**Materials and Methods:** Restless legs syndrome (RLS) and Periodic Limb Movements (PLM) associated with frequent blood donation have been described as a cause of iron deficiency or, conversely, in patients with hemochromatosis. The presence of PLMs in polysomnographic studies is a common finding in patients referred for other sleep disorders and is more frequent in older patients. It is increasingly common in sleep units to evaluate patients with polyglobulia to rule out a sleep-disordered breathing. However, there are no data regarding the presence of PLMs in these patients with polycythemia, nor if there is a relationship with therapeutic bleeding.

**Results:** Of the 7333 PSG, 95 were performed in patients with polyglobulia to rule out Obstructive Sleep Apnea (OSA). A PLM index greater than 15 was found in 20 patients. The mean PLM rate was 28 / hour ( range : 15 to 80 ) Of those 20 (95%) were considered Polyglobulia secondary to Obstructive Sleep Apnea. Polycythemia Vera was found in one case. 90% were male, with an average age of 60.6 years( range 47 to 81 ), 90% being asymptomatic for any motor disorder at the time of the test; Sleep Apnea was diagnosed in 85%, With an AHI average 34 / hour.(range : 5 to 85 ) The appearance of PLM from the third bleeding as an average and of ferritin values with a mean of 75 ng/ml ( range : 9-131 ) . No relationship was found between the severity of PLM and sleep apnea syndrome.

**Conclusions:** Therapeutic bleeding is related to PLM in patients with polyglobulia, especially after the third therapeutic bleeding.

**Acknowledgements:** To the workers of the Sleep Unit of the Hospital Universitario La Ribera, Valencia, Spain

## NON-PARAMETRIC ACTIGRAPHY-DERIVED MEASURES DIFFER IN DEMENTIA WITH LEWY BODIES COMPARED TO ALZHEIMER'S DEMENTIA: A FEASIBILITY STUDY

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**Introduction:** Dementia with Lewy bodies (DLB) is the second most common form of dementia. Sleep disturbances are highly prevalent in DLB and are more severe relative to other neurodegenerative dementias including Alzheimer's dementia (AD).

DLB studies typically use subjective informant measures to assess sleep. Where objective sleep has been assessed, this has normally been done within a sleep laboratory or hospital environment on a single night, which can be disruptive, unrepresentative of habitual sleep and cause patient and caregiver burden.

One possibility is the use of actigraphy. This is a validated marker of the sleep-wake cycle and is a feasible method of assessing sleep in dementia populations, including DLB. To date, no studies have specifically examined non-parametric methods of actigraphy analysis in DLB. These can provide a comprehensive description of the circadian rest-activity pattern. This is important as non-parametric measures may be more sensitive to change than standard actigraphic measures of sleep continuity, and therefore have utility as a diagnostic/prognostic tool, or clinical trial outcome measure. The aim of this study was to: 1) assess the feasibility of deriving non-parametric measures from DLB actigraphy data, and 2) compare these to an AD group. It was hypothesised that non-parametric measures would differ between DLB and AD.

**Methods:** One week of actigraphy data was continuously collected from mild-to-moderate probable DLB participants ( $n = 8$ ) and probable AD participants ( $n = 6$ ), using wrist-worn accelerometers (GENEActiv, Activinsights, UK)

Non-parametric measures were derived from actigraphy data using the nparACT package (v0.8; Blume et al., 2016) for R (R Core Team, 2021). Specifically, interdaily stability (IS), intradaily variability (IV), relative amplitude of activity (RA), 5 hours with the lowest actigraphy amplitude (L5) and 10 hours with the highest average amplitude (M10) values were calculated. These were compared between DLB and AD groups using non-parametric Mann-Whitney  $U$ -tests.

**Results:** All participants tolerated wearing accelerometers and it was feasible to obtain non-parametric rest-activity values from actigraphy data. Relative to AD, RA values were significantly lower (DLB:  $M = 0.34$ ,  $SD = 0.25$ ; AD:  $M = 0.69$ ,  $SD = 0.14$ ;  $p = .01$ ) and M10 values were also lower in DLB (DLB:  $M = 32.72$ ,  $SD = 24.40$ ; AD:  $M = 89.29$ ,  $SD = 22.31$ ;  $p < .01$ ). There were no significant between-group differences in IS, IV or L5 values.

**Conclusions:** It is feasible to derive non-parametric rest-activity measures from actigraphic data collected from individuals with DLB. The relative amplitude of activity, and 10 hours with the highest average amplitude were significantly lower in DLB compared to AD. This suggests that specific circadian markers derived from actigraphy may be differentially affected in DLB. This is clinically relevant and further work should examine if these measures are potentially a suitable DLB prognostic or diagnostic target, or if they represent a sensitive outcome measure in future clinical trials.

**Acknowledgements:** This study was funded by Alzheimer's Research UK, Alzheimer's Research UK North Network Centre, British Sleep Society, Northumbria University Graduate Futures, and the NIHR Newcastle Biomedical Research Centre.

## SLEEP RHYTHMIC MOVEMENT DISORDER ASSOCIATED WITH THE VARIANT OF RESTLESS LEG SYNDROME: A CASE REPORT

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**Introduction:** Rhythmic movement disorder (RMD) is a stereotyped movement disorder of sleep characterized by rhythmic oscillations such as head banging, body rocking or head rolling. It has rarely been described in association with other sleep disorders such as sleep disordered breathing,

periodic limb movements, narcolepsy and restless legs syndrome (RLS). We report an interesting case in a child affected with SRMD-RLS with abnormal sensation not previously described in the literature.

**Materials and Methods:** Case report: An 14-year-old male presented to our sleep center with concerns about unusual movements during sleep. The patient reported his head hot and itchy before falling asleep, and he began to rub and scratch his head and back. The episodes occur always half an hour before his sleep and consist three forms including banging his head on the mattress or the wall, rocking his body rhythmically and clapping his head and hand, in addition to attention deficits, excessive daytime sleepiness and poor school performance. Past medical History: he was born one week late birth. His feeding history was negative. He has poor sports performance and average academic performance. Neurological and neuropsychological assessments, full-night video electroencephalogram (VEEG), repeated video-polysomnography (PSG), multiple sleep latency test (MSLT), and extended laboratory testing for serum ferritin were performed.

**Results:** The neurological examination was normal. The Epworth Sleepiness Scale (ESS) was 14. The serum ferritin level was normal. Plain and contrast-enhanced cervical MRI showed that the spinal cord was thickened and abnormal signal at the level of cervical 3-5, with adjacent enhanced vascular shadows. A video-PSG recording showed a disrupted and fragmented sleep with a reduced sleep latency (3 min) and a reduction of REM sleep (16.5%), elevated WASO (234min), and a reduced sleep efficiency index (56.9%). The PSG monitoring confirmed the presence of RMD such as rhythmic movements of the head, body rocking and head rolling at the wake-sleep transition of the total sleep. He was treated with pramipexole (dose: 0.36 mg) and clonazepam (dose: 1 mg). At one-year follow-up, both RLS and RMD symptoms dramatically improved and sleep onset and maintenance insomnia disappeared.

**Conclusions:** Nocturnal events have similar clinical features and high comorbidity rate, which increases the difficulty of accurate diagnosis. We should recognize that RLS could involve not only legs but also other body parts to varying degrees in each patient. Serum iron, ferritin and other related examination, sleep scale assessment, Neuroimaging, polysomnography, and overnight VEEG monitoring can help to diagnosis and guide an eventual treatment option. Regarding the sensorimotor symptoms of this patient, the relationship between the sleep-related rhythmic movement disorder and restless legs syndrome should be further explored.

**Acknowledgements:** We would like to thank the patient for his participation and his informed consent to the study.

## STRUCTURAL CHANGES OF THE SUBCORTICAL GRAY STRUCTURES IN RESTLESS LEGS SYNDROME

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**Introduction:** Several studies have shown the involvement of specific structures of the central nervous system, the dopaminergic system, and iron metabolism in restless legs syndrome (RLS), but the exact location and extent of its anatomical substrate is not yet known. The scope of this new study was to investigate the brain subcortical gray structures, by means of structural magnetic resonance imaging (MRI) studies, in RLS patients in order to assess the presence of any volume or shape abnormalities involving them.

**Materials and Methods:** Thirty-three normal controls (24 females and nine males) and 45 RLS patients (34 females and 11 males) were retrospectively recruited and underwent a 1.5 Tesla MRI study with two-dimensional T1 sequences in the sagittal plane. Post-processing was performed by means of the Functional Magnetic Resonance Imaging of the Brain Analysis Group Integrated Registration and Segmentation Tool (FIRST) software, and both volumetric and morphological analyses of the thalamus, caudate, putamen, globus pallidus, brainstem, hippocampus, and amygdala, bilaterally, were carried out.

**Results:** A statistically significant volumetric reduction in the left

amygdala and left globus pallidus was found in subjects with RLS, as well as large surface morphological alterations affecting the amygdala bilaterally and other less widespread surface changes in both hippocampi, the right caudate, the left globus pallidus, and the left putamen. These findings could not be explained by small vessel disease or other cerebrovascular damage previously reported in RLS.

**Conclusions:** These findings seem to indicate that the basic mechanisms of RLS might include a pathway involving not only the hypothalamus–spinal dopaminergic circuit (nucleus A11), but also pathways including the basal ganglia and structures that are part of the limbic system; moreover, structural alterations in RLS seem to concern the morphology as well as the volume of the above structures. The role of basal ganglia in the complex neurophysiological and neurochemical mechanism of RLS needs to be carefully reconsidered

**Acknowledgements:** The authors would like to express their deepest appreciation to all participants who gave their informed consent to use their clinical and imaging data for the purposes of this study.

### TONGUE BITING AND SUDDEN LIMB MOVEMENTS DURING SLEEP IN CHILDHOOD - ARE WE TALKING ABOUT EPILEPSY? NOT ALWAYS!

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**Introduction:** Sleep-related movement disorders (SRMD) are characterized by simple, usually stereotyped movements that disturb sleep. Some of these movements can mimic sleep-related epilepsy syndromes (SRES). We describe two cases of anomalous movements during sleep that were initially suspicious of epilepsy.

**Case report 1:** A 2-years-old boy referred due to recurrent tongue biting during sleep since 12-months-old. Irrelevant past medical history with normal neurodevelopment. No family history of movement disorders. Parents described movements like hypnic jerks followed by tongue biting and awakening and crying episodes with swelling and bleeding lacerations at lateral sides of his tongue. His physical examination, including neurological examination was normal except for the tongue lesions. Two EEG were normal. Video-polysomnography (video-PSG) with expanded electroencephalogram (EEG) montage and masseters electromyography showed: 15.9 arousals per hour and 35 awakenings coincident with increased masseter and chin tonus, without visible anomalous movements, epileptic activity or increased periodic limb movements of sleep (PLMS) index. Although tongue lesions improved, awakenings were still very frequent, so a low dose of oral clonazepam was started. After 2 months he sleeps thirteen hours per day without awakenings.

**Case report 2:** An 18-months-old boy referred due to limb movements during sleep, suspicious of epilepsy. No significant past medical history. His father had anomalous movements during sleep and his mother restless legs syndrome. Movements were described as pedalling, kicking, sudden upper and lower limbs movements that "look like bumps", before falling asleep and during sleep. A restless sleep with frequent awakenings has been reported. No anomalous movements when he is awake. Irrelevant physical examination. EEG was normal and a video-PSG with expanded EEG montage showed elevated PLMS index (50.1 per hour) with arousals (14.8 per hour) and exuberant hypnic jerks, without epileptic activity. Ferritin was below 50 ng/mL (27 ng/mL) and iron supplementation was started. Although bad adherence during the first months, improvement was noted (his mother reported a decrease of sleep movements and awakenings). After a correct iron supplementation, ferritin has risen (58 ng/ml). Now, he is 4-years-old, and despite not having insomnia, he reported leg discomfort ("pricks in my legs") at the end of the day, at rest. There were also school complaints of agitated and inattentive behaviours, so he started gabapentin.

**Conclusions:** Tongue biting during sleep is an uncommon cause of sleep disturbance. It is highly suggestive of an epileptic seizure, but it's not specific. Given the child's age and clinical evolution, geniospasm would be the most likely hypothesis and could justify these events. Sleep-related

faciomandibular myoclonus cause similar injuries but is more frequent in middle age patients. Periodic limb movement disorder and exuberant hypnic jerks can be mistaken with nocturnal frontal lobe epilepsy, characterized by hypermotor behaviour during sleep, which may be in the form of kicking, trashing or pedalling movements, as we saw in case 2. Treatment and evolution of SRMD are quite different from those from epilepsy syndromes. Recognition and adequate treatment are essential to improve sleep and life quality of these children and their families

### WHAT IS THE BEST WAY TO ASSESS THE SEVERITY OF RHYTHMIC MOVEMENT DISORDER? EXPERIENCE FROM A SPECIALIST PAEDIATRIC SLEEP CENTRE

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Sleep Related Rhythmic Movement Disorder (RMD) is a rare sleep disorder which involves stereotypical, repetitive and rhythmic large motor actions at the time of sleep onset and/or during the sleep period. Classically, this involves body rocking or rolling at a frequency 0.5–2 Hz, often impacting with a surface such as a bed or wall. Whilst the diagnostic criteria of RMD are described in the International Classification of Sleep Disorders (III), there is no consensus about how to assess the severity of this disorder. We propose that there should be standardised, internationally agreed thresholds to evaluate the severity of RMD, in the same way AHI is used for obstructive sleep apnoea.

Southampton sleep clinic has a specialist interest in RMD and currently manages 61 children. Experience informs us that there is a wide spectrum of severity at presentation and response to treatment. We use multi-modal investigations to characterise the nature and severity of RMD: actigraphy, home videosomnography (VSG) and in-laboratory polysomnography (PSG).

Two cases are presented to highlight the range in severity of RMD and to demonstrate the data yield from our standard investigations. The advantages and disadvantages of each modality will be presented. For example, actigraphy enables prolonged, non-invasive assessment of the duration and frequency of movements. Polysomnography enables detailed assessment and importantly, whether the movements originate from wakefulness or sleep (and which sleep stage). Home videosomnography provides less invasive but highly accurate assessment of the frequency and duration of movements. It also enables more detailed analysis such as the movement phenotype. Like other sleep disorders, night to night variability is seen in RMD. This can be captured on actigraphy and extended home videosomnography.

#### Conclusions:

- There is a wide range of severity of RMD.
- A multi-modal investigation approach is required to accurately characterise RMD.
- There is currently no international consensus regarding thresholds for diagnosis and severity rating of this sleep disorder.
- Our novel Rhythmic Movement Index and semiology categories are examples that could be further developed to address this deficit.

### Narcolepsy

#### AN ESTIMATION OF THE BURDEN OF ILLNESS AND HEALTHCARE RESOURCE UTILIZATION DUE TO NARCOLEPSY AND IDIOPATHIC HYPERSOMNIA IN THE UNITED STATES

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**Introduction:** Narcolepsy and idiopathic hypersomnia (IH) are associated with significant clinical, humanistic, and economic burden borne collectively by patients, their families, and society at large. Few studies have evaluated the burden of narcolepsy type 1 (NT1), narcolepsy type 2 (NT2)

and IH in the healthcare system using real world data. The objective of this study was to estimate the burden attributable to testing, treatment, and care for narcolepsy and IH in the United States.

**Materials and Methods:** A non-interventional cohort design was employed to identify patients with claims relating to narcolepsy or IH in the IBM MarketScan commercial claims database between January 2015 and December 2019. Cases (aged 18 to  $\leq 64$  years) were required to have qualifying medical claims ( $\geq 2$  medical claims occurring  $\geq 60$  days but not more than 12 months apart) for the same type of central disorder of hypersomnolence (CDH), i.e., NT1, NT2 or IH. The date of the first qualifying medical claim was set as the index date. Cohort assignment was based on the condition listed on the last observed CDH claim. Controls, individuals in the database without a diagnosis of narcolepsy or IH, were randomly selected at a 1:3 (cases: controls) ratio, and matched on age, gender, region/state, calendar quarter, and insurance plan type. Demographic and clinical characteristics were captured during the 12-month pre-index period, and treatment patterns, costs and healthcare resource utilization were captured during the 12-month post-index period.

**Results:** The cohort consisted of 7,799 patients overall. There were 1,137 NT1, 4,849 NT2 and 1,694 IH patients. 119 patients had  $>1$  type of CDH diagnoses. The mean age was 41.5 years and 65.2% were female. Less than half (45.5%) of the total study sample had evidence of diagnostic laboratory sleep testing during the 365 days before or 90 days after the index date: 34.9% had nocturnal polysomnography and 25.3% had a Multiple Sleep Latency Test (MSLT). More than half of patients received antidepressants (54.3%), stimulants (53.8%) or wakefulness-promoting agents (52.6%) during the follow-up period. Polypharmacy, defined as prescriptions for two or more medications with different mechanisms of action for NT1, NT2 or IH at the same time, was observed in 59.5% of patients. Compared to matched controls, mean annual all-cause healthcare costs were significantly greater ( $p < 0.0001$ ) for patients with NT1 (NT1: \$40,599 vs control: \$8,239), NT2 (\$26,893 vs \$8,924), and IH (\$18,067 vs. \$8,394). The mean number of outpatient visits was significantly greater for patients with NT1, NT2 and IH compared to controls (NT1: 21.9 vs. 10.3, NT2: 22.4 vs 10.9, and IH: 24.1 vs 11.0).

**Conclusions:** Patients with narcolepsy and IH have a substantial healthcare burden in the United States, which was demonstrated in this study by notably higher all-cause healthcare resource utilization, and healthcare costs that were 2- to 5-fold higher compared with patients without narcolepsy or IH. Patients were frequently prescribed multiple concurrent treatments to manage their disorder. Approaches to lower the burden of these diseases may be helpful.

**Acknowledgements:** The study was funded by Takeda Development Center Americas, Inc.

#### ANTI-HYPOTHALAMIC AUTOANTIBODIES IN PATIENTS WITH NARCOLEPSY

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**Introduction:** Narcolepsy is a rare disease characterized by excessive daytime sleepiness, hallucinations, sleep paralysis and sleep disorders. Cerebral spinal fluid (CSF) orexin's level reduction and the presence of cataplexy differentiate narcolepsy type one (NT1) from narcolepsy type two (NT2). Association with HLA DQB1\*06:02 was found, that strongly suggests an autoimmune basis. How the autoimmune mechanism could be involved in initiation and/or progression of the disease is not clear. Many studies have shown T-cell mediated process against orexin neurons (hypocretin-specific CD4<sup>+</sup> T cells were found), but also humoral mechanism may be involved. The aim of this study was to search for autoantibodies against primate hypothalamic neurons in narcolepsy.

**Materials and Methods:** Twelve patients affected by Narcolepsy according to current diagnostic criteria (AASM, 2014) (11 NT1 and one NT2; mean age 28 $\pm$ 16.5, range 11-62, 4 females) were enrolled. The differentiation

between NT1 and NT2 was performed by the clinical assessment of cataplexy and/or by dosing CSF orexin's levels. A control group of 18 healthy volunteers, aged 18-51, was included. All subjects underwent a blood sampling to perform immunofluorescence analysis. The detection of anti-hypothalamic autoantibodies was performed with an indirect immunofluorescence (IIF) method using Euroimmun AG kits (Lubeck, Germany). In detail, each sample was analysed at a serum dilution of 1:10 on a section of primate hypothalamus. A pool of conjugate fluorescent anti-human IgG and IgM was used as detecting antibodies. Positive and negative control serum was analysed in each analytical session. The intensity of the fluorescence was determined by a visual scale (VS) score from 0 to 3 (0 no reaction, 1 weak fluorescence, 2 intermediate fluorescence, 3 strong fluorescence). Samples were positive if scores of 2 or 3 were attributed.

**Results:** Ten patients showed a positive immunoreaction (four patients with a VS score of 3 and six patients with a VS score of 2). Two patients showed a VS score of 1, and no one had a VS score of 0 (no reaction). One NT2 and one NT1 patients showed a weak fluorescence (VS 1). Among the 18 healthy controls, two of them showed a weak fluorescence (VS 1), and the remaining no reaction at all (VS 0).

**Conclusions:** Although this is a preliminary study, the majority of the tested narcoleptic patients showed autoantibody reactivity against hypothalamic antigens. Interestingly, the patients showing poor reactivity, suggesting that the autoimmune activity may be weak or incomplete, were the only NT2 patient and an NT1 patient with low frequency cataplexy. Several literature data are suggesting that the NT2 may be an incomplete form of narcolepsy or even a prodromal stage of NT1, considering that often NT2 patients develop cataplexy over time. Further evidence is needed to confirm our result, including additional analysis to better define the localization of the antigen and the nature of antibodies, as well as increase the sample size, in particular NT2 patients.

#### APPLICABILITY OF THE SUSTAINED ATTENTION TO RESPONSE TASK (SART) IN CLINICAL PRACTICE: EXPERIENCE AND RESULTS FROM A TERTIARY REFERRAL CENTER

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**Introduction:** Evaluation of disorders of hypersomnolence should include assessment of disturbed vigilance, which can be quantified using the computerized, short and objective Sustained Attention to Response Task (SART), assessed five times over the course of the day. Here we describe our experience with the SART in a tertiary referral center.

**Materials and Methods:** We analyzed clinical data of 317 patients with hypersomnolence complaints, diagnosed with narcolepsy type 1 (NT1; n=102), narcolepsy type 2 (NT2; n=21), idiopathic hypersomnia (IH; n=46), obstructive sleep apnea syndrome (OSAS; n=28) and complaints of EDS without explanatory diagnosis (CEDs; n=120). Multiple sleep latency test (MSLT), polysomnography (PSG), Epworth Sleepiness Scale (ESS), Hospital Anxiety and Depression Scale (HADS) and SART outcomes (reaction time, total errors, commission and omission errors) were compared between diagnostic groups and with each other, corrected for age.

**Results:** SART-outcomes did not correlate with the MSLT, PSG or HADS. Higher ESS-scores were associated with longer reaction times and more commission errors ( $p < .01$ ). Reaction times were significantly longer in the morning with more omission errors ( $p < .05$ ). OSAS patients has slower reaction times than the NT1, IH and CEDs groups (median 428 ms,  $p < .05$ ).

**Conclusions:** The SART quantifies disturbed vigilance, which is a different dimension of disorders of hypersomnolence than measured by the MSLT or PSG. It does not differentiate between sleep disorders and is not affected by symptoms of anxiety or depression. In the clinical practice for the diagnosis and clinical monitoring of hypersomnolence patients, multiple testing times during the day and a practice session are advised, for example before each MSLT nap opportunity.

## ASSESSMENT OF THE DIAGNOSED PREVALENCE OF NARCOLEPSY AND IDIOPATHIC HYPERSOMNIA IN THE UNITED STATES USING REAL WORLD DATA

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**Introduction:** Primary central disorders of hypersomnolence (CDH) including narcolepsy and idiopathic hypersomnia (IH) are chronic, debilitating, neurological conditions characterized by excessive daytime sleepiness. Considerable symptom overlap with other medical, neurological, and psychiatric conditions mean they are often underdiagnosed or misdiagnosed, leading to significant prolonged clinical and economic burden due to insufficient/inappropriate treatment. Well-conducted, up-to-date studies describing the epidemiology of these conditions may inform health policy and clinical decision-making. The objective of this study was to evaluate the diagnosed prevalence of narcolepsy and IH using real world data.

**Materials and Methods:** A non-interventional cross-sectional study was conducted to assess the diagnosed prevalence and incidence of narcolepsy and IH using data from the IBM MarketScan Commercial Claims and Encounters database from January 2017 to December 2019. The population was limited to individuals aged  $\leq 64$  years continuously enrolled for medical and pharmacy benefits during the year under study. Prevalent cases were individuals with  $\geq 2$  medical claims (occurring  $\geq 60$  days but not more than 12 months apart) for the same type of CDH (i.e., narcolepsy type 1 [NT1], narcolepsy type 2 [NT2] or IH).

**Results:** The diagnosed prevalence of narcolepsy per 100,000 people was 49.3 in 2017, 51.6 in 2018 and 53.3 in 2019. Of those with narcolepsy, the prevalence of NT1 was 9.7 in 2017, 10.4 in 2018 and 10.7 in 2019, while the diagnosed prevalence of NT2 was 38.8 in 2017, 40.4 in 2018 and 41.7 in 2019. The diagnosed prevalence of IH per 100,000 was 13.9 in 2017, 14.5 in 2018 and 14.6 in 2019. The prevalence of narcolepsy and IH was higher in females than males (narcolepsy: 60.8 vs. 37.1; IH: 18.1 vs. 9.3, in 2017), and highest in individuals aged between 35 and 44 years compared with other age groups. The diagnosed incidence of narcolepsy per 100,000 person years was 7.6 in 2017, 7.7 in 2018 and 5.5 in 2019, while the diagnosed incidence of IH was 2.7 in 2017, 2.7 in 2018 and 1.8 in 2019. The incidence of narcolepsy and IH was higher in females than males (narcolepsy: 9.0 vs. 6.0; IH: 3.5 vs. 1.9, in 2017), and the incidence of narcolepsy was highest in individuals aged between 18 and 34 years compared with other age groups, and incidence of IH was highest among individuals aged between 35 and 44 years compared with other age groups. The trend of prevalence and incidence estimates by sex and age groups were generally consistent across the years under study.

**Conclusions:** Narcolepsy and IH are rare conditions, affecting  $\sim 50/100,000$  individuals. In this study, prevalence of narcolepsy and IH increased slightly from 2017 to 2019; however, incidence rates remained similar. Prevalence estimates for narcolepsy were consistent with findings from previous studies, though the estimates in this study were based on diagnoses logged as part of routine clinical care for the administration of insurance claims. Further studies to validate the approach for selecting cases in US administrative claims databases are recommended.

**Acknowledgements:** The study was funded by Takeda Development Center Americas, Inc.

## CARDIOVASCULAR BURDEN OF NARCOLEPSY DISEASE (CV-BOND): A REAL-WORLD EVIDENCE STUDY

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**Introduction:** Narcolepsy is a rare, central disorder of hypersomnolence that requires long-term treatment and is associated with multiple comorbidities. Many treatments for narcolepsy symptoms have

cardiovascular-related warnings and precautions in their labels. The objective of this study was to estimate the risk of cardiovascular comorbidities in US adults with narcolepsy.

**Materials and Methods:** Claims from IBM® MarketScan®, an administrative claims database, between January 2014 and June 2019 were analysed. Eligible patients were  $\geq 18$  years of age and had continuous medical and prescription coverage (gaps  $\leq 30$  days allowed). The narcolepsy cohort was defined by  $\geq 2$  outpatient claims containing a diagnosis of narcolepsy type 1 or type 2 on separate days and no more than 6 months apart;  $\geq 1$  claim must have been nondiagnostic (ie, not for diagnostic sleep testing). Patients without narcolepsy were matched 3:1 to patients with narcolepsy by calendar date of cohort entry, age, gender, US geographic region, and insurance type. Outcomes included incidences of any stroke; atrial fibrillation; heart failure; ischaemic stroke; major adverse cardiac event (MACE); myocardial infarction; grouped instances of stroke, atrial fibrillation, or oedema; any cardiovascular disease; and any cardiovascular disease excluding hypertension. Each incidence calculation required a 6-month outcome-free period prior to cohort entry. Differences between cohorts were evaluated using a Cox proportional hazard model adjusted for age, gender, region, insurance type, and relevant morbidities/comorbidities and medications in the baseline period.

**Results:** Of 54,239,110 adults in the database, 12,816 and 38,441 were included in the narcolepsy and matched non-narcolepsy cohorts, respectively. Approximately 67% were female, and mean age was approximately 38 years in both cohorts. Adjusted hazard ratios (HRs), derived from incidence rates, suggested significantly increased risk of the following outcomes in the narcolepsy cohort compared with matched non-narcolepsy controls (nominal  $P < 0.05$ ): any stroke (HR [95% CI]: 1.71 [1.24, 2.34]); heart failure (1.35 [1.03, 1.76]); ischaemic stroke (1.67 [1.19, 2.34]); MACE (1.45 [1.20, 1.74]); grouped instances of stroke, atrial fibrillation, or oedema (1.48 [1.25, 1.74]); and any cardiovascular disease excluding hypertension (1.30 [1.08, 1.56]).

**Conclusions:** Physicians should consider increased cardiovascular risk when weighing risk modification strategies and treatment options for narcolepsy.

**Acknowledgements:** Supported by Jazz Pharmaceuticals.

## CHILDREN, ADOLESCENTS, AND THEIR PROVIDERS: THE NARCOLEPSY ASSESSMENT PARTNERSHIP (CATNAP™) PAEDIATRIC NARCOLEPSY REGISTRY: STUDY DESIGN

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**Introduction:** Limited information is available on the natural history, presentation, and management of paediatric narcolepsy. *Children, Adolescents, and Their providers: the Narcolepsy Assessment Partnership (CATNAP™)* is a retrospective and prospective longitudinal, multicentre, web-based paediatric narcolepsy registry (ClinicalTrials.gov identifier: NCT04899947). CATNAP is a next-generation registry that collects relevant real-world clinical information from patients, caregivers, and clinicians. The primary objectives are to improve understanding of the natural history of paediatric narcolepsy, characterise symptom presentation and diagnosis in paediatric patients, and understand treatment practices and outcomes. Secondary objectives are to understand the quality of life of paediatric patients and their caregivers, burden of disease and healthcare resource utilisation of patients, caregiver burden, and impact on patients' social development and academic/educational outcomes.

**Materials and Methods:** Eligible children/adolescents ( $< 18$  years of age) with a confirmed diagnosis of narcolepsy will be invited to participate by registry site personnel or the treating physician. Using web-based portals, patients, caregivers, and clinicians will complete an initial survey and annual follow-up surveys. Patients and caregivers will provide information on sociodemographic characteristics (including race/ethnicity and geographic location); diagnostic, medical, and treatment history; comorbidities; and disease progression. In addition, they will complete validated

instruments assessing the patient's daytime sleepiness, quality of life, psychological/behavioural health, and social functioning. Caregivers will also complete instruments assessing the impact of the patient's narcolepsy on the caregiver's well-being, social support, sleep, and work. Clinicians will provide information on signs/symptoms/testing at diagnosis, anthropometrics, comorbidities, disease progression, treatment history, and clinical outcomes, as well as medical records, to further understanding of the natural history of paediatric narcolepsy.

**Results:** CATNAP enrolment opened in October 2020. Data are anticipated to be presented starting in 2022.

**Conclusions:** CATNAP will be the first longitudinal study in paediatric narcolepsy of key determinants of patient management and outcomes, including the patient experience and patient/caregiver burden. These data will facilitate education of patients and caregivers, inform clinical decision-making, and potentially contribute to the development of new treatment strategies with a better understanding of patient impact.

**Acknowledgements:** Supported by Jazz Pharmaceuticals.

### DEVELOPMENT AND VALIDATION OF THE PEDIATRIC HYPERSOMNIA SURVEY (PHS)

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**Introduction:** Narcolepsy and idiopathic hypersomnia usually begin in early adolescence, but diagnostic delays ranging 5–10 years are common, impacting disease burden. To improve early identification of these treatable conditions, we developed and validated the Pediatric Hypersomnia Survey (PHS).

**Materials and Methods:** Content was developed through literature review, patient focus groups, interviews with experts in the field, and field testing. We then validated the 14-item survey across three hospitals and web recruitment from patient groups. In the validation phase, we recruited a total of 331 participants (patients with narcolepsy type 1 (n=64), narcolepsy type 2 (n=34), idiopathic hypersomnia (n=36), and other sleep disorders (n=97), and healthy controls (n=100), ages 8–18 years. We assessed a range of psychometric properties, including discriminant diagnostic validity for CNS disorders of hypersomnolence using ROC analysis and reliability across a 1 week period.

**Results:** Confirmatory Factor Analysis indicated a 4-domain solution with good reliability expressed by satisfactory Omega values. Across groups, the PHS total score showed appropriate positive correlations with other validated surveys of sleepiness ( $r$ 's =0.65–0.78,  $p$ 's<0.001) and negative correlations with Multiple Sleep Latency Test measures (mean sleep latency:  $r$ =–0.27,  $p$ =0.006 number of sleep onset REM periods:  $r$ =0.26,  $p$ =0.007. Compared to controls and patients with other sleep disorders, the AUC for narcolepsy or idiopathic hypersomnia was 0.87(0.02), 95% CI 0.83–0.91 with high sensitivity (81.3, 95% CI 73.7–87.5) and specificity (81.2, 95% CI:75.1–86.4). Test-retest reliability was  $r$ =0.87.

**Conclusions:** The PHS is a valid and reliable tool for clinicians to identify pediatric patients with narcolepsy and idiopathic hypersomnia. Implemented in clinical practice, the PHS will potentially decrease diagnostic delays and time to treatment, ultimately reduce disease burden for these debilitating conditions.

### DRUG THERAPY FOR PATIENTS WITH NARCOLEPSY IN A REAL WORLD IN JAPAN: A DESCRIPTIVE OBSERVATIONAL STUDY USING HEALTHCARE CLAIMS DATA

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**Introduction:** Prior epidemiological studies of narcolepsy in Japan were conducted a few decades ago. Additionally, to the best of our knowledge, little nationwide epidemiological data are available to understand the actual situation of drug therapy in Japan, while new therapies have been developed. The objectives of this study were to describe prevalence, incidence, and drugs among patients who were diagnosed with narcolepsy in Japan using nationwide healthcare claims data from January 2010 to December 2019.

**Materials and Methods:** Patients diagnosed as narcolepsy were identified from January 2010 to December 2019 using an employment-based health insurance claims data compiled by JMDC Inc. The patients were selected according to the following inclusion criteria. Patients 1) with both disease names (Japanese disease name) and diagnosis records (ICD-10 code [G474]) of narcolepsy in 2 consecutive months during the study period and 2) with any data records for 1 year before index date, as which the date of the first diagnosis was defined, were included. Annual prevalence and incidence of narcolepsy were estimated in the overall population and by age and sex among employees and their dependents aged <75 years. Drugs examined were modafinil, methylphenidate, pemoline, tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRI), and serotonin-norepinephrine reuptake inhibitors (SNRI) in the overall population quarterly each year. Each of these drugs is used for the patients and three of them (modafinil, methylphenidate, pemoline) have an indication for treatment of narcolepsy in Japan.

**Results:** We identified 1,539 patients with narcolepsy (sex; 966 males and 573 females, age; 31.5 ±13.5 years old, median follow-up; 2.0 years). The overall annual prevalence increased from 5.7 to 18.5/100,000 persons in 2010 and 2019, and the large increase was found in patients aged 20–29 years and 10–19 years, with the highest prevalence in 2019 (9.7 to 37.5/100,000 persons in 2010 and 2019, 5.0 to 27.1/100,000 persons). The overall incidence slightly increased from 3.6 to 4.3/100,000 person-year in 2010 and 2019, and the highest incidence was found in patients aged 20–29 years and 10–19 years (5.8 to 11.3/100,000 person-year in 2010 and 2019, 3.8 to 7.4/100,000 person-year). Methylphenidate and modafinil were commonly prescribed in 2010 (27.3%–38.9% [min-max, quarterly], 17.5%–45.5%, respectively). Methylphenidate was prescribed more commonly than modafinil until early 2012. On the contrary, modafinil was used more commonly than methylphenidate from late 2012. Methylphenidate prescription declined in ten years, whereas modafinil prescription increased (15.6%–17.1% in 2019, 43.8%–45.8% in 2019). Pemoline followed above two drugs (12.4%–12.9% in 2019). While SSRI prescription declined in ten years (0.0%–22.5% in 2010, 7.4%–8.3% in 2019), SNRI prescription increased in ten years (0.0%–3.0% in 2010, 13.0%–13.4% in 2019).

**Conclusions:** Our prevalence and incidence estimate especially in teens and young adults increased from 2010 to 2019. Prevalence gradually increased over ten years, and although overall incidence rate changed little. The prescription of modafinil was increased and modafinil was most prescribed in 2019, followed by methylphenidate and pemoline.

**Acknowledgements:** We are grateful to Japan Narcolepsy Association.

### EARLY EFFICACY WITH ONCE-NIGHTLY SODIUM OXYBATE (ON-SXB; FT218): POST-HOC ANALYSES FROM REST-ON

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**Introduction:** Once-nightly sodium oxybate (ON-SXB; FT218) is an investigational, extended-release formulation of SXB for the treatment of adults with narcolepsy. In the phase 3 REST-ON clinical trial, significant improvements for ON-SXB vs placebo were observed at weeks 3 (6-g dose), 8 (7.5-g dose), and 13 (9-g dose) for the 3 coprimary endpoints of mean sleep latency on the Maintenance of Wakefulness test, Clinical Global Impression of Improvement rating, and number of weekly cataplexy episodes (all  $P$ <0.001), as well as the secondary endpoints Epworth Sleepiness Scale (ESS) score (all  $P$ <0.001), disturbed nocturnal sleep ( $P$ <0.05, ON-SXB 6 g;  $P$ <0.001 ON-SXB 7.5 and 9 g), sleep paralysis (all

$P < 0.05$ ), and patient-reported sleep quality and refreshing nature of sleep on visual analog scales (VAS; all  $P < 0.001$ ). A post hoc analysis revealed that ON-SXB 4.5 g significantly reduced the number of weekly cataplexy episodes vs placebo at week 1 of treatment ( $P < 0.05$ ). Additional post hoc analyses were conducted to investigate the efficacy of ON-SXB on other endpoints with recorded values at weeks 1 and 2.

**Materials and Methods:** In REST-ON (NCT02720744), individuals  $\geq 16$  years of age with narcolepsy type 1 or 2 were randomized 1:1 to receive double-blind ON-SXB (4.5 g, 1 week; 6 g, 2 weeks; 7.5 g, 5 weeks; 9 g, 5 weeks) or matching placebo. Randomization was stratified by narcolepsy type. ESS score, VAS sleep quality, and VAS refreshing nature of sleep were recorded in an electronic diary. VAS was a 1–100 scale with 1 indicating poor quality/unrefreshing sleep and 100 indicating good quality/refreshing sleep. Least squares mean differences (LSMD) in change from baseline to weeks 1 and 2, associated 95% confidence intervals (CIs), and  $P$ -values were calculated post hoc using a mixed-effects model for repeated measures in the modified intent-to-treat (mITT) population, defined as all participants who received  $\geq 1$  dose of study drug and had an efficacy assessment at week 3. No imputation was done for missing data.

**Results:** The mITT population comprised 190 participants (ON-SXB, 97; placebo, 93). Baseline ESS scores were 16.6 and 17.5 for the ON-SXB and placebo arms, respectively. A significant improvement in ESS score for ON-SXB vs placebo was observed at week 2 (LSMD,  $-1.3$  [95% CI:  $-2.4, -0.2$ ];  $P < 0.02$ ) with numerical improvement seen at week 1 ( $-0.7$  [ $-1.6, 0.2$ ]). For the ON-SXB and placebo arms, respectively, baseline VAS sleep quality was 53.8 and 55.9, and baseline VAS refreshing nature of sleep was 46.5 and 49.9. Significantly greater improvement was observed with ON-SXB vs placebo for sleep quality at week 1 (3.6 [1.1, 6.1];  $P < 0.01$ ) and week 2 (7.0 [3.8, 10.1];  $P < 0.001$ ) and refreshing nature of sleep at week 1 (3.2 [0.5, 5.9];  $P < 0.05$ ) and week 2 (5.8 [2.3, 9.4];  $P = 0.001$ ).

**Conclusions:** ON-SXB demonstrated improvement vs placebo in subjective measures of daytime sleepiness and in sleep quality and refreshing nature of sleep as early as week 1. If approved, ON-SXB will be a treatment option that may provide early relief of narcolepsy symptoms for some patients.

**Acknowledgements:** This study was funded by Avadel Pharmaceuticals.

#### EFFECTS OF LOWER-SODIUM OXYBATE ON SLEEP TIME IN A PLACEBO-CONTROLLED, DOUBLE-BLIND, RANDOMISED WITHDRAWAL STUDY IN ADULTS WITH IDIOPATHIC HYPERSOMNIA

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**Introduction:** Idiopathic hypersomnia is a debilitating central hypersomnolence disorder characterised by excessive daytime sleepiness; severe sleep inertia and long nocturnal sleep time are key symptoms. The first approved treatment is lower-sodium oxybate (LXB; Xywav®). The efficacy and safety of LXB for the treatment of idiopathic hypersomnia in adults was established in a double-blind randomised withdrawal study (NCT03533114). This analysis evaluated the effect of LXB treatment on sleep time in the study.

**Materials and Methods:** Eligible participants 18–75 years of age with idiopathic hypersomnia per *International Classification of Sleep Disorders*, 2nd or 3rd Edition criteria began LXB treatment in an open-label titration and optimisation period (OLT; 10–14 weeks), followed by a 2-week, open-label, stable-dose period (SDP), and were then randomised to placebo or to continue LXB treatment during a 2-week, double-blind, randomised withdrawal period (DBRWP). This post hoc analysis utilised participant-recorded electronic daily sleep diary data from screening week 2 to SDP week 2, and DBRWP week 2. Sleep parameters were assessed after exclusion of erroneous records (incorrect clock time); assessments included 24-hour total sleep time (TST; nocturnal TST plus duration of nap [s]), nocturnal TST (time from trying to sleep until final awakening, subtracting duration of awakenings at night), and duration of naps. Results are reported for participants who were treatment naive at entry or taking alerting agents (AAs; stimulants and wake-promoting agents) at study entry; AA treatment was to remain stable throughout the study.

Participants treated with sodium oxybate at entry were not included in this analysis.

**Results:** The study enrolled 154 participants (mean  $\pm$  SD age,  $40 \pm 14$  years; 68% female); 3917 of 4596 daily sleep diary records were analysed. During open-label LXB treatment, decreases in 24-hour TST were observed from baseline to end of open-label period (SDP) in both treatment groups. The estimated median reduction was 61 minutes (baseline, 535; end of SDP, 486) in treatment-naïve participants, and 28 minutes (504; 468) in participants receiving AA at baseline. Reduction in nocturnal TST was also observed: estimated median decrease was 32 minutes (508; 486) in treatment-naïve participants and 23 minutes (475; 460) in participants receiving AA at baseline. Total nap duration was also decreased: estimated median reduction was 11.3 minutes (19.6; 0.0) in treatment-naïve participants and 8.4 minutes (15.0; 7.5) in participants receiving AA at baseline. From end of SDP to end of the 2-week DBRWP, 24-hour TST increased in participants randomised to placebo (median, 469; 498 minutes, respectively) but remained stable in participants continuing LXB treatment (467; 461 minutes); estimated median difference in change (95% CI) was  $-23$  minutes ( $-58, 10$ ;  $P = 0.0864$ ). Common treatment-emergent adverse events (reported by  $\geq 10\%$  of total participants across all study periods, excluding placebo data) were nausea, headache, dizziness, anxiety, and vomiting.

**Conclusions:** LXB treatment in adults with idiopathic hypersomnia resulted in reductions in 24-hour total sleep time, nocturnal sleep time, and nap duration during the open-label treatment phase in both baseline treatment groups. Total sleep time worsened when participants switched to placebo in this controlled, randomised study.

**Acknowledgements:** Supported by Jazz Pharmaceuticals.

#### EFFICACY OF FT218, A ONCE-NIGHTLY SODIUM OXYBATE FORMULATION, IN PATIENTS WITH NARCOLEPSY: POST-HOC SENSITIVITY ANALYSES FROM THE REST-ON TRIAL

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**Introduction:** In REST-ON (NCT02720744), once-nightly sodium oxybate (ON-SXB; FT218) treatment resulted in significant improvement vs placebo for coprimary endpoints mean sleep latency on the Maintenance of Wakefulness test (MWT), Clinical Global Impression of Improvement (CGI-I) rating of “much” or “very much” improved, and weekly number of cataplexy attacks (NCA) (all  $P < 0.001$ ). Post-hoc sensitivity analyses using different methods to handle missing data were conducted to support the robustness of the primary data.

**Materials and Methods:** Individuals aged  $\geq 16$  years with narcolepsy type 1 or 2 were randomized 1:1 to receive ON-SXB (1 week, 4.5 g; 2 weeks, 6 g; 5 weeks, 7.5 g; 5 weeks, 9 g) or placebo. Sensitivity analyses included completer population; placebo-based multiple imputation (MI) with missing not at random assumption (missing values in both arms imputed from observed placebo-arm values); analysis of covariance (ANCOVA); and tipping point-based MI of worsening values until  $P > 0.05$ . For MWT and NCA, mean differences and  $P$  values were calculated. For CGI-I, odds ratios (OR) and  $P$  values were calculated for completers; mean differences (1–7 points; lower values indicate greater improvement) and  $P$  values were calculated using ANCOVA.

**Results:** For completers (ON-SXB,  $n = 69$ ; placebo,  $n = 79$ ), significant improvement was observed with 6, 7.5, and 9 g ON-SXB vs placebo on all coprimary endpoints (all  $P < 0.001$ ); with 9-g dose, mean difference vs placebo on MWT was 6.0 min (95% CI: 3.3–8.7), CGI-I responder proportions for ON-SXB and placebo were 72.3% and 31.6% (OR, 5.7 [95% CI: 2.8–11.6]), and mean difference in NCA was  $-6.6$  (95% CI:  $-9.6$  to  $-3.6$ ). With placebo-based MI, all ON-SXB doses were associated with significant improvement vs placebo on all coprimary endpoints (all  $P < 0.001$ ); with 9-g dose, mean difference vs placebo on MWT was 5.4 min (95% CI: 2.8–8.0), CGI-I responder proportions for ON-SXB and placebo were 63.0% and 28.5% (OR, 4.3 [95% CI: 2.3–8.0]), and mean difference in NCA was  $-6.4$  (95% CI:  $-11.3$  to  $-3.7$ ). With ANCOVA, all ON-SXB doses were associated with

significant improvement vs placebo on all coprimary endpoints (all  $P < 0.001$ ); for the 9-g dose, mean difference vs placebo on the MWT was 6.0 min (95% CI: 3.6–8.5), CGI-I rating difference was  $-1.0$  (95% CI:  $-1.3$  to  $-0.7$ ), and mean NCA was  $-6.4$  (95% CI:  $-9.0$  to  $-3.8$ ). With MWT tipping point MI, differences between ON-SXB and placebo lost significance with worsening of 7.0, 5.2, and 4.3 min from baseline for 6, 7.5, and 9 g, respectively, which was implausible for the 7.5- and 9-g doses as baseline MWT was 5 min. When participants who withdrew from the ON-SXB arm were imputed as “not improved,” CGI-I remained significant in favor of ON-SXB (all 3 doses,  $P < 0.001$ ). Mean NCA remained significant for all 3 ON-SXB doses vs placebo with worsening trajectories imputed; positive results could not be tipped over with plausible values.

**Conclusions:** These post-hoc results are consistent with the coprimary endpoints and further confirm the efficacy of ON-SXB as a treatment for narcolepsy symptoms.

**Acknowledgements:** This study was funded by Avadel Pharmaceuticals.

#### EFFICACY OF ONCE-NIGHTLY SODIUM OXYBATE (ON-SXB; FT218) ACROSS STIMULANT USE SUBGROUPS: POST-HOC ANALYSES FROM THE REST-ON TRIAL

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**Introduction:** In REST-ON (NCT02720744), once-nightly sodium oxybate (ON-SXB; FT218) resulted in significant improvement vs placebo for the coprimary endpoints of mean sleep latency on the Maintenance of Wakefulness test (MWT), Clinical Global Impression of Improvement (CGI-I) rating, and number of weekly cataplexy attacks (NCA) overall ( $P < 0.001$ ) and in subgroups based on concomitant stimulant use for MWT and CGI-I (all  $P < 0.05$ ). Post-hoc analyses to investigate ON-SXB efficacy on the secondary REST-ON endpoints of disturbed nocturnal sleep (DNS) and the Epworth Sleepiness Scale (ESS) score were similarly conducted.

**Materials and Methods:** Individuals aged  $\geq 16$  years with narcolepsy type 1 or 2 were randomized 1:1 to receive ON-SXB (1 week, 4.5 g; 2 weeks, 6 g; 5 weeks, 7.5 g; 5 weeks, 9 g) or placebo.  $P$  values for change from baseline vs placebo at weeks 3 (6 g), 8 (7.5 g), and 13 (9 g) in ESS score, sleep shifts (ie, the number of shifts from stages N1, N2, N3 and rapid eye movement [REM] sleep to Wake and from N2, N3 and REM sleep to N1), nocturnal arousals (NA), and patient-reported outcomes of sleep quality and refreshing nature of sleep on a 100-point visual analog scale were calculated using a mixed-effects model for repeated measures.

**Results:** Of the 190 participants in the modified intent-to-treat population, 119 were taking concomitant stimulants (ON-SXB,  $n=66$ ; placebo,  $n=53$ ) including modafinil (ON-SXB, 21.5%; placebo, 21.0%), armodafinil (ON-SXB, 12.1%; placebo, 6.7%), amphetamine (various; ON-SXB, 10.3%; placebo, 5.7%), and methylphenidate (ON-SXB, 10.3%; placebo, 6.7%), and 71 were not taking stimulants (ON-SXB,  $n=31$ ; placebo,  $n=40$ ). Improvements with ON-SXB vs placebo were observed regardless of stimulant-use subgroup for ESS (stimulants: all doses,  $P \leq 0.01$ ; no stimulants: 6 g, directional improvement; 7.5 g,  $P < 0.01$ ; 9 g,  $P < 0.001$ ), sleep shifts (stimulants: 6 g,  $P < 0.01$ ; 7.5 and 9 g,  $P < 0.001$ ; no stimulants: all doses,  $P < 0.001$ ), and NA (stimulants: directional improvement, 6 g; 7.5 g,  $P < 0.01$ ; 9 g,  $P = 0.001$ ; no stimulants: 6 and 7.5 g,  $P < 0.05$ ; 9 g,  $P = 0.01$ ). Improvements with ON-SXB vs placebo were also observed on the patient-reported outcomes of sleep quality (stimulants: 6 and 7.5 g,  $P < 0.01$ ; 9 g,  $P < 0.05$ ; no stimulants: all doses  $P < 0.001$ ) and refreshing nature of sleep (stimulants: 6 and 9 g,  $P < 0.05$ ; 7.5 g,  $P < 0.001$ ; no stimulants: 6 and 7.5 g,  $P < 0.01$ ; 9 g,  $P = 0.001$ ).

**Conclusions:** The results of these post-hoc analyses were consistent with the previously reported statistically significant coprimary endpoint results from REST-ON. These data support the efficacy of ON-SXB for EDS and DNS in adults, as measured by objective and subjective endpoints, regardless of concurrent stimulant use.

**Acknowledgements:** This study was funded by Avadel Pharmaceuticals.  
**EFFICACY OF ONCE-NIGHTLY SODIUM OXYBATE (ON-SXB; FT218) BY NARCOLEPSY TYPE: POST-HOC ANALYSES FROM THE REST-ON TRIAL**

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**Introduction:** In REST-ON (NCT02720744), once-nightly sodium oxybate (ON-SXB; FT218) treatment resulted in significant improvement vs placebo for the coprimary endpoints mean sleep latency on the Maintenance of Wakefulness test (MWT), Clinical Global Impression of Improvement (CGI-I) rating of “much” or “very much” improved, and weekly number of cataplexy attacks (NCA) overall (all  $P < 0.001$ ) and in post-hoc analyses of subgroups of narcolepsy type 1 or 2 (NT1/NT2) for MWT and CGI-I (all  $P < 0.05$ ). Secondary REST-ON endpoints included polysomnographic measures of sleep stage shifts and nocturnal arousals (NAs) and patient-reported assessments of sleep quality and refreshing nature of sleep. Post-hoc analyses to investigate ON-SXB efficacy based on secondary REST-ON endpoints measuring effects on objective and subjective measures of disrupted nighttime sleep and daytime sleepiness in patient subgroups based on narcolepsy type were conducted.

**Materials and Methods:** Individuals aged  $\geq 16$  years with NT1 or NT2 were randomized 1:1 to receive ON-SXB (1 week, 4.5 g; 2 weeks, 6 g; 5 weeks, 7.5 g; 5 weeks, 9 g) or placebo.  $P$  values for change from baseline vs placebo at weeks 3 (6 g), 8 (7.5 g), and 13 (9 g) in Epworth sleepiness scale (ESS) score, sleep shifts (ie, the number of shifts from stages N1, N2, N3 and rapid eye movement [REM] sleep to Wake and from N2, N3 and REM sleep to N1), nocturnal arousals (NA), and patient-reported outcomes of sleep quality and refreshing nature of sleep on a 100-point visual analog scale were calculated using a mixed-effects model for repeated measures.

**Results:** Of the 190 participants in the modified intent-to-treat population, 145 had NT1 (ON-SXB,  $n=73$ ; placebo,  $n=72$ ) and 45 had NT2 (ON-SXB,  $n=24$ ; placebo,  $n=21$ ). Significant improvements with ON-SXB vs placebo were observed for both narcolepsy types for shifts to a lighter stage of sleep (NT1: 6, 7.5, and 9 g, all  $P < 0.001$ ; NT2: 6 and 7.5 g, both  $P < 0.05$ , 9 g,  $P < 0.001$ ), NA (NT1, 6 g,  $P < 0.05$ , 7.5 and 9 g,  $P < 0.01$ ; NT2, 7.5 and 9 g,  $P < 0.05$ ), and sleep quality (NT1, 6, 7.5, and 9 g, all  $P < 0.001$ ; NT2, 6, 7.5, and 9 g, all  $P < 0.05$ ). For both ESS and refreshing nature of sleep, significant improvements with ON-SXB vs placebo were observed for NT1 (6, 7.5, and 9 g,  $P \leq 0.001$ ). The NT2 subgroup showed directional improvements for these endpoints but did not achieve statistical significance.

**Conclusions:** Stratifying objective and subjective measures of disrupted nighttime sleep and daytime sleepiness by NT1 and NT2 allows for subgroup efficacy analyses. Lack of statistical significance on some endpoints for the NT2 subgroup may be due to underpowering. The results of these post-hoc analyses are generally consistent with the previously reported positive endpoints from REST-ON and provide further support for the efficacy of ON-SXB as a treatment for narcolepsy symptoms in adults with either NT1 or NT2.

**Acknowledgements:** This study was funded by Avadel Pharmaceuticals.

#### EFFICACY OF ONCE-NIGHTLY SODIUM OXYBATE (ON-SXB; FT218) FOR EXCESSIVE DAYTIME SLEEPINESS AND CATAPLEXY: POST-HOC NUMBER NEEDED TO TREAT AND EFFECT SIZE ANALYSES FROM REST-ON

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**Introduction:** Narcolepsy is a chronic neurologic disease; symptoms

include excessive daytime sleepiness (EDS) and cataplexy. FT218 is an extended-release, once-nightly formulation of sodium oxybate (ON-SXB) that is in development for treatment of adults with narcolepsy. Treatment with ON-SXB resulted in significant improvement vs placebo (6 g, 7.5 g, and 9 g, all  $P < 0.001$ ) for the coprimary endpoints of mean sleep latency on the Maintenance of Wakefulness test (MWT), Clinical Global Impression of Improvement rating, and number of weekly cataplexy episodes, as well as the secondary endpoint Epworth sleepiness scale (ESS) score, in the phase 3 REST-ON clinical trial (NCT02720744). Post-hoc analyses of numbers needed to treat (NNT) and effect sizes were performed to provide further context into the effectiveness of ON-SXB.

**Materials and Methods:** Individuals aged  $\geq 16$  years with narcolepsy type 1 or 2 were randomized 1:1 to receive ON-SXB (1 week, 4.5 g; 2 weeks, 6 g; 5 weeks, 7.5 g; 5 weeks, 9 g) or placebo. For the post-hoc analyses, response on the MWT was defined as  $\geq 5$  min increase from baseline in mean sleep latency, response on the ESS was defined as a score  $\leq 10$ , and cataplexy response was defined as  $\geq 50\%$  reduction from baseline in the mean number of weekly.

**Results:** In total, 222 participants were randomized and 190 comprised the modified intent-to-treat population (ON-SXB,  $n=97$  [NT1,  $n=73$ ]; placebo,  $n=93$  [NT1,  $n=72$ ]). For MWT response, all doses of ON-SXB (6 g at week 3, 7.5 g at week 8, and 9 g at week 13) had NNTs of 3 and effect sizes ranging from 0.7–0.9. For ESS response, NNTs ranged from 3 to 6, with a dose-response effect. As a decrease signifies response, effect sizes were between  $-0.5$  to  $-0.7$  for the 3 doses. For cataplexy response, NNT was 6 for the 6-g dose and 3 for the 7.5-g and 9-g doses, and the effect sizes were between  $-0.7$  to  $-0.8$ .

**Conclusions:** NNTs provide a useful interpretation of the expected effectiveness of a medication. As defined by these measures, only 3–6 patients need to be treated with ON-SXB to achieve  $\geq 5$  minutes increased sleep latency on the MWT or an ESS of  $\leq 10$ , with the same number needed to achieve a 50% or greater reduction in cataplexy. Effect size provides a useful interpretation, as this calculation relies upon the standard deviation; an effect size of 0.50 or more is generally regarded as a moderate effect and 0.80 as a large effect. These post-hoc analyses provide further confidence in the strength of ON-SXB efficacy and may be useful to clinicians in discussing treatment expectations.

**Acknowledgements:** This study was funded by Avadel Pharmaceuticals.

#### ENHANCEMENT OF A MACHINE LEARNING ALGORITHM TO ALERT SLEEP CLINICIANS OF PATIENTS AT RISK FOR NARCOLEPSY, USING NOCTURNAL POLYSOMNOGRAPHY IN GENERAL SLEEP MEDICINE CLINICS

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**Introduction:** Narcolepsy frequently remains undiagnosed for many years following symptom onset (Thorpy MJ, Krieger AC. *Sleep Med.* 2014;15(5):502-7). A combination of clinician lack of narcolepsy-specific education and experience, combined with substantial medical comorbidity such as sleep apnoea, contributes to this underdiagnosis. Polysomnography (PSG) has been previously shown to contain quantitative information that, using machine learning algorithms, may aid the identification of narcolepsy type 1 (Stephansen JB, et al. *Nat Commun.* 2018;9(1):5229). The current study evaluated the practical clinical application of these algorithms and further enhanced them in a large sleep clinic population to create a tool with high sensitivity and specificity to alert sleep clinicians about patients at risk for narcolepsy.

**Materials and Methods:** A total of 21,837 nocturnal PSG studies from a random sample of sleep clinic patients (narcolepsy-related PSG studies,  $n=302$ ; non-narcolepsy control PSG studies,  $n=21,535$ ) were randomly split (1:1) into a training set and a testing set. Multiple Sleep Latency Test results were used as a proxy for diagnosis of narcolepsy type 1 (NT1;  $\geq 3$  sleep onset rapid eye movement periods [SOREMPs] and mean sleep

latency [MSL]  $\leq 5$  minutes;  $n=137$ ) or narcolepsy type 2 (NT2;  $\geq 2$  SOREMPs and MSL  $\leq 8$  minutes [but not meeting criteria for NT1];  $n=165$ ). Sleep stage probability graphs, or hypnodensities, were estimated from the PSGs on 15-second epochs using a previously developed convolutional neural network. A Gaussian process (GP) model was then designed to identify patients with a high probability of having narcolepsy using these hypnodensities as input. This model's performance (ability to distinguish between narcolepsy and healthy controls based on sensitivity and specificity) considered receiver operating characteristics (ROC) with the goal of achieving an area under the curve (AUC)  $\geq 0.80$  when plotting specificity versus sensitivity. An additional goal, based on sleep medicine clinician feedback, was to confirm narcolepsy diagnosis in at least 3 of each 4 algorithm-identified patients with narcolepsy (ie,  $\geq 75\%$  specificity) while having the system identify at least half of the patients with narcolepsy in the overall sample (ie,  $\geq 50\%$  sensitivity).

**Results:** When trained to evaluate narcolepsy according to either NT1 or NT2 criteria, the GP model had an AUC=0.9960 and AUC=0.8014 for classifying narcolepsy in the training and testing sets, respectively. Sensitivity in the testing set ranged from 73% to 65% for specificities between 75% and 80%. The classifier's performance improved in the testing set when trained to evaluate narcolepsy according to NT1 criteria only (AUC=0.9997 and AUC=0.8154 for the training and testing sets, respectively; sensitivity ranged from 75% to 72% for specificities between 75% and 80%).

**Conclusions:** Results of this study support further efforts to develop a machine learning-based algorithm that can offer an objective, sensitive, and specific tool to alert sleep clinicians about patients at risk for narcolepsy, using nocturnal polysomnography in general sleep medicine clinics.

**Acknowledgements:** Supported by Jazz Pharmaceuticals.

#### EPIGENETIC REGULATION OF OREXIN NEURONS BY MIRNAS

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Narcolepsy type 1 is a sleep disorder characterized by excessive daytime sleepiness and cataplexy (sudden loss of muscle tone triggered by positive emotions). Genetic studies showed that narcolepsy is associated with the human leukocyte antigen (HLA) locus. Postmortem brain analysis showed a large reduction of orexin-producing neurons in the lateral hypothalamus of narcolepsy patients. Narcolepsy patients show a deficiency of orexin-A neuropeptide in the cerebrospinal fluid (CSF). This deficiency is supposed to be due to an autoimmune attack targeting hypothalamic orexin neurons. An alternative possibility is a decreased or absence of orexin gene expression. Transcriptional control of orexin is not well-known. In this study the role of miRNAs as epigenetic regulators of orexin gene expression were tested. MicroRNAs (miRNAs) are small, non-coding, highly conserved RNAs which can block mRNA translation into protein. Dicer is an essential protein in the production of mature and functional miRNAs that can regulate or silence expression of target genes. Thus, we inactivated miRNAs in orexin neurons by deleting the floxed-Dicer alleles in orexin-Cre-ki mice (Orexin-Dicer-ko). We found that orexin expression is completely lost in Orexin-Dicer-ko mice, both at mRNA and protein levels, resulting in the typical narcolepsy symptoms such as cataplexy, sleepiness, difficulties to maintain long wakefulness and shorter Rapid-Eyes-Movements (REM) sleep latency. Interestingly, conditional deletion of miRNAs maturation in adult mice by using a tet-off system (Orexin-Dicer-cko) did not lead to the loss of orexin neurons 4 weeks after shutting down of miRNA maturation but a decrease of orexin neurons is observed 8 weeks after Dicer deletion. These results suggest that orexin neurons could survive without mature miRNAs during 4 weeks but not 8 weeks. Our findings suggest a major role for miRNAs in the development and maintenance of orexin neurons and add Orexin-Dicer-ko and Orexin-Dicer-cko as new mouse models of narcolepsy.

**Keywords:** microRNA, Gene expression, Dicer, Cataplexy

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## EXTRACTING REAL-WORLD INSIGHTS FROM SOCIAL MEDIA TO UNDERSTAND NARCOLEPSY AND THE IMPACT OF BRAIN FOG

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**Introduction:** The ability to listen to and interpret the patient experience is necessary to understand how to address the needs of a particular community. The TREND analytics engine identifies the most discussed concepts and terms from social media to better understand a disease from the patient's perspective using natural language processing (NLP). The resulting data provide many unique opportunities for both patient community partners and industry sponsors to bridge the communication divide between the community lexicon and medical terminology to improve care delivery. In the narcolepsy community, unmet needs around the issue of brain fog can be served by this approach.

**Materials and Methods:** The TREND analytics engine, Krystie™, was used to map the information shared in 2 narcolepsy communities: a private Facebook group, PWN4PWN, and a Reddit thread, r/Narcolepsy, together containing 40,163 comments from July 2020–July 2021. Krystie uses NLP techniques to analyze complex, real-world conversations and identify key terms and concepts from social media conversations. The concepts are the words and phrases—including misspellings, colloquialisms, and abbreviations—that denote an idea.

**Results:** Krystie identified the top 200 terms used in narcolepsy social media forums and ranked 12 overarching concepts (ie, clinical findings, substances, bodily/mental function) based on the number of conversations surrounding each one in this investigation. It then created a co-occurrence network for brain fog by isolating conversations that included brain “fog” and “help” language (eg, “improved symptoms”, “reduced brain fog”). The network further revealed 3 medications, “Xyrem”, “Adderal”, and “modafinil”, with high connectivity to the central network of brain “fog” and “help”.

**Conclusions:** Using NLP techniques, this analysis brings further understanding to the impact of narcolepsy, and the associated unmet needs with brain fog, to the patient experience and highlights the richness of conversations shared among community members. In the context of rare disease, where real-world information is often limited, the ability to interrogate social media conversation data can be valuable to patients and their caregivers, physicians, researchers, and pharmaceutical developers. The data that formed the basis of this analysis can be further explored to gain additional clarity from this first assessment and can prompt collaborative health initiatives to address community needs, thus representing an important contribution to the field of real-world evidence collection for the medical community.

**Acknowledgments:** TREND Community thanks our cosponsors Harmony Biosciences and Takeda for amplifying the voices of people living with narcolepsy, PWN4PWN for providing access to data, and Wake Up Narcolepsy and Sleep Consortium for their consultation during the review process.

## HETEROGENEOUS NEUROPSYCHIATRIC SYMPTOMS AND OUTCOME IN VERY EARLY-ONSET NARCOLEPSY TYPE 1: A CASE SERIES

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Narcolepsy type 1 is a central disorder of hypersomnolence characterized by excessive daytime sleepiness, cataplexy (i.e., sudden loss of muscle tone during wakefulness triggered by emotions), and additional rapid eye movement sleep-related manifestations with a peculiar phenotype when arising at pediatric age. Several features of childhood Narcolepsy type 1 are common to neuropsychiatric conditions; discrete neuropsychiatric comorbidity has also been demonstrated.

Here we report on three children with very early Narcolepsy type 1 onset, observed close to symptoms' onset. All three patients had psychiatric features since Narcolepsy symptoms' onset coupled with peculiar motor disturbances, and the course of narcolepsy symptoms paralleled neuropsychiatric aspects, suggesting a possible intrinsic link between sleep and psychological features.

Multidisciplinary management is mandatory for pediatric Narcolepsy type 1 since prompt disease management taking into account neuropsychiatric symptoms could lead to a better clinical outcome and improve quality of life.

## IDLING FOR DECADES: A EUROPEAN STUDY ON RISK FACTORS ASSOCIATED WITH LONG TIME TO NARCOLEPSY DIAGNOSIS

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**Introduction:** Narcolepsy type-1 (NT1) is a rare chronic neurological disorder with excessive daytime sleepiness (EDS) as usual first and cataplexy as pathognomonic symptoms. Most NT1 patients have a delay up to several years or even decades between symptom onset and correct diagnosis. The long diagnostic delay in narcolepsy may lead to a substantial medical and socioeconomic burden. Shortening the NT1 diagnostic delay is the key to reduce disease burden and related low quality of life. Here we investigated the changes of diagnostic delay over the diagnostic years (1990–2018) and the factors associated with the delay in Europe.

**Materials and Methods:** We analyzed 580 NT1 patients from 12 European countries using the European Narcolepsy Network database. The diagnostic delays between patients diagnosed in different years were compared using Kruskal-Wallis rank sum test (P-value<0.05). Post-hoc pairwise comparisons were done using the non-parametric Conover's test (P-value<0.05) with P-values adjusted by Benjamini & Hochberg method. The same tests were also applied to the stratified data, i.e., the diagnostic years were stratified to 1990–1999 (n=47), 2000–2009 (n=164), 2010–2013 (n=234) and 2014–2018 (n=135), and the diagnostic delays between the 12 countries. We then combined machine learning and linear mixed-effect model (LMM) to identify factors associated with the delay.

**Results:** We did not find significant differences in the diagnostic delay over years in the whole dataset (P-value=0.263), although the delay showed significant country differences (P-value<0.0001). The number of patients with short (≤2-year) and long (≥13-year) diagnostic delay equally increased over decades, suggesting that subgroups of NT1 patients with variable disease progression may co-exist. At Younger age of cataplexy

onset ( $P$ -value=0.017), longer interval between EDS and cataplexy onsets ( $P$ -value<0.0001), lower cataplexy frequency ( $P$ -value<0.0001), shorter duration of irresistible daytime sleep ( $P$ -value=0.031), lower daytime REM sleep propensity ( $P$ -value=0.0026) and females ( $P$ -value=0.0043) are associated with longer diagnostic delay.

**Conclusions:** Our findings contrast the results of previous studies reporting shorter delay over time which is confounded by calendar year, because they characterized the changes in diagnostic delay over the symptom onset year. Our study indicates that new strategies such as increasing media attention/awareness and developing new biomarkers are needed that better detect EDS, cataplexy and changes of nocturnal sleep in narcolepsy, in order to shorten the diagnostic interval.

**Acknowledgements:** The EU-NN database is financed by the EU-NN. The EU-NN has received financial support from UCB Pharma Brussels for developing the EU-NN database.

### IS THERE ANY CONSISTENT STRUCTURAL AND FUNCTIONAL BRAIN ABNORMALITY IN NARCOLEPSY? A META-ANALYTIC PERSPECTIVE

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**Introduction:** Narcolepsy is characterized by excessive daytime sleepiness, loss of muscle tone (cataplexy), sleep paralysis and hallucinations. Several neuroimaging studies have been conducted to investigate its underlying pathophysiology, but indicated divergent results. This quantitative meta-analysis aimed to identify consistent structural and functional abnormality in narcolepsy.

**Materials and Methods:** We performed a pre-registered Activation likelihood estimation (ALE) meta-analysis on both structural and functional neuroimaging experiments, while adhering to the best-practice guidelines for conducting neuroimaging meta-analysis. We searched PubMed, Web of Science and Embase in September 2020, performed reference tracking of relevant publications, and after screening 2577 records, read 121 full papers and finally included 15 whole-brain neuroimaging experiments. Next, we extracted the peak coordinates of the significant regions reported in the included experiments and performed ALE meta-analyses. We corrected for multiple comparisons using  $cFWE$  at  $p < 0.05$  and excluded coordinates from ROI-based experiments. In addition, we identified studies using overlapping samples and merged their coordinates to prevent them from overly influencing the results.

**Results:** Our ALE analysis revealed no significant regional convergence across all the experiments ( $p_{cFWE} > 0.326$ ), as well as across the subset of experiments reporting decreased grey matter volume, activity or connectivity [ $N = 13$ ] ( $p_{cFWE} > 0.215$ ). No modality-specific ALE analysis was performed due to the small number of experiments within each modality.

**Conclusions:** In the present study, we found no convergent regional abnormality. This study highlights the need for an updated and robust neuroimaging meta-analysis on narcolepsy once more studies are available in the future.

**Acknowledgements:** -

### LINKING CLINICAL COMPLAINTS AND OBJECTIVE MEASURES OF DISRUPTED NIGHTTIME SLEEP IN NARCOLEPSY TYPE 1

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**Introduction:** Despite its high frequency in narcolepsy type 1 (NT1), disrupted nocturnal sleep (DNS) remains an understudied symptom, and its

determinants have been poorly assessed. We aimed to determine the clinical, polysomnographic (PSG), and laboratory variables associated with DNS in a large sample of patients with NT1 in drug-free and treated conditions; and to evaluate the effect of medication intake on DNS complaint and its severity.

**Materials and Methods:** Two hundred forty-eight consecutive adult patients with NT1 (145 untreated, 103 treated) diagnosed according to ICSD-3 criteria; at the National Reference Center for Narcolepsy-France were included. A subgroup of 51 drug-free patients was evaluated again during stable treatment. DNS was assessed with a single item of the Narcolepsy Severity Scale, and categorized in four levels (absent, mild, moderate, severe). Clinical characteristics, self-report rating scales, PSG parameters (especially sleep fragmentation markers: sleep bouts (SB), wake bouts (WB), sleep/wake transitions), objective sleepiness (on multiple sleep latency test (MSLT) or maintenance of wakefulness test (MWT)) and cerebrospinal fluid orexin-A levels were assessed.

**Results:** In drug-free patients, DNS severity was highly associated with a more severe disease, more cataplexy, hallucinations, sleepiness, anxiety/depressive symptoms, autonomic dysfunction, and a worse quality of life (QoL). Patients with moderate/severe DNS (59%) had increased sleep onset REM periods on MSLT, lower sleep efficiency on PSG, more N1, longer wake after sleep onset, more SB and WB, of shorter duration, more Rapid Eye Movement (REM) and non-REM sleep instability, and more transitions. In treated patients, DNS severity also was associated with more severe disease, subjective sleepiness, anxiety/depressive symptoms, worse QoL, and also with antidepressant intake. No PSG parameter was associated with DNS, except a longer REM sleep latency, but daytime wakefulness measured objectively by MWT was impaired in patients with moderate/severe DNS (mean sleep latency difference of 7 min compared with patients without DNS,  $p=0.005$ ). In the longitudinal sample, subjective sleepiness, NT1 severity, and depressive symptoms were reduced during treatment, as well as total sleep time, WB, SB, and sleep-wake transitions. Upon treatment, DNS improved in 55% of patients. No parameter to predict this improvement was identified, except higher baseline anxiety level.

**Conclusions:** DNS complaint is frequent in patients with NT1 and is associated with disease severity, several PSG parameters and objective sleepiness in untreated and treated conditions. DNS improves with treatment. We advocate the systematic assessment of this symptom and its inclusion in NT1 management strategy.

**Acknowledgements:** to all study participants, patients and their families, and the French Association of Narcoleptic patients (ANC, Association Française de Narcolepsie Cataplexie et d'Hypersomnies rares)

### LONG-TERM SAFETY OF ONCE-NIGHTLY SODIUM OXYBATE: INTERIM DATA FROM RESTORE

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**Introduction:** Sodium oxybate (SXB) is an established standard-of-care treatment for adults with narcolepsy. Existing oxybate formulations are immediate release and require patients to awaken for a second dose 2.5–4 h after the first bedtime dose. Once-nightly SXB (ON-SXB; FT218), an extended-release formulation, is under FDA review for the treatment of adults with narcolepsy. The efficacy and safety of ON-SXB at doses of 6, 7.5, and 9 g in patients with narcolepsy type 1 (NT1) or type 2 (NT2) were assessed in the 13-week, phase 3, randomized, placebo-controlled REST-ON clinical trial (NCT02720744). The coprimary endpoints of improvement in mean sleep latency on the Maintenance of Wakefulness test, Clinical Global Impression of Improvement rating (% much/very much improved), and number of weekly cataplexy attacks were all met (all doses,  $P < 0.001$  vs placebo). Safety and adverse drug reactions (ADRs) were consistent with the known safety profile of immediate-release SXB. RESTORE is an ongoing open-label study (NCT04451668) designed to assess the long-term safety

and tolerability of ON-SXB.

**Materials and Methods:** In RESTORE, an open-label extension/switch study, participants aged  $\geq 16$  years with a confirmed diagnosis of NT1 or NT2 are eligible for enrollment. Participant eligibility includes those who completed the REST-ON trial, who are receiving a stable dose of twice-nightly SXB, or who are naïve to oxybate treatment are eligible. Initial ON-SXB doses for those switching from stable immediate-release oxybate therapy are the equivalent/closest dose to their previous total nightly dose. Initial dose for others is 4.5 g/night. Investigators may titrate the ON-SXB dose by 1.5-g increments weekly as needed. Adverse events (AEs) are collected including treatment-emergent AEs and ADRs (AEs assessed by the investigator to be related or possibly related to study drug). Interim safety data from RESTORE were analyzed descriptively using the safety population, which included all enrolled participants who received  $\geq 1$  dose of ON-SXB.

**Results:** At an interim data cutoff date of November 7, 2021, a total of 103 participants were enrolled (not currently taking oxybate,  $n=27$ ; switch,  $n=76$ ). Most participants are white ( $n=83$  [80.6%]) females ( $n=68$  [66.0%]) with a mean (range) age of 34 (16–72) years. As of this data cutoff date, 1 patient had 2 serious AEs (fractured ribs and pneumothorax after slipping in a puddle during the day) that were deemed unrelated to ON-SXB; the patient continued in the study. Fifty-four (52.4%) participants have experienced an AE and 32 (31.1%) participants have experienced an ADR. Most ADRs have been considered mild (68.5%) or moderate (27.4%) in severity. The most frequently reported ADRs ( $\geq 2\%$ ) thus far are nausea (5.8%), fall (4.9%), dizziness (3.9%), enuresis (3.9%), tremor (3.9%), headache (2.9%), paresthesia (2.9%), somnambulism (2.9%), and somnolence (2.9%).

**Conclusions:** ON-SXB has been generally well tolerated, and no new safety signals have been observed. These interim data indicate that the safety profile of ON-SXB is consistent with that of SXB. If approved, ON-SXB will offer a new once-nightly treatment option for adults with narcolepsy.

**Acknowledgements:** This study is funded by Avadel Pharmaceuticals.

#### MACHINE LEARNING MODEL ON POLYSOMNOGRAPHY FEATURES THROUGHOUT THE NIGHT TO BETTER CHARACTERIZE NARCOLEPSY TYPE 1

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**Introduction:** Narcolepsy type 1 (NT1) is characterized by excessive daytime sleepiness, cataplexy, disrupted nighttime sleep, hypnagogic/hypnopompic hallucinations, and sleep paralysis. Low levels of CSF orexin is the best diagnostic biomarker for NT1; however, this invasive test is infrequently used. To date, polysomnography (PSG) biomarkers that can be used reliably for diagnostic purposes are lacking. Here we examine the changes in sleep architecture throughout the night to better discriminate patients with NT1 from clinical controls (Co).

**Materials and Methods:** PSG features were derived from 159 drug-free nocturnal PSG records (NT1:  $n=112$ , age  $37 \pm 14$  years; Co:  $n=45$ , age  $41 \pm 15$  years). Control PSGs were selected using: total sleep time  $\geq 5$ h, sleep efficiency  $\geq 70\%$ , and both apnea-hypopnea index and periodic leg movements index  $< 15$ . Features were derived from hypnograms and the output of a deep learning model that estimates the probabilities of each sleep stage, so-called “hypnodensities”. Basic sleep metrics (e.g. REM onset, duration of each sleep stage) and sleep state transition matrices were calculated from hypnograms, while marginal and mixed-stage probabilities were calculated from hypnodensities. In addition to whole-night metrics ( $n=11$ ), the night was divided into quarters in which all features were averaged. Specific groups of quarter-night features (sleep metrics,  $n=44$ ; transition matrices,  $n=100$ ; stage probabilities,  $n=60$ ) and all features combined were individually used to train/test/validate a Gaussian process classifier to differentiate between the two groups. The dataset was randomly divided into training/testing and validation sets, representing 70% and 30% of the subjects respectively. Class imbalance, present in our data due to the smaller number of controls, was addressed via data augmentation. The area under the receiver operating curve (AUC) was computed as a measure of classifier performance, and the most discriminative features were identified.

**Results:** Classification results show the benefit of computing sleep metrics by quarter-night, increasing AUC to 0.96 compared to 0.89 when using whole-night sleep metrics. The AUC increased to 0.97 when only quarter-night hypnodensities were used. No further change in AUC was observed when combining all features together. Transition matrices provided the lowest AUC of 0.77. The most discriminative features involved REM-sleep in the first quarter-night, as shown by feature importance rankings for each tested classifier. When hypnodensity features were used, the probability of REM-sleep in the first quarter was the top feature. Similarly, the fraction of time spent in REM in the first quarter was the second most important feature for the quarter-night sleep metrics. Similarly, classification using transition matrices showed REM-to-REM transitions as the main feature.

**Conclusions:** Our findings demonstrate the value of analyzing the evolution of sleep architecture per quarter-night period, as differences between NT1 subjects and clinical controls are most clearly seen in the early hours of the night. REM-related metrics early in the night are particularly informative for NT1 classification, consistent with prior studies. In future work, we will apply these tools to understand features of other hypersomnolence disorders.

**Acknowledgements:** This work was conducted by Takeda Pharmaceuticals and Sleep-Unit, Montpellier-France, which was partially supported by Takeda

#### MEASUREMENT OF NARCOLEPSY SYMPTOMS IN SCHOOL-AGED CHILDREN AND ADOLESCENTS

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**Introduction:** Available validated instruments to assess and monitor Narcolepsy type 1 (NT1) symptoms in pediatric population are limited. Several daytime sleepiness scales are used, together with daily diary or questionnaires to capture cataplexy frequency and intensity. However a comprehensive tool that quantifies all NT1 symptoms with a single instrument is seriously lacking in children. We previously validated the Narcolepsy Severity Scale (NSS) in adults to quantify the severity, frequency, and consequences of the 5 key narcolepsy symptoms over the last month, and we now developed the Pediatric NSS (NSS-P). The aims of this study were to assess NSS-P psychometric properties, validity, and reliability, and to evaluate its responsiveness to treatment in a well-characterized sample of children and adolescents with NT1.

**Materials and Methods:** The NSS was reformulated for children, with adapted wording, and the item about driving was removed. The total score of the 14-item NSS-P ranges from 0 to 54, the higher scores reflecting a more severe disease. Children and adolescents ( $n = 209$ , 6–17 years of age) with a clear diagnosis of NT1, followed in two Reference Centers for Narcolepsy in France (Paris, Montpellier) were consecutively included, and were asked to fill in the NSS-P. The scale was fully and correctly completed by 160 patients (10–18 years of age, 68 drug-free). Moreover, 65 participants completed it twice (33 before/during treatment, and 32 under the same treatment). The NSS-P psychometric properties, score changes before/during treatment, and convergent validity with other clinical parameters were assessed.

**Results:** The NSS-P showed adequate psychometric properties with significant item-total score correlations. Factor analysis indicated a 4-factor solution with good reliability. The NSS-P total score was lower in treated than untreated patients with a mean difference of  $3.71 \pm 1.45$ , with a minimum clinically important difference between untreated and treated patients in the longitudinal sample estimated at 4 points. Four severity levels were defined (mild, moderate, severe, very severe) with between-group differences related to treatment. The NSS-P total score was associated with self-reported sleepiness, insomnia, and depressive symptoms. The temporal stability of the scale was satisfactory.

**Conclusions:** We validated a brief instrument to assess NT1 symptom

frequency, severity, and consequences in  $\geq 10$ -year-old children and adolescents, with 4 clinically relevant severity score ranges. This scale constitutes a relevant tool to improve and provide guidance for NT1 management in pediatric populations. The ease of administration, its good psychometric properties, and its sensitivity to detect symptom changes after management ensure future use of this questionnaire in clinical and research settings.

**Acknowledgements:** The authors are indebted to all study participants, patients and their families, and the French Association of patients (ANC, Association Française de Narcolepsie Cataplexie).

#### MODEL OF NAP DETECTION FROM ACCELEROMETRY DATA AND ITS APPLICATION TO A STUDY WITH NARCOLEPSY TYPE 1 AND HEALTHY PARTICIPANTS

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**Introduction:** Excessive daytime sleepiness (EDS) is one of the defining symptoms of narcolepsy, affecting daily functioning and quality of life. To complement often biased self-reports and enable more accurate clinical follow-up, we developed an objective measure of daytime naps, representing a key manifestation of EDS. Our automated nap detection algorithm is based on actigraphy, which is a well-established approach that leverages wearable devices to approximate sleep–wake transitions and extract summaries of sleep. Following algorithm development/validation using the Multi-Ethnic Study of Atherosclerosis (MESA) dataset, we applied it in the context of a Phase 0 clinical trial (NCT04445129) that included patients with narcolepsy type 1 (NT1) and healthy participants.

**Materials and Methods:** MESA consists of 2,237 participants who wore wrist-worn actigraphy devices across seven days. We restricted our attention to the daytime hours of 8 a.m.– 6 p.m. and defined ground-truth naps as sustained periods ( $\geq 5$  minutes) of hand-scored sleep. We developed an integrated pipeline that predicts sleep–wake epochs from activity counts, groups these predictions into naps, then post-processes these naps using pruning and fusion. Sleep–wake epochs are predicted using simpler sleep wake scoring methods (e.g., Cole-Kripke) as well as deep learning models (e.g., convolutional neural networks [CNNs]). Following validation, our algorithm was applied in a Phase 0 study that collected accelerometry and other physiological measurements (e.g., heart rate, polysomnography) for 16 Patients with narcolepsy type 1 (NT1) and 16 healthy sex and age matched controls. All participants wore a wrist accelerometer on their non-dominant hand at screening and throughout the study. Nap predictions were compared to subjective self-reports collected electronically (ePRO).

**Results:** Our nap detection algorithm yielded high sensitivity (88.9%) and F1 area (84.4%) in the MESA validation dataset. Although Cole-Kripke and CNN produced similar results, we favored the former as computationally cheaper, more interpretable, and easily extendable to other studies. In the clinical trial, the nap detection algorithm had poor agreement with ePRO (F1 area = 0.20, ICC = 0.32). Unlike the algorithm, ePRO did not show a clear contrast within versus outside a nap, suggesting its accuracy for both the timing and duration of a nap was limited. We found that the odds of experiencing a day without a nap were tenfold higher in controls relative to NT1, and that the rate of naps was 47% higher in cases than controls. While the duration of naps was the same among the two groups according to both the ePRO and algorithm, the latter provided an estimate with much smaller variance.

**Conclusions:** Past studies have indicated that actigraphy is a highly sensitive instrument for quantifying daytime naps. In this work we developed an actigraphy-based algorithm for detecting naps that has both high sensitivity and specificity. Future studies will incorporate additional physiological measurements such as heart rate with physical activity, as the combination might provide a more accurate and robust measure for naps.

**Acknowledgements:** Dr. Ghosal's postdoctoral fellowship is partially supported by Takeda.

#### NEW NARCOLEPSY-ATAXIA AND NEUROPATHY PHENOTYPE NOT ASSOCIATED WITH DNMT1

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**Introduction:** Autosomal Dominant Cerebellar Ataxia-Deafness and Narcolepsy (ADCA-DN, OMIM #604121) and Hereditary Sensory Neuropathy with Dementia and Hearing Loss (HSN-IE, OMIM #614116) are two neurodegenerative syndromes caused by dominant mutations in the replication foci targeting sequence on the DNA methyltransferase 1 gene. The wide spectrum of phenotypes due to DNMT1 mutations is termed as DNMT1- complex disorder but typically mutations in exon 21 give rise to cerebellar ataxia, with deafness and narcolepsy and mutations in exon 20 to peripheral neuropathy with sensory and autonomic involvement. All cases reported to date have mutations in the targeting sequence domain of DNMT1. We present a new phenotype not associated with DNMT1.

**Materials and Methods:** Neurophysiologic testing, brain imaging, laboratory test, high resolution HLA typing, phenotypic and genotypic characterizations were performed. A panel of 150 genes related to dominant and recessive ataxias was analyzed using WES (SureSelect Human All Exon V6 / Illumina sequencing). The sequences obtained were alignment against the GRCh38/hg38 reference sequence. The competitive Elisa Kit Orexin A EIA Kit EK-003-30 (Phoenix Pharmaceuticals) was used for Hypocretin-1 determination.

**Results:** The patient is a male currently aged 71 years. Started with CPAP for OSAS in 2015 after polysomnography with AHI 20,5 but EDS didn't improve. Narcolepsy type 1 diagnosed in 2016. Cataplexy occurred 3–4 times a week since 2013 -at age of 64- with laughter and other emotions, mainly generalized, of 10 seconds, with rapid recovery. Sleep paralysis 3–4 times a week. Not hallucinations. Treatment with Sodium oxybate (SXB; Xyrem) and later, with Lower-sodium oxybate (LXB; JZP-258) produced a significant reduction in all patient symptoms. Polysomnography with REM sleep onset 2,5 minutes and multiple latency test with mean latency of 3,5 min and two SOREMs. HLA DRB1\*15:01, HLA\*06:02 and HLA\*01:02 positive. Hypocretin in CSF 83,3 pg/ml, around ¼ of values for controls in the kit. In 2018 – 5 years after cataplexy begins - progressive deterioration of gait along with sexual impotence and orthostatic hypotension appeared. In the exploration, a cerebellar ataxia of predominance in the lower limbs is evident without other relevant findings. Brain MRI showed no structural pathology. CSF without inflammation data and with negative neurodegeneration markers (Amiloid- $\beta$  and Tau). Electromyography showed a mild distal motor axonal neuropathy. New polysomnography showed REM sleep behavior disorder consistent with clinical data. No pathogenic genetic variants, including the DNMT1 gene, were identified. The picture has advanced progressively, with severe difficulty in ambulation and standing without support, without evidence of any new symptoms, nor the appearance of any other pathological findings.

**Conclusions:** A late onset case of narcolepsy, ataxia and peripheral neuropathy -not sensitive- and without deafness not linked to any genetic described mutation is shown. Due to the clinical similarities with the pictures associated with DNMT1 mutations, the case indicates that some phenotype of the so-called DNMT1- complex disorder might not always be related with the targeting sequence domain of DNMT1.

**Acknowledgements:** The hypocretin determinations of this patient were made with the FI19058 FEDER grant support.

#### NOVEL GENES ASSOCIATED WITH HYPOCRETIN-PRODUCING NEURONS IDENTIFIED BY GENE EXPRESSION PROFILING

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**Introduction:** for the last 20 years, research on the autoimmune hypothesis of narcolepsy has focused on autoreactivity against hypocretin, the absence of which is causing the disorder's symptoms. So far, no such autoreactivity has been definitively shown. It is largely unknown whether other genes exist that are expressed exclusively in hypocretin-producing neurons and therefore represent a potential alternative auto-antigen for the immune response leading to narcolepsy. We assess the merit of genes from literature associated with narcolepsy using novel *in silico* methods that utilize available gene expression information in humans and animals. Additionally, using the same methods, we aim to identify genes of interest that might be alternative candidates to hypocretin for the auto-immune response leading to the destruction of the hypocretin-producing neurons.

**Materials and Methods:** a search on genes associated with hypocretin-producing neurons was built in Pubmed using guidelines on performing an exhaustive literature review published before by McKeever et al. (2015). References of the search results were used to add missed publications to the search results. A list of genes associated with narcolepsy was retrieved from DisGeNet v3.0, a database that integrates human gene-disease associations from different expert curated sources and text-mining of literature. Spatial gene expression data from six adult human brains were obtained from the Allen Human Brain Atlas database. Semi-quantitative information on gene expression was provided by the Genotype Tissue Expression (GTEx) project and its portal (gtexportal.org): expression data were derived from 54 different tissues of almost 1000 healthy donors.

**Results:** using both Pubmed search and DisGeNet a total of 321 genes associated with narcolepsy were identified. Cross-referencing these findings with Allen Brain Atlas and GTEx portal expression profiles did not show a clear co-expression of any of these genes with hypocretin.

Cross-reference of the 150 genes with an expression profile most similar to hypocretin in GTEx portal rendered 49 genes that also showed expression in the hypothalamus in sufficient quantities in that database. Based on the function of these genes derived from the literature and expression in other tissues 31 genes were ruled out for being involved in the autoimmune hypothesis of narcolepsy type 1, rendering 18 potential novel candidate genes.

**Conclusions:** most candidate genes derived from genome-wide association studies were found unlikely to be a target for the autoimmune response leading to narcolepsy type 1 based on their expression profile that differs considerably from that of hypocretin. Novel open access expression profiling databases allow for searching for candidate auto-antigens that represent alternative targets for the autoimmune response leading to narcolepsy type 1. The *in vivo* expression of the 18 identified candidate genes from this study in hypocretin-producing neurons can be validated in post mortem brains of healthy controls and narcolepsy patients and subsequently used to broaden the view on possible auto-immune mechanisms in narcolepsy.

#### PATIENT AND HEALTHCARE PROVIDER SURVEYS OF NARCOLEPSY DISEASE BURDEN AND OXYBATE TREATMENT EXPERIENCE

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**Introduction:** Sodium oxybate (SXB) has long been recommended as a narcolepsy treatment by the American Academy of Sleep Medicine, including in the 2021 clinical practice guidelines. However, for nearly 2 decades, only immediate-release oxybates have been available, requiring patients to awaken for a second dose 2.5–4 h after the first bedtime dose. FT218 is an extended-release, once-nightly SXB formulation (ON-SXB)

currently in development for treatment of adults with narcolepsy. A survey was undertaken to evaluate patient and healthcare provider (HCP) perspectives on narcolepsy disease burden, treatment approaches, and satisfaction with current narcolepsy treatment options.

**Materials and Methods:** Thirty-minute, web-based surveys were separately fielded to individuals with narcolepsy and HCPs who treat patients with narcolepsy. Adults with self-reported, physician-diagnosed narcolepsy for  $\geq 1$  year with or without prior or current oxybate use, or those who were oxybate naïve, were eligible. HCPs were board-certified or board-eligible with pulmonology, sleep medicine, neurology, or psychiatry specialties, or who had nurse practitioner or physician assistant roles. All participants responded to survey questions using 9-point scales; higher scores indicated greater severity/agreement/satisfaction/importance/preference.

**Results:** Of the patient participants (n=120), most were white (81%) and female (79%); mean age was 40 years; 86 were current/past users of twice-nightly SXB; 56 were current/past users of mixed-salt oxybates; and 26 were oxybate naïve. HCPs (n=100) were mostly sleep medicine specialists (37%) or neurologists (30%) and male (68%); 91% and 83% had experience prescribing twice-nightly SXB and mixed-salt oxybates, respectively. Both patients and HCPs strongly agreed that patients preferred a narcolepsy treatment taken a lesser number of times (rated 6.7 and 7.7, respectively). Patients reported that the most common narcolepsy symptoms they experienced daily/almost daily were tiredness/fatigue (63% at initial presentation, 64% at time of diagnosis), excessive daytime sleepiness (EDS; 60% at initial presentation, 68% at time of diagnosis), and poor nighttime sleep (44% at initial presentation, 47% at time of diagnosis). HCPs most commonly prescribed stimulants (modafinil, 20%; armodafinil, 15%) and oxybates (twice-nightly SXB, 17%; mixed-salt oxybates, 12%). Both HCPs and patients expressed moderate-to-high satisfaction with mixed-salt oxybates (both rated 7.1) and twice-nightly SXB (6.8 and 6.6, respectively). HCPs were more satisfied than patients with modafinil (6.9 vs 4.5), armodafinil (6.9 vs 4.8), solriamfetol (6.8 vs 5.4), and pitolisant (6.6 vs 5.2). Twice-nightly SXB and mixed-salt oxybates received moderate-to-high ratings from both patients and HCPs for cataplexy reduction (patients: 7.3 and 7.4; HCPs, 6.7 and 6.8) and EDS (patients: both 7.0; HCPs, both 6.9) and consistency in taking the same amount each night (patients, both 7.3; HCPs, 6.3 and 6.7). Twice-nightly SXB and mixed-salt oxybates had lower satisfaction scores for dosing frequency (patients, 5.4 and 6.0; HCPs, 5.9 and 6.3) and medication taste (patients, 5.3 and 5.7; HCPs, 5.9 and 6.2).

**Conclusions:** While both individuals with narcolepsy and HCPs had moderate-to-high satisfaction with current narcolepsy treatment options, unmet needs remain regarding aspects of treatment such as dosing frequency. If approved, ON-SXB may address a significant unmet need in eliminating the middle-of-the-night dose.

**Acknowledgements:** This study was funded by Avadel Pharmaceuticals.

#### PATIENT AND PROVIDER PREFERENCES FOR OXYBATE TREATMENT FOR NARCOLEPSY: A DISCRETE CHOICE EXPERIMENT

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**Introduction:** Immediate-release sodium oxybate (SXB) and mixed-salt oxybates require twice-nightly dosing, with a second dose taken 2.5–4 hours after the first bedtime dose. FT218 is an investigational, extended-release, once-nightly formulation of SXB (ON-SXB) for treatment of adults with narcolepsy. Discrete choice experiments (DCEs) were performed separately for patients and healthcare providers (HCPs) to characterize and quantify drivers of preferences for attributes associated with oxybate treatments for narcolepsy.

**Materials and Methods:** A 30-minute web-based survey was fielded to patients and HCPs. Patients were adults with self-reported physician-diagnosed narcolepsy for  $\geq 1$  year and prior/current use of twice-nightly

SXB, mixed-salt oxybates, or were oxybate naïve. HCPs were board-certified or board-eligible HCPs with pulmonology, sleep medicine, neurology, or psychiatry specialties or nurse practitioner or physician assistant roles; active clinical practice 3–35 years; and managed  $\geq 200$  unique patients and  $\geq 5$  unique narcolepsy patients in the last month. Choice sets with 2 hypothetical treatment profiles were generated in the DCE, each combining attributes of twice-nightly SXB, mixed-salts oxybate, and ON-SXB. Participants viewed 12 choice sets each and were asked to indicate their most preferred product overall, one that would improve quality of life (QoL), and one that would result in less stress/anxiety. The DCE was analyzed using a mixed logit model.

**Results:** In total, 120 patients and 100 HCPs participated in the DCEs. For both patients and HCPs, the most important attribute of oxybate treatment for narcolepsy driving overall product choice was dosing frequency (relative attribute importance, 26.0 and 46.1, respectively), with once-nightly strongly preferred over twice-nightly dosing (relative preference weights,  $\pm 25.6$  and  $\pm 43.6$ ). Other important attributes that drove overall product choice were clinical efficacy and sodium content (relative attribute importance, 23.5 and 20.8) for patients and adverse reactions and sodium content for HCPs (relative attribute importance, 19.7 and 18.6). For patient quality of life (QoL), dosing frequency was again the most important product attribute for both patients and HCPs (relative attribute importance, 28.7 and 41.7), with once-nightly dosing preferred over twice-nightly (relative preference weight,  $\pm 25.7$  and  $\pm 38.5$ ). Additional important drivers of QoL preference were clinical efficacy and sodium content (relative attribute importance, 28.3 and 20.9) for patients and adverse reactions and clinical efficacy (relative attribute importance, 21.5 and 18.6) for HCPs. For reducing patient anxiety/stress, the most important product attribute remained dosing frequency for both patients and HCPs (relative attribute importance, 26.7 and 44.0), with once-nightly dosing again preferred over twice-nightly dosing (relative preference weight,  $\pm 23.9$  and  $\pm 41.6$ ). Additional important attributes for reducing anxiety and stress for patients were clinical efficacy and sodium content (relative attribute importance, 17.4 and 17.3); for HCPs, these were adverse reactions and sodium content (relative attribute importance, 18.2 and 14.2).

**Conclusions:** For both patients and HCPs, dosing frequency was the most important attribute driving preference for overall product choice, patient QoL, and reducing patient anxiety/stress; it was a more important driver than adverse reactions, clinical efficacy, and sodium content. For all 3 categories, once-nightly dosing was preferred over twice-nightly dosing.

**Acknowledgements:** This study was funded by Avadel Pharmaceuticals.

#### PREVALENCE OF NARCOLEPSY TYPE 1 AND TYPE 2 IN REPRESENTATIVE SAMPLES OF THE GENERAL POPULATION OF NORTH AMERICA, EUROPE AND SOUTH KOREA

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**Introduction:** Narcolepsy, a lifelong debilitating neurological disorder, is characterized by hypersomnolence, sleep fragmentation and manifestations of various REM-like sleep phenomena (cataplexy, sleep paralysis, and hypnagogic hallucinations). It is a rare disorder and therefore, previous studies on prevalence of the disease are essentially based upon estimates from small samples: very few studies were conducted with large representative general population samples. The objective of this study was to assess the prevalence of narcolepsy in a large sample representative of general populations over several countries and continents.

**Materials and Methods:** This cross-sectional epidemiological study involved 61,754 individuals representative of the general population of their respective country. A total of 35,368 individuals were from Europe, 20,130 were from North America and 6,256 were from South Korea. Individuals were aged between 15 and 102 years old. Data were collected from 1993 to 2016. The Sleep-Eval Expert System was used to collect data in all 10 participating countries. All interviews were conducted over the telephone. The Sleep-Eval questionnaire was the same in all the studies with some additions in the most recent years to cover other health aspects

indirectly related to sleep such as nutrition or expanded pain section. For the purpose of this study, an algorithm was created using the answers provided for each symptom to reach a diagnostic conclusion of Narcolepsy type 1, i.e. with cataplexy episodes (NT1) or Narcolepsy type 2, without cataplexy (NT2) according to ICSD3.

**Results:** Overall, prevalence of NT1 was 0.0191% (95% CI: 0.008–0.030%) for the whole sample. Prevalence was similar between settings: USA 0.0126% (95% CI: 0.000–0.0300%); Europe 0.0197% (95% CI: 0.0051–0.0343%); Canada 0.0283% (95% CI: 0.000–0.0792), South Korea 0.0257 (95% CI: 0.000–0.0654%). NT1 prevalence was comparable between men and women, and was higher among  $\leq 35$  y.o. (0.0318% [95% CI: 0.008–0.056%]), compared with 35–54 y.o. (0.0161% [95% CI: 0.000–0.033%]) and  $\geq 55$  y.o. (0.0079% [95% CI: 0.000–0.021%]). NT2 prevalence overall was 0.0233% (95% CI: 0.0113–0.0353%), and was comparable between settings: USA 0.0251% (95% CI: 0.0005–0.0497%); Europe 0.0209 (95% CI: 0.0059–0.0360%); Canada 0.0322% (95% CI: 0.000–0.0864%); South Korea 0.0271% (95% CI: 0.000–0.0679%). NT2 prevalence was similar between men and women, and was higher among 35–54 y.o. (0.0039% [95% CI: 0.013–0.066%]) compared with  $\geq 55$  y.o. (0.0045% [95% CI: 0.000–0.014%]) and  $< 35$  y.o. (0.0236% [95% CI: 0.003–0.044%]). In total, only 26.9% of narcolepsy individuals in the sample, mostly NT1, were already diagnosed with the disorder.

**Conclusions:** Our study shows that narcolepsy is indeed a rare disorder affecting 42.4 individuals per 100,000 inhabitants. It is a disorder that can take years to be diagnosed and is often difficult to recognize. As such, it is not surprising that only a quarter of the individuals identified as being narcoleptic by us were previously diagnosed by a physician.

**Acknowledgements:** Data collection was funded by the John-Arrillaga Foundation and analysis study by Takeda Development Center Americas. We would like to thank Yelena Pyatkevich and Dana Teltsch for their contributions.

#### QUALITY OF LIFE IN ADOLESCENTS WITH TYPE-1 NARCOLEPSY – A TRANSVERSAL STUDY IN A TERTIARY HOSPITAL

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**Introduction:** Type-1 narcolepsy is a rare chronic disease characterized by excessive daytime sleepiness (EDS) and cataplexy that usually starts by adolescence or beginning of adult life.

It is commonly associated with an increased risk of depression, aggressive behavior, social issues and lower school performance among other conditions.

The authors propose themselves to evaluate quality of life related to health in adolescents with narcolepsy and to compare it with healthy controls.

**Materials and Methods:** Transversal and descriptive study performed in April/2021. Application of the Portuguese version of the questionnaires KIDSCREEN-27 and Pediatric Daytime Sleepiness Scale to patients with type-1 narcolepsy, followed in regular appointments in a tertiary hospital, and a sample of convenience of healthy controls aged 11 to 18 years old.

**Results:** Our sample consisted of 22 adolescents with narcolepsy (13 ♀, 9 ♂), with a median age of 15.0 years old (IQR 13.0–16.0). The median age at diagnosis was 11 years old (IQR 9.8–13.5). Beyond EDS, all presented with cataplexy at the time of diagnosis, with 14 (63.6%) currently presenting more than one episode per month. Twenty of the 22 patients (90.9%) claimed taking regular medication for symptomatic control and 19 (86.4%) maintained routine appointments with a psychologist.

The control group included 23 adolescents (13 ♀, 10 ♂), with median age of 15.0 years old (IQR 13.0–17.0).

The self-reported quality of sleep was similar between the two groups. The degree of daytime sleepiness was significantly higher ( $p=0.032$ ) in patients with narcolepsy (median 16; IQR 11–20.3), comparatively to controls (median 13; IQR 13–16). EDS was identified in 7 (31.8%) of the adolescents with narcolepsy and none of the controls.

Considering the quality of life dimensions evaluated, scores were lower in patients with narcolepsy for peer and social support ( $p=0.063$ ) and physical well-being ( $p=0.001$ ). Scores were similar between the two groups for psychological well-being, autonomy and parent relation, and

school environment.

When questioned about future life perspectives, patients with narcolepsy presented overlapping results, except for a lower probability of taking a driver's license, despite no statistical significance ( $p=0.104$ ).

**Conclusions:** The reported quality of life in the different dimensions was significantly lower in patients with narcolepsy only for the physical well-being dimension. Despite having regular appointments and taking medication, daytime sleepiness is difficult to control in these patients.

In 3 of the 5 domains of quality of life that were evaluated, results were similar between both groups. We believe specialized psychological support may have had an important role in achieving these scores.

We should be aware of all the aspects that integrate quality of life in these patients, particularly during the important period of adolescence.

Given the small number of patients, owing to the rarity of the disease, it would be important to widen the sample through a multicentric study.

#### RELIABILITY OF A COMPETITIVE ENZYME-LINKED IMMUNOSORBENT ASSAY (ELISA) IN DETECTION OF NARCOLEPSY

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**Introduction:** Low or undetectable levels of Hypocretin-1 (Hcrt1) peptide in cerebrospinal fluid (CSF) constitutes a diagnostic criterion for Narcolepsy Type I (NT1). Radioimmunoassay is the usual method of Hcrt1 measurement for human CSF analyses, although attempts are being made to find accurate but simpler and less expensive techniques, including the competitive enzyme-linked immunosorbent assay (ELISA). We have examined with a blinded study the reliability of a competitive ELISA in detection of narcolepsy.

**Materials and Methods:** The competitive ELISA kit "Orexin A EIA Kit EK-003-30" (Phoenix Pharmaceuticals) was used. ELISAs were done with CSF samples obtained from 17 patients with different types of central hypersomnia and 3 controls before knowing the clinical condition of the patients, for which the researchers were totally blind so far. After having the results of the blind assays, correlations were made considering the patient clinical diagnosis. Medians and ranges and non-parametrical statistical tests were used for statistical analyses.

**Results:** A first ELISA with CSF samples from 8 patients in which Hcrt1 solid phase extraction was previously done produced very low peptide values. Therefore, the following two trials with the CSF samples from the 20 patients were done without Hcrt1 prior extraction. Hcrt1 concentrations of significantly different magnitudes were obtained in these two essays (medians = 110.7 vs. 282.5 pg/ml; ranks 49.5-343.1 vs. 119.2-567.0 pg/ml, respectively;  $p = .0001$ ). However, despite the notable inter-assay differences, a good correspondence between the values of the two trials occurred (Spearman rank correlation coefficient  $p = .0031$ ; multiple regression analysis  $F_{1,19} = 12,863$ ;  $p = .0021$ ). Hcrt1 values of the blind ELISAs and the clinical diagnosis of the 17 patients with central hypersomnia were contrasted. Ten patients diagnosed with clear-cut cataplexy (6 with typical NT1 together with 4 having secondary narcolepsy but meeting all the clinical and neurophysiological criteria for NT1) displayed the lowest Hcrt1 medians in the two trials (98.9 and 190.0 pg/ml). Contrarily, 5 patients with other central hypersomnia (2 with idiopathic hypersomnia, 2 with Narcolepsy Type 2 and the remaining 1 with Kleine-Levin syndrome) had the highest Hcrt1 medians in the two trials (290.7 and 453.4 pg/ml). The remaining 2 patients with idiopathic hypersomnia presented Hcrt1 mismatching values. Finally, statistical comparisons between Hcrt1 values in the 10 patients with clear-cut cataplexy and the rest of the patients including controls resulted in statistically significant values ( $p = .0016$ , Mann-Whitney U test).

**Conclusions:** Competitive ELISA without prior solid phase extraction of Hcrt1 is a methodology that allows the discrimination of patients with narcolepsy with cataplexy (NT1) or secondary narcolepsy meeting the clinical and neurophysiological criteria for NT1). However, a notable degree of inter-assay variability can occur. Therefore, it is essential to have clearly identified reference control samples in each ELISA determination

(positive and negative controls).

**Acknowledgements:** This study was supported by FI19058 FEDER grant.

#### SAMELISANT (SUVN-G3031): A PHASE-2, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY TO EVALUATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND EFFICACY IN PATIENTS WITH NARCOLEPSY WITH AND WITHOUT CATAPLEXY

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**Introduction:** Samelisant (SUVN-G3031) is a potent, selective, brain-penetrating and orally active inverse agonist at histaminergic H3 receptor (H3R). It is selective against 70 other targets which includes GPCRs, ion channels, transporters, enzymes, peptides, steroids, second messengers, growth factors and prostaglandins. Samelisant exhibits dose dependent H3R occupancy in rats. It has robust wake-promoting and anticataplectic effects in orexin knockout mice. This suggests that Samelisant has potential therapeutic utility in the treatment of excessive daytime sleepiness (EDS) and cataplexy associated with narcolepsy. Safety and tolerability studies in animals and healthy human subjects suggested a favorable risk/benefit profile.

**Materials and Methods:** Samelisant is currently being evaluated as a monotherapy in a double-blind, placebo-controlled, parallel-group, multicenter, proof of concept Phase-2 study for safety, tolerability, pharmacokinetics and efficacy in patients with narcolepsy with and without cataplexy (Clinical Trials.gov identifier NCT04072380).

Narcolepsy patients with or without cataplexy as per the international classification of sleep disorders – third edition (ICSD-3), Epworth sleepiness scale (ESS) score of  $\geq 12$ , and mean maintenance of wakefulness test (MWT) time of  $< 12$  min are being randomized to 2 mg Samelisant, 4 mg Samelisant or placebo treatment arms in 1:1:1 ratio. Patients are being stratified based on the type of narcolepsy, with and without cataplexy. Each patient would receive study drug once daily for 2 weeks. Efficacy assessments include MWT, ESS, clinical global impression of severity, clinical global impression of change, and patient global impression of change, nocturnal overnight polysomnography and sleep diary. Safety assessments include vital signs, physical examinations, electrocardiogram, laboratory assessments, Columbia suicide severity rating scale and adverse events.

**Results:** The study is currently enrolling patients with narcolepsy across several sleep study centers in the United States and Canada.

**Conclusions:** Safety and efficacy results from this phase-2 proof of concept study are expected in Q3 2022.

**Acknowledgements:** None

#### SKIN TEMPERATURE IS ASSOCIATED WITH ON-THE-ROAD DRIVING PERFORMANCE IN PATIENTS WITH CENTRAL DISORDERS OF HYPERSOMNOLENCE

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**Introduction:** Excessive daytime sleepiness is one of the core symptoms of central disorders of hypersomnolence (i.e. narcolepsy and idiopathic hypersomnia). This can directly impair driving performance. Increased sleepiness is also known to be reflected in relative alterations in distal and proximal skin temperature. We therefore examined the association between skin temperature and on-the-road driving performance in patients with central disorders of hypersomnolence.

**Materials and Methods:** Distal ( $T_{dist}$ ) and proximal ( $T_{prox}$ ) skin temperature of patients with narcolepsy ( $n = 39$ ) or idiopathic hypersomnia ( $n = 5$ ) was continuously measured during a standard one-hour driving test. Driving performance was assessed by calculating the standard deviation of the lateral position (SDLP) of the vehicle over segments of five kilometers. The distal to proximal skin temperature gradient (DPG) was calculated and all three skin temperature measures were averaged over each driving

segment. Participants with an average SDLP above the cut-off and/or who discontinued the driving test prematurely were considered to have increased risk of impaired driving performance.

**Results:** Average DPG values were not significantly different between those who were or were not at increased risk of impaired driving. The DPG was however significantly associated with SDLP. For every degree increase in DPG, the SDLP increased by 0.69 cm (SEM = 0.0539,  $p < 0.001$ ).  $T_{prox}$  had the strongest association with SDLP: every degree increase in  $T_{prox}$  was associated with a significant SDLP decrease of 0.85 cm (SEM = 0.0486,  $p < 0.001$ ).  $T_{dist}$  showed no significant association with driving performance.

**Conclusions:** These preliminary results show an association between skin temperature and on-the-road driving performance in patients with central disorders of hypersomnolence. Further research on the predictive value of these temperature measures should reveal their use in real-time monitoring of driving performance.

**Acknowledgements:** We thank the Dutch Ministry of Infrastructure and Water Management for their financial support of this study. We thank Bas Schottert for performing the MWT and SART.

### SLEEP-RELATED HALLUCINATION IS A RISK FACTOR FOR ADOLESCENT NARCOLEPSY'S DEPRESSION FEELINGS

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**Introduction:** To evaluate the association between depression symptoms, clinical features (disease onset-age, disease duration, sleep-related hallucination), sleepiness and polysomnography parameters in adolescent narcolepsy type 1 patients.

**Materials and Methods:** Eighty-three adolescent narcolepsy type 1 patients were involved in this cross-sectional study. Patients completed questionnaires evaluating depression symptoms (Center for Epidemiologic Studies Depression Scale) and sleepiness (Epworth Sleepiness Scale). Parameters from polysomnography and multiple sleep latency test were also collected.

**Results:** Patients with depression symptoms (62.7%) have later disease onset-age. Depression symptoms were associated with sleep-related hallucination (OR = 2.75). Six independent variables were associated with sub-dimension depression symptoms, including sleep latency, sleep efficiency, sleep-related hallucination, Epworth sleepiness scale, disease duration and disease onset-age.

**Conclusions:** Sleep-related hallucination is associated with total depression symptoms in adolescent narcolepsy. Subjective sleepiness is associated with depressed affect, somatic symptoms and interpersonal problems. Lower sleep efficiency is associated with lack of positive affect.

**Acknowledgements:** This work was supported by the National Natural Science Foundation of China (81700088), National Natural Science Foundation of China (82070091), International Cooperation and Exchange of the National Natural Science Foundation of China (82020108001), Dongcheng District Talents Project of Beijing (DCQYYRC-789-01-DR), Youth Foundation of Beijing Tiantan Hospital (No.2018-YQN-18) and Youth Talent Support Project from China Association for Science and Technology.

### SOLRIAMFETOL REAL WORLD EXPERIENCE STUDY (SURVEY): INITIATION AND TITRATION STRATEGIES AMONG PHYSICIANS PRESCRIBING SOLRIAMFETOL FOR PATIENTS WITH NARCOLEPSY FROM GERMANY

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**Introduction:** Excessive daytime sleepiness (EDS) is a core symptom of narcolepsy that may be managed with wake-promoting agents or sodium oxybate. Solriamfetol (Sunosi™) is a dopamine/norepinephrine reuptake inhibitor approved in the EU and the US to treat EDS associated with narcolepsy (75–150 mg/day) and obstructive sleep apnoea (OSA) (37.5–150 mg/day). This study characterises real-world dosing and titration strategies used by European physicians when initiating solriamfetol treatment.

**Methods:** The SURWEY study is an ongoing retrospective chart review conducted by sleep physicians in Germany, France, and Italy. Here, we report initial data from a cohort of patients with narcolepsy from Germany. Physicians who prescribed solriamfetol to  $\geq 10$  patients with narcolepsy provided data from medical records of approximately 10 patients. Eligible patients were  $\geq 18$  years old, diagnosed with EDS (as determined by the physician) due to narcolepsy, had reached a stable solriamfetol dose, and had completed  $\geq 6$  weeks of treatment. Patients were classified into 1 of 3 groups based on solriamfetol initiation strategy: changeover (switched/switching from existing EDS medications onto solriamfetol), add-on (adding solriamfetol to current EDS medication), or new-to-therapy (no current EDS medication prior to solriamfetol).

**Results:** Data are reported for 70 patients with narcolepsy. Patients' mean $\pm$ SD age was 36.9 $\pm$ 13.9 years and mean $\pm$ SD body mass index (BMI) was 26.7 $\pm$ 5.2 kg/m<sup>2</sup>; 56% female, 57% had cataplexy, and most (84%) were treated in sleep centres. Anxiety/depression was the most commonly reported comorbidity (36%). Changeover was the most common initiation strategy ( $n=43$ ), followed by add-on ( $n=19$ ) and new-to-therapy ( $n=8$ ). Patients in the changeover group commonly switched from sodium oxybate (23%), modafinil (16%), pitolisant (9%), or other wake-promoting medications (23%). In the add-on group, solriamfetol was commonly added to pitolisant (42%) and sodium oxybate (37%). In the changeover group, most patients (88%) switched due to lack of efficacy of previous medications. Switching was managed using an abrupt (1 day to the next) approach for 88% of patients and overlapping (tapered) for 9%; physicians indicated they would recommend the switching strategy they had used for 95% of patients. Solriamfetol was typically prescribed for once-daily administration (99%), and the most common starting doses were 75 mg/day (69%) or 150 mg/day (20%); these starting doses were used for 67% and 28% of the changeover group, 68% and 11% of the add-on group, and 75% and 0% of the new-to-therapy group; most of the remaining patients were initiated at 37.5 mg. In 29 patients (41%), solriamfetol was titrated; 27/29 (93%) completed titration as prescribed, most of whom (17/27 [63%]) completed titration within 7 days.

**Conclusion:** This study provides the first multicentre real-world data describing the use of solriamfetol in a cohort of patients with narcolepsy in Germany. Most patients in this study were switched from a prior medication to solriamfetol, with lack of efficacy cited as the most common reason for switching. Solriamfetol was typically initiated at 75 mg/day; titration after initiation was common.

**Acknowledgements:** This study was supported by Jazz Pharmaceuticals.

### SOLRIAMFETOL REAL WORLD EXPERIENCE STUDY (SURVEY): SAFETY, EFFECTIVENESS, AND EXPERIENCE DURING FOLLOW-UP FOR PATIENTS WITH NARCOLEPSY FROM GERMANY

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**Introduction:** Solriamfetol (Sunosi™) is a dopamine/norepinephrine reuptake inhibitor approved in the EU and the US to treat excessive daytime sleepiness (EDS) associated with narcolepsy (75–150 mg/day) and obstructive sleep apnoea (OSA) (37.5–150 mg/day). Previous research

examined solriamfetol in clinical trials, but research in real-world settings is limited. This real-world study characterises outcomes for patients with narcolepsy following initiation of solriamfetol treatment by European physicians.

**Methods:** SURVEY is an ongoing retrospective chart review conducted by sleep physicians in Germany, France, and Italy. Here, we report initial data from a cohort of patients with narcolepsy from Germany. Physicians who prescribed solriamfetol to  $\geq 10$  patients provided data from medical records of approximately 10 patients with narcolepsy. Eligible patients were  $\geq 18$  years old with EDS (as determined by the physician) due to narcolepsy, had reached a stable solriamfetol dose, and had completed  $\geq 6$  weeks of treatment. Patients were classified into 1 of 3 groups based on solriamfetol initiation: changeover (switched/switching from existing EDS medications onto solriamfetol), add-on (adding solriamfetol to current EDS medication), or new-to-therapy (no current EDS medication prior to solriamfetol). Epworth Sleepiness Scale (ESS) scores, patient and physician impressions of the patient's condition, and adverse events were assessed.

**Results:** Data are currently available for 70 patients with narcolepsy (mean $\pm$ SD age, 36.9 $\pm$ 13.9 years; mean $\pm$ SD body mass index, 26.7 $\pm$ 5.2 kg/m<sup>2</sup>; 56% female, 57% with cataplexy, and 84% treated in sleep centres). Changeover was the most common initiation strategy (n=43), followed by add-on (n=19) and new-to-therapy (n=8). Final follow-up visits were mean $\pm$ SD 15.3 $\pm$ 7.6, 17.1 $\pm$ 6.3, and 16.0 $\pm$ 5.7 weeks after solriamfetol initiation for the 3 groups, respectively. For the overall group, mean $\pm$ SD ESS score at initiation of solriamfetol treatment was 17.6 $\pm$ 3.1 (n=61) and 13.6 $\pm$ 3.8 at follow-up (n=51), with a mean $\pm$ SD decrease of 4.3 $\pm$ 2.9, indicating improvement in EDS. Improvements in ESS scores were seen regardless of initiation strategy, with mean $\pm$ SD decreases of changeover 4.1 $\pm$ 2.9 (n=28), add-on 3.7 $\pm$ 2.6 (n=15), and new-to-therapy 6.1 $\pm$ 3.0 (n=8) points at follow-up. Overall, most patients perceived slight or strong improvements of their condition after initiating solriamfetol (physician report, 94%; patient report, 91%), with similar results across subgroups. Most patients (62%) reported a duration of effect of solriamfetol of 6 to <10 hours; 47% of patients reported experiencing a gradual wearing off of solriamfetol at the end of the day, and 26% reported no wearing off. Most patients (72%) reported no change in their perceived night-time sleep quality. The most common adverse events were headache (9%), decreased appetite (6%), and insomnia (6%); no cardiovascular events were reported.

**Conclusion:** This study provides the first multicentre real-world data regarding outcomes following initiation of solriamfetol in a cohort of German patients with narcolepsy. ESS scores improved after solriamfetol initiation across all subgroups (changeover, add on, and new-to-therapy), and over 90% of patients and physicians perceived improvement in EDS. Common adverse events were consistent with those reported for solriamfetol in the clinical trial setting.

**Acknowledgements:** Supported by Jazz Pharmaceuticals.

#### SPHYNCS: GUT MICROBIOTA COMPOSITION IS DIFFERENT IN NARCOLEPSY TYPE 1 AND NARCOLEPSY BORDERLAND

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**Introduction:** The Swiss Primary Hypersomnolence and Narcolepsy Cohort Study (SPHYNCS) has the aim to identify new biomarkers for narcolepsy (NT1, NT2) and its borderland (NBL). Through the brain-gut-axis the microbiome is able to affect microglia development and CNS inflammation. Considering the hypothesis of an immune-mediated etiology of narcolepsy and only two small studies in the literature, assessment of gut microbiota profile in patients with narcolepsy and NBL maybe of interest.

**Materials and Methods:** Fecal samples were prospectively collected from the ongoing SPHYNCS cohort (Dietmann, J Sleep Res 2021). We performed an amplicon sequencing approach on V5/V6 regions of 16s rRNA genes with Ion 316™ Chip V2 in the Ion PGM™ System. Raw sequences were first loaded into the QIIME v2 pipeline. Then calculation of the  $\alpha$ -diversity

using Shannon index, b-diversity with Bray-Curtis genus-level community dissimilarities, and statistical analysis of clustering using Mann-Whitney U tests for alpha diversity and Adonis (PERMANOVA) for beta diversity to confirm that the strength and statistical significance of groups were tested with downstream analysis using *phyloseq* in R. Multivariate analysis by linear models (MaAsLin2) R package was used to find associations between clinical metadata (diagnosis, age, gender, BMI, diet, and others) and microbial community abundance.

**Results:** So far (July 2020–September 2021), 41 patients (12 NT1, 25 NBL, 9 healthy controls) were included, of whom 69% were female and with a mean age of 28 years (range 17–44 years). There were no differences in alpha and beta diversity between the diagnosis groups. When compared to controls, patients with Narcolepsy type 1 showed a trend towards higher species richness (p<0.1). There were also significant differences in the abundance of several operational taxonomic units: the most robust was a higher prevalence of *Eggerthellaceae* family in patients in both NT1 and NBL when compared to controls (p < 0.05).

**Conclusions:** Preliminary findings of this ongoing study suggest differences in the gut microbiota composition of patients with NT1 and NBL when compared to controls. These results only partially support 2 previous publications on the topic and stress the importance of further systematic studies on larger patients series.

**Acknowledgements:** This study is funded by Swiss National Science Foundation (SNF Grand ID 320030\_185362) and by two non-product-related investigator initiated study grants from UCB Biopharma SRL (IIS-2017-120409) and Jazz Pharmaceuticals (IST-18-10975)

#### SURFACE-BASED MORPHOMETRY ANALYSIS AND NEURODEVELOPMENT IN NARCOLEPSY'S BRAIN

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**Introduction:** The cortical morphology and neurodevelopment are rarely examined in narcolepsy, despite an overall young age at onset. Here we investigated structural and maturational changes in the cortex of patients with narcolepsy by surface-based morphometry analysis.

**Materials and Methods:** Fifty-one narcolepsy patients (25 adolescences and 26 adults) and 60 typically developing group-matched healthy controls (30 adolescences and 30 adults) provided resting-state functional and high-resolution 3T anatomical magnetic resonance imaging scans. The FreeSurfer image analysis suite quantified vertex-level cortical thickness and gyrification. Voxel-wise resting-state functional connectivity was also calculated.

**Results:** There were cortical thickness decreases localized to bilateral frontal cortex and left precuneus in adolescent narcolepsy patients. Adolescent narcolepsy demonstrated increased gyrification in left occipital lobe, left precuneus and right fusiform but decreased gyrification in left postcentral gyrus. Whilst, adult narcolepsy exhibited increased gyrification in left inferior temporal gyrus and right anterior cingulate cortex. Furthermore, altered cortical thickness and gyrification were associated with sleepiness severity. Increased gyrification was associated with reduced long-range functional connectivity. In adolescent narcolepsy patients, those with more severity of sleepiness showed increased right postcentral gyrification. Decreased bilateral frontal and occipital gyrification was found in cases with hallucination.

In adult patients with adolescent-onset compared with patients with adult-onset of the disease, a wide range of regions showed reduced gyrification. Narcolepsy showed impact on brain development, especially in frontal lobe and this effect was augmented during adolescence, continuing into adulthood.

**Conclusions:** Particularly the frontal lobe showed altered brain morphology, being a thinner cortex and more gyri. Enhanced gyrification was moreover associated with reduced long-distance connectivity, altering functional connectivity among cortices. The impact of narcolepsy on brain development could remain from adolescence to adulthood and it was especially exacerbated in adolescents, which may partially relate to the cognitive and behavioral problems exhibited.

**Acknowledgements:** This work was supported by the National Natural

Science Foundation of China (81700088), National Natural Science Foundation of China (82070091), International Cooperation and Exchange of the National Natural Science Foundation of China (82020108001), Youth Talent Support Project from China Association for Science and Technology.

### THE ITALIAN MULTICENTER COHORT OF THE POST AUTHORIZATION SAFETY STUDY ON PITOLISANT (PASS-PITOLISANT) IN NARCOLEPSY: RESPONSE TO TREATMENT

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**Introduction:** 14 Italian Sleep Centers enrolled 191 narcoleptic patients in the observational PASS-Pitolisant. Besides drug's safety, the study analyzed variations of narcolepsy symptoms, depression, quality of life and disease burden.

**Materials and Methods:** from PASS-Pitolisant's 3<sup>rd</sup> Interim report we extracted detailed clinical data on patients who concluded the 1-year follow-up (FU) visit. Clinical Global Impression (CGI) for Excessive Daytime Sleepiness (EDS) and cataplexy severity were judged by sleep experts. Validated questionnaires were administered to evaluate EDS (Epworth Sleepiness Scale, ESS), depression (Beck Depression Inventory, BDI), quality of life (EQ-5D-5L) and disease burden (Functional Outcome of sleep questionnaire, FOSQ10).

**Results:** of the 191 patients (76.4% narcolepsy type I and 23.6% narcolepsy type II) enrolled, 96 completed the 1-year FU visit. ESS decreased from 15.2±4.4 at baseline to 12.4±4.5 and responders (ESS≤10 or ESS decrease≥3) were 57.3%. Other main narcoleptic symptoms including cataplexy, sleep attacks, sleep paralysis and hypnagogic hallucinations ameliorated in 39.7%, 49.4%, 15.6% and 21.5% of patients, respectively. According to CGI, 87.5% of patients had improvement of EDS and 64.5% of cataplexy. Moreover, at FU visit an increase of EQ-5D-5L score (baseline: 64.7; FU: 73.6%), an increase of FOSQ-10 score (baseline: 13.7±3.8; FU:15.6±3.4), and no worsening of BDI score for 96.3% of patients were observed.

**Conclusions:** According to PASS-Pitolisant interim report, patients recruited from the Italian centers reported improvement of narcolepsy symptoms at 1-year FU. Treatment favorably impacted on quality of life and on depressive symptoms, mitigating the burden of disease.

### THE REM-SLEEP RELATED CHARACTERISTICS OF NARCOLEPSY: A NATION-WIDE MULTI-CENTER STUDY IN TURKEY, THE REMCON STUDY

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**Introduction:** Narcolepsy type 1 (NT1) is caused by hypocretin deficiency, the pathophysiology of narcolepsy type 2 (NT2) has not been delineated. Except for the hypocretin deficiency and cataplexy, all clinical and laboratory features used in the diagnosis of NT2 are identical to those used for NT1. The aim of this study was to assess the REM sleep-related characteristics in the patients with narcolepsy; the characteristics of REM sleep in PSG and MSLT recordings, the quantification of RSWA and atonia index, and the analysis of rapid eye movements (REMs) during REM sleep.

**Materials and Methods:** This study was planned by the Sleep Medicine Study Group of the Turkish Neurology Society, and conducted in eleven centers in eight cities in Turkey. The analysis of RSWA was analyzed by reviewing all REM sleep periods on PSG and MSLT recordings per standard criteria. The total duration of the increased muscle tone during REM sleep in the chin and bilateral leg EMG recordings was calculated as RSWA index. The REMs index was also investigated the relation to the RSWA.

**Results:** A total of 274 Patients were involved; 147 patients (53.6%) were males and 127 patients (46.4%) were females; the mean age was 29.1±12.0 years. The diagnosis of NT1 was made in 166 patients (60.6%), and 108 patients (39.4%) were diagnosed as having NT2. Epworth sleepiness scale was significantly higher in patients with NT1 than the patients with NT2 (p=0.001). The diagnosis of RBD was made in 19.3% of the patients with NT1 versus in 2.8% of the patients with NT2 (p<0.001). The percentage of SOREMP in PSG recordings was significantly higher in patients with NT1 (37.1%) than those with NT2 (18.9%, p=0.001). MSLT showed that the mean sleep latency was shorter in patients with NT1 compared to those with NT2 (p<0.001). The total duration of REMs on electrooculography recordings was also significantly higher in patients with RSWA in compared with the patients without RSWA (p=0.002). Total duration of REMs was significantly and positively correlated with the duration of RSWA on chin-EMG and leg-EMG recordings (p=0.001). ROC analyses showed an RSWA index of ≥2% for the RSWA on chin-EMG with a sensitivity of 86.7% and a specificity of 71.3% (p<0.001). The REMs index ≥20% was associated with the presence of RSWA with a sensitivity of 70.0% and a specificity of 57.1% (p=0.008).

**Conclusions:** In this nation-wide study, we introduced for the first time that the increase in the density REMs during REM sleep may be one of the indicators of the RSWA. Significant positive correlations were demonstrated between the total duration of REMs on electrooculography recordings and the mean durations of RSWA in both chin and leg EMG recordings. A REMs index of >20% was demonstrated to have a moderate sensitivity and specificity in the diagnosis of RSWA. As observed in chin RSWA index, REMs index also showed a significantly high association with RBD, in compared to RSWA per standard criteria.

**Acknowledgments:** None

### THE STUDY ON BRAIN FUNCTION STATE OF NARCOLEPSY PATIENTS

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**Introduction:** The study was to evaluate the night sleep quality and daytime function of narcolepsy patients by the scales, polysomnography, multiple sleep latency test and brain function state quantitative monitoring.

**Materials and Methods:** In the study, 30 patients with narcolepsy diagnosed in the sleep outpatient department of the First Bethune Hospital of Jilin University from March 2019 to January 2021 by scales and PSG+MSLT were selected as the study group, and 30 healthy volunteers as the control group. All patients in the study group were in accordance with the diagnostic criteria of narcolepsy in ICSD-3 and were examined with General Hospital Anxiety/Depression Scale (HAD), Patient Health Questionnaire-9 (PHQ-9), Epworth sleepiness scale (ESS) and brain function state before and 3 months after taking medicine. The control group received PSG+MSLT and brain function state examination. The brain waves in resting state were collected and wavelet analysis was used for data processing to compare the

characteristics of night sleep quality and daytime brain function state between narcolepsy group and control group. Objective to evaluate the night sleep quality and daytime function state of narcolepsy patients by studying the correlation between HAD, PHQ-9, ESS scales, polysomnography+ multiple sleep latency test related parameters and daytime function state.

#### Results:

1. In addition to typical tetralogy, narcolepsy patients were often complicated with obstructive sleep apnea hypopnea syndrome (OSAHS), REM sleep without atonia (RSWA) and REM sleep behavior disorder (RBD).
2. Compared with the control group, the sleep structure of PSG in narcolepsy group were as follows: Sleep efficiency decreased ( $P < 0.001$ ), N1% increased ( $P < 0.001$ ), N2% decreased ( $P < 0.05$ ), N3% decreased ( $P < 0.001$ ), REM% decreased ( $P < 0.05$ ).
3. The correlation between PSG+MSLT and daytime brain function in narcolepsy group showed that the average sleep latency of MSLT was negatively correlated with brain fatigue index (correlation coefficient was  $-0.513$ ,  $P < 0.05$ ).
4. The score of PHQ-9 increased, the anxiety tendency index increased ( $P < 0.001$ ), the internal focus index increased ( $P < 0.05$ ), and the alertness index decreased ( $P < 0.05$ ) in patients with narcolepsy. There was a negative correlation between HAD depression score and alertness index (correlation coefficient was  $-0.267$ ,  $P < 0.05$ ), anxiety tendency index was positively correlated with sleep apnea hypopnea index(AHI) (correlation coefficient was  $0.403$ ,  $P < 0.05$ ).
5. After treatment for 3 months, ESS score and brain fatigue index of narcolepsy patients decreased ( $P < 0.05$ ).

#### Conclusions:

1. Narcolepsy patients were easy to be complicated with OSAHS, RSWA and RBD.
2. The nocturnal sleep efficiency of narcolepsy patients decreased, N1% increased, N2% decreased, N3% decreased, REM% decreased. The average sleep latency in MSLT was negatively correlated with brain fatigue index in narcolepsy patients.
3. There was a negative correlation between depression tendency and alertness index in narcolepsy patients. ESS score and brain fatigue index decreased after 3 months of narcolepsy treatment.

#### Acknowledgements:

### UNSUPERVISED CLUSTERING OF CENTRAL HYPERSOMNOLENCE DISORDERS ENABLES DATA-DRIVEN PHENOTYPING: TOWARD MORE RELIABLE DIAGNOSTIC CRITERIA

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**Introduction:** Recent studies fueled doubts as to whether all currently defined central disorders of hypersomnolence are stable entities, especially narcolepsy type 2 and idiopathic hypersomnia. New reliable biomarkers are needed and the question arises whether current diagnostic criteria of hypersomnolence disorders should be reassessed. The main aim of this data-driven study was to confirm clear separation of narcolepsy type 1 and identify more reliable subgrouping with new clinical biomarkers of individuals without cataplexy.

**Materials and Methods:** We used agglomerative hierarchical clustering, an unsupervised machine learning algorithm, to identify distinct hypersomnolence clusters in the large-scale European Narcolepsy Network database. For this study, we newly developed the open-source python-based package Bowerbird, which integrates widely used agglomerative hierarchical clustering algorithms with clustering validation methods and intuitive data visualization options. We included 1078 unmedicated adolescents and adults and 97 variables, covering all aspects of central hypersomnolence disorders such as symptom presence and characteristics, demographics, objective and subjective sleep measures, and laboratory biomarkers. We specifically focused on subgrouping of patients without cataplexy. The number of clusters was chosen to be the minimal number for which patients without cataplexy were put in distinct groups. Researchers were blinded for current diagnosis until the clustering algorithm was completed.

**Results:** Seven clusters were identified, of which four clusters included predominantly individuals with cataplexy. These four clusters indicate subtypes of individuals with cataplexy and likely reflect different disease severities. The two most distinct clusters consisted of 158 and 157 patients respectively and were dominated by those without cataplexy. Amongst other variables, these two clusters significantly differed in presence of sleep drunkenness (96.2% vs. 1.3%,  $p < 0.0001$ , respectively), subjective difficulty awakening (difficult or nearly impossible to wake up: 63.4% vs. 21.5%,  $p < 0.0001$ , respectively) and weekend-week sleep length difference (median [IQR]: 1 hour [0.0–2.5] vs. 0.1 hour [0.0–1.5],  $p = 0.0086$ , respectively). Patients formally diagnosed as narcolepsy type 2 and idiopathic hypersomnia were evenly mixed in these two clusters.

**Conclusions:** In the largest study on hypersomnolence disorders to date, we identify a robust data-driven set of clinical biomarkers that results in distinct and consistent subgrouping of all forms of central disorders of hypersomnolence. Our results confirm subgrouping of individuals with narcolepsy type 1 and contest inclusion of sleep-onset rapid eye moment periods (SOREMPs) in diagnostic criteria for individuals without cataplexy. The results support a fundamental transformation of the diagnostic process and provide promising new variables for reliable diagnostic categories that better resemble different patient phenotypes of individuals without cataplexy, including sleep drunkenness, subjective difficulty awakening and weekend-week sleep length difference. Cluster-guided classification

will result in a more solid hypersomnolence classification system that is less vulnerable to instability of single features.

**Acknowledgements:** Jari K. Gool, Zhongxing Zhang and Martijn S.S.L. Oei contributed equally to this work as first authors. Ramin Khatami and Gert Jan Lammers contributed equally to this work as last authors.

### Neurological Sleep Disorders Affecting Sleep

#### ASSOCIATION OF CIRCADIAN DISTRIBUTION OF SEIZURES WITH SLEEP ARCHITECTURE AND ABNORMAL SLEEP PHENOMENA IN EPILEPSY

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**Introduction:** Epilepsy is a neurological disorder characterized by abnormal cortical activity and recurrent seizures. The bidirectional relationship between sleep and epilepsy is known, as sleep disorders frequently accompany epilepsy. Obstructive sleep apnea and restless legs syndrome are more often reported in patients with epilepsy (PWE) and confirmed through objective measures. On the other hand, sleep structure may be affected due to the course of the disease, as well as other contributing factors.

Our aim was to compare the polysomnographic variables between PWE with sleep-only seizures and PWE with a mixed distribution pattern of seizures.

**Materials and Methods:** Adult ( $\geq 18$  y.o.) PWE underwent clinical interview and polysomnography (PSG) with a full electroencephalographic montage in a tertiary sleep and epilepsy center. According to the overall history of seizure distribution throughout the day, the patients were further divided into those with sleep-related seizures only (sleep-related seizure group - SSG) and those with either exclusively daytime seizures or seizures occurring at any time (mixed seizure group - MSG). Main sleep parameters such as sleep stage latencies and percentages, limb movement indices (limb movement index - LMI, periodic limb movement index - PLMI), apnea-hypopnea index (AHI), and other indices were scored according to the American Academy of Sleep Medicine Scoring Manual ver. 2.3. Mann-Whitney U test was used for statistical analysis.

**Results:** We involved 84 PWE (mean age - 35.5 years, SD - 13.4; age range 18–69; F - 51.2%) and further divided the sample in two groups: SSG - 28.6% (n=24); MSG - 71.4% (n=60).

Major sleep phenomena were derived from PSG studies in both groups. In regards to limb movements in sleep, LMI and PLMI were significantly higher in SSG (LMI, 10.2/h vs 19.3/h,  $p < 0.07$ ; PLMI, 10.2/h vs 3.9/h,  $p = 0.07$ ). Sleep-disordered breathing did not differ between study groups (SSG/MSG): AHI - 6.9/7.0, ODI - 7.2/7.7, respectively ( $p > 0.05$ ).

In SSG there is a tendency towards shorter mean latencies for NREM1 (20.1 vs 27.7,  $p > 0.05$ ), NREM2 (15.9 vs 31.0,  $p < 0.05$ ), and NREM3 (32.2 vs 58.4,  $p < 0.05$ ). REM latency was prolonged within SSG (171.5 vs 157.6;  $p > 0.05$ ). No differences were noted between both groups in regards to percentages of sleep stages in relation to total sleep time: NREM1, 11.05% vs 12.15%; NREM2, 41.8% vs 40.7%; NREM3, 33.8% vs 32.7%; REM, 13.3% vs 13.8%;  $p > 0.05$ ).

**Conclusions:** According to our study results, there may be a connection between exclusively sleep-related seizures and disturbed sleep architecture, as well as associated polysomnographic abnormal sleep phenomena. Limb movements in sleep may be associated with sleep-related seizures in a stronger manner, compared to patients with only or predominantly daytime seizures. The described findings may play an important role in the management of patients with epilepsy depending on the circadian distribution of seizures.

#### CHARACTERISTICS OF CENTRAL SLEEP APNEA IN HAWAII ETHNIC GROUPS

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**Introduction:** Central Sleep Apnea (CSA) is a sleeping disorder in which the brain sends improper signals to muscles responsible for breathing. As CSA is an uncommon, complex sleep disorder, a better understanding of various sociodemographic and biological risk factors for CSA is warranted, especially in underrepresented, at-risk populations. This pilot study investigates factors associated with CSA amongst patients of different racial and cultural backgrounds, with a focus on those of Asian and Hawaiian ancestry.

**Materials and Methods:** A retrospective case-controlled study was conducted at a neuro-clinic based in Hawaii. Sociodemographic, cardiovascular, psychiatric, and neurological comorbidities were collected from 35 patients with CSA. Patients below the age of 18 were excluded. Two sets of randomized matched and unmatched controls were collected in a 4:1 ratio.

**Results:** Patients with CSA are more likely to have private insurance than patients without (OR = 2.46 95% CI: 1.10 to 5.62,  $p = 0.02515$ ). Patients with CSA were found to have greater BMIs than patients without (95% CI: 1.57 to 6.30,  $W = 3297.5$ ,  $p = 0.00158$ ), with a mean difference of 3.98. Significant factors included atrial fibrillation (OR = 3.60, 95% CI: 1.05 to 11.96,  $p = 0.030$ ), hypercholesterolemia (OR = 3.60, 95% CI: 1.05 to 11.96,  $p = 0.030$ ), autoimmune disorder (OR = 6.43, 95% CI: 1.94 to 22.25,  $p = 0.00052$ ), periodic limb movement syndrome (OR = 20.34, 95% CI: 2.99 to 551.28,  $p = 0.00061$ ), and insomnia (OR = 3.87, 95% CI: 1.36 to 10.82,  $p = 0.0090$ ).

**Conclusions:** These findings show that patients with CSA are more likely to have complications such as increased BMI, atrial fibrillation, hypercholesterolemia, autoimmune disorder, periodic limb movement syndrome, and insomnia. They are also more likely to have private insurance, suggesting that socioeconomic status may play a role in the likelihood of patients seeking treatment. A larger prospective study could be conducted for a compelling area of future study.

**Acknowledgments:** Thank you to our mentors, Dr. Liow, Dr. Viereck, Dr. Vajjala, Dr. Carrazana, Catherine, Ena, and all HPN staff.

#### CHARACTERIZATION OF NEURODEGENERATIVE DISORDER SUBTYPES BASED ON NON-REM HYPERTONIA AND SLEEP SPINDLE DURATION

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**Introduction:** Increased non-REM hypertonía (NRH) and decreased sleep spindle durations (SpD) were found to be independently associated with patients broadly characterized as presumed Parkinsonian-spectrum disorder [i.e., dementia with Lewy Bodies/Parkinson Disease Dementia (DLB/PDD), Parkinson Disease (PD), progressive supranuclear palsy (PSP), or isolated REM sleep behavior disorder (iRBD)] when compared to subjects with Alzheimer Disease dementia (AD), mild cognitive impairment (MCI) and normal cognition (NC). We aimed to analyze combined features of NRH and SpD and determine whether these characteristics could distinguish neurodegenerative disorder (NDD) subtypes.

**Materials and Methods:** This multicenter investigation included analysis of several neurodegenerative disorderpatient subtypes including: DLB/PDD (n=16), PD (n=16), iRBD (n=19), PSP (n=13), AD (n=22), MCI (n=35), and NC (n=61).

Sleep Profiler (SP) recordings were simultaneously acquired from EEG sensor sites AF7-AF8, AF7-Fpz and AF8-Fpz (Advanced Brain Monitoring, Carlsbad, CA, USA). The SP records were auto-staged using within-epoch temporal power spectral characterization with combined detection of individual slow waves, sleep spindles and cortical arousals, and then technically reviewed for final sleep stage assignments.

NRH was auto-detected based on patterns of persistently elevated electromyographic (EMG) power relative to delta, theta, and sigma bands. Variability thresholds were applied to each epoch to ensure EMG bursts attributed to sleep disordered breathing arousals were not

mischaracterized as NRH. The percent-time NRH was based solely on auto-detected block, no edits were made to add or remove NRH.

Sleep spindles were characterized by temporalexursions in the absolute and relative alpha and sigma power relative to the beta and EMG power, and with a minimum spindle length of 250 milliseconds. Spindle duration was tallied as the sum of all spindle lengths.

With NRH  $\geq 5\%$  of sleep-time and spindle-duration  $\leq 1$ -minute considered abnormal, tallies were compared across neurodegenerative disorder subtypes with Fisher Exact tests.

**Results:** Combined SP features of normal-NRH/normal spindle-duration were greater in the NC (56%), AD (46%), and MCI (43%) subtypes versus PSP (8%) and DLB/PDD (6%), and when iRBD (21%) was compared to NC (all  $P < 0.05$ ). Abnormal-NRH/abnormal spindle-duration was more frequent in PSP (85%) and DLB/PDD (75%) subtypes versus iRBD (26%), PD (25%), MCI (11%), AD (9%), and NC (8%) (all  $P < 0.02$ ). Abnormal-NRH/normal spindle-duration was greater in iRBD (47%) compared to MCI (14%), NC (8%), PSP (8%), DLB/PDD (6%), and AD (5%) subtypes, and in PD (31%) versus NC (all  $P < 0.05$ ). Normal-NRH/abnormal spindle-duration occurred more often in AD (41%) than iRBD (5%) and PSP (0%) (both  $P < 0.05$ ).

**Conclusions:** The combination of NRH and spindle-duration abnormality occurred more frequently in DLB/PDD and PSP subtypes. Abnormal NRH with normal spindle-duration was more frequent in iRBD and PD subtypes. Normal NRH and spindle-duration occurred most often in NC and MCI types. AD exhibited normal NRH with isolated cases of either normal or abnormal spindle-duration. Our preliminary findings suggest that auto-detected sleep biomarkers may aid in the characterization of neurodegenerative disorder subtypes. Larger prospective cohort studies are needed.

**Acknowledgements:** Support provided by National Institute of Health grants: R44AG050326, R44AG054256, AG062677, NS100620, AG056639, RO1AG060477, P50AG005131, R21AG064271, ULRR024150, and R34AG056639.

#### CLINICAL IMPACT AND POLYSOMNOGRAPHIC FEATURES OF SLEEP DISTURBANCES IN MULTIPLE SCLEROSIS

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**Introduction:** Multiple sclerosis (MS) represents a risk factor for sleep disorders, especially insomnia and restless legs syndrome (RLS). Despite this, sleep is yet underinvestigated in patients with MS. Only few studies have evaluated sleep by polysomnography (PSG), and most available data come from self-administered questionnaires. This study aimed to estimate prevalence and polysomnographic features of sleep disturbances in MS. It also evaluated the relationship between sleep disturbances and critical symptoms of MS such as fatigue, drowsiness, and depression.

**Materials and Methods:** Cross-sectional, observational, controlled, polysomnographic investigation. Eighty-six patients with a diagnosis of MS or CIS were subjected to a sleep check and fulfilled clinical questionnaires. Seventy-six patients also underwent home PSG and maintenance of wakefulness test (MWT). One hundred five healthy controls (HC) and 35 patients with idiopathic RLS (iRLS) were recruited to compare sleep architecture, respiratory parameters and sleep related leg movement activity (LMA) with patients affected by MS. A subgroup analyses was than performed, evaluating the influence of brainstem lesions at neuroimaging on instrumental and clinical data.

**Results:** MS patients had increased sleep latency, percentage of sleep stage N1, reduced sleep efficiency ( $p < 0.001$ ) and total sleep time compared to healthy controls. Prevalence of RLS and PLMS (PLMSI  $\geq 15/h$ ) in MS group was of 31.4% and 31.6% respectively. Among MS patients with RLS, only 37.5% had a PLMSI  $\geq 15/h$  versus the 71.4% of iRLS. PLMS in RLS secondary to MS were fewer, shorter, less periodic and bilateral when compared to iRLS. RLS and PLMS were independently correlated to fatigue. The frequency of sleep-related breathing disorders (SRBD) was comparable in MS patients and HC, also in the subgroup with brainstem lesions. No MS patient had a central apnea index  $\geq 2/h$ . The respiratory disturbance index (RDI) did not correlate to clinical parameters such as fatigue and depression. Patients with MS were drowsier than HC, but there was not a correspondence between subjective and objective (MWT) sleepiness.

**Conclusions:** In comparison to healthy patients, MS is a risk factor for RLS, PLMS, lower sleep quality. MS seems to be a candidate pathological model of dissociation between the sensory and motor component of RLS, with possible treatment implications. Particular attention should be given to symptoms of RLS in fatigued MS patients. The study does not provide evidence of an association between MS specific symptoms such as fatigue, sleepiness, depression and central or obstructive apneas, even in the presence of brainstem lesions.

**Funding:** Grant ABREOC from Ente Ospedaliero Cantonale (EOC); Grant Swiss MS Society (SMSS); Swiss National Science Foundation, grant number: 320030\_160250.

#### HIGH RISK OF SLEEP DISORDERS IN PATIENTS WITH PAINFUL TEMPOROMANDIBULAR DYSFUNCTION: A CASE CONTROL STUDY

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**Introduction:** Sleep disturbances and chronic pain are highly prevalent conditions compromising health and well-being. Among the many and complex functions of sleep, it ameliorates pain which in turn favors sleep. Interactions between inadequate or insufficient sleep on pain modulatory pathways frequently result in adverse clinical outcomes affecting people at an individual and societal level. Therefore, a better understanding of such interactions may help to improve clinical outcomes and allow to establish standards of care for improving health systems efficacy.

This study aimed to evaluate whether disturbed sleep is more common in patients with painful temporomandibular disorders (TMD) compared to otherwise healthy controls.

**Material and Methods:** The sample consisted of 108 consecutive patients attending for the first time in a TMD and Orofacial Pain (OP) specialized university center from January 2018 to February 2020. Diagnosis of TMD was based on Research Diagnostic Criteria for TMD. Sleep quality and sleep complaints were assessed by the Pittsburgh Sleep Quality Index (PSQI) and compared among subjects with MD (TMD+) and without (TMD-). Poor sleep quality was defined by a PSQI score equal or greater than 5 and sleep disturbance by a PSQI score equal or greater than 10.

**Results:** Overall 70 patients (64,8%; 90% females) with a mean age of  $42,34 \pm 13,57$  were diagnosed with TMD within the two-year period. The mean PSQI score was significantly higher in the TMD+ group ( $8,91 \pm 4,1$  versus  $6,15 \pm 2,78$ ;  $p < ,05$ ). Poor sleep quality was observed in 80% of the patients within the TMD+ group versus 74% in TMD- ( $p < ,05$ ). The rate of PSQI assessed sleep disturbance was higher ( $p < ,05$ ) in TMD+ (36%) compared to the TMD- (5%).

**Conclusion:** Results from this study confirms an important prevalence of sleep dissatisfaction among patients seeking care at a TMD/OP unit. Although sleep complaints were common among the general population in the present study, they were even more frequent and severe in patients

with clinically diagnosed painful TMD. The high frequency of sleep disorders in TMD patients suggests a high risk of sleep disorder. This study finding likely has relevant clinical impact and deserves further exploration, both regarding possible mechanisms of sleep-pain interaction and regarding clinical diagnosis and care.

### NIEMANN-PICK TYPE C WITH SLEEP DISORDERS: CENTRAL SLEEP APNEA AND CATAPLEXY

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**Introduction:** Niemann-Pick type C(NPC) is a set of autosomal recessive inheritance diseases that sheath phospholipids and cholesterol deposit in body organs. The manifestations are highly diverse, but sleep disorders are rarely reported in NPC. Here, we report 2 cases of NPC disease with sleep disorders and discuss clinical features and possible pathogenesis of sleep disorders in NPC patients.

**Materials and Methods:** The sleep symptoms, polysomnography, and genetic characteristics of the two patients with NPC were analyzed. And the related literature was reviewed to explore the possible pathological mechanism of sleep disorders in patients with NPC.

**Results:** Case 1 was a young man with physical clumsiness, glossolalia, excessive sleepiness, and cataplexy. His polysomnography indicated severe central sleep apnea, and multiple sleep latency tests(MSLT) suggested sleep latency on average was 3.9 minutes; 2 SOREMPs(sleep-onset REM period) were found in five times. Case 2 was a child with cataplexy, intelligence impairment, and episodic jerking. The MSLT showed 3 SOREMPs in 5 naps, the mean REM latency was 2.3 minutes, and the mean sleep latency was 15.2 minutes, and orexin in cerebrospinal fluid was 45.61 pg/ml. Both Patients were confirmed Niemann Pick disease by bone marrow puncture and gene tests.

**Conclusions:** Sleep disorders of patients with NPC significantly influence patients' life quality and are not easy to be identified. In this paper, two patients suffered sleep disorders such as central sleep apnea, sleepiness, and cataplexy. Other sleep disorders such as obstructive sleep apnea, REM sleep behavior disorder, and restless leg syndrome have also been reported. The mechanism may be related to sheath phospholipids and cholesterol deposits in brain tissue associated with sleep-wake regulating, but it doesn't have enough evidence. The pathological mechanism needs to be discussed in the future.

### NON-REM SLEEP HYPERTONIA IN PARKINSONIAN-SPECTRUM DISORDERS

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**Introduction:** Non-REM hypertonia (NRH) was recently reported to be independently associated with the synucleinopathy-mediated neurodegenerative disorders: dementia with Lewy Bodies/Parkinson Disease Dementia (DLB/PDD), Parkinson Disease (PD), and isolated REM sleep behavior disorder (iRBD) [1]. In this NRH investigation, we included progressive supranuclear palsy (PSP), a Parkinsonian-spectrum disorder caused by tau pathology.

**Materials and Methods:** In this multicenter study, patients broadly characterized as presumed Parkinsonian-spectrum disorders (PSD) included DLB/PDD (n=16), PD (n=16), iRBD (n=19), and PSP (n=13). Presumed non-PSD subjects included Alzheimer's Disease dementia (AD=22), mild cognitive impairment (MCI=35), and normal cognition (NC=61).

Sleep Profiler studies (Advanced Brain Monitoring, Carlsbad, CA, USA) were acquired in all participants.

Sleep was auto-staged using machine-learning algorithms applied to recording from the frontopolar sites Af7, Af8 and Fpz. The auto-staging was then visually inspected according to the neurodegenerative disease technical editing guide [2]. In the 75% of in-home with two-nights of data, sleep metrics were weight-averaged based on sleep time.

NRH was auto-detected based on patterns of persistently elevated electromyographic (EMG) power relative to delta, theta, and sigma bands. Variability thresholds were applied to each epoch to ensure EMG bursts attributed to sleep disordered breathing arousals were not mischaracterized as NRH. A NRH block required four of six contiguous epochs having satisfied the threshold criteria. Finally, NRH blocks were extended to link blocks with  $\leq 2$ -second gaps. The percent-time NRH was based solely on auto-detected block, no edits were made to add or remove NRH. A  $\geq 5\%$  threshold characterized abnormal-NRH. Twenty-nine NC were longitudinally retested after 364- to 563-days. Statistical analyses included inter-class correlations (ICC), Bland-Altman plots, multiple logistic regression, and receiver-operating-characteristic curves (ROC).

**Results:** In the PSD=41 and non-PSD=95 records with two-nights of data, NRH-severity demonstrated moderate consistency (ICC=0.78, bias=0.6 $\pm$ 6.2%, P<0.0001). Across the two-nights, NRH was classified consistently as normal or abnormal in 59.6% and 27.2% of the records, vs. normal/abnormal=4.4% or abnormal/normal=8.8%. The test-retest reliability of NRH-severity was good (ICC=0.84, bias=0.06 $\pm$ 3.8%, P<0.0001), with all retest comparisons repeating as normal (73%) or abnormal (27%). The frequency of abnormal-NRH in PSP=92% was significantly greater than MCI=26%, AD=14%, and NC=16% (all P<0.0001) and PD=56% (P<0.05), but not DLB/PDD=81% and iRBD=74%. Abnormal-NRH was significantly associated with the PSD group (P<0.0001) and it differentiated PSD versus non-PSD group with an area under the curve of 0.78 (95%CI: 0.72-0.85) based on a sensitivity of 0.75 (95%CI: 0.63-0.84) and a specificity of 0.81 (85%CI: 0.73-0.87).

**Conclusions:** NRH independently discriminated PSD patients from age-sex similar non-PSD subjects, suggesting that NRH is a common sleep motor signature across clinical PSD phenotypes. We speculate that NRH could be related to pathological changes within key non-REM sleep motor modulating center in synucleinopathies and PSP.

#### Reference:

Non-REM Sleep with Hypertonia: A Potential Prodromal Biomarker For  $\alpha$ -Synuclein-Related Neurodegenerative Disease. Levendowski DJ, et al. *Neurology* 2021. 96(15):1943

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**Acknowledgements:** Support provided by National Institute of Health grants: R44AG050326, R44AG054256, AG062677, NS100620, AG056639, RO1AG060477, P50AG005131, R21AG064271, ULRR024150, and R34AG056639.

### SAFE AND EFFECTIVE USE OF SUVOREXANT IN CHILDREN WITH NEURODEVELOPMENTAL DISORDERS: A SINGLE-CENTER, RETROSPECTIVE STUDY OF CLINICAL PRACTICE

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**Background:** Sleep problems in children with certain neurodevelopmental disorders (NDD) are nearly ubiquitous, with prevalence in Autism Spectrum Disorder, ADHD, Tuberous Sclerosis Complex, Rett Syndrome, Angelman Syndrome, and Prader-Willi Syndrome approaching 50–80%, 25–50% 73%, 80%, 80%, and 70%, respectively [1–7]. Chronic insomnia and circadian rhythm disorders are often seen. Treatment of primary sleep disorders in children with atypical neural development can be particularly recalcitrant to first-line behavioral and pharmacologic interventions that are effectively used to treat typically developing children. This is in part because sleep disorders in children with neurodevelopmental disorders are often the result of a complex interplay between multiple molecular mechanisms. Furthermore, children with neurodevelopmental disorders can be particularly sensitive to medications that are without significant adverse effects in typically developing children. The continual development and assessment of sleep-promoting drugs with novel mechanisms of actions are necessary to expand treatment options. Suvorexant reversibly antagonizes the binding of wake-promoting neuropeptides orexin A and orexin B to receptors OX1R and OX2R and suppresses wakefulness. Initially approved and recommended for treatment of chronic insomnia in adults [8], suvorexant was released in November 2014 in Japan and in February 2015 in the U.S. Kawabe et al [9] documented its safe and effective use in adolescents. Its safety and efficacy in children with neurodevelopmental abnormalities, however, remains uncertain.

**Methods:** A retrospective analysis was performed in pediatric patients who were prescribed suvorexant between 2015 and 2021 and were treated at Cincinnati Children's Hospital Medical Center. Primary sleep diagnoses and NDD diagnoses made by developmental specialists, psychiatrists, neurologists, and psychologists were identified and demographic information collected. Starting suvorexant dose was recorded. Adverse effects and statements of efficacy were catalogued. Descriptive statistics were applied. Normal data reported as mean[SD], while non-normal data reported as median[Q<sub>1</sub>,Q<sub>3</sub>].

**Results:** 159 individuals with a neurodevelopmental disorder diagnosis (most common: developmental delay, autism, intellectual disability) were administered suvorexant. N by y age group: 2–5y 16, 5–12y 50, 12–18y 20, and 18–22y 23. Patients were 12.2[7.7,18.3] years old (median[Q<sub>1</sub>,Q<sub>3</sub>]), and 40.9% female, with a weight of 22.6[14.1,42.8] kg at the time of suvorexant initiation. Weights by y age group were: 2–5y 6.7[5.1,10.1] kg, 5–12y 17.2 [14.3,23.0] kg, 12–18y 42.2[25.7] kg (mean[SD]), and 18–22y 54.8[14.9] kg (mean[SD]). Starting doses were as follows for the following age ranges: 2–5y:5[2.5,6.3] mg (median[Q<sub>1</sub>,Q<sub>3</sub>]), 5–12y:5[2.5,5] mg, 12–18y:5[5,10] mg, and 18–22y:10[10,10] mg. Suvorexant was safe; no significant adverse events that required an in-patient hospitalization or prolongation of an existing hospitalization, that resulted in significant disability/incapacity, that was life-threatening, or that resulted in death, were recorded. Suvorexant was well-tolerated, with only a small proportion discontinuing due to adverse effects (chiefly irritability). Certain patients continued to use suvorexant for months after initiation, supporting its efficacy for select individuals.

**Conclusions:** We report the use of an orexin-receptor antagonist, suvorexant, is safe, well-tolerated and efficacious in the treatment of insomnia and circadian rhythm sleep-wake disorders in children with neurodevelopmental disorders.

**Acknowledgements:** This work was supported by the Cincinnati Children's Research Foundation

## SLEEP AND STROKE-RELATED DELIRIUM: A SYSTEMATIC REVIEW AND META-ANALYSIS

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**Introduction:** Sleep and circadian rhythms disorders are frequent in the acute phase of stroke, with various manifestations, such as sleep-disordered breathing, insomnia, hypersomnia, and periodic limb movements. Sleep modifications are likely to contribute to the development of stroke-related delirium, a common neuropsychiatric complication of acute stroke. The purposes of the current study are: 1) to systematically review the

medical literature assessing the role of sleep modifications associated with delirium in acute stroke patients, and 2) to evaluate the efficacy of sleep interventions to prevent or mitigate delirium in acute stroke patients by means of meta-analysis.

**Materials and Methods:** The study was performed according to the latest Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement. Eligibility criteria for study selection were established according to PICO methodology. Only studies reporting data about sleep in acute stroke, and in which delirium was formally evaluated with a validated tool, were included. The search was performed on PubMed, and Scopus databases. The last search was conducted on November 30<sup>th</sup>, 2021. Studies were evaluated by means of "Quality assessment tools for quantitative studies" developed by Effective Public Healthcare Practice Project (EPHPP), which allows the studies to be rated as *strong*, *moderate* or *weak*. Only studies that evaluated the effect of sleep interventions on prevention of stroke-related delirium were included in meta-analysis, which was achieved with Cochrane Review Manager Web.

**Results:** The literature search allowed to identify 15 studies, highly heterogeneous in terms of study design, setting, sleep assessments, delirium measures, and types of sleep intervention. The number of patients included ranged from 18 to 573. Mean age of enrolled patients ranged from 54 (34–88) to 81 (64–94). In most of cases, sleep was subjectively assessed by the patients or rated by clinicians. None of the studies performed polysomnography for evaluation of sleep. Sleep interventions were heterogeneous across studies. Pharmacological intervention was the most common strategy, with various drugs acting on sleep and circadian rhythms. In one study, a 4-week treatment with CPAP was performed, whereas in two studies sleep intervention was evaluated in terms of frequent night-time care. In the study quality assessment, most studies were rated as *weak* or *moderate*. Four studies were entered into meta-analysis. The meta-analysis revealed that sleep interventions reduced the incidence of stroke-related delirium (pooled OR=0.43; 95% CI=0.30–0.61; p<0.001). Indeed, the pooled incidence in the intervention group was 16.3% versus 35.6% in the control group.

**Conclusions:** This systematic review suggests that sleep disruption is a possible risk factor for stroke-related delirium. This evidence should be considered weak, due to the poor overall quality of the papers. Nevertheless, this limited evidence supports the adoption of measures to promote sleep in the prevention of stroke-related delirium. Among such interventions, exogenous circadian rhythm synchronizers, such as melatonin, and the adoption of sleep hygiene measures may diminish delirium occurrence in acute stroke. Randomized clinical trials, with objective sleep assessment, are needed to establish a high-quality recommendation for the prevention of stroke-related delirium.

**Acknowledgements:** none.

## SLEEP BEHAVIOR AND SLEEP DURATION MATTERS WITH WAKE UP ONSET OF ISCHEMIC STROKE IN NON SNORING PATIENTS

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**Introduction:** One third of stroke patients have occurred symptom at awakening. That is called wake up onset stroke (WUS). Hazard of sleep disorders such as sleep breathing disorders, non-apnea sleep disturbances, and circadian rhythm disorder on ischemic stroke have been established. Among these sleep disorders, obstructive sleep apnea (OSA) is known to be more frequent in patients with WUS. Recently, sleep behavior such as weekend catch-up sleep (WUS) and chronotype has highlighted in reducing vascular risk factors including hypertension, dyslipidemia and obesity. So, we aim to determine the association between sleep behavior such as weekend CUS and chronotype and acute WUS.

**Materials and Methods:** A cross-sectional study consisted of 250 mild to moderate stroke patients referred to a Korean Stroke registry about Dongtan sacred heart hospital patients. Also, we screened questionnaire including STOP-Bang questionnaire and other factor-related sleep disturbance such as sleep duration. Patients were classified into high and low risk of obstructive sleep apnea(OSA) and subsequently divided by WUS (Wake-up stroke) and non-WUS. Demographic data, sleep respiratory data, heart rate variability, stroke risk factors, stroke classification and

sleep-related scales were recorded. We compared the differences in the variables between the two groups and determined the independent variables associated with WUS.

**Results:** Of 250 participants who completed the interview, 70 (28.0%) reported stroke onset during sleep (WUS) and high risk OSA (STOP-bang score >2) was prevalent in 80.4% of participants. There was no significant differences in age, gender, stroke risk factors, and stroke classification according to WUS in a total of patients. However, among low risk OSA patients, short average sleep duration, lack of weekend CUS, and early chronotype were associated with WUS independent of age, gender, and other sleep risk factor (OR 1.4, 1.7, and 1.6, respectively) Also conventional stroke risk factor such as diabetes and dyslipidemia was associated with borderline significance.

**Conclusions:** The overall prevalence of WUS in our cohort was present in 28.0%. Without effects of OSA, sleep behaviors relating sleep insufficiency such as lack of weekend catch-up sleep, short sleep duration, earlier chronotype was significant association with the prevalence of WUS. Insufficient sleep and lack of compensation can be negative effects on cardiovascular disease, especially onset during sleep of ischemic stroke.

### SLEEP DISORDERS IN MYASTHENIA GRAVIS

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**Introduction:** Myasthenia gravis (MG) is an autoimmune disease (AD) that affects the neuromuscular junction, resulting in muscular fatigue that may involve the diaphragm and accessory respiratory muscles and lead to respiratory failure. Recent studies have shown a high prevalence of obstructive sleep apnea (OSA) in myasthenia gravis when compared to the general population.

**Case presentation:** A 67-y-old man, obese (body mass index 33 Kg/m<sup>2</sup>), reported complaints of loud snoring, witnessed apnoeas, excessive daytime sleepiness and sexual dysfunction. The patient underwent level 1 polysomnography revealing severe OSA, with an apnoea/hypopnoea index (AHI) of 47.5/h (predominance of obstructive apnoeas and hypopnoeas). The oxygen desaturation index (ODI) was 51/h. Automatic positive airway pressure (APAP) therapy (pressure range 6–12 cmH<sub>2</sub>O) was effective in reducing AHI to 2.4/h (average 95th percentile pressure was 8.5 cmH<sub>2</sub>O). A few months later, the patient's adherence to the therapy decreased. Seven years later, he was hospitalized for dysphagia and difficulty in chewing. While a nasogastric tube was being introduced, the patient had an episode of sudden respiratory distress, with respiratory arrest requiring endotracheal intubation and mechanical invasive ventilation. Anti-acetylcholine receptor antibodies were positive and an electromyography described disturbances of the neuromuscular transmission compatible with MG. He started treatment with prednisolone, immunoglobulin and pyridostigmine with clinical improvement. At discharge, arterial blood gas confirmed the presence of hypercapnic respiratory failure, probably secondary to his neuromuscular disease, requiring the introduction of bi-level non-invasive ventilation (NIV) [inspiratory positive airway pressure (IPAP) of 20 cmH<sub>2</sub>O; expiratory positive airway pressure (EPAP) of 10 cmH<sub>2</sub>O]. On a follow-up visit, the patient presented good adherence to NIV, without respiratory failure in the blood gas analysis. Nevertheless, he complained of muscle weakness in the cervical region and maintained a residual AHI of 5.8/h. The parameters were adjusted (IPAP 21, EPAP 12 cmH<sub>2</sub>O), resulting in an improvement of the AHI to 0.7/h.

**Conclusion:** It is important to raise awareness about the possible sleep disorders associated with neuromuscular diseases such as MG. In this patient, oropharyngeal weakness associated with MG may have worsened the preexisting OSA syndrome. Furthermore, the respiratory muscle dysfunction that characterizes MG may have contributed to sleep hypoventilation to the point of requiring assisted ventilation.

Additionally, it is important to highlight the possible role of OSA in modulating the immune system, especially considering that MG is an AD. Although the direct relationship between OSA and MG in immune-modulation is still unknown, the cellular injury caused by sleep apnea-induced hypoxia triggers an immune response that may increase the long-term risk of developing or worsening autoimmune diseases.

### SLEEP HABITS, CIRCADIAN RHYTHM, AND SLEEP RELATED SYMPTOMS IN ADULT GLIOMA PATIENTS. A PROSPECTIVE, CROSS-SECTIONAL STUDY

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**Introduction:** Most knowledge on sleep disorders in adult glioma patients derives from clinical trials using health-related quality of life scores depicting various aspects of sleep disturbance. Although these scores allow estimation of sleep quality, factors leading to sleep disruption remain unclear and comprehensive sleep assessments are still lacking. The aim of the current study was the description of sleep habits, circadian rhythm and sleep related symptoms in a large group of adult glioma patients.

**Materials and Methods:** In this prospective cross-sectional study 79 adult glioma patients (49% female; 17 Grade II, 19 Grade III, 43 Grade IV, according to the WHO 2016 classification) underwent a standardized semi-structured interview evaluating sleep habits and sleep related phenomena as well as a set of validated sleep specific questionnaires (PSQI, ISI, MEQ, ESS, STOP-BANG, RBDI). Clinical information as well as PHQ-9 and FSS were analysed as co-factors.

**Results:** For the whole sample median bedtimes ranged from 22:00 (19:00–01:00) to 07:00 (03:30–10:00), median sleep latency was 12 minutes (1–120), median sleep duration was 8.5 h (4.0–11.00 h), 33% of patients reported regular daytime sleep, none of these values differed with regards to glioma grade or localisation (all  $p > 0.05$ ). Most common circadian type was a moderate morning type (54%), while definite morning type and an intermediate type were almost equally distributed (23% and 20% respectively). Circadian preference was significantly associated with glioma grade and localisation ( $p = 0.025$  and  $p = 0.003$  respectively). Median ESS was 6 (0–19), 18% of patients reported excessive daytime sleepiness, there was a trend towards lower ESS values in Grade II patients ( $p = 0.057$ ). Median PSQI value was 3 (0–14), 23% had a score >5 indicating poor sleep, significant differences for the PSQI were found when comparing tumour localisations ( $p = 0.019$ ). While median score on STOP-BANG questionnaire was 2 (0–7), 43% of patients had at least intermediate risk for OSA, there was a significant association of OSA risk and glioma localisation ( $p = 0.043$ ). Seven patients (9%) were positive for the core criteria of RLS. Nine patients (11%) screened positive on the RBDI.

**Conclusions:** This study demonstrates a broad spectrum of sleep related symptoms in adult glioma patients. The results suggest a complex association between tumour specific factors and presence of sleep complaint.

### SLEEP MODULATION IN PARKINSON'S DISEASE PATIENTS WITH DEEP BRAIN STIMULATION: THE ROLE OF FREQUENCY VARIATIONS

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**Introduction:** Deep Brain Stimulation (DBS) is an effective treatment for motor symptom in Parkinson's Disease (PD). Since sleep alterations are a frequent non-motor symptom in PD, DBS is shown to modify also sleep parameters. Low frequencies stimulation are used in Subthalamic Nucleus (STN) DBS in PD patients to improve gait disorders and the hypothesis of a possible involvement of these frequencies of the Pedunculo Pontine Nucleus (PPN) was advanced. PPN is a brainstem nucleus involved in locomotion but also in sleep modulation, especially in REM sleep.

The aim of our study was to investigate the differences between low (60Hz) versus high (130Hz) frequencies of STN DBS in PD patients (PD-

(DBS) in sleep parameters. We also explored differences in sleep parameters between PD-DBS patients and PD patients with only medical treatment (PD-MED) and healthy controls (HC).

**Materials and Methods:** PD-DBS and PD-MED non demented patients were recruited at the Movement Disorders Clinic of our Hospital. Also HC age-matched were recruited. All patients underwent a full night laboratory polysomnography, while PD-DBS performed two recordings in different non consecutive days: a night with 60Hz frequency of stimulation, one night with 130Hz frequency of stimulation. Sleep conventional macrostructure and microstructure analysis was performed. Motor symptoms were evaluated with validated scale and with a wrist Actigraphy. EEG quantitative variables and sleep slow oscillation (SSO) analysis were explored for PD-DBS patients.

**Results:** In our study 10 PD-DBS patients, 10 PD-MED and 10 HC were enrolled. Two PD-DBS patients were subsequently excluded from the analysis due to the presence of artifacts in the recordings. No differences in age or disease duration were found among groups. PD-DBS patients presented increased REM sleep duration during 60Hz stimulation compared to 130Hz. Phasic EMG activity during REM sleep was not different in the two stimulation conditions. NREM sleep (macrostructure and microstructure) was not significantly modified in the two stimulation conditions. When 60Hz frequency was used, an increase in Theta activity in EEG quantitative analysis was found during both REM and NREM sleep. No significant differences were found in SSO between the two stimulation conditions. Tremor was significantly higher at 60Hz frequency of stimulation than 130Hz. When the three groups were compared: PD-MED presented a significant lower number of REM periods and a trend towards significant of lower REM percentage than HC; PD-DBS patients when stimulated with 60Hz showed REM percentage and number of REM periods higher than PD-MED and with values similar than HC. Considering sleep microstructure PD-MED presented a reduced Total CAP Rate % than HC and A3 index was reduced in PD-MED and in PD-DBS 130Hz (but not at 60Hz) compared to HC.

**Conclusions:** Low frequencies stimulation of STN could modulate sleep in PD patients increasing REM sleep, suggesting a possible involvement of other brain structures as PPN, as proposed for motor improvement with these stimulation setting. STN stimulation at 60Hz seems to not cause major modification of NREM sleep and microstructure of sleep, while DBS shows globally a modulation effect on sleep improving sleep parameters compared to PD-MED patients.

#### SLEEP-WAKE MISPERCEPTION. A COMPREHENSIVE ANALYSIS OF A LARGE SLEEP LAB COHORT

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**Introduction:** Since almost half a century, sleep researchers have noted a substantial discrepancy between subjective sleep/wake estimations and sleep laboratory findings. Underestimation of one's sleep duration appeared to be particularly common in patients suffering from insomnia, including cases of subjective total insomnia. The observation of largely reduced subjective sleep perception despite normal or only mildly disturbed sleep led to the proposition of a new diagnostic term, sleep state misperception, and of a new insomnia subcategory, paradoxical insomnia. Sleep-wake misperception is, however, not limited to insomnia, but has been reported for other sleep disorders, including sleep apnea, periodic limb movement disorder, post-traumatic sleep-wake disturbances, and sleep restriction. In addition, sleep disorders rarely manifest as purely isolated entities, but often overlap and coexist with other sleep disorders, eg, comorbidity of insomnia and sleep apnea. In the case of narcolepsy, several sleep disorders may co-occur in the same patient (eg, insomnia, sleep apnea, sleep paralysis, rapid eye movement (REM) sleep behavior disorder). Eventually, it also became clear that sleep state misperception not only involves underestimation but also overestimation of sleep. Despite considerable efforts to understand the underlying mechanisms contributing to sleep state misperception, and the awareness of the high distress it exerts on affected patients, the prevalence, magnitude and types of sleep-wake misperception remains unknown in many sleep-wake

disorders. A recent study, however, identified the type of sleep disorder as the most significant predictor of the subjective-objective discrepancy in total sleep time. Overall, subjective-objective discrepancy of sleep-wake variables has rarely been examined in a large sleep laboratory cohort that included careful diagnostic ascertainment along the third version of the International Classification of Sleep Disorders (ICSD-3). Hence, the present study aimed to assess the prevalence and correlates of sleep-wake misperception in a large cohort of patients with various sleep-wake disorders, all diagnosed along the third version of the International Classification of Sleep Disorders.

**Materials and Methods:** We retrospectively included 2738 patients examined by polysomnography, who in addition estimated upon awakening their total sleep time, sleep onset latency and Wake after sleep onset (WASO). We computed subjective-objective mismatch by the formula (subjective e objective value)/objective value 100; negative and positive values indicated under- and overestimation, respectively.

**Results:** In the entire sample, the magnitude of under- and overestimation of total sleep time was similar, but varied significantly between diagnostic groups, with insomnia and insufficient sleep syndrome showing the most pronounced underestimation and REM parasomnia and circadian rhythm disorders showing the most pronounced overestimation of total sleep time. In all diagnostic categories, a majority tended to overestimate their sleep onset latency and to underestimate the amount of WASO. Younger age was independently correlated with underestimation of total sleep time and WASO, and with over-estimation of sleep onset latency. Overestimation of sleep onset latency independently correlated to an increased latency to N3 sleep stage on polysomnography.

**Conclusions:** While sleep-wake misperception is highly prevalent in all sleep-wake disorders, significant differences exist in magnitude of under- and overestimation between distinct diagnostic groups.

**Acknowledgements:** none

#### VALIDATION STUDY OF THE RICHARD'S CAMPBELL SLEEP QUESTIONNAIRE IN PATIENTS WITH ACUTE STROKE

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**Introduction:** Sleep disorders, such as insomnia, sleep disordered breathing, and restless legs syndrome, are frequent in the acute phase of stroke, with an estimated prevalence of over 50%. Sleep-wake disorders in stroke survivors are associated with increased mortality, stroke recurrence, and worse neurological and cognitive recovery. Despite this, a low percentage of patients with acute stroke undergoes a formal sleep testing, partially due to difficult access and high costs of routinary polysomnography (PSG) assessment. Therefore, subjective survey instruments are needed for sleep disorders screening in stroke units. The Richards-Campbell Sleep Questionnaire (RCSQ) is a simple, validated scale for measuring sleep quality in intensive care unit patients. The aim of the present study is to validate RCSQ for use in patients with acute stroke in the setting of a stroke unit.

**Materials and Methods:** The study is a prospective observational cohort study. Patients were consecutively enrolled from the stroke unit of the Fondazione Policlinico Universitario Agostino Gemelli, Rome. Inclusion criteria were: age  $\geq$  18 years; diagnosis of ischemic or hemorrhagic stroke; NIHSS  $\geq$  1. Exclusion criteria were: stroke mimics; absence of neuroimaging evidence of brain lesion; aphasia; extreme severity of conditions; inability of the patient to undergo PSG. All patients underwent overnight unattended bed-side PSG, which was scored by sleep expert physicians, blinded to the RCSQ. The morning after PSG recordings, patients were administered the RCSQ by stroke physicians. The cut-off value for good sleep was a RCSQ score of 59. The validation study was performed comparing the answers given by the patients to the questionnaire with the corresponding parameters of PSG. In particular:

- Total score of the scale compared with Sleep Efficiency Index (SEI).

- Perceived sleep depth compared with time spent in stage N3 (N3).
- Subjective time to fall asleep compared with sleep latency (SL).
- Perceived time spent awake compared with wake after sleep onset (WASO).

Difficulty to fall asleep again after waking up compared with duration of awakenings.

- Perceived quality of sleep compared with SEI.

The Bland–Altman analysis was performed to evaluate the inter-method agreement between RCSQ and PSG parameters. Moreover, accuracy, sensitivity and specificity were obtained for the total score and for each item of the questionnaire.

**Results:** The final cohort consisted of 25 patients, 11 men. Mean age was 73.6±13.8 years. Mean RCSQ score was 63.6±22.9. In the Bland–Altman analysis, the mean difference found between the RCSQ and polysomnography was -13.4 (95% limits of agreement -56.7 – 29.9). The level of agreement was statistically significant ( $p < 0.01$ ). Compared to PSG, accuracy of the RCSQ was 60%, sensitivity 50%, and specificity 78%. Each item of the questionnaire was consistent with the corresponding PSG parameters. **Conclusions:** The RCSQ showed to be a reliable instrument to subjectively assess sleep in acute stroke patients, with only a mild underestimation of sleep quality and quantity compared to PSG. Indeed, the total score and the different items of the questionnaire showed a high level of agreement with objective PSG parameters. Therefore, the study allows to validate RCSQ for use in stroke unit.

**Acknowledgements:** none.

## Other

### A CROSS-SECTIONAL STUDY OF THE ASSOCIATION BETWEEN SLEEP QUALITY AND ANXIETY IN POSTSECONDARY STUDENTS IN ONTARIO

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**Introduction:** Postsecondary students frequently report high rates of anxiety and poor sleep quality. The association between poor sleep quality and anxiety and the potential role other covariates have in this association is poorly understood in this population. Therefore, the purpose of this study was to assess the association between poor sleep quality and moderate to extremely severe anxiety in post-secondary students in Ontario as well as assess the impact of any covariates.

**Materials and Methods:** This cross-sectional study enrolled students from two faculties: Faculty of Health Sciences (FHS) and Faculty of Education (FEEd) at Ontario Tech University (OTU), and students attending the Canadian Memorial Chiropractic College (CMCC) during the fall of 2017. Participants completed self-report questionnaires to measure sleep quality (PSQI), anxiety (DASS-21), socio-demographic, lifestyle and health-related variables. Multivariable logistic regression was used to measure the association between poor sleep quality (PSQI score  $\geq 7$ ) and moderate to extremely severe anxiety (DASS-21 anxiety subscale score  $\geq 10$ ) while controlling for covariates (e.g. biological gender, age, socioeconomic status, medical co-morbidities, depression, stress, and food insecurity).

**Results:** The sample included 882 students from OTU (77% female) and 510 participants from CMCC (60% female). For students attending OTU, the prevalence of poor sleep quality was 61.8% (95% CI: 9.52 – 9.93) with a mean global score of 7.75/21 (95% CI: 7.54 – 7.97). The majority of students in this sample (73.7%) obtained less than 7 hours of sleep per night and 41.7% reported daytime sleepiness. The one-week prevalence of moderate to extremely severe anxiety was 58.3% (95% CI 14.85 – 16.11), with the mean DASS-21 score of 10.37/21 (95% CI 9.81–10.91). A significant correlation between PSQI scores and DASS-21 anxiety scores ( $r = 0.30$ ,  $p < 0.001$ ) was found. Similarly, in the sample of CMCC students the prevalence of poor sleep quality was 59.8% (95% CI: 9.26 – 9.81) with a mean PSQI score of 7.42/21 (95% CI: 7.13 – 7.71). 75.5% of students reported obtaining less

than 7 hours of sleep and 32.4% reported daytime sleepiness. For CMCC students, the one-week prevalence of moderate to extremely severe anxiety was 41% (95% CI 14.64 – 16.46) and the mean DASS-21 score was 7.43/21 (95% CI 6.83 – 8.04). A significant correlation between PSQI scores and DASS-21 anxiety scores ( $r = 0.32$ ,  $p < 0.001$ ) was also found within this sample. Students who reported poor sleep quality were more likely to report moderate to extremely severe anxiety (OTU: OR = 3.22 [95% CI 2.41 – 4.30] and CMCC: OR = 3.83 [95% CI 2.49 – 5.91]). This association decreased but still remained high even after controlling for covariates (biological gender, stress, and depression) that were found to be important (OTU: OR = 1.55 [95% CI 1.10 – 2.18] and CMCC: OR = 2.61 [95% CI 1.61 – 4.24]).

**Conclusions:** Poor sleep quality is associated with moderate to extremely severe anxiety in students within the postsecondary population. Implications for policy development and campus wellness are encouraged.

**Acknowledgements:** University of Ontario Institute of Technology; Institute of Disability and Rehabilitation Research, Ontario Trillium Foundation.

### A LONGITUDINAL STUDY OF WORK TIME SCHEDULE AND PRESCRIBED SLEEP MEDICATION USE IN NORWEGIAN NURSES

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**Introduction:** Shift work normally disrupts the sleep-wake cycle and can cause acute symptoms such as sleepiness at work, as well as curtailed and disturbed sleep. About 64% of nurses in Norway have shift work. Compared to the general population, a larger proportion of nurses struggle with sleep problems, but there is a dearth of knowledge about how workers cope with these problems. The aim of this study was to explore whether a change from a work schedule with nights to a work schedule without nights was associated with a change in the probability of prescribed sleep medication use.

**Materials and Methods:** A longitudinal study with annual questionnaire data (2008/2009–2021, no questionnaire in 2019) on 2028 Norwegian nurses who participated in the ongoing Survey of Shift Work, Sleep and Health (SUSSH). In each wave, the nurses were asked about their work schedule (only day work, shift work without nights and shift work with nights) and whether they have used any prescribed sleep medication the last year. Associations were estimated using a random effects model and a fixed effects regression model in which nurses were included as their own control. The fixed effects regression model accounts for all unobserved potential confounding that are constant within an individual throughout follow-up (such as stable personality traits, chronotype and health behaviors).

**Results:** A total of 291 nurses (14.3% of total sample) reported to have used prescribed sleep medication the last year in at least one wave. Throughout the follow-up period, the proportion of nurses who reported sleep medication use increased. In both the random and the fixed effects regression models, a change from shift work with nights to only day work resulted in a more than 50% reduced probability of reporting sleep medication use in the next wave (adjusted OR (aOR) 0.46, 95% CI 0.24–0.86 in the random effects model, and aOR 0.32, 95% CI 0.14–0.70 in the fixed effects regression model). A non-statistically significant reduction in sleep medication use was found within nurses who changed from shift work with nights to shift work without nights in the fixed effects regression model (aOR 0.66, 95% CI 0.37–1.20).

**Conclusions:** A change in work schedule from shift work with nights to day work was associated with a significant reduced probability of prescribed sleep medication use. This suggests that shift work, in particular night work, puts nurses at risk of developing sleep disturbances that deserves treatment/interventions.

**Acknowledgements:** We are grateful to all nurses participating in the study and to the Norwegian Nurses Organization (NSF) for funding and help with recruitment.

## ASSOCIATIONS BETWEEN DAILY SLEEP AND AFFECTIVE EXPERIENCES: A SYSTEMATIC REVIEW

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**Introduction:** This work reviews empirical research investigating the bidirectional relationship between daily sleep and affective experiences. In particular, the review focuses on ambulatory assessments such as experience sampling (ESM) and daily diaries. This review of daily sleep-emotion dyads considered a broad approach to mood disorder diagnosis (bipolar, depression, anxiety), work schedules, and shift work. Interchangeable affective definitions are considered, along with the situational context and ecological validity of daily assessments. Studies published since 2017 are included, thus expanding prior reviews such as Konjarski et al. (2018) and Ong et al. (2017).

**Materials and Methods:** The International Prospective Register for Systematic Reviews (PROSPERO) and four electronic databases were searched to October 2021: EMBASE (Ovid), Ovid MEDLINE(R), PsycINFO (Ovid), and Scopus (Elsevier). Additional studies were identified through reference checking and hand searching. Records were deduplicated on EndNote and uploaded to Rayyan.

**Results:** 2,078 studies were identified and 69 met the full inclusion criteria. Studies predominantly included healthy populations (N=58), of which six involved shift workers; remaining studies investigated mood disorders (N=11). Studies with only self-report sleep measures were most common (N=41) but a high number incorporated actigraphy (N=29). Overall, 18 studies used both actigraphy (objective) and self-report (subjective) sleep markers. Sleep diaries (N=17), the Pittsburgh Sleep Quality Index (PSQI; N=12), and Positive and Negative Affect Schedule (PANAS; N=27) were the most widely used measures. The majority of studies (N=55) incorporated at least one electronic device or digital technology to capture ambulatory sleep and affect outcomes. In general, findings support a mutual relationship between sleep and next-day affective experiences among healthy populations, shift workers, and individuals diagnosed with a mood disorder.

**Conclusions:** Studies varied considerably in how 'sleep' and 'affect' were defined and operationalised. The type of momentary assessment technique, frequency and timing of daily measures, and study duration were also wide-ranging. Relatively few studies utilised both objective and subjective sleep markers. Further research is needed among those with non-standard work schedules, shift workers, and affective disorders; for which sleep-wake and circadian disruption are common and may confer vulnerability to mood perturbations.

**Acknowledgements:** This study represents independent research [part] funded by the National Institute for Health Research (NIHR) Maudsley Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

## BEFORE AND AFTER A SLEEP PROGRAMME AT THE START OF THE PANDEMIC: HUNROSA SLEEP CONSULTANCY

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**Introduction:** Hunrosa Sleep Consultancy is unique in the UK as a private provider of sleep services to the National Health Service. In our commissioned contracts we work with young people who have sleep difficulties and complex health needs. The main diagnosis is autism however there are comorbidities including cerebral palsy, epilepsy and rare conditions. Hunrosa wished to investigate the impact of the pandemic on the quality of its services, having pivoted to deliver the service via telehealth.

**Materials and Methods:** Hunrosa worked alongside the Community Paediatric Team who maintained medical oversight of the cases. After a detailed referral, Hunrosa contacted the young people and families and explained the service and the sleep diaries. Of the 63 referrals made, 50 went on to treatment with Hunrosa. Each young person submitted two weeks of sleep diary for consideration. Intervention then involved a

detailed assessment, a draft report was compiled and goals agreed with the young person/family. The report was then used to create a plan of action. The young person and family were given ongoing support for an average of 2 months to achieve results. In addition a further 20 families were enrolled onto the Sleep Wise parents webinar, referred by the paediatricians. Each participant had the opportunity to discuss a pre recorded sleep diary in a 30 minute consultation after the training.

**Results:** After a Sleep Wise input as above, 80% of young people resolved their sleep problem. 84% of families followed the sleep intervention to completion, just 5% stated that they had stopped due to issues with the pandemic. There was a big reduction in sleep disturbance: from 6 out of 12 to 2 out of 12. Almost three quarters did not need sleep medication as their sleep improved naturally. Quality of life scores improved across the board. The training was well received: "The course was highly informative. I found it incredibly useful. it was presented in such a good way. I got so much from it".

**Conclusions:** Hunrosa believes that this feedback gathered during the pandemic, impacted by the first and second lockdowns in the UK, shows that treatment of sleeplessness in young people with challenging health conditions is not unduly disadvantaged by delivery through online and telehealth means. indeed it is still possible to achieve a high degree of success and engagement.

**Acknowledgements:** Hunrosa wishes to thank the Kernow CCG in the NHS for the opportunities provided by this project.

## CHANGES IN SLEEP ARCHITECTURE DURING LONG-DURATION SPACEFLIGHT

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**Introduction:** Previous projects have shown that astronauts sleep significantly worse in space than on Earth. However, it is unclear how spaceflight influences sleep architecture. Such information could inform our understanding of the adaptive mechanisms of NREM and REM sleep. We investigated how sleep architecture is affected during spaceflight relative to on Earth.

**Materials and Methods:** We recorded the sleep of four cosmonauts and one astronaut using the Nightcap sleep monitor before (preflight, n=112 nights), during (spaceflight, n=83 night), and after (postflight, n=61 nights) long-duration missions aboard the Mir space station. We compared hand-scored REM, NREM, and wakefulness during spaceflight to sleep on Earth, both pre- and postflight using mixed-effects regression models to account for subject variability. We also used mixed-effects modeling to assess if sleep efficiency and architecture evolved with more time spent in space.

**Results:** Participants averaged an hour less sleep during spaceflight ( $5.7 \pm 0.6$ ) compared to preflight ( $6.7 \pm 0.7$ ;  $p \leq 0.0001$ ) and spent significantly more time awake in bed, leading to a 17.7% reduction in sleep efficiency. Sleep architecture was also affected by spaceflight: the share of the total recording spent in NREM and REM showed significant percentage decreases of 14.1% and 25.8%, respectively. REM latency increased by nearly 50% during spaceflight. Sleep latency increased significantly from the start to finish of the missions ( $\beta: 0.40$ ;  $p < 0.0001$ ), and the percentage of sleep spent in REM recovered over time ( $\beta: 0.04$ ;  $p = 0.01$ ).

**Conclusions:** These data substantiate previous findings focused on sleep continuity in microgravity. A variety of metrics demonstrate worse sleep in space. NREM and REM time significantly decreased alongside an increase in wakefulness, but the relative proportion of these stages also changed significantly: REM sleep suffered more than NREM in spaceflight conditions. These longitudinal data add value to our nebulous understanding of how sleep functions in microgravity.

**Acknowledgements:** Mary Gordon Roberts Fellowship, NAS 9-19406, NIMH #MH-48,832, the MacArthur Foundation Mind-Body Network, and Healthdyne Technologies

## COMPARATIVE EFFICACY OF OSA PATIENTS UNDERGOING MULTILEVEL SURGERY FOLLOWED BY UPPER AIRWAY STIMULATION VERSUS ISOLATED UPPER AIRWAY STIMULATION

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**Introduction:** Upper Airway Stimulation (UAS) of the hypoglossal nerve is a growing management option for patients with obstructive sleep apnea (OSA). Currently, exclusion criteria for UAS includes an apnea-hypopnea index (AHI) above 65 or concentric collapse of the velum with drug-induced sedation endoscopy (DISE). We describe the treatment efficacy of subjects who were initially ineligible for UAS treatment, but who then met inclusion criteria following multi-level upper airway surgery. We then compared this cohort to subjects with isolated UAS.

**Materials and Methods:** The design in a single-center, retrospective study. Data collection include demographics, body mass index (BMI), AHI, oxygen desaturation index (ODI), Drug Induced Sedation Endoscopy (DISE) results, Epworth sleepiness score (ESS), and Fatigue severity score (FSS), and UAS titration results.

**Results:** Thirty-six subjects underwent UAS implantation (Inspire system, Minnesota, USA) from 2016 to 2019. Eighteen subjects who were initially ineligible for UAS underwent multi-level surgery, including uvulopalatopharyngoplasty (UPPP) with genioglossus advancement, distraction osteogenesis maxillary expansion (DOME), or maxillomandibular advancement (MMA). Mean age was 62.3±9 years with 28% being female. Mean BMI was 29±4 kg/m<sup>2</sup>. The cohort of seventeen subjects who met criteria for UAS from the start had mean age of 62.9±14 years and mean BMI of 26.7±4 kg/m<sup>2</sup> with 12% being female. Mean pre-treatment AHI for the multi-level cohort was 49±3 events per hour, which was reduced to 3.6±5 events per hour with mean voltage of 1.8V±0.9. Mean pre-treatment AHI for UAS only cohort was reduced from 33±14 events per hour to 5.3±6 events per hour with mean voltage of 1.9V±0.3.

**Conclusions:** For patients who are ineligible for UAS due to severity of OSA or concentric collapse of the velum, multilevel surgery including MMA followed by UAS confers effective post treatment results that in our cohort was superior to the UAS only group.

**Acknowledgements:** None

## DISRUPTED SLEEP IN RETT SYNDROME ANIMAL MODELS

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**Introduction:** Sleep problems are reported to be prevalent in individuals with Rett Syndrome (RTT, MIM 312750). RTT is a rare, progressive neurodevelopmental disease, characterized by loss of acquired language skills, stereotypic hand movements, and comprehensive cognitive, social, motor skill impairments. Typical and atypical variants have been defined, framing RTT when clinical features vary subtly. Due to the discovery of RTT genetic mutations, who are mostly located in the genes of methyl-CpG binding protein 2 (MECP2), cyclin dependent kinase like 5 (CDKL5) and forkhead box G1 (FOXP1), animal models have been developed. We will systematically review studies investigating sleep in animal models of RTT.

**Materials and Methods:** Five electronic databases PubMed, Web of Science, PsycINFO, Ebsco and Scopus, were searched up till March 06 2020. Inclusion and Exclusion Criteria: sleep studies in RTT animal models including variants of MeCP2, Cdkl5 and Foxg1. Review papers, conference proceedings, thesis works and studies reporting "sleep" but not presenting data were excluded.

**Results:** From 2005 to 2020, 13 studies investigating sleep in RTT animal models have been published. Five countries established an animal model

for sleep: one in monkey, two in *Drosophila* and 10 in mouse. Disrupted sleep in these animal models presented to be enhanced waking state with increased fragmented sleep bouts, but no altered sleep duration/proportion within 24-h cycles. Findings in EEG spectral analysis revealed lower 4 Hz frequency wave (slow wave sleep) and decrease in the average number of delta cycles in 24-h cycles. Irregular circadian rhythm was displayed as decreased amount and rhythm amplitude of sleep-activity. Animal models also exhibited sleep breathing abnormalities particularly during NREM sleep.

**Conclusions:** We found disturbed efficacy and continuity of sleep in all genetically mutated models of mice, cynomolgus monkeys and *Drosophila*. Models also presented circadian arrhythmicity. Overall, animal models mimic sleep complaints reported in individuals with RTT. Animal models investigating sleep may unravel novel neural mechanisms for this severe neurodevelopmental rare disease.

**Acknowledgements:** The financial support (NO. 201806180064) provided by China Scholarship Council (CSC) is acknowledged.

## EFFECTIVENESS OF DIGITALLY DELIVERED SLEEP INTERVENTIONS ON SLEEP AND MENTAL HEALTH OUTCOMES IN POSTSECONDARY STUDENTS: A SYSTEMATIC REVIEW

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**Introduction:** Students pursuing postsecondary education are a population at significant risk for both sleep problems and poor mental health outcomes such as depression and anxiety. Interventions such as sleep hygiene education and cognitive behavioural therapy (CBT) are commonly used treatments for sleep problems and have been effective in improving sleep and mental health in the university student population. Digitally-delivered CBT has also been shown to be effective in improving sleep in youth, however it has not been evaluated in the postsecondary student population.

**Materials and Methods:** We conducted a systematic review of the quantitative and qualitative evidence on the effectiveness and user experiences of digital sleep interventions to improve sleep and mental health outcomes in postsecondary students. We searched MEDLINE, CINAHL, Embase, and APA PsycInfo for studies published from 2000 to 2021. We included randomized controlled trials (RCTs), cohort studies, case-control studies, qualitative studies, and mixed methods studies. Pairs of reviewers independently screened and critically appraised studies, and extracted data. We aimed to use a sequential approach at the review level to synthesize and integrate data across qualitative and quantitative research studies.

**Results:** We screened 5361 citations and 58 full text articles. Eight relevant RCTs and one cohort study were critically appraised. Three interventions were assessed including CBT, digital sleep hygiene education, and relaxation music. Most studies were assessed as high risk of bias. Given the methodological limitations of the included studies, we are unable to conclude on the effectiveness of digital sleep interventions for postsecondary students. We did not identify any qualitative studies.

**Conclusions:** Methodological limitations preclude firm conclusions. Further research is needed to assess the effectiveness of digital alternatives for delivering sleep interventions to improve sleep and mental health outcomes in postsecondary students. Qualitative studies exploring the views and preferences of students and providers are required to inform the development of novel interventions that are acceptable in this population.

**Acknowledgements:** Canadian Institutes of Health Science (CIHR) Operating Grant: Knowledge Synthesis: COVID-19 in Mental Health & Substance Use

## EFFECTS OF EPILEPSY SURGERY ON SLEEP MACROSTRUCTURE AND MICROSTRUCTURE IN PATIENTS WITH DRUG-RESISTANT TEMPORAL LOBE EPILEPSY DUE TO HIPPOCAMPAL SCLEROSIS: A PROSPECTIVE CONTROLLED POLYSOMNOGRAPHIC STUDY

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**Introduction** Temporal lobe epilepsy due to hippocampal sclerosis (TLE-HS) is one of the most common drug-resistant epilepsy. Surgery is an effective approach for epilepsy compared with ASMs in TLE-HS. The aim of the study is to evaluate the effect of surgical treatment of TLE-HS due on sleep profile and architecture by subjective and objective evaluation of sleep in basal condition, after 1 month and 1 year.

**Methods** Thirteen patients affected by TLE-HS were recruited to undergo overnight polysomnography and a subjective evaluation of nocturnal sleep utilizing the Pittsburgh Sleep Quality Index (PSQI) and daytime somnolence through the Epworth Sleepiness Scale (ESS) in basal condition (T0), one month after epilepsy surgery (T1) and one year after surgery (T2). Thirteen healthy controls (HC) matched for age, sex and BMI were recruited. Scoring and analysis of sleep macrostructure and cyclic alternating pattern (CAP) parameters were performed.

**Results:** The comparison between patients in basal condition (T0) and HC showed a significant lower sleep efficiency ( $p = 0.003$ ), REM percentage ( $p < 0.001$ ). Regarding CAP, patients at T0 showed higher CAP rate ( $p < 0.001$ ), CAP rate in N2 ( $p < 0.001$ ), higher A3 (%) ( $p = 0.001$ ), higher mean duration of A1 ( $p = 0.002$ ), A3 index ( $p < 0.001$ ), cycle in sequences ( $p < 0.001$ ), lower B duration ( $p < 0.001$ ), cycle mean duration ( $p < 0.001$ ) than HC. Surgery did not induce any significant changes in nocturnal macrostructural polysomnographic variables in T1 and T2. Lower CAP rate (T1 vs T0 and T2 vs T0  $p < 0.001$ ), CAP rate in N3 (T1 vs T0 and T2 vs T0  $p < 0.001$ ), A3 (%) (T1 vs T0 and T2 vs T0  $p < 0.001$ ); lower phase A2 (T1 vs T0  $p < 0.001$ ) and A3 index (T1 vs T0  $p < 0.001$ ), higher phase A1 index (T2 vs T0  $p < 0.001$ ) and B mean duration (T2 vs T0  $p = 0.002$ ) and lower cycle in sequences (T2 vs T0  $p = 0.002$ ). No significant differences were found between T1 and T2 in CAP parameters.

**Conclusion:** We found a significant fragmentation in patients affected by TLE-HS compared with HC. In addition, ATL induced a significant improvement in sleep continuity as evaluated by cyclic alternating pattern already one month later and this effect persisted after one year. ALT seem to restore a more resilient sleeping brain.

## EFFECTS OF SLEEP RESTRICTION AND TIME OF THE DAY ON BALANCE CONTROL IN HEALTHY OLDER MEN AND WOMEN

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**Introduction:** Falls represent a major public health problem leading to injuries and hospitalization. The frequency of falls increases with age and frailty level. Studies suggest that sleep deprivation reduces stability of body balance and this destabilizing effect is greater in older individuals. The contribution of sleep-wake homeostasis and circadian rhythmicity on postural control (PC) and their interaction with sex is unknown. We aimed to investigate the impact of sleep loss and time of the day on PC under different sensorial feedback conditions in healthy elderly women and men.

**Methods:** Thirty-seven healthy elderly participants (20 females, age=63±3) underwent a 2.5-days-long laboratory session in dim light condition (<10lx) in the Sleep and Brain Research Unit of the University of East Anglia. After a baseline night, participants were randomly assigned to either a 40-h sleep deprivation (SD) or a multi-nap (MN) experimental condition comprising consecutive intervals of 160-mins of wake in dim light (<10 lx) and 80-mins of sleep. PC was tested regularly on a 4-hourly-basis. Each PC test session included 8 consecutive 20-sec-long trials standing on a force plate with eyes open or closed and with fingertip light touch or no touch sensorial feedback. In the current analyses, we focused

on the dynamics of the sway estimated through the ellipse area fitted to the center of pressure (CoP) stabilogram.

**Results:** Our analysis returned a significant main effect of sensorial feedback modality on PC ( $P < 0.0001$ ) with fingertip feedback producing a much larger stabilization in PC compared to visual feedback independent of age, sex and experimental condition. Interestingly, the effect of experimental condition on PC was modulated by sensorial feedback modality in men who performed significantly worse in SD compared to MN in the open eyes feedback modality ( $P = < 0.0187$ ). We also found a significant interaction between experimental condition and time of the day with PC being significantly impaired in SD compared to MN during the circadian night only ( $P = < 0.0016$ ). Interestingly these effects were present again in the open eyes feedback modality ( $P = < 0.0007$ ) and in men only ( $P = < 0.0003$ ).

**Discussion:** Here we show for the first time that the effect of sleep loss on balance control is modulated by interactions between sensorial feedback modality, time of the day and sex. The greater impact of sleep loss on balance control observed when participants rely on visual feedback may be due to an intersensorial conflict between vision and other sensorial modalities important for balance control, such as vestibular and somatosensory sensation, induced by the dim light conditions. In other words, although the visual channel is engaged it may not provide reliable feedback about body sway when the individual is sleep deprived. Our results imply that older men characterized by disturbed sleep may be at increased falls risk particularly during the night and dim lit environment.

**Acknowledgment:** This study was supported by the Wellcome trust to Dr. Lazar (207799/Z/17/Z).

## EXAMINING THE INTERACTIVE EFFECTS OF FAMILY- AND NEIGHBOURHOOD-LEVEL SOCIO-ECONOMIC CHARACTERISTICS ON CHILD SLEEP OUTCOMES

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**Introduction:** Family socio-economic status is a well-established risk factor of adverse sleep outcomes in children. At the neighbourhood-level, the effects of socio-economic characteristics (SECs) on sleep outcomes are mixed. However, the interactive effects of neighbourhood- and family-level SECs have not been examined. This study filled this gap.

**Materials and Methods:** Secondary data analyses were completed on a sample of children (aged 4 to 11;  $N = 6,264$ ) from the 2014 Ontario Child Health Study, a cross-sectional, province-wide sample of 10,802 children aged 4 to 17. Multi-level modelling was used to assess the relationship between child- (i.e., age, sex, internalizing problems, externalizing problems, chronic illness, negative parenting behaviours), family- (i.e., marital status, parent education level, family poverty, parent mental health symptomatology, number of years lived in the neighbourhood) and neighbourhood-level factors (i.e., neighbourhood residency, neighbourhood antisocial behaviour, neighbourhood poverty level) and their relationship to sleep outcome variables: problems falling asleep, problems staying asleep, weekday sleep duration and weekend sleep duration.

**Results:** Results showed ( $M$  age = 7.5, 50% male) neighbourhood antisocial behaviour predicted more problems falling asleep ( $\beta = 0.13$ ,  $p < .01$ ). Neighbourhood poverty ( $\beta = -0.01$ ,  $p < .01$ ) predicted significantly shorter weekday sleep duration and the interactive effects of family and neighbourhood poverty significantly predicted weekend sleep duration ( $\beta = 0.01$ ,  $p < .05$ ). Interestingly, children living in low poverty neighbourhoods without family poverty and children living in high poverty neighbourhoods with household poverty had the shortest weekend sleep durations (9.7 hours).

**Conclusions:** There is a compound effect of family and neighbourhood poverty on children's sleep. Different levels of SECs may interact to influence child sleep and relate to sleep outcomes differentially. Clinicians should assess neighbourhood-level factors (e.g., noise) that may be influencing child sleep, as neighbourhood-level variables predicted sleep outcomes above and beyond child- and family-level factors.

## FIVE-YEAR TRANSITIONS OF SYMPTOM SUBTYPES IN UNTREATED OBSTRUCTIVE SLEEP APNEA

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**Introduction:** Symptom subtypes have been consistently identified in mild and moderate-severe OSA in cross-sectional studies. The objectives of this study were to determine how often participants transition between symptom subtypes over 5 years and whether baseline clinical factors were associated with observed transitions.

**Materials and Methods:** We analyzed demographic, clinical, polysomnographic and symptom data from 2,643 participants of the Sleep Heart Health Study (53.7% women; mean age 62.4 years) with complete baseline and follow-up visits (5.2 years between visits). Latent transition analysis was conducted using 14 daytime and nighttime symptom items in individuals with OSA diagnosis (apnea-hypopnea index [AHI]≥5) to determine symptom subtypes at baseline and follow-up as well as their transition probabilities over time. Individuals without OSA (AHI<5) were incorporated as a known class at each time point. Multinomial logistic regression was conducted to assess the effect of age and sex on class transitions between baseline and follow-up visits.

**Results:** We identified four OSA symptom subtypes at both baseline and follow-up visits: minimally symptomatic, disturbed sleep, moderately sleepy and excessively sleepy. Most participants did not transition subtypes between visits (55.8%). Of participants whose subtype remained the same between visits, 54.1% had minimal symptoms at baseline; 48.5% were in moderately sleepy; 31.5% were excessively sleepy and 34.6% were in disturbed sleep. A transition to moderately sleepy was the most common. Excessively sleepy participants transitioned most often to moderately sleepy (37.9%). One-year increase in baseline age was associated with a 7% increase in odds to transition from excessively sleepy to disturbed sleep (OR=1.07; 95%CI=1.01-1.15) and about 6% increase in odds to transit from excessively sleepy to moderately sleepy (OR=1.06 (95% CI=1.02-1.12)). Women had higher odds to transit from moderately sleepy to minimal symptoms (OR=2.35; 95%CI: 1.27-3.27) and to transit from minimal symptoms to no longer having an OSA diagnosis (OR = 2.30; 95%CI=1.40-3.80).

**Conclusions:** Approximately half of the participants transitioned their symptom subtypes over a period of 5 years, with most transitioning to minimal symptoms. Increasing age and sex may affect the transitions.

**Acknowledgements:** Research grant support (U01HL53916, U01HL53931, U01HL53934, U01HL53937, U01HL53938, U01HL53940, U01HL53941, U01HL64360) from the National Institutes of Health.

## IMPACT OF SLEEP DURATION ON THE RESPONSE TO VACCINATION: A META-ANALYSIS

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**Introduction:** The SARS-COV-2 pandemic has resulted in over than 5 millions confirmed deaths. Although vaccination is a major strategy to control this pandemic, to date, only 54% of the world population has received at least one dose of a COVID-19 vaccine. Booster inoculations are increasingly recommended. Thus, the vaccination effort may need to continue for several years before the epidemic can be considered as contained. Although antibody response is just one facet of the adaptive immune system's response to vaccination, it is considered to be a clinically significant biomarker of protection. The role of insufficient sleep duration in individual differences in antibody responses to vaccination against influenza or hepatitis has been examined in a number of studies, with somewhat mixed results. In order to summarize and clarify these findings, we have used a meta-analytical approach to determine whether the current body of evidence suggests that optimizing sleep duration may be an

easily modifiable behavior that could increase the efficacy of anti-viral vaccination.

**Materials and Methods:** The PubMed database was searched with the combination “sleep\*” and “vaccin\*” keywords. Studies were selected if they met the following criteria: (1) were performed on healthy human adults; (2) assessed vaccine efficacy by antibody titers or protection status; (3) performed subjective (survey items, questionnaire, sleep diary, interview) and/or objective (actigraphy, polysomnography) measures of sleep duration; (4) were laboratory-conducted studies of manipulation of sleep duration over 1 or more nights; (5) were cohort studies; (6) were peer reviewed original research papers. Since the number of available studies was small, we have engaged in a collaborative effort with the authors of all publications to obtain the information needed to optimize the estimation of the pooled effect size (ES) and the 95% confidence intervals: log transformed data when non parametric testing was used; calculation of separate ES for men and women; analyses corrected for age and overweight/obesity status whenever appropriate; sleep data no more than one week apart from inoculation. Number of participants, mean, beta or odd ratio and their respective dispersion were collected. The ES was interpreted as small when ≤0.20, moderate when >0.50 - ≤ 0.80 or large when >0.80.

**Results:** No relationship was observed between self-reported short sleep and vaccine efficacy (n=504; overall ES=0.16 [-0.12, 0.44]). In contrast, when studies that used objective measures of sleep were examined, a robust adverse impact of short sleep on vaccine efficacy was detected (n=282; overall ES=0.96 [0.15, 1.78]). The pooled ES for experimental studies (n=111) was 0.84 [0.20, 1.49] and 1.08 [0.10, 2.06] for prospective studies (n=171). The meta-analysis did not find significant differences in ES between women and men.

**Conclusions:** When assessed objectively, short sleep duration was associated with a clinically relevant decrease in efficacy of anti-viral vaccination. These findings suggest that achieving adequate amount of sleep during the time window surrounding the time of inoculation may increase the efficacy of vaccines against diverse strains of viruses, possibly including strains of SARS-CoV-2.

**Acknowledgements:** Collectively, the authors acknowledge the support of their respective institutions in these challenging times.

## LATENT PROFILE ANALYSIS WITH MMPI-2 RESPONSES IN MILITARY RECRUITS REFERRED FOR PSYCHIATRIC SYMPTOMS IN KOREA

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**Introduction:** Since South Korea has adopted the conscription system, medical and psychiatric evaluation is essential before military enlistment. The purpose of this study was to examine young men based on various symptoms in clinical dimensions of MMPI-2 who were referred due to psychiatric screening failure.

**Materials and Methods:** Subjects were 92 males aged 18 to 28 years who visited the psychiatry department of the university hospital for psychiatric evaluation. Of the total 92 subjects, 52 had depressive disorders, 29 had anxiety disorders, and 11 had other psychiatric disorders. Latent profile analysis (LPA) of MMPI-2 clinical scales was conducted to examine types and characters of latent class groups with clinically useful profiles among the subjects.

**Results:** The most frequent complaint was sleep disturbance. Three latent classes, 'mild maladjustment group (MM)', 'neurotic depression and anxiety group (NDA)', and 'hypersensitive and hypervigilant group (HH)' were identified. Each group differed in their clinical characteristics. The MM (15.2%) showed low scores of around 50 on all of MMPI-2 clinical scales. The NDA (39.1%) presented a clinically high score distribution in internalizing problems such as depression, anxiety, helplessness, social discomfort, and so on. Compared to the NDA, the HH (45.7%) complained of internalizing problems more strongly and at the same time, experienced a high level of paranoid idea, anger, and hostility.

**Conclusions:** This study suggests that classifying the military recruits with psychological maladjustment into three subgroups based on clinical

responses from MMPI-2 might be helpful for further treatment.

#### Acknowledgements:

### METHODOLOGICAL QUALITY IN THE MOST CITED META-ANALYSES IN SLEEP MEDICINE

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**Introduction:** Systematic reviews and meta-analyses are usually regarded as the research design that generates the highest level of scientific evidence. However, this assumption is only valid when the procedures and analyses are performed considering the best and most rigorous methodological standards. Meta-analyses that are poorly reported or are performed with substandard methods might have the opposite effect, impairing the process of evidence synthesis. Previous studies have reported that meta-analyses in the field of Sleep Medicine are frequently of low methodological quality. The current study aimed to analyse if the problem related to methodological quality is also observed in the most cited sleep-related meta-analyses.

**Materials and Methods:** A bibliometric search was performed in Web of Science (all databases collection), to retrieve sleep-related meta-analyses. The search records were sorted by citation count and the top 300 meta-analyses were extracted. As Web of Science does not have any specific category related to Sleep Medicine, this search strategy might lead into false-positive results. Therefore, all records were initially evaluated to assure they belong to the field of Sleep Medicine (i.e.: their population, intervention or main outcome is related to sleep). The meta-analyses confirmed to be related to sleep were analysed in two aspects: 1. citation information was extracted directly from Web of Science for all included studies, and 2. The top 100 most-cited meta-analyses were evaluated according to AMSTAR 2.0 for methodological quality. Data extraction and methodological quality assessment was performed by two independent reviewers and discrepancies were solved by consensus.

**Results:** Out of the 300 exported meta-analysis, 194 (65%) were related to sleep. Among these, the relationship of meta-analyses with sleep were due to the population in 25 studies (13%), to the intervention in 148 studies (76%) and to the outcomes in 104 studies (53%). The single year with most meta-analysis published was 2015 (n=36, 19%); 46 meta-analyses (24%) were published from 2020-2016, 95 (49%) from 2011-2015, 35 (18%) from 2006-2010, 11 (6%) from 2011-2005 and 7 (4%) up to 2000. The most-cited meta-analysis in the sample had 4.116 citations, the average citation rate was of 198.0±341.6 and the average citations per year was 20.6±23.9. Regarding AMSTAR 2.0 assessment, 2 meta-analyses were considered as of high methodological quality, 3 as of moderate quality, 27 as of moderate quality and 68 as of critically low quality.

**Conclusions:** The overall methodological quality among the most cited meta-analyses in the field of Sleep Medicine was remarkably low. Considering we were dealing with the most-cited meta-analyses, which are likely to be the ones with more impact and relevance in an area, one would expect a higher quality level. This is an important concern, considering the surge in the publication of this type of study in the last two years. These results corroborate previous studies regarding the low methodological quality of meta-analysis in Sleep Medicine and reinforce the need to promote the use of the most rigorous systematic methods and tools in this field.

**Acknowledgements:** AFIP, CNPq, CAPES

### MORE THAN SLEEP AND WAKE DISTURBANCES: AN ACTIGRAPHIC STUDY SHOWING THE SLEEP-WAKE PATTERN DYSREGULATION IN EPILEPSY

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**Introduction:** This study aimed to assess the sleep-wake pattern in patients with epilepsy compared to controls.

**Materials and Methods:** Patients with epilepsy and controls underwent a 14-day actigraphic recording to evaluate the rest-activity cycle. A sleep medicine interview was performed to exclude conditions interfering with the sleep-wake cycle in both patients and controls. Patients presenting seizures during the actigraphic recording were excluded. Daytime activity, nocturnal sleep, and non-parametric circadian rhythm activity (NPCRA) were analysed.

**Results:** Twenty-two patients (mean age 49.5±19.84 years; 50% female) and 17 controls were included. Patients showed lower sleep efficiency and longer sleep latency than controls. NPCRA analysis showed lower inter-daily stability and higher intra-daily variability in patients, who also presented lower daytime activity and a longer central phase measure (CPM) than controls.

**Conclusions:** Patients showed a significant alteration of the sleep-wake pattern, featured by lower synchronization and higher fragmentation of the rest-activity rhythm. Moreover, patients showed a delayed CPM than controls, corresponding to an evening chronotype tendency.

Nocturnal sleep alteration and lower daytime activity were also evident. Therefore, patients with epilepsy present an alteration of the sleep-wake pattern and clinicians should increase their awareness about circadian rhythmicity dysregulation in epilepsy.

### NAPPING IMPROVES WAKEFULNESS IN ATHLETES BUT HAS NO INFLUENCE ON ENDURANCE PERFORMANCE

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**Introduction:** The sleep quality of athletes is often poor or reduced because of stress, travel within different time zones and competition fear. Therefore we examined the effects of napping after partial sleep deprivation (PSD) on endurance performance in athletes.

**Materials and Methods:** Twelve healthy and trained participants (7 female and 5 male) underwent three test sessions. After one control night (eight hours of sleep) the participants slept randomized 5 hours without nap (NoNap) and with a 30-minute nap opportunity (Nap30). PSD and the nap were quantified with pupillography (pupillary unrest index, PUI), a subjective level of sleepiness questionnaire (Karolinska Sleepiness Scale, KSS) and polysomnography. After each night the participants performed a maximal cycling ergometry test, which determines time to exhaustion (TTE) and maximal oxygen uptake (VO2max).

**Results:** The main results include a significant increase in the KSS after 5h of sleep compared with the control condition ( $p < 0.01$ ,  $\eta^2 = 0.52$ ). From pre to post nap the KSS decreased significantly (5.4 vs 3.2,  $p = 0.004$ ). Aside from that PUI decreased pre-post nap significantly (7.9 vs 4.3 mm/min,  $p = 0.048$ ). There was no significant effect of sleeping condition on TTE ( $p = 0.601$ ,  $\eta^2 = 0.125$ ) and VO2max ( $p = 0.364$ ,  $\eta^2 = 0.088$ ).

**Conclusions:** The results of the study indicate that napping or PSD has no influence on pure endurance performance. We conclude that exercise performance is a multidimensional construct where the condition of sleep is less relevant. However, napping is a good method to increase wakefulness and concentration, which can be beneficial for game sports.

**Acknowledgements:** We want to thank the study participants.

### POOR CORRELATION OF SUBJECTIVE SLEEP QUALITY ASSESSED BY PITTSBURGH SLEEP QUALITY INDEX WITH MEASURES OF SLEEP QUALITY DETERMINED BY POLYSOMNOGRAPHY IN ISCHEMIC STROKE PATIENTS

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**Introduction:** Sleep disturbances are common in stroke patients, but they are often neglected. Pittsburgh Sleep Quality Index (PSQI) is a widely used

questionnaire for assessing subjective sleep quality. Sleep efficiency and duration and proportion of deep sleep and REM are considered to be polysomnographic (PSG) measures of sleep quality. There are very few studies comparing PSQI with PSG.

**Aim:** To compare the subjective and objective measures of sleep quality in ischemic stroke patients.

**Materials and methods:** Pittsburgh Sleep Quality Index was administered in a prospectively recruited ischemic stroke patient who underwent polysomnography. Sleep was scored according to AASM guidelines.

**Results:** Hundred and two-stroke patients were recruited with a mean age of 50 (SD: 12) of which 78.4% were male. The median NIHSS score was 1 (IQR: 0,3), modified Rankin Scale was 1 (IQR: 0,2) and AHI was 18 (IQR: 7,34). The mean PSQI global score was 5 (SD: 2). Objective measures of sleep quality like sleep efficiency ( $r=0.168$ ) and proportion of deep sleep ( $r=0.057$ ) did not correlate with the PSQI score. There was poor correlation of PSQI score with REM duration ( $r=-0.140$ ), REM% ( $r=-0.266$ ), N2 duration ( $r=0.314$ ) and N2% ( $r=0.011$ ). Subjective sleep onset latency determined by PSQI and sleep onset latency determined by polysomnography had no correlation ( $r=0.018$ ).

**Conclusion:** This study showed a poor correlation between PSQI determined quality of sleep with objective measures of sleep quality determined by polysomnography in ischemic stroke patients. Pittsburgh Sleep Quality Index is not a reliable tool in assessing sleep quality in ischemic stroke survivors.

**Acknowledgments:** I thank the funding agency ICMR for the financial support and the Department of Neurology, NIMHANS, Bangalore, India for providing a platform to perform the polysomnography studies.

#### QUANTITATIVE MEASUREMENT OF UPPER AIRWAY DIMENSIONS DURING DRUG-INDUCED SLEEP ENDOSCOPY TO STUDY ORAL APPLIANCE OUTCOME IN OBSTRUCTIVE SLEEP APNEA

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**Introduction:** Mandibular advancement devices (MAD) are proven to be effective in selected patients with obstructive sleep apnea (OSA). The predominant mode of action of MAD is to protrude the mandible, resulting in opening of the upper airway and increasing its volume. The aim of this study is to visually investigate the effect of MAD therapy on upper airway dimensions during drug-induced sleep endoscopy (DISE).

**Methods:** Data of 56 OSA patients, treated with an MAD fixed at 75% of maximal protrusion and with polysomnography baseline apnea-hypopnea index (AHI)  $\geq 10$  /h sleep, were included. All patients underwent a DISE with and without MAD during their treatment time frame and completed 3-month follow-up polysomnography with MAD. Three snapshots were selected at beginning of inspiration from the DISE video-footage for each patient at the level of the tongue-base both at baseline and with MAD in situ. Cross-sectional areas were digitally measured on retroglottal and retro-epiglottic level before and after mandibular advancement, using the polygon selection tool in ImageJ, following the airway lumen transversally with attention to light-dark interfaces to ensure a constant anatomical level. To correct for possible differences in scope-positioning, calibration according to the lateral epiglottis-length was performed. Intraclass correlation coefficients (IC) were calculated in 60 images ( $n = 10$  patients) for the retroglottal and retro-epiglottic area while the MAD was present and without MAD, to assess agreement with an independent second observer.

Linear mixed effects models were built to define the effect of MAD on upper airway dimensions. The presence or absence of MAD was included as fixed effect. Correlation between repeated measures on a certain outcome referring to the same individual patient was accounted for through random effects. Moreover, expansion ratios were calculated by dividing cross-sectional areas during mandibular advancement by areas at baseline. Treatment response was defined as reduction in AHI  $\geq 50\%$ . To determine the

association between MAD treatment response and expansion ratios, independent samples t-tests were used.

**Results:** A total of 336 images (168/168, baseline/MAD) in 56 OSA patients was scored (82.1% male; age:  $48.6 \pm 7.9$  years; BMI  $25.9 \pm 7.9$  kg/m<sup>2</sup>; baseline AHI 19.0 (12.9 – 25.7) events/h sleep).

Interobserver reliability measuring retroglottal and retro-epiglottic areas was excellent (IC = 0.97).

A significant difference was seen between the retroglottal cross-sectional area at baseline ( $47,823.36 \pm 2,357.58$  pixels) and with MAD presence ( $55,818.52 \pm 2,357.58$  pixels) ( $p \leq 0.0001$ ); no significant difference was found at the retro-epiglottic area ( $p = 0.1074$ ). More interestingly, greater expansion ratios for retroglottal area were seen in responders ( $1.31 \pm 0.49$ ) compared to non-responders ( $1.12 \pm 0.31$ ), although non-significant ( $p = 0.0876$ ). No significant association was found between treatment response and retro-epiglottic area.

**Conclusions:** These findings demonstrate an increase in upper airway dimensions at retroglottal level during drug-induced sleep with MAD presence. Furthermore, a more pronounced increase in retroglottal expansion ratios is observed in responders for MAD treatment compared to non-responders. However, larger sample sizes are needed to confirm these results. Finally, the utility of DISE in evaluating MAD treatment outcome is emphasized.

#### RIGHT AND LEFT ASYMMETRY IN SLEEP EFFICIENCY IN POLYSOMNOGRAPHY OF HEMISPHERIC ISCHEMIC STROKE – PRELIMINARY EVIDENCE

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**Introduction:** Topography of stroke lesions and their effect on the sleep macro architecture remains unclear. There is scant literature on studies comparing the macroarchitecture of sleep between left and right hemispheric Middle Cerebral Artery (MCA) territory ischemic stroke survivors. **Aim:** To evaluate the sleep macroarchitecture in patients with hemispheric ischemic stroke.

**Materials and methods:** We selected MCA territory ischemic stroke patients from prospectively recruited ischemic stroke survivors who were evaluated for sleep-disordered breathing. Patients underwent overnight polysomnography and the sleep was scored according to AASM criteria. The brain lesions were mapped into various territories adapting the schema as described in the Alberta stroke programme early CT score (ASPECTS).

**Results:** Sixty-six CT/MRI-proven MCA territory stroke patients were selected from 104 patients with ischemic stroke. The mean age of the patients was 50.5 (SD 12.7). 78% of patients were of the male gender. The median modified Rankin Scale was 1 (IQR: 1, 2) and the median NIHSS was 1 (IQR: 1,3). PSG scored median AHI was 7.4 (IQR: 2.9, 19.1). The mean ASPECT score was 8 (SD 1). Right MCA stroke had reduced sleep efficiency (mean 60.6, SD 19.4) compared to left MCA stroke (mean 76.4, SD 11.9). Fourteen patients had basal ganglia infarcts. When patients with basal ganglia lesions were excluded from the MCA territory stroke the sleep efficiency between right and left hemispheric stroke was 59.9 (SD 18.7) vs 75.9 (SD 12.4). When the posterior MCA territory defined as ASPECT lesion in M3 and M6 were excluded from the analysis the sleep efficiency was 61.1 (SD 13.5) vs 75.6 (SD 13.3) for right and left hemispheric strokes respectively. In this group, N 2 % (28.2, SD 15.1 vs 51.5, SD 20.3) and REM % (10.3, SD 6.8 vs 16.6, SD 9.2) were reduced in right side lesion. Stage N3 was reduced in both groups.

There was no significant difference in ASPECT score, ESS, and PSQI between the right and left anterior hemispheric stroke. NIHSS and mRS did not differ between the groups, Basal ganglia lesion did not show any laterality of sleep abnormalities.

**Conclusion:** Right MCA hemispheric stroke patients had a greater degree of sleep alterations compared to the left. The difference was pronounced in patients with lesions in anterior part of MCA territory. The right-left difference was not noted in lesions limited to basal ganglia. Larger sample of patients with voxel-based volumetric lesion mapping would verify the robustness of the present study.

**Acknowledgments:** I thank the funding agency Indian Council for Medical Research (ICMR) for the financial support and the Department of Neurology, NIMHANS, Bangalore, India for providing a platform to perform the polysomnography studies.

### SLEEP AS AN OUTCOME MEASURE IN ADHD RANDOMIZED CONTROLLED TRIALS>

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**Introduction:** Sleep disturbances are highly prevalent among children with Attention Deficit Hyperactivity Disorder (ADHD). Emerging literature is demonstrating the intrinsic role of sleep in ADHD, including the recently described ADHD sleep phenotypes and ADHD-related sleep disorders. Yet, despite the high prevalence of sleep disturbances in children with ADHD, the diagnostic and treatment regimens are primarily focussed on daytime symptomatology. Randomized controlled trials (RCTs) mainly focus on outcome measures pertaining to daytime functioning, and consequently, sleep outcome measures are not often utilized in such trials. Thus, the goals of this scoping review are to (1) identify interventional RCTs that have utilized a sleep-specific outcome measure and (2) review the validity and applicability of tools used to capture sleep.

**Materials and Methods:** This scoping review follows the methodological framework outlined by Arksey & O'Malley. A search was carried out in CINAHL, Embase, Medline, and PsycINFO in June, 2020 using variations of the following search terms: ADHD AND Sleep AND RCT. Criteria for inclusion was (1) diagnosis of ADHD according to e.g. DSM or ICD, (2) Sleep as a primary or secondary outcome, (3) RCT study design as is defined by the *Cochrane Handbook*.

**Results:** Out of the 2265 records screened, only 71 RCTs used a sleep-specific primary or secondary outcome measure. As a primary outcome measure, sleep was used in 40/71. Of these 40 RCTs, the most commonly employed tool was actigraphy (n=18) followed by sleep log/diary (n=16), Children's Sleep Habits Questionnaire (CSHQ; n=13), and polysomnography (n=10). In the remaining 31 RCTs, sleep was used as a secondary outcome measure. The most common tool was the Pittsburgh Sleep Quality Index (PSQI; n=15), followed by CSHQ (n=5), Pediatric Daytime Sleepiness Scale (PDSS; n=3), Epworth Sleepiness Scale (ESS; n=3), and actigraphy (n=3). Of the 50 RCTs that were targeting ADHD symptoms (e.g. using stimulants), adverse sleep outcomes were seen in 19/50 studies.

**Conclusions:** Despite the fact that sleep disturbance is a comorbid and/or intrinsic characteristic of ADHD, affecting 25-50% of this population, the number of RCTs utilizing sleep-specific outcome measures is limited. Further, given the well-known adverse effects of certain ADHD medications (e.g. stimulants) on sleep, sleep has to be included, not only as an adverse event measure, but also as an outcome measure using both objective and subjective measures.

### SLEEP KNOWLEDGE, BELIEFS AND PRACTICES IN YOUTH SPORTS COACHES AND SCIENCE SUPPORT STAFF

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**Introduction:** Sleep is a crucial aspect of youth athletes' development, recovery, and performance. Due to time requirements for school and homework, training schedules, and social interactions, it has been shown that youth athletes may not meet guidelines for adequate sleep. Youth athletes' coaches and science support staff seem to play an essential role in supporting athlete health and well-being, including sleep habits. The main purpose of this study was to assess the sleep hygiene knowledge of

coaches and sports science support staff working with youth athletes, their sleep practices implemented with athletes and their sleep education.

**Materials and Methods:** A sample of 139 Polish coaches and sports science support staff working with youth athletes volunteered to complete a survey focused on sleep monitoring and hygiene practices, as well as sleep education. The Sleep Beliefs Scale (SBS) was also included. Differences in scores based upon categorical variables for the job position (coach vs support staff), a sports discipline (team vs individual), and working experience ( $\leq 5$  years vs  $> 5$  years) were calculated by the Mann-Whitney U-test.

**Results:** Overall sleep hygiene knowledge was inadequate for the whole sample ( $14.86 \pm 2.70$ , score range 0 - 20; mean  $\pm$  SD). However, the overall score of the SBS for science support staff was adequate ( $15.44 \pm 2.71$ ) and significantly higher than the inadequate result obtained by coaches ( $14.48 \pm 2.65$ ,  $p = 0.013$ ). Similarly, the result for the "sleep-wake cycle behaviours" factor was adequate for science support staff ( $5.91 \pm 1.64$ ) and significantly higher than coaches' results considered inadequate ( $5.24 \pm 1.56$ ;  $p = 0.017$ ). "Sleep-incompatible behaviours" factor was adequate for both the science support staff and coaches ( $6.74 \pm 1.25$  vs  $6.49 \pm 1.31$ , respectively;  $p = 0.206$ ), while the "thoughts and attitudes to sleep" factor was inadequate ( $3.24 \pm 0.95$  vs  $3.05 \pm 0.95$ , respectively;  $p = 0.178$ ) without significant differences between groups. Additionally, there was a significant difference in knowledge of "sleep-wake cycle behaviours" between those working  $\leq 5$  years compared to those working  $> 5$  years ( $5.84 \pm 1.49$  vs  $5.25 \pm 1.66$ , respectively;  $p = 0.048$ ). Less than half (48%) of coaches and science support staff promoted or administered sleep hygiene strategies, and only 17% monitored the sleep of youth athletes. Most coaches and science support staff (only 35% of "yes" responses) were not educated in sleep knowledge. However, there were significant differences between coaches and science support staff (28% vs 46%, respectively;  $p = 0.030$ ) in their education in the sleep field.

**Conclusions:** Coaches working with youth athletes had inadequate overall sleep hygiene knowledge, while knowledge of sports science support staff was adequate. However, the factor "thoughts and attitudes to sleep" should be improved for both groups. Sleep hygiene strategies and sleep monitoring seemed to be not common practices of youth coaches and science support staff. The sleep education of coaches and science support staff was rather limited. Based on the findings, we suggest that a broader approach to sleep education of coaches and science support staff might be necessary to improve sleep practices for youth athletes.

### SLEEP MACROSTRUCTURE AND MICROSTRUCTURE IN PSYCHOGENIC NON EPILEPTIC SEIZURES: COMPARISON BETWEEN PNES AND TEMPORAL LOBE EPILEPSY

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**Introduction:** Sleep complaints are commonly reported in patients with PNES (Psychogenic Non-epileptic Seizure) but few studies have addressed this issue. In addition, the lack of clear markers makes PNES diagnosis still difficult and often late. We investigated the differences in sleep macrostructure and microstructure (cycling alternating pattern CAP, sleep spindles, slow-oscillations SO and coupling) between documented PNES patients and temporal lobe epilepsy (TLE) patients with hippocampal sclerosis, with the aim of finding a neurophysiological marker for the PNES diagnosis.

**Materials and Methods:** 13 patients with PNES and 13 patients with TLE were recruited and underwent two 48-h ambulatory polysomnography (A-PSG) monitoring sessions. Scoring and analysis of sleep macrostructure and sleep microstructure (cyclic alternating pattern CAP, fast and slow spindles and slow oscillations SO) were performed.

**Results:** No differences were found in sleep macrostructure between the two groups of patients. PNES patients presented a higher CAP rate in N1, a lower in N3, a longer mean CAP duration of phase B and a higher number of CAP cycles compared to the TLE group. PNES patients had higher

amplitude of frontal slow spindles and central fast spindles. PNES had also higher density, amplitude and rate of slow oscillation (SO) but shorter mean duration of Slow Oscillation (SO) on frontal and central regions. Coupling between SO and spindle was higher in PNES patients compared to TLE group.

**Conclusions:** PNES seem to induce a less fragmented sleep as shown by microstructural analysis compared to TLE. This finding may be the expression of more resilient strategies of sleep in PNES than TLE.

#### STRENGTHS OF ASSOCIATIONS BETWEEN POTENTIAL RISK FACTORS AND DEPRESSIVE SYMPTOMS ACROSS LEVELS OF SLEEP QUALITY IN UNIVERSITY STUDENTS: A CROSS-SECTIONAL STUDY

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**Introduction:** Depression is a multi-causal disorder with a complex etiology. It has been proposed that the multiple causes of depression are best understood as a system of interacting causal mechanisms. Sleep disturbances have been consistently identified as a risk factor for depression. Sleep disturbances are also known to impair emotion regulation abilities, which could potentially increase the negative effects of other risk factors on depression. In this study we aim to test the hypothesis that sleep quality interacts with several other potential risk factors in relation to depressive symptoms.

**Objectives:** First, we aim to determine whether sleep quality statistically interacts with the potential risk factors loneliness, risky alcohol use, perfectionistic concerns and physical inactivity in relation to depressive symptoms. Second, we aim to explore the functional form of these potential statistical interactions and associations.

#### Materials and Methods:

**Design.** Cross-sectional study. **Participants.** Swedish university students (n=4262). **Measures.** All measures were self-rated and collected with a web-survey. Sleep quality was measured with the Pittsburgh Sleep Quality Index and depressive symptoms with the short-form Depression, Anxiety and Stress Scale. **Statistical analysis.** Regression models of increasing complexity (linear and non-linear, with and without interactions) were compared to determine the presence of associations and statistical interactions, and to explore the best functional form for these associations and interactions. Out-of-sample R<sup>2</sup> from repeated cross-validation was used to select the final models.

**Results:** Sleep quality was associated to depressive symptoms in all models. Sleep quality showed a linear interaction with perfectionistic concerns in relation to depressive symptoms. Loneliness, risky alcohol use and physical inactivity showed non-linear associations to depressive symptoms, but no interactions with sleep quality.

**Conclusions:** Of the four investigated potential risk factors, only perfectionistic concerns interacted with sleep quality in relation to depressive symptoms. This interaction was weak and explained little of the overall variance in depressive symptoms. We conclude that sleep quality may statistically interact with some, but not all, potential risk factors in relation to depressive symptoms and that non-linear associations should be taken into consideration when examining interaction effects.

**Acknowledgements:** This research project was funded by the Swedish Research Council for Health, Working Life and Welfare (FORTE), grant number FORTE2018-00402.

#### TARGETED MEMORY REACTIVATION TO AUGMENT TRAUMA TREATMENT DURING SLEEP

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**Introduction:** Post-traumatic stress disorder (PTSD) is a severe mental

disorder with traumatic memories at its core. Currently, first-choice treatment, consisting of exposure-based psychotherapy, such as eye movement desensitization and reprocessing (EMDR), proves ineffective in half of PTSD-patients(1). Post-treatment sleep represents an unique time-window to increase therapeutic efficacy. Updated traumatic memories then get consolidated during sleep, solidifying the treatment effect(2). Recent advances in basic memory research show that memory consolidation can be enhanced by presenting reminder cues (sounds/scents that were linked to the memory at encoding) during subsequent sleep (targeted memory reactivation, (TMR))(3,4). Here, we apply TMR for the first time in PTSD patients to increase therapeutic effectiveness.

**Materials and Methods:** We tested whether re-administering auditory EMDR cues during post-EMDR sleep would increase therapeutic outcome in PTSD patients, using a 2X3 ANOVA (2 group (TMR > no-TMR) X 3 (time, pre > post 1 day > post 1 week)). This was measured as reduced subjective and physiological fear during script driven imagery (SDI) of the traumatic event during fMRI, as well as reduced overall PTSD symptom level. Besides, patients kept a daily sleep- and intrusion diary pre and post-intervention. Polysomnography was recorded overnight during post-EMDR sleep .

**Results:** A main effect of time on RSDI re-experiencing and avoidance was found across groups (p<0.001). A time x group interaction was demonstrated for avoidance, showing a larger reduction in avoidance after TMR when exposed to the traumatic memory the next day (pre > post-TMR x TMR > no TMR, p=0.024). No effects of TMR were found on the PTSD symptom level, sleep- or intrusion diary.

**Conclusions:** Results so far show a modest additive effect of TMR: Patients in the TMR group are less inclined to avoid when exposed to the traumatic memory after sleep. This effect depends on how often the memory is reactivated during sleep (trend-level). Since analysis of heartrate, fMRI-data and sleep/EEG-data are still ongoing, no final conclusions can be drawn regarding the additive effect of TMR on PTSD treatment. Findings do show that it is technically possible and safe to apply TMR in patients with PTSD, as as no increases in PTSD symptomatology were found.

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#### THE ASSOCIATION BETWEEN SCHOOL START TIMES, SCHOOL DAY SLEEP DURATION AND SOCIAL JETLAG AMONG NORWEGIAN HIGH SCHOOL STUDENTS. RESULTS FROM A LARGE-SCALE, CROSS-SECTIONAL STUDY

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**Introduction:** The present study aimed to explore the association between school start times, school day sleep duration, and social jetlag in a large-scale sample of Norwegian adolescents.

**Materials and methods:** A total of 4010 Norwegian high school students aged 16-17 years (mean age 16.4 years ± 0.5; 54% females) participated in a survey on sleep, school start time, and health. The survey included, among others, items from the Munich ChronoType Questionnaire (addresses sleep habits on schooldays and free days and can be used to calculate social jetlag), with additional items on wakefulness in bed for a detailed estimation of sleep duration. In the present study, we report data on school day sleep duration and social jetlag in relation to school start time. One-way ANOVAs were performed, with students categorized into five groups according to habitual school start time (earlier than 8.00, 8.00, 8.15, 8.30,

and later than 8.30). Significant overall effects were further investigated by Tukey HSD post-hoc tests. Regression analyses were performed for school day sleep duration with school start time as an independent, continuous parameter, both crude and adjusted for sex, circadian preference (measured by the short version of the Horne-Ostberg Morningness-Eveningness Questionnaire), and scores of anxiety and depression (measured by the General Anxiety Disorder-7 and Patient Health Questionnaire-9, respectively).

**Results:** Analyses showed overall differences in school day sleep duration in relation to school start time,  $F(4,3946)=10.911$ ,  $p<.001$ , with the later starting students generally obtaining more sleep than earlier starting students. Students starting at 8.30 slept 6:56 hours ( $\pm 1:22$ ), significantly longer than students starting at 8.15 (6:42 hours  $\pm 1:26$ ,  $p=.010$ ), at 8.00 (6:40 hours  $\pm 1:25$ ,  $p=.005$ ) and earlier than 8.00 (6:15 hours  $\pm 1:56$ ,  $p<.001$ ). Students starting later than 8.30 slept 7:03 hours  $\pm 1:20$  ( $p=.859$  compared to students starting at 8.30). Similarly, results showed overall differences in social jetlag according to school start time,  $F(4, 3946) = 18.111$ ,  $p<.001$ , with the later starting students generally having shorter social jetlag than the earlier starting students. Students starting school at 8.30 had a social jetlag of 2:34 hours  $\pm 1:03$ , significantly shorter than that in students starting at 8.00 (2:50  $\pm 1:12$ ,  $p<.001$ ) and earlier than 8.00 (3:02  $\pm 1:15$ ,  $p<.001$ ) and longer than that in students starting later than 8.30 (2:17 hours  $\pm 1:09$ ,  $p=.011$ ). Students starting at 8.15 had a social jetlag of 2:43  $\pm 1:04$  ( $p=.093$  compared to students starting at 8.30). In the crude regression analysis, school start time predicted 8% ( $p<.001$ ) of the variance in school day sleep duration. The association between sleep duration and school start remained significant when adjusted for sex, circadian preference, and anxiety- and depression scores.

**Conclusion:** Our findings indicate that school start time represents a key determinant for school day sleep duration and the degree of social jetlag among older adolescents.

#### THE ASSOCIATION BETWEEN SLEEP QUALITY AND ANXIETY IN POSTSECONDARY STUDENTS: A SYSTEMATIC REVIEW OF THE LITERATURE

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**Introduction:** Mental health conditions such as anxiety represent a growing health concern for students in institutions of higher education. Postsecondary students are a vulnerable population that is increasingly recognized to be at risk for both mental health problems and significant sleep problems. While it has been hypothesized that poor sleep quality may be a risk factor for developing anxiety, little is known about the frequency and severity of sleep problems and their association with anxiety within the postsecondary student population. The aim of this systematic review was to synthesize the best evidence on the association between sleep quality and anxiety in postsecondary students.

**Materials and Methods:** An experienced librarian developed systematic search strategies in four databases: MEDLINE, Embase, APA PsycInfo (through Ovid Technologies Inc.) and CINAHL, Cumulative Index to Nursing and Allied Health Literature (through EBSCOhost). Databases were searched from inception to September 2020. Random pairs of independent reviewers screened titles and abstracts for eligibility and critically appraised all eligible studies. We assessed the quality of studies using the Scottish Intercollegiate Guidelines Network (SIGN) criteria for cohort studies, and the Hoy tool for cross-sectional studies. One author extracted and synthesized the results from all of the low and moderate risk of bias studies. We synthesized our results by study design and population.

**Results:** Once duplicates were removed, a total of 3203 unique citations were screened. Fifty-one articles were eligible and critically appraised. Studies with low and moderate risk of bias were included in our final synthesis of which 24 were cross-sectional studies and four were cohort

studies. With the exception of one study, all cross-sectional studies reported a statistically significant association between poor sleep quality and anxiety. All four of the cohort studies found that students who reported poor sleep quality were more likely to develop future anxiety and students with anxiety were more likely to develop future poor sleep quality.

**Conclusions:** Poor sleep quality is associated with anxiety in post-secondary students. Due to the cross-sectional nature of most studies, we cannot determine the direction of this association. Future studies should focus on developing high-quality prospective cohort or longitudinal studies to help understand the impact and direction that this association has in postsecondary populations. This research has the potential to inform the development and design of mental health policies and programs that are created by postsecondary institutions to address the increasing rates of student mental health issues.

**Acknowledgements:** Canadian Institutes of Health Research (CIHR) Operating Grant: Knowledge synthesis: COVID-19 in Mental Health & Substance Use; University of Ontario Institute of Technology; Institute of Disability and Rehabilitation Research.

#### THE CROSS-SECTIONAL ASSOCIATION OF OBSTRUCTIVE SLEEP APNEA WITH FRAILTY STATUS IN HIGH NEED, HIGH RISK VETERANS

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**Introduction:** High-Need High-Risk (HNHR) represents a heterogeneous group of individuals with high prevalence of multimorbidity, disability and frailty leading to poor clinical outcomes and increase healthcare utilization. Frailty is characterized by a vulnerability to stressors resulting from loss of physiological reserve across multiple physiological systems. Frailty is associated with multimorbidity, disability and mortality. Obstructive Sleep Apnea (OSA) and frailty are common conditions in older adults and often coexist. Complicated OSA may lead to the development of frailty through a combination of hypertension, strokes, arrhythmias, chronic hypoxemia, metabolic syndrome, and cognitive impairment. The aim of this population-based study was to determine the cross-sectional association of OSA with frailty in High Need, High Risk Veterans.

**Materials and Methods:** Cross-sectional, population-based study of HNHR adults  $\geq 24$  years old, from seven Veterans Healthcare Administration hospitals in Florida and Puerto Rico identified through quarterly reports generated by the VHA using predictive modeling. OSA was ascertained based on the presence or absence of OSA diagnosis in VA electronic health records (CPR Vista) of specific International Classification of Diseases, 10<sup>th</sup> Revision (ICD-10) codes. Frailty was operationalized with a 31-item VA Frailty Index (VA-FI) generated as a proportion based on the number of items in several domains (morbidity, function, sensory loss, cognition/mood, and other variables) present. The VA-FI was divided into tertiles (0.0–0.267, 0.268–0.40, 0.40–0.8). After adjusting for age, gender, ethnicity, race, marital status, BMI, polypharmacy ( $\geq 5$  drugs), alcohol and substance abuse, we performed an ordinal logistic regression using odds ratios (OR) with 95% confidence intervals (CI) with obstructive sleep apnea as the independent variable and frailty as the dependent variable.

**Results:** A total of 10,916 HNHR Veterans were included in the analysis, mean age 68.45 (SD=11.79, range 24–103), 93.4% male, 74.7% Caucasian, 88.4% Non-Hispanic, mean VA-FI .34 (SD=.15, range .00–.81), mean BMI 29.87 (SD=6.97, range 11.12–100) and 4,825 (44.2%) had obstructive sleep apnea. After ordinal logistic regression, compared with the lowest, the upper tertile of VA-FI Scores was associated with obstructive sleep apnea, unadjusted OR 2.06, 95%CI: 1.92–2.21,  $p<0.001$  and after adjustment, OR 2.50, 95%CI: 2.30–2.72,  $p<0.001$ .

**Conclusions:** This study shows that in HNHR patients, OSA was cross-sectionally associated with frailty. Future prospective studies are needed in order to clarify the strength of this association. These findings suggest that earlier detection and treatment of OSA in HNHR Veterans may prevent or reverse frailty status.

**Acknowledgements:** This material is the result of work supported with resources and the use of facilities at the Miami VA Healthcare System GRECC.

## THE EFFECT OF NIGHT-TIME SLEEP DURATION ON HAND GRIP STRENGTH OF MIDDLE-AGED AND ELDERLY PATIENTS WITH COPD

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**Introduction:** The studies regarding the relationship between night-time sleep duration and hand grip strength (HGS) among chronic obstructive pulmonary disease (COPD) individuals were limited. Current study aimed to evaluate the impact of night-time sleep duration on HGS among COPD subjects.

**Materials and Methods:** Using data from the China Health and Retirement Longitudinal Study wave 3, a nationally population-based survey conducted in 2015, we performed a cross-sectional study to examine the relationship between sleep duration per night and HGS among middle-aged and older COPD patients. HGS was measured using dynamometers. The sleep duration per night was divided into 5 subgroups: <5h, 5–7h, 7h, 7–9h and >9h. Independent samples *t*-tests, chi-square tests, and Fisher's exact tests were used to determine differences in patients' sociodemographic characteristics and health-related information among 5 subgroups. Multivariate linear regression models were used to determine the association between sleep duration per night and HGS.

**Results:** Among men with COPD, shortest (<5h) sleep duration correlated with lower HGS. Among women with COPD, shortest (<5h) or longest sleep duration (>9h) showed significant association with weaker HGS.

**Conclusions:** Current study observed that night-time sleep duration has closely relationship with HGS among middle-aged and elderly with COPD. The results indicated that healthcare providers should focus on the influence of sleep duration on HGS among COPD patients. Future longitudinal studies are necessary to investigate the causal relationship between sleep duration and muscle strength measured by HGS in COPD individuals with different gender.

**Acknowledgements:** none

## THE IMPACT OF PAIN ON DEPRESSION-RELATED STATES MAY BE IMPROVED WITH GOOD SLEEP QUALITY IN PEOPLE WITH CHRONIC PAIN CONDITIONS: A MODERATION ANALYSIS

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**Introduction:** Individuals with chronic pain conditions experience high levels of co-existing sleep problems and depression. There are several predictors of depression among this population including pain severity, pain interference, and perception of illness. In addition, sleep problems have been identified as a risk factor for the initiation and maintenance of depression. Given that pain, sleep, and depression interrelate, this study sought to cross-sectionally examine the relationships between these health outcomes. This research also explored whether sleep quality moderated the relationship between pain and depression, among individuals with chronic pain.

**Materials and Methods:** A community-dwelling sample of 1059 individuals aged 18 and over, with self-reported chronic pain conditions completed a survey between February and March 2020 with prior consent. Participants completed validated measures relating to pain severity, pain interference, sleep quality, and depression outcomes, in addition to demographic indicators. *T*-tests were used to examine any differences in pain, sleep or depression scores based on demographic characteristics. Moderation analyses were used to examine whether sleep quality moderated the relationship between pain outcomes and depression, whilst controlling for age, gender, and pain condition.

**Results:** A total of 97% of participants were in range for 'poor sleep quality'. Less than half the sample scored within 'normal' range for depression (indicating no symptoms), and 63% scored within range for either 'mild', 'moderate' or 'severe' depression symptoms. Results from *t*-test analyses revealed no significant gender differences for pain or sleep outcomes, however men reported slightly higher depression scores than women ( $t(1057) = 2.19, p = 0.03, d = 0.23$ ).

A moderation analysis using pain interference as an independent variable

accounted for a significant amount of variance in depression;  $R^2 = 0.29, F(6, 1052) = 72.76, p < 0.001$ . Pain interference, sleep quality, gender, SEP, and chronic widespread pain were all independently significantly associated with depression. In addition, there was a significant interaction between pain interference and sleep quality;  $\Delta R^2 = .003, \Delta F(1, 1052) = 2.82, p = 0.028$ . Upon examining an interaction plot, we demonstrated there was a positive relationship between pain interference and depression meaning as pain interference scores increased, depression scores increased. This linear relationship was observed when sleep quality scores were one SD below the average;  $b = 0.66, 95\%CI [0.52, 0.80], t = 9.04, p < 0.001$ , when sleep quality scores were average;  $b = 0.77, 95\%CI [0.65, 0.89], t = 12.80, p < 0.001$ , and when sleep quality scores one SD above the average;  $b = 0.88, 95\%CI [0.72, 1.04], t = 10.60, p < 0.001$ . This suggested that good sleep quality attenuated the effect of pain interference on depression scores, and equally, poor sleep quality amplified the effect of pain on depression scores.

**Conclusions:** Sleep problems should be routinely screened for during consultations with chronic pain patients to improve care outcomes. Structured sleep interventions such as CBTI should be considered within combined treatment approaches for individuals with co-existing sleep problems and depression.

**Acknowledgements:** This study was funded by the Economic and Social Research Council, part of Innovation & Research UK.

## THE INTERPLAY BETWEEN SLEEP, COGNITION AND COPY NUMBER VARIATIONS

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**Introduction:** Sleep disturbances (e.g., insomnia, shorter sleep duration and lower sleep efficiency) are commonly reported in individuals with Neurodevelopmental Disorders (NDDs) and are suggested to exacerbate cognitive impairments in NDD populations, like executive functioning, which enables goal directed thought and behavior. Chromosomal microarray is recommended as first tier diagnostic testing for NDDs and pathogenic Copy Number Variants (CNVs; large deletions or duplications in the genome) are identified in 8 to 15% of individuals. However, the relationship between these CNVs, sleep problems and cognitive disturbances remains understudied. Investigating CNVs related to NDDs in a sample of clinically unaffected carriers provides an opportunity to disentangle the relationship between sleep and cognition.

**b** to examine if CNVs that confer risk for NDDs in a general population are related to sleep and executive functioning performance. We further investigated if the interaction between NDD CNVs and sleep are linked to executive functioning performance.

**Method:** We analyzed 424,278 individuals from the UKBiobank (Mean Age = 62, 56% females) with self-reported insomnia symptoms and sleep duration. Sleep duration and efficiency derived from actigraphy (N = 86,721) was available for a subset of individuals. Insomnia is reported as a binary variable (0 = no symptoms, 1 = symptoms occur often) and duration in minutes. Executive functioning performance was captured using the completion speed on a computerized trail making test (TMT, N = 96,224). Subtest TMTB removing motor speed from subtest TMTA was *z* scored. Microarray technology was used to identify 4668 carriers of deletions and duplications at 50 and 34 genomic loci respectively. CNVs were selected based on previously reported associations with NDDs. Separate general linear models controlling for age and sex were applied to examine associations between CNVs, sleep and executive functioning traits. FDR corrections accounted for multiple comparisons.

**Results:** Carriers of any NDD duplication or deletion compared to non-carriers did not differ significantly on sleep or cognitive measures. However, individual CNV analyses showed significant associations. Carriers of a 22q11.2 Proximal (LCRA) duplication, along with 16p13.3 and 22q11.2

Distal deletions self-reported sleeping more than non CNV carriers ( $\beta = 12.6-18.6$ ,  $p < 0.01$ ). However, carriers of a 10q11.21 deletion reported sleeping less ( $\beta = -30.0$ ,  $p = 0.007$ ). 22q11.2 Distal deletions ( $\beta = 48.7$ ,  $p < 0.003$ ) were associated with longer sleep duration reported with actigraphy, however no significant difference was found for shorter duration or sleep efficiency. 1q21.1TAR duplication carriers were 1.3 times more likely to experience insomnia symptoms (CI95%[1.1-1.5],  $p = 0.04$ ). Poorer performance on the trail making task was associated with a DMRT1 duplication and deletions of 1q21.1 Distal regions ( $z = 0.05-0.30$ ,  $P < 0.01$ ). Regressions revealed only shorter sleep duration ( $z = -0.03$ ) and lower sleep efficiency ( $z = -0.55$ ) measured by actigraphy was related to poorer trail making task performance ( $p = < 0.006$ ). No interactions between CNVs and sleep measures were observed to influence executive functioning performance.

**Conclusion:** Distinct NDD CNVs significantly decrease cognitive functioning, while significantly influencing physiological and self-reported sleep in both directions. These results provide further evidence of the complex relationship between sleep and cognitive abilities. How these findings fit within a clinical context and existing literature of sleep genetics will be discussed.

**Acknowledgements:** FRQS, Brain Canada, ACAR

## Parasomnia

### DISORDERS OF AROUSAL IN ELDERLY: LEARNING FROM CLINICAL PRACTICE

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**Introduction:** Disorders of Arousal (DoA) are behaviors occurring during an incomplete arousal from non-rapid eye movement (NREM) sleep, including confusional arousals (CA), sleepwalking (SW) and sleep terrors (ST). DoA are common and benign sleep disorder of the childhood. In the elderly DoA are often drug-induced or comorbid with other sleep disorders (i.e., sleep breathing or Parasomnia Overlap Disorders). In the middle-aged patients it is of relevance to distinguish DoA from other nocturnal motor behaviors with certainty, in particular from REM sleep behavior disorder (RBD) which is linked to alpha-synucleinopathies. Even though DoA require an accurate diagnosis in the elderly, they have seldom been investigated. We report 5 cases of DoA in older patients, aiming at describing the clinical and video-polysomnographic features in this age group.

**Materials and Methods:** 5 consecutive elderly patients (4 males, 1 female), complaining of nocturnal motor behaviors, underwent a clinical interview and a 24-48h Video-Polysomnography (VPSG). Two patients repeated 48h VPSG at 6 months follow-up.

**Results:** Patients were 65 - 72 years old at the time of our examination and nocturnal episodes had started when they were 10 - 60 years old. Three patients complained of diurnal consequences (excessive daytime sleepiness, fatigue); one of them referred dangerous behaviors. Three patients had DoA positive family history and among them one suffered from Parkinson's Disease which had onset 38-years after the nocturnal episodes' appearance. The events occurred mainly in the first part of the night, with a variable frequency throughout the years. The episodes description by eyewitness began with the patients abruptly raising the head or trunk and sitting in bed and included vocalizations (screaming, speaking), gesturing and, in only one patient, sleepwalking. During the episodes all patients seemed confused and when questioned were not immediately fully alert and rarely reported any dream-like content. VPSG at the baseline detected 25 DoA episodes with semeiological features consistent with 21 CA and 4 ST. VPSG during the follow-up documented 3 CA and 1 ST episodes. All episodes arose from NREM sleep; during REM sleep a physiological muscle atonia was recorded. After the diagnosis one patient refused any medications; two patients, one treated with Trazodone 75 mg while another with Clonazepam 1 mg/nightly, reported no significant clinical changes. Two

patients, respectively treated with Melatonin 2 mg and Clonazepam 1 mg at bedtime, reported a reduction in frequency of motor behaviors.

**Conclusions:** DoA may arise or persist with fluctuating trend in the elderly presenting with motor manifestations analogous to those described in younger subjects. A detailed clinical interview and examination together with the support of VPSG recording are required to assess an accurate DoA diagnosis in elderly subjects. A correct diagnosis distinguishing DoA from RBD is particularly relevant for the disease's prognosis.

**Acknowledgements:** The study has no financial support.

### EEG ACTIVATION IN SIMPLE AND COMPLEX EPISODES OF DISORDERS OF AROUSAL: A SPECTRAL ANALYSIS STUDY

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**Introduction:** Disorders of Arousal (DoA) are NREM parasomnias characterized by the admixture of both deep sleep and wake EEG activity. Recently, three different motor patterns of increasing complexity have been described in DoA, ranging from simple arousal movements (SAMs) to more elaborate behaviours including rising arousal movements (RAMs) and complex arousal movements (CAMs) which involve sleepwalking. The aim of this work is to characterize, by means of a spectral EEG analysis, the EEG activity preceding DoA episodes in comparison to a preceding baseline stable period of deep sleep. In addition, we compare the EEG preceding the more complex episodes to the simpler ones, in order to analyse eventual differences in the EEG activity preceding the two types of episodes.

**Materials and Methods:** We analysed 104 consecutive video-polysomnographic recordings of DoA patients, identifying and classifying all DoA episodes. For each episode we computed the spectral density for 6 frequency ranges (delta, theta, alpha, sigma, beta, gamma), evaluating a time window of 5 seconds before each episode and a time frame of 60 seconds from 2 to 3 minutes before the episodes (baseline stable N3 sleep). The software MATLAB was used for spectral analysis.

**Results:** EEG analysis comprised 363 DoA episodes. Spectral analysis before the episodes showed an absolute significant increase over the whole scalp in all frequency bands with the exception of sigma, which showed a significant decrease. In normalized maps, the increase was relatively higher over the central/anterior areas in comparison to the posterior ones for slow frequency bands. A relative increase over the central/anterior areas was also detected for rapid frequency bands. When comparing SAMs with RAMs and CAMs, no significant differences emerged from spectral analysis.

**Conclusions:** Our results indicate a dissociation between antero-posterior areas for slow frequency bands, with persistence of deep sleep rhythms over the anterior ones, in accordance with literature data. In addition, the coexistence of rapid rhythms (more typical of wakefulness) over the central/anterior areas suggests an alteration of local sleep mechanisms, possibly responsible for the motor behaviours. The simpler and the more complex episodes are preceded by a similar EEG activation, confirming that SAMs correspond to the smaller fragments of the longer and more elaborate episodes, both sharing a similar pathophysiological mechanism.

**Acknowledgements:** none.

### EFFECTS OF SLEEP DEPRIVATION ON SLEEPWALKING: ROLE OF SLEEPWALKERS' CLINICAL CHARACTERISTICS

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**Introduction:** Several studies have shown that adult sleepwalkers experience more frequent and complex forms of sleepwalking during recovery sleep following sleep deprivation than during normal polysomnographic (PSG) recordings. While this work suggests that sleep deprivation could be used to establish a PSG-based diagnosis of sleepwalking in predisposed patients, samples sizes have been too limited to delineate patient characteristics of those who experience greater episode frequency following sleep deprivation. The objectives of the present study were to retrospectively analyze the effects of sleep deprivation in a large cohort of adult sleepwalkers and to study patients' clinical characteristics that could distinguish those who respond to the effects of sleep deprivation from those who do not. Based on clinical reports, we expected sleep deprivation to facilitate the occurrence of behavioral episodes in patients' recovery sleep with greater effects observed in sleepwalkers with a childhood onset of the disorder as well as those with a family history of sleepwalking.

**Materials and Methods:** 124 adults (45 men, 79 women) with a mean age of 32 years and an ICDSD-based diagnosis of sleepwalking underwent one night of continuous PSG recording in the laboratory (baseline recording). They returned to the laboratory the next evening for a standard sleep deprivation protocol and spent the remainder of the night in their room under video supervision. Recovery sleep began the next morning after 21 to 28 hours of continuous wakefulness.

**Results:** A greater number of sleepwalking episodes were recorded during recovery sleep (227) than at baseline (143). Seventy-eight of the 124 patients (63%) experienced at least one episode during recovery sleep compared to 60 patients (48%) at baseline ( $\chi^2_1=5.29$ ,  $P=0.02$ ). A  $2 \times 2$ , group (childhood-onset, adulthood-onset)  $\times$  night (baseline, recovery) ANOVA showed that patients with childhood versus adulthood onset of the disorder did not differ significantly in their pre- to post-sleep deprivation increase in sleepwalking episodes ( $F_{1,122}=13.22$ ,  $P<0.01$ ). Similarly, a  $2 \times 2$ , group (familial history, no familial history)  $\times$  night (baseline, recovery) ANOVA showed that patients both with and without a family history for the disorder showed the same level of pre- to post-sleep deprivation increases in sleepwalking ( $F_{1,122}=18.06$ ,  $P<0.01$ ).

**Conclusions:** This study indicates that sleep deprivation is effective in facilitating the occurrence of behavioral episodes in adult sleepwalkers with varying clinical histories. However, the costs and benefits of this protocol need to be considered given that over a third of sleepwalkers did not experience an episode during their recovery sleep. Furthermore, extended sleep deprivation can be difficult on some patients and requires added lab resources. One alternative is the presentation of auditory stimuli during sleepwalkers' N3 sleep, a method previously shown to be effective in triggering sleepwalking episodes in predisposed patients.

**Acknowledgements:** This research was supported by the Canadian Institutes of Health Research (grant # MOP 49515) to AZ and JM.

## INFREQUENT "PARASOMNIAS AND PARASOMNIAS-LIKE" EVENTS. DIAGNOSTIC AND THERAPEUTIC MANAGEMENT

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**Introduction:** Parasomnias are experiences, behaviors or autonomic responses that arise from sleep, they are classified according to the sleep phase they are related to. There are other events that could present in our office that we should be aware of. We will present cases that exemplify such conditions.

**Case Report/Case History:** 1. A 51-year-old woman, she is at follow up for insomnia that doesn't respond to the initial treatment, it's initiated zolpidem 5 mg at bedtime and later augmented to 10 mg. At follow up, she complained of a 5 kg weight gain, waking up to find misplaced dishes, the fire of the kitchen was on. A sleep eating disorder was diagnosed, and zolpidem suspended. There were no new reports of this episodes.

2. A 46-year-old man, without comorbidities, come to our consult as a part of an investigations for a judicial case of sexual harassment. He is a security worker, with 12 hours night shifts since more than ten years ago, and he

sleeps 8 hours during the day, non-restorative sleep. The PSG shows an AHI of 26.6, ODI 31.4 T88% 8.3%, REM sleep behavior disorder nor other parasomnias were observed during the test. We make the diagnosis of obstructive sleep apnea and sexsomnia. CPAP therapy was initiated and there are no new reports of sexsomnia episodes, the patients remain pending on ruling of court.

3. A 74-year-old man, consults for episodes of abrupt awakening at night with an intense sensation of fear, tachycardia, these episodes occur about 3-5 times a week, for the last 30 years, after a traumatic event. The PSG is normal, but several episodes like the ones told by the patients were registered. Clinical diagnosis of nocturnal panic attacks is made and referred to the psychiatrist who initiated pharmacological treatment with flurazepam, the frequency of the episodes has decreased over the follow up months.

4. A 50 years old man, works as a jailer, with complaints of maintenance insomnia related to episodes of rude awakening with tachycardia. Nocturnal PSG showed 12 episodes similar to those the patient described. Psychiatric treatment with doxepin and paroxetine were started with improvement of nocturnal symptoms.

5. A 63-year-old woman, consults for nocturnal episodes of uncomfortable sensations on the clitoris, described like electric, pinching sensations that irradiate to the thighs, the sensation diminishes standing up and walking. Clinical diagnosis of possible persistent genital arousal disorder was made, the diagnosis was explained to the patient, an EMG test and blood samples were requested but the patients refuse all interventions.

**Conclusion:** The cases described above have very low prevalence, these disorders should be kept in mind and be part of the differential diagnosis in our consult, that way a correct diagnosis and treatment is made which could have major implications in our patients life.

## LOW SPECIFICITY OF SCREENING QUESTIONNAIRES FOR REM SLEEP BEHAVIOR DISORDER

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**Introduction:** Screening questionnaires for REM sleep behavior disorder (RBD) have been validated with good sensibility and sensitivity but included a large number of diagnosed RBD patients, who were likely aware of typical symptoms. Subsequent studies reported limited usefulness of these questionnaires outside the context of validation studies. Aim of this study was to assess the diagnostic value of RBD screening questionnaires in a large sample of patients referred to a sleep center.

**Methods:** This prospective study was conducted in Innsbruck, Austria and Barcelona, Spain. From January 2017, 200 consecutive patients referred for the first time for evaluation of any type of sleep disorder to each center were included. Patients filled consecutively by themselves and prior to the routine clinical interview the following questionnaires (RBD screening questionnaire (RBDSQ), the RBD single question (RBD1Q) and the Innsbruck RBD inventory). Questionnaires were presented in a random order and all possible random orders were equally represented. All patients positive for at least one RBD questionnaire were invited to undergo video-poly-somnography (V-PSG) with the SINBAR montage, whereas patients negative for all three questionnaires underwent a V-PSG whenever clinically indicated and the VPSG data was also included in the analysis. RBD was diagnosed based on V-PSG according to the International Classification of Sleep Disorders (3<sup>rd</sup> edition). Sensitivity, specificity, accuracy, negative and positive predictive value of the RBD questionnaires were calculated.

**Results:** One patient from each center refused to participate, so that data are available for 398 patients. Mean age was  $50.4 \pm 17.1$  years, 54.8% were male. In the whole sample, 59.5% (N=237) were positive for at least one questionnaire. Two-hundred-ten of them (88.6%) underwent V-PSG; RBD was diagnosed in 28/210 (13.3%). Of the 161 patients negative for all RBD questionnaires, 92 underwent V-PSG for other reasons; one (1.1%) was diagnosed with RBD. Sensitivity, specificity and accuracy were: 79.3%, 47.3% and 50.3% for the RBDSQ; 75.9%, 66.1% and 67% for the RBD1Q; 89.7%, 54.6% and 57.9% for the Innsbruck RBD inventory. Combining the three questionnaires, sensitivity was 96.6%, specificity 33.3%, accuracy 39.4%. Although negative predictive value was 98.9%, the positive predictive value was only 13.3%. Of note, sleep experts identified RBD through clinical interview with 72.4% sensitivity, 96.3% specificity and 94.2% accuracy.

**Conclusions:** Specificity and positive predictive value of the RBD screening questionnaires were low to very low in this cohort, underlying the need of a V-PSG for RBD diagnosis and that questionnaires should not be used to select “probable RBD” patients to be included in studies.

**Acknowledgements:** We are thankful to Mr. Heinz Hackner for accurate V-PSG scoring and technical support.

#### PAROXYSMAL AROUSALS IN SLEEP-RELATED HYPERMOTOR EPILEPSY (SHE) AND SIMPLE AROUSAL MOVEMENTS IN DISORDERS OF AROUSAL (DOA): SEMIOLOGICAL AND CLINICAL FEATURES MAKE A DIFFERENCE

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**Introduction:** Sleep-related hypermotor epilepsy (SHE) is a focal epilepsy characterized by seizures occurring mostly during sleep, ranging from brief paroxysmal arousals (PAs) to hyperkinetic seizures and ambulatory behaviors. PAs are brief and stereotypic seizures representing the beginning of a major seizure. A correct PAs characterization is clinically relevant for many reasons, although the most recent Consensus Conference has underscored that if the captured episodes are minor motor events or PAs, the clinical diagnosis may be unreliable. PAs recognition could be useful for SHE diagnosis when video-polysomnography (VPSG) does not allow recording major seizures, and a correct identification of PAs should be important to define the frequency of SHE seizures and targeting of therapy. Furthermore, PAs need to be distinguished from brief episodes typical of disorders of arousal (DOAs), a group of non-rapid eye movement (NREM) parasomnias that require totally different management in comparison with SHE. DOAs, which include Sleepwalking, Sleep terrors and Confusional arousals, are characterized by recurrent episodes of incomplete awakening from sleep with abnormal sleep-related complex movements and behaviors and partial to complete amnesia for the episodes. A recent VPSG study showed that DOAs are characterized by events of increasing intensity and complexity with briefer episodes appearing in addition to major ones. These episodes, characterized by head, head and limbs, or head and trunk movements, have been called simple arousal movements (SAMs). In these cases, distinguishing PAs from SAMs remains difficult even for epilepsy and sleep experts. We performed a characterization of PAs and SAMs to identify VPSG features that can contribute to the diagnosis of SHE or DOAs.

**Materials and Methods:** Fifteen SHE, 30 DOAs adult patients, and 15 healthy subjects underwent full-night VPSG. Two neurologist experts in sleep disorders and epilepsy classified all the sleep-related movements and episodes recorded. For each PAs and SAMs, sleep stage at onset, duration, limb involvement, progression, and semiology have been identified.

**Results:** A total of 121 PAs were recorded, emerging mostly during stage 1-2 NREM sleep (median duration: 5 seconds). At the beginning, 78 (64%) PAs were characterized by hyperkinetic movements and 43 (36%) by tonic/dystonic postures, involving more than three non-contiguous or all body parts. The standard was a constant progression of movements during PAs without any motor arrests. In DOAs patients a total of 140 SAMs were recorded (median duration: 12 seconds) mostly emerging during stage 3 NREM sleep. In SAMs, we did not observe any tonic/dystonic or hypermotor patterns or stereotypy; motor arrest was present over the course of about half of the episodes. In comparison with both DOA and healthy subjects, SHE patients showed a higher number of sleep-related movements per night and a reduction of sleep efficiency.

**Conclusions:** PAs and SAMs present different semiological and clinical features. Their recognition could be useful to drive the diagnosis when major episodes are not recorded during VPSG in patients with a clear clinical history of SHE or DOAs.

#### SLEEP TALKING AS DREAM ENACTING BEHAVIOR: A NEW PERSPECTIVE TO STUDY COGNITION DURING SLEEP

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**Introduction:** Sleep Talking (ST) is characterized by the production of unaware linguistic vocalizations (STs) during sleep. On the one hand, ST could allow researchers the direct observation of cognitive processes during sleep. Interestingly, recent findings reported the replay of verbal material learned during an episode of ST. This phenomenon was considered as an “overt replay” of high cognitive processes and may help sleep-related memory consolidation. However, data on this issue are still lacking, and the role of ST in memory consolidation is poorly understood.

On the other hand, the vocal activations also showed the incorporations of waking experiences. Besides, some studies reported a high concordance between vocalizations and oneiric contents (Dream Enactment Behavior), providing a potential access to mental activity during sleep. It is known that the waking-life experiences could be incorporated according to the day-residue effect or dream-lag effect. Therefore, the incorporations of the verbal task or daily experiences could represent a reprocessing of semantic and/or autobiographical memories. Overall, the STs might permit the direct observation of these cognitive processes ongoing.

Our explorative study had two independent aims:

1. The investigation of autobiographical incorporations into dream reports and STs. According to the “continuity hypothesis,” the incorporations into STs could represent “day-residue effect” or “the dream-lag effect”;
2. The assessment of ST's impact on memory consolidation, according to two alternative hypotheses: (A) the replay of verbal content on STs increases the sleep-dependent gain (defined as the difference between morning and evening recall) in the ST group, or (B) the sleep fragmentation due to STs is associated to a decreased gain.

**Materials and Methods:** We recruited N=28 participants with ST (F=23; age mean: 23.71) and N=27 controls (F=21; age mean: 24.44). For eight days, participants performed home monitoring. They were instructed to complete daily logs (for seven evenings), sleep logs, and record their oneiric contents every morning. On the 8th day, a word-pair task was administered. ST subjects audio-recorded their vocal activations.

**Results:** Results showed a higher gain in the control than ST group ( $t=2.103$ ;  $p=0.04$ ), but no significant correlation was observed between the number of STs and gain. Notably, one ST subject produced a word semantically related to the task and revealed an increase in the gain. The incorporations of wake-experiences in dream content revealed a dream lag effect of personally significant events in both groups ( $F=3.510$ ;  $p=0.04$ ). There was no correspondence between the daily activities, dream content, and STs, although some semantic correspondences were observed between STs and dream recalls ( $N=4$ ).

**Conclusions:** In conclusion, our results supported the idea that STs could represent the overt expression of semantic memories consolidation. The worst performance of the ST group seems coherent with the hypothesis that sleep fragmentation due to STs is associated with a decreased sleep-dependent gain, although a polysomnographic assessment is needed.

Consistently with literature, STs represent a window towards the dream activity, and multiple awaking protocols immediately after STs could provide more information about correspondence between STs and dream reports and the reprocessing of autobiographical memories.

#### THE AROUSAL DISORDERS QUESTIONNAIRE: A NEW AND EFFECTIVE SCREENING TOOL

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**Introduction:** Arousal Disorders (DoA) include Confusional Arousals, Sleepwalking and Sleep Terrors and are often characterized by abnormal sleep-related complex behaviors sometimes resulting in sleep injuries, sleep disruption and adverse health and psychosocial effects. These consequences can affect both patients and bedpartners. When particularly frequent and violent, DoA may be mistaken for seizures, especially Sleep-related Hypermotor Epilepsy (SHE), which is a rare form of focal epilepsy characterized by brief and stereotyped seizures occurring predominantly during sleep. A correct diagnosis of sleep-related motor behaviors in adults is essential not only to set up a correct therapy and to prevent sleep-related injuries and/or relevant daytime consequences but also for the prognosis. DoA diagnosis is mainly clinical but no validated questionnaires exist for DoA screening according to the criteria of the International Classification of Sleep Disorders, Third Edition. Recently our group proposed the Arousal Disorders Questionnaire (ADQ) as a new diagnostic tool for DoA diagnosis. The objective of this study was to evaluate the diagnostic accuracy of the ADQ in a sleep and epilepsy center.

**Materials and Methods:** One interviewer blinded to clinical and video-polysomnographic (VPSG) data administered the ADQ to 150 patients consecutively admitted to our Sleep and Epilepsy Centers. The final diagnosis, according to VPSG recordings of at least one major episode, classified patients either with DoA (DoA group) or with other sleep-related motor behaviors confounding for DoA (nDoA group). Parental or another observer's input was collected for 93 subjects to improve the accuracy of lifelong history.

**Results:** 47 patients (31%) composed the DoA group; 56 patients with Rem Sleep Behaviour Disorder (RBD), 39 with SHE, six with night eating syndrome, and two with drug-induced DoA composed the nDoA group. The ADQ had a sensitivity of 72% (95% CI: 60–82) and a specificity of 96% (95% CI: 89–98) for DoA diagnosis; excluding the items regarding consciousness and episode recall, sensitivity was 83% (95% CI: 71–90) and specificity 93% (95% CI: 86–97)

**Conclusions:** The ADQ showed good accuracy in screening patients with DoA in a sleep and epilepsy center setting. Diagnostic criteria related to cognition and episode recall reduced ADQ sensitivity, therefore a better definition of these criteria is required, especially in adults.

## THE PHENOMENOLOGY OF PARASOMNIAS BASED ON INTERNET DATABASES

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**Introduction:** Parasomnias deeply impact individuals' quality of life and may cause injuries. We analyzed videos on sleep movement and behavioral episodes for clarifying if there are group phenotypes, allowing identifying risk-types for preventing sleep-related injuries.

**Materials and methods:** We used internet video databases such as YouTube and other public video stores and searched for keywords such as “sleepwalking”, “sleep eating” “sleep sex”, “somnambulism”, and “aggression in sleep” in several languages (English, Portuguese, French, German, Hungarian and Russian). The videos provided no information on the history or diagnosis of the presented individuals. We could characterize sleep-related phenomena and behaviors, by a self-made questionnaire of 10 questions. The data was estimated by logistic regression analysis, associating sleep behavior, gender, and age groups (0–16, 18–50, and 50+ years) by STATA statistical package.

**Results:** Two hundred twenty-four videos (102 women and 122 male) were estimated by Chi-square test and logistic regression at a 95% confidence interval, ( $P < 0.05$ ). The odds of sleepwalking (including those resulting in dangerous behavior) were significantly higher in adults, children, and adolescents compared to the elderly. Women's odds were double compared to the children for complex activities during sleepwalking carrying risk of injury. Sleep talking (uttering full sentences) was ~3 times more likely in adults than in the children group. Women and girls were most likely to manifest emotional behaviors (be scared, crying, or

laughing) compared to the rest of the groups. The risk of violent movements in bed was significantly more often in elderly males.

**Conclusion:** Our results have allowed identifying sleep behavior types across age and gender groups. The existence of sleep-activity phenotypes (if confirmed by further studies on larger and representative patient populations) might help predict types of injuries thus providing possibilities to protect those affected. Based on our study, elderly males with sleep-related activities (possibly REM sleep behavior disorder patients) may need the protection of their bed partner and themselves by softening sleeping facilities; sleepwalking adults and children need window and door-grates, no fragile or sharp surfaces in the bedroom. Sleepwalking women need to be protected against easy (unaware) use of the kitchen, and electric devices during sleep. Our approach may allow considering personality, and brain-network backgrounds of parasomnias.

**Acknowledgment:** Stipendium Hungaricum

## Pediatric

### ACADEMIC PERFORMANCE IN SCHOOL-AGE CHILDREN: ASSOCIATION WITH SLEEP DURATION, BUT NOT STUDY TIME

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**Introduction:** In Singapore, Confucian beliefs in hard work and endurance for academic excellence are prevalent. Consequently, school-age children spend prolonged hours on academically related activities, leaving little time for sleep. This study aimed to characterise sleep duration and time use on weekdays and weekends in school-age children in Singapore, and to investigate their associations with academic performance.

**Materials and Methods:** In an online survey, 155 parents with a school-age child aged 7–12 years in Singapore reported the amount of time their child slept and spent on various activities (e.g. study) on weekdays and weekends, as well as their child's academic performance. Paired-sample *t* tests were used to determine differences in sleep durations and time use between weekdays and weekends. Multiple regression analyses were conducted to examine the association of time spent on each activity with sleep duration after controlling for children's age, gender, body mass index, and monthly household income.

**Results:** Sleep duration increased from 8.25 h on weekdays to 9.42 h on weekends ( $p < .001$ ). Relative to weekdays, school-age children spent more time on face-to-face interaction with family and friends, social media, gaming, watching TV / videos, and sports, while time spent on school classes and co- / extra-curricular activities decreased ( $ps < .001$ ). On both weekdays and weekends, children spent 2.22–2.25 h studying outside of school hours (homework and tuition;  $p = .79$ ). Critically, better academic performance was significantly associated with longer sleep duration on weekdays ( $p = .03$ ), but not time spent on studying or other activities ( $p > .06$ ), after controlling for the contribution of demographic variables.

**Conclusions:** These data collected in Singapore – a hard-driving society under strong influence of Confucian values that emphasise hard work as the key to success, refute the idea that longer study hours are required for better academic performance among school-age children. Instead, our findings support the important role of sleep in optimising cognitive functions and learning.

**Acknowledgements:** This study was supported by the start-up grant from the National University of Singapore awarded to Dr Lo.

### ACCELEROMETER-MEASURED PHYSICAL ACTIVITY, SEDENTARY BEHAVIOUR, AND SLEEP IN CHILDREN WITH CEREBRAL PALSY AND THEIR ADHERENCE TO THE 24-HOUR ACTIVITY GUIDELINES

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**Introduction:** Physical activity (PA), sedentary behaviour (SB), and sleep, collectively known as activity behaviours, are modifiable lifestyle factors affecting child health and wellbeing. Children with Cerebral Palsy (CP), the most common physical disability in childhood, tend to have inactive lifestyles (i.e. reduced PA levels, and high SB levels) and are more likely to experience sleep problems compared to their typically developing peers. To promote healthy lifestyle behaviours throughout the entire 24-hour period, we recently developed a clinical practice guide containing 24-hour activity guidelines for children with CP. This study aimed to: 1) measure and describe the 24-hour activities (i.e. PA, SB, and sleep); and 2) examine adherence to the 24-hour activity guidelines among children with CP using actigraphy.

**Materials and Methods:** The study population consisted of ambulatory children with CP classified at Gross Motor Function Classification System (GMFCS) levels I–III, and between the age of 3–12 years. Children's 24-hour activities (i.e. PA, SB, and sleep) were recorded over seven consecutive days using hip- and wrist-worn ActiGraph wGT3X-BT accelerometers.

**Results:** In total, 362 days and 340 nights from 54 children with CP (44% girls; median age, 6.5 years; GMFCS distribution: level I, n=30; level II, n=15; level III, n=9) were included in the analyses. Average daily wear time was 746.2 ± 48.9 min, of which children spent on average 33.8% in light PA (251.6 ± 58.7 min/day), 5.2% in moderate-to-vigorous PA (38.5 ± 20.1 min/day), and the remaining 61.1% being sedentary (456.1 ± 80.4 min/day). PA decreased while SB increased with increasing GMFCS level. Although preschool aged children (3–5y, 11.4 ± 0.6h) spent significantly more hours in bed compared to school-aged children (6–12y, 10.7 ± 0.7h), both groups showed a similar total sleep time (9.3 ± 0.7h and 8.9 ± 0.9h, respectively). The majority of all children (78.4%) had a sleep onset latency <30 minutes, and the average sleep efficiency of the total study sample was 82.4% ± 6.0%. In total, 13% of all children met the PA recommendations, and 35% met the age-appropriate sleep duration recommendation. The proportion of children meeting the combined 24-hour activity guidelines for PA and sleep was low (5.9%), especially in preschool aged children and in those classified at GMFCS level III (both 0%).

**Conclusions:** Our findings contribute to our understanding of the 24-hour activities of ambulatory children with CP. The observed low 24-hour activity guideline adherence rates underscore the importance of considering the entire continuum of movement behaviours (i.e. PA, SB, and sleep) in the care of children with CP, in efforts to promote healthy lifestyle behaviours and prevent negative health outcomes.

**Acknowledgements:** This study was kindly supported by a grant from JFK Kinderfonds and Kinderrevalidatiefonds Adriaanstichting, foundations aimed at improving the quality of life of children and adolescents with physical disabilities in The Netherlands. The authors are grateful to each of the children and their parents for participation in this study. We thank the healthcare professionals from the rehabilitation settings for their kind assistance in participant recruitment.

#### A COMPARISON OF SIDS/SUID BEHAVIORAL RISK AMONG USERS OF A RESPONSIVE BASSINET

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**Introduction:** Each year, approximately 3,500 infants die of Sudden Infant Death Syndrome (SIDS) or Sudden Unexpected Infant Death (SUID). SIDS/SUID deaths usually occur in the infant's sleep area, with about 40% of the deaths attributed to SIDS, another 40% to unknown causes, and about 20% due to accidental suffocation and strangulation in bed. Studies have identified three primary risk factors associated with SIDS/SUID deaths: prone sleep positioning, sharing a sleep surface with a parent or caregiver, and the presence of soft bedding.

The American Academy of Pediatrics recommends the promotion of safe sleep environments to reduce the risk of SIDS/SUID. However, since 2000 there has been no significant reduction in annual SIDS/SUID incidence in the U.S., suggesting that greater intervention is needed beyond educational campaigns. Additionally, systematic review has found that even when

parents are aware of the risk of bedsharing, many choose to co-sleep with their infant to improve sleep, comforting, and bonding.

**Materials and Methods:** SNOO is a responsive bassinet that uses motion, white noise, and swaddling to calm infants and improve sleep duration and quality from birth through six months of age. SNOO also has an anchored swaddling apparatus that secures the baby on its back and prevents rolling to an unsafe, non-supine position.

This was a single-arm observational study for SNOO in U.S. subjects, 0 to 6 months of age, including 1,012 SNOO users. Non-supine sleep, bedsharing and use of soft bedding were self-reported by caregivers in an online survey among individuals, ages 18+ years of age, who purchased or rented a SNOO.

The prevalence of unsafe sleep practices was compared between SNOO users and historical rates reported in the lowest risk available cohort (non-Hispanic White mothers) from the Centers for Disease Control and Prevention (CDC) Pregnancy Risk Assessment Monitoring System (PRAMS). For each endpoint (non-supine sleep, bedsharing, and use of soft bedding), an Objective Performance Criteria (OPC) was determined by the lower bound of the 95% confidence interval, in accordance with guidelines established by the FDA (*FDA Guidance: "Design Considerations for Pivotal Clinical Investigations for Medical Devices"* December 4, 2013).

**Results:** Surveyed SNOO users were found to be significantly less likely to engage in SIDS/SUIDS risk behaviors across the below three domains when compared to the lowest risk available cohort 2009–2015 PRAMS respondents:

- Non-supine sleep: 1.3% SNOO versus 15.3% OPC
- Any bedsharing: 29.4% SNOO versus 50.9% OPC
- Any soft bedding: 10.8% SNOO versus 31.6% OPC

**Conclusions:** The results from this observational study support the conclusion that SNOO users are significantly less likely to engage in risky sleep behaviors. Although the "Safe to Sleep" campaign was widely disseminated, infant caregivers continue to engage in unsafe sleeping practices. New tools may help promote adherence to safe sleep practices by avoiding non-supine positioning, bedsharing, and the use of soft bedding.

**Acknowledgements:** This study received financial and administrative support from Happiest Baby, Inc.

#### ACTIVE INVOLVEMENT OF CHILDREN IN ADHD RANDOMIZED CONTROL TRIALS ASSESSING SLEEP

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**Introduction:** Sleep disturbances are an intrinsic characteristic of ADHD, and interventions to treat ADHD can alleviate or aggravate intrinsic sleep problems. The treated subjects' voice, here the pediatric patient, may or may not be captured during their treatment. The goals of this secondary analysis are to 1) determine if children were involved in research investigating interventions for ADHD and sleep, 2) and to what degree their reporting was acknowledged.

**Materials and Methods:** We performed a secondary analysis of a dataset from a previous scoping literature review (DOI 10.17605/OSF.IO/VWRPT) which screened 2265 studies to identify 71 interventional ADHD RCTs that measured sleep as a primary or secondary outcome. In this analysis we reviewed the 52/71 RCTs carried out in pediatric populations. The research questions were: 1) how was the child involved in the consenting process, and 2) was the child directly involved in the tools used to measure ADHD, sleep, miscellaneous outcomes, and reporting of adverse events.

**Results:** A total of 6488 subjects aged 2–17 (mean= 9.5) were enrolled between the years 1995–2020. 32,11,9 studies targeted ADHD, sleep, and ADHD and sleep, respectively. 3/52 RCTs did not mention consent or assent (age range: 6–12, mean=9.5) and 5 did not specify the participant (5–14, m=9.8). The children and parents gave consent in 6 RCTs (5–15, m=10.2), 30 RCTs had the children give assent with parental consent (5–17, m=9.6),

only the parents gave consent in 8 RCTS (2–12,  $m=8.5$ ), respectively. The children were not included in the reporting of ADHD, sleep, or miscellaneous outcomes in 30/52 RCTS (3–15,  $m=9.4$ ). When participating, children were more frequently involved in the reporting of nighttime outcomes ( $n=12$ ; 2–17,  $m=10.0$ ) compared to daytime outcomes ( $n=5$ ; 5–13,  $m=8.6$ ) and 1 RCT had children reporting both (13–17,  $m=14.5$ ). Children were involved in the reporting of adverse events in 15/52 RCTS (2–17,  $m=12.4$ ).

**Conclusions:** We conclude that tools used to measure outcomes in ADHD RCTS sparsely involved the input of children. These findings suggest not only the need for a consensus approach to obtaining consent/assent in pediatric ADHD RCTS, but also the involvement of children can be improved through incorporating more child friendly tools in order to comply with the United Nations Convention on the Rights of the Child.

**Acknowledgements:** BC Children's Hospital Foundation and Research Institute

### ARE SOME CHILDREN GENETICALLY PREDISPOSED TO POOR SLEEP? A POLYGENIC RISK STUDY

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**Introduction:** Insomnia is considered to be driven by learned maladaptive sleep habits which can be unlearned with cognitive behavioral therapy. Twin studies, however, show that sleep traits are moderately heritable: 40% for insomnia symptoms and 46% for sleep duration. Genome-wide association studies (GWAS) have identified genetic variants involved in insomnia and sleep duration in adults, but it is unknown whether these variants affect sleep during early development. We assessed whether polygenic risk scores for insomnia (PRS-I) and sleep duration (PRS-SD) affect sleep throughout early childhood to adolescence.

**Materials and Methods:** We included 2,458 children of European ancestry from the Generation R Study for whom genotype and sleep data were available. PRS-I (higher scores indicate genetic susceptibility for insomnia) and PRS-SD (higher scores indicate genetic susceptibility for longer sleep duration) were based on the largest GWAS studies to date. Sleep was reported by mothers at child's age 1.5, 3, 6 and 10–15 years, and in a subsample ( $N=975$ ) estimated with actigraphy at age 10–15 years.

**Results:** Children with higher PRS-I had more mother-reported sleep problems at 1.5 years ( $B_{PRS-I<0.001}=0.13$ , 95%CI: 0.04;0.22) and at 6 years ( $B_{PRS-I<0.008}=0.09$ , 95%CI: 0.02;0.16). PRS-SD was not associated with mother-reported sleep problems. A higher PRS-SD was in turn associated with longer actigraphically estimated sleep duration ( $B_{PRS-SD<0.008}=0.05$ , 95%CI: 0.001;0.09) but also more wake after sleep onset ( $B_{PRS-SD<0.005}=0.25$ , 95%CI:0.04;0.47) at 10–15 years.

**Conclusions:** Children who are genetically predisposed to insomnia have more insomnia-like sleep problems, whereas those that are genetically predisposed to longer sleep, have longer sleep duration, but are also more awake during the night in adolescence. This indicates that polygenic risk for sleep traits, based on GWAS in adults, affects sleep already in children. The findings may offer opportunities for early risk estimation, detection and prevention.

### ASSOCIATION BETWEEN SLEEP CHANGES AND SYMPTOM RECOVERY FOLLOWING PEDIATRIC CONCUSSION

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**Introduction:** Mild traumatic brain injuries, such as concussion, are one of the most common causes of neurological morbidities in children. In addition to physical, cognitive, and emotional symptoms, one of the most common complaints following a concussion is the presence of sleep disturbances, such as trouble falling asleep. Post-concussive sleep disturbances in youth have been associated with more severe symptom severity and prolonged recovery time. Nevertheless, very limited research has investigated the exact relationship between sleep and post-concussive symptoms in pediatric concussion. The goal of the present study was to longitudinally assess the nature of sleep changes following concussion in a pediatric sample.

**Materials and Methods:** Secondary analysis were done based on the Predicting Persistent Post-Concussive Problems in Pediatrics (5P) study, a multicenter cohort of 3,029 children between the ages of 5–17 years presenting to an emergency department with concussion from 2013–2015. Post-concussive symptom ratings and sleep disturbances were obtained at 5 pre-defined time points following concussion (weeks 1, 2, 4, 8, 12), using the Post-Concussion Symptom Inventory (PCSI) and the sleep item of the Pediatric Quality of Life Inventory, respectively. Symptom severity and recovery trajectories were measured using delta scores on the PCSI for each time point (post-injury symptoms minus retrospectively assessed pre-injury symptoms). Linear mixed models were fitted separately for the PCSI total score and the physical, cognitive and emotional symptom subscales, adjusting for random participant effects. Model predictors included sleep, time, and time x sleep interaction. The model also accounted for age, sex, maximum duration of previous concussion symptoms, prior diagnosis of developmental disorder, depression, anxiety, and prior diagnosis of sleep disorders as they are known risk factors for prolonged recovery.

**Results:** A total of 591 participants were included in the analysis (mean age=12 years,  $SD=3.3$ ; 38% female). There was an overall improvement in sleep scores over the 12-week period, with the sharpest improvement occurring at the early stages, from week 1 to 2. The time x sleep interaction was a significant predictor of recovery for both the PCSI total score and physical subscale. More specifically, higher sleep improvements over time were associated with greater reductions in post-concussive symptoms, and this effect was most pronounced early in the course of recovery. Furthermore, longer symptom duration from previous concussions, female sex, anxiety, and the presence of developmental disorders were significant predictors of higher global post-concussive symptom severity, while female sex and anxiety were significant predictors of higher physical symptom severity. In addition, poor sleep and female sex were significant predictors of higher cognitive and emotional symptom severity.

**Conclusions:** The present findings reveal that the evolution of sleep changes over time is a strong predictor of post-concussion symptom recovery, particularly in the early stages following the injury. The temporal relationship between sleep improvements and the alleviation of post-concussive symptoms appears to be heavily driven by physical symptoms. Nevertheless, sleep was also strongly linked to the cognitive and emotional symptoms. This highlights the importance of protecting sleep during recovery from concussion in children and adolescents.

**Acknowledgements:**

### A SURVEY AND INTERVIEW STUDY EXPLORING UK PRACTICING PRIMARY CARE PROVIDERS' MANAGEMENT OF CHRONIC INSOMNIA IN CHILDREN

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**Introduction:** Chronic insomnia (CI), specifically behavioural insomnia, is a common childhood sleep problem, with potential to impact many domains for the child/family. Behavioural interventions are effective management approaches. Limited research has specifically explored the management of CI in UK primary care. This study aimed to explore UK primary care practitioners' (PCP) views, knowledge, and practice for managing CI in children  $\leq 5$  years old.

**Materials and Methods:** A mixed-methods study (online survey and qualitative interviews). Participants were UK general practice PCPs such as general practitioner doctors (GPs) and practice nurses, or community PCPs such as health visitors (HVs) and nursery nurses. A link to an online survey was distributed to general practice PCPs in multiple regions of England, through one NHS trust to community PCPs, and in the community. The survey included closed/Likert scale questions (using questions or basing/adapting questions from existing published literature) and data were analysed with descriptive statistics. Survey participants could express an interest in taking part in a semi-structured interview. Transcribed interviews were analysed based on reflexive thematic analysis.

**Results:** There were 355 survey participants. Of 319 who reported their role, 76% were GPs, 9.7% practice nurses, 5.3% advanced nurse practitioners, 2.2% HVs and 0.6% nursery nurses. 86.7% of participants agreed or strongly agreed that CI impacts the children, and 97.4% the family. 90.8% agreed or strongly agreed that it is important to use behavioural interventions, compared to 21.5% for pharmacological interventions. CI is not often discussed in consultation. For the likelihood of making individual recommendations for 3 different age groups (<6 months, 6–12 months, 1–5 years), more than 85% reported 'positive bedtime routines' most of the / every time, in comparison to less than 50% for any other recommendations. 68.9% did not know of other resources for parents. Knowledge and confidence for the management of CI varied, and only 5.4% had received teaching about this topic when training to qualify as a health professional. 80.3% of participants expressed interest for further training opportunities. From 21 qualitative interviews (18 GPs, 3 HVs), findings were similar and highlighted further detail. Although infrequent with GPs, discussion about CI is more common with HVs, and GPs perceived some barriers to discussion/management in primary care. Participants also perceived general practice to be more suited to general assessment, basic advice and signposting, whereas HVs were also perceived as better suited to detailed management. GP knowledge and confidence varied, and any knowledge was generally due to personal experience instead of professional teaching. GPs expressed an interest in suitable brief training opportunities.

**Conclusions:** It would be helpful to increase GP knowledge/confidence for managing paediatric CI by increasing GP training opportunities and awareness of evidence-based resources for signposting families to. In GP consultations, it would also be helpful to increase discussion about CI.

**Acknowledgements:** This study/project is funded by the National Institute for Health Research (NIHR) School for Primary Care Research. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

#### CENTRAL SLEEP APNEA IN FULL TERM NEONATE AS AN INITIAL PRESENTATION OF EARLY INFANTILE EPILEPTIC ENCEPHALOPATHY

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**Introduction:** Central sleep apnea is a rare entity in full term neonate. It can represent the first sign of several neurologic and non-neurologic disorders. Genetic disorders, metabolic conditions and brain abnormalities are also among the differential diagnosis in patients with this presentation. The literatures have evolved overtime, and earlier diagnosis has allowed to treatment of this entity, including new and advanced modalities of ventilatory support medications. Genetic analysis allows us to detect the conditions that responsible for the presence of central apnea in this patient.

The authors present a case of severe central sleep apnea in a neonate, discussing the findings of serial polysomnograms, genetic testing, differential diagnosis and some of treatment modalities approached during illness of our patient.

**Case report:** Female patient born full term at 39 weeks via C section to a 23-year-old G2P2, pregnancy complicated by scant prenatal care. Apgar score were 5 and 8 respectively. She was transferred to the NICU due to respiratory distress requiring CPAP 5 cm of water. Despite no apparent pulmonary cause, patient requiring persistent respiratory support and NICU team was unable to wean the patient to room air. At 33 days of life, she was on oxygen via nasal cannula 0.7 L FiO2 21%. During physical exam, her respiratory rate ranged from 21–44 breaths/minute, and her oxygen

saturation was 92–100% while on oxygen. Her appearance showed no distress, no noisy breathing, normal work of breathing, no retractions, and normal sounds on auscultation. Her extremities showed right club foot. Neurological exam demonstrated hypertonicity and exaggerated Moro reflexes with excessive jitteriness. Patient underwent polysomnogram which revealed severe central sleep apnea with apnea hypopnea index (AHI)121.1/ hour and central apnea index (CAI) 116/hr. EEG recording during the polysomnogram showed evidence of discontinuous background which was dysmature for age. Patient was started empirically with caffeine 20 mg/kg as initial dose, continued by caffeine 10 mg/kg/day, as well as continued with oxygen supply. On repeat polysomnogram on day 10 of therapy, we noted marked improvement of central sleep apnea (AHI 11.2/hr., CAI 10.8/hr.).

Patient later developed movements concerning for seizures, EEG showed recurrent spasm-tonic seizures, with burst-suppression background consistent with Early infantile epileptic encephalopathy (EIEE). Epilepsy gene panel revealed a pathogenic variant in KCNQ2 gene (c.523G>T (p. Val175Leu), heterozygous). Patient started on ox carbamazepine with the addition of other antiepileptic medications for better seizure control.

**Conclusions:** Prompt diagnosis of central sleep apnea and etiology identification is the key for the successful treatment of this life threatening condition. The presentation in neonates is subtle and requires further investigation, as the treatment of other conditions, as in this patient's case with EIEE. Multimodality treatments allow for a better outcome of central apnea.

**Acknowledgements:** We would like to thank the sleep technicians and all the staff in the Sleep disorders center, our neonatologists and epileptologists at the University of Chicago for their continuous support.

#### CHILDREN HOME UNATTENDED POLYSOMNOGRAPHY IN A TOWN OFFICE PRACTICE: FEASIBILITY, QUALITY AND PATIENTS AND CAREGIVERS' SATISFACTION

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**Introduction:** Laboratory polysomnography is the gold standard to measure sleep objectively, however, is cumbersome as children and parents sleep longer and with higher sleep quality at home than at the hospital (Marcus 2014). Home unattended polysomnography (U-PSG) represents a less stressful alternative for families, a more affordable sleep study type in terms of resources and costs, as well as a potential option in reducing the waiting lists burden.

**The study objective** is to present the feasibility, tolerance, and children and parents' satisfaction of U-PSG in a large series of children.

**Materials and Methods:** We conducted a retrospective analysis of home-based consecutive children's U-PSGs between January 2018 and June 2021. All parents read and signed an informed consent form. U-PSG was installed and analyzed following the AASM criteria with a Nox A1 polysomnographer at the doctor's office by a certified sleep technician. The recording was made at home. In the morning, parents and children filled out analog visual scales to assess their satisfaction with the home recording (from 0 to 10, 10 being best) and parents' preference to perform the PSG at home (0) or at hospital (10). For each recording, global quality (0–100%) of the study was generated.

**Results:** 363 consecutive children aged  $8.9 \pm 3.3$  years (range 2–17 years) underwent a U-PSG. The most important symptoms were snoring (42%), awakenings (41%), fatigue (40%), and kicking (29%). 75 patients were previously diagnosed of a ADD, ADHD or other learning disorders, and 12 with an epilepsy. PSG results with mean  $\pm$  SD were: total sleep time  $549.5 \pm 81.7$  min.; arousal index  $11.7 \pm 5.1$  / hour; sleep efficiency was  $91.2 \pm 6.6$  %; N1:  $5.5 \pm 3.1$  %; N2:  $51.0 \pm 5.9$  %; N3:  $20.3 \pm 4.8$  %; REM  $23.2 \pm 4.3$  % . Mean global quality of the PSG recording was 81.2%. Four out of 363 PSG recording should be repeated because of technical problems. Mean parent's satisfaction with ambulatory recording was 9.0/10, mean children's satisfaction was 8.8/10 and most parents would prefer to perform a home U-PSG rather than a hospital PSG (2.1/10). 347 patients had an AIH more than 1 and 120 of the patients had more than 5 periodic leg movements (PLMs) per hour of sleep. Among patients with ADD, ADHD or other learning disorders, 90.7% had an AIH > 1, 38.7% had more than 5 PLMs per

hour of sleep, and 34.7% had both.

**Conclusions:** The results of this study show the preference of parents and their children for home U-PSG, provides further validity U-PSG in children, by achieving very good quality of signals and allowing accurate diagnoses, and reinforces the eventual potential usability of home U-PSG in children.

**Reference:** Marcus CL, Traylor J, Biggs SN, et al. Feasibility of Comprehensive, Unattended Ambulatory Polysomnography in School-Aged Children. *J Clin Sleep Med JCSM Off Publ Am Acad Sleep Med.* 2014;10(8):913–918.

#### COMORBID INSOMNIA AND OBSTRUCTIVE SLEEP APNEA IN SCHOOL AGE CHILDREN AND ADOLESCENTS: A DESCRIPTIVE ANALYSIS WITH FOCUS ON POLYSOMNOGRAPHIC DATA

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**Introduction:** Insomnia and obstructive sleep apnea (OSA) are the most common sleep disorders among the different age groups, and therefore can co-occur. When insomnia and OSA co-exist (COMISA), they may interact and mutually potentiate some of the downstream morbidities associated with either one of these sleep disorders. Indeed, the risk of cardiovascular and metabolic disorders (CMD) is often independently associated with either insomnia or OSA, and such risk seems to be aggravated in adult COMISA patients. However, there is a remarkable scarcity of evidence regarding how COMISA may affect the pediatric population. This study aimed to objectively assess Insomnia, OSA and COMISA in a sample of school age children and adolescents, and evaluate how anthropometric measurements including body mass index (BMI), neck circumference (NC) and abdominal perimeter (AP) correlate with each condition.

**Materials and Methods:** PSG recordings performed during 2019 in school age children and adolescents living in Salvador, Brazil were retrieved, and divided into otherwise healthy children (SL < 24 min and AHI ≤ 1), those with objectively assessed insomnia (sleep latency - SL > 24 min), OSA (AHI > 1/hr TST) and COMISA (SL > 24 min and AHI > 1).

**Results:** Among 60 children (53% males), 47 (73.4%) were school age (31.7%, > 5 to 7 years; 46.7% > 7–12 years; 21.7% were > 12 years). In the cohort, 29 children (48.3%) suffered from no sleep disorder, while 11 (18.3%) fulfilled clinical criteria for insomnia, 14 (23.3%) presented with isolated OSA, and 6 children (10%) were diagnosed with COMISA. Patients with COMISA were all from female gender and had longer sleep latencies when compared with either insomnia, OSA or controls (54.0 min vs. 35.0 min vs. 3.8 min vs. 6.5 min, respectively;  $p=0.001$ ). Total sleep time (TST) and sleep efficiency (SE) were also increased in COMISA groups compared to all the other groups ( $p=0.01$ ); There were no significant differences regarding BMI, NC and AP across the groups.

**Conclusions:** These preliminary findings suggest that pediatric COMISA can be detected in the pediatric age range and appears to exhibit some discernible PSG-related differences. Such findings justify more expansive exploration of the epidemiology and clinical characteristics and morbidities associated with COMISA in children.

#### COMPARISON OF POLYSOMNOGRAPHIC CHARACTERISTICS BETWEEN LOW BIRTHWEIGHT AND NORMAL BIRTHWEIGHT CHILDREN IN THE NORTHERN TERRITORY OF AUSTRALIA

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**Introduction:** Low birthweight (LBW, <2500g) is recognised as a significant risk factor for a range of chronic health conditions and has recently been implicated in the development of sleep disorders. However, information on polysomnographic (PSG) characteristics in children born with LBW has yet to be reported.

**Materials and Methods:** Demographic, clinical and PSG parameters of children born LBW were compared against children born with normal birthweight (>2500g, NBW) in a cohort of children attending paediatric sleep laboratory in the Northern Territory of Australia between 2015 and 2020.

**Results:** One hundred and seventy-two paediatric patients had birthweight data available, (37% female, 30% Indigenous Australian). Of these, 19 (11%) were LBW (median birthweight 2300 g (IQR 1713, 2410)). LBW children had a significantly higher prevalence of obesity (33% vs. 14%), though no other demographic features differed. LBW children showed a significantly higher amount of time spent awake after sleep onset (125 minutes (IQR 54.4, 164) vs. 63.2 minutes (IQR 36, 107),  $p=0.032$ ) and a significantly lower sleep efficiency than NBW children (78% (IQR 73, 83) vs. 84% (IQR 79, 90),  $p=0.002$ ) which held following adjustment for demographic and clinical factors in multivariate regression.

**Conclusions:** LBW is associated with increased sleep disruption and reduced sleep efficiency. This sleep health deficit may contribute to development of chronic disease in this vulnerable population, and thus should be monitored to provide avenues for early intervention.

#### CORTICAL HEMODYNAMIC CHANGES ASSOCIATED WITH SLEEP SLOW WAVES IN SCHOOL-AGE CHILDREN

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**Introduction:** Slow waves (0.5–4 Hz), the most prominent EEG hallmark of NREM sleep, undergo relevant changes as a function of experience-dependent plasticity and maturational brain adaptations. Indeed, previous scalp EEG studies showed that the maximal slow wave activity shifts from posterior to anterior brain regions from childhood to adulthood, paralleling brain structural changes and the acquisition of behavioral and cognitive skills. By using EEG and simultaneous event-related fMRI, we recently demonstrated in adults that slow waves are associated with hemodynamic changes in the bilateral somatomotor cortex, suggesting that this region may play a key role in the generation and expression of slow waves (Betta et al., *NeuroImage*, 2021). Here we sought to determine whether slow waves of school-age children are associated with similar hemodynamic changes relative to adults or are instead characterized by a different (more posterior) cortical involvement in line with previous scalp EEG findings.

**Materials and Methods:** We analyzed data collected from fourteen children (12 males, age 6–11 yrs) with a diagnosis of childhood epilepsy with centrotemporal spikes (CTS) who fell asleep during simultaneous EEG (32 electrodes) and fMRI (3T) recordings. EEG artifacts were removed using EEGLAB (FMRIB-plugin and Independent Component Analysis). Sleep scoring was performed according to standard criteria. Automated algorithms were used to detect slow waves and spindles as described in previous work, while CTS were manually scored by two expert neurophysiologists. Brain regions associated with slow wave occurrence were identified through a voxel-wise regression that included CTS as a regressor of no-interest. To exclude any potential confounding effects related to the occurrence of sleep spindles another analysis was run including these events as an additional regressor of no-interest. A within-run permutation procedure ( $N=1000$ ) was used to estimate the strength of BOLD-signal changes ( $z$ -score), and a mixed effect linear model was used

for group-level analysis. A cluster correction procedure was implemented to account for multiple comparisons.

**Results:** Slow waves were associated with significant (corrected  $p < 0.05$ ) BOLD-signal decreases in bilateral somatomotor and parietal areas (right, 1138 voxels,  $x = -36.6$ ,  $y = +22.8$ ,  $z = +48.3$ ; left, 497 voxels,  $x = +49.7$ ,  $y = +20.0$ ,  $z = +43.3$ ). Similar results were obtained after the inclusion of spindles in the model. A direct comparison of present results with those previously obtained in adults (conjunction map, uncorrected  $p < 0.01$  in both datasets) revealed areas of overlap within the bilateral somatomotor cortex (Betta et al., *NeuroImage*, 2021). However, BOLD-signal changes observed in adults tended to involve more anterior (frontal) areas, whereas, in children, they extended more posteriorly, within parietal regions. No significant BOLD-signal changes were found in thalamus, brainstem and cerebellum, where a positive hemodynamic modulation was previously observed in adults.

**Conclusions:** Present findings are in line with evidence indicating that the cortical distribution of sleep slow waves changes with maturation, from a stronger parietal involvement in school-age children to a predominant frontal one in adult individuals. However, they also suggest that the somatomotor cortex could serve an important role for the expression of sleep slow waves throughout the lifespan.

#### DAYTIME POLYSOMNOGRAPHY IN CHILDREN: A USEFUL TOOL?

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**INTRODUCTION:** Nocturnal polysomnography (nPSG) is a useful tool and the gold standard for the assessment of sleep architecture and sleep disorders. However, nPSG may have some limitations: it is not widely available, it requires qualified staff and has a longer duration. This causes large waiting lists and higher economic costs.

Daytime polysomnography (dPSG) could be an alternative to evaluate sleep in children. It has less duration but with the same quality standards. Nevertheless, little is known regarding children's sleep parameters during daytime.

The aim of this work is to describe the different sleep parameters recorded in daytime polysomnography in healthy children aged 1-6 years.

**Materials and methods:** We performed a retrospective and descriptive study of 89 healthy children classified into 3 groups according to age (1-2, 3-4 y 5-6 years old) and who were studied using a daytime PSG, in our Hospital (Ramón y Cajal Hospital, Madrid) between 2019-2020. Patients were excluded from the analysis if total sleep time were lower than 150 minutes or they documented obstructive sleep apnea (OSA), periodic leg movement (PLM) or epilepsy during polysomnography.

We analyzed demographic data and polysomnographic measures such as study duration, total sleep time, stage distribution (%), sleep efficiency, sleep efficacy, arousal index and WASO (wake after sleep onset). We used AASM diagnostic criteria to assess these measures.

**RESULTS:** Daytime PSG lasted an average of 240 minutes and mean total sleep time was 207 minutes.

The percentage of total sleep time spent in sleep stages N1, N2, N3 and REM were 5.83%, 26.68%, 46.02%, 21.48%, respectively. There were no differences between age groups.

The mean efficiency was 87.15%. The mean efficiency in the different age groups (1-2, 3-4 y 5-6 years old) were 91.46%, 85.98%, 86.18%, respectively. Also, total sleep time was higher in the group of 1-2 years old, which means better efficiency and worse wake after sleep onset (WASO).

**CONCLUSIONS:** We have observed in this study that daytime PSG shows values of sleep architecture similar to those observed in nPSG, regardless of the age group. Moreover, a higher sleep efficiency is detected in the younger age group (1-2 years)

Therefore, daytime PSG could be useful, and a screening alternative tool to nPSG for sleep disorders in children under 6 years.

#### EFFECT OF A STANDARDIZED MASSAGE ROUTINE ON POLYSOMNOGRAPHY IN EX-TERM INFANTS AT 4 MONTHS OF AGE: A RANDOMISED CONTROL TRIAL

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**Introduction:** Massage is a form of environmental enrichment with proven benefits for preterm health and brain maturation. However, there is a paucity of evidence about the benefits of massage for term infants. The dynamic development of sleep during early infancy is a valuable instrument to assess brain maturation. This study investigates the effect of routine parent-led daily massage on the sleep EEG of healthy term-born infants at 4 months of age.

**Materials and Methods:** Healthy ex-term infants were recruited at Cork University Maternity Hospital, Ireland. At 2 weeks of age, infants were randomised to the control or intervention group; parents in the intervention group were asked to perform the massage routine 3-times daily and to keep a massage diary. For each infant, a daytime sleep EEG with extra polysomnographic channels was recorded at 4 months and EEG features measured. Sleep spindles were manually annotated on the EEG over the left and right fronto-central regions. Mean frequency, Brain Symmetry Index, synchrony and spectral power of the sleep spindles were calculated with MATLAB R2020a. Spindle number and density were also analysed. EEG quantitative (qEEG) features included measures of inter-hemispherical connectivity, EEG power, discontinuity and spectral distribution obtained through a bespoke Matlab Toolbox NEURAL. qEEG results were compartmentalised into sleep stages and frequency ranges. A comparison of EEG features between groups was performed. Due to poor compliance with the massage routine, a subgroup comparison of regularly massaged participants (daily massage of  $\geq 5$  minutes for  $\geq 4$  days/week for  $\geq 10$  weeks) and never-massage controls was also performed. Mann-Whitney U test was used to compare sleep parameters between groups.

**Results:** EEGs of 179 infants were included in the analysis (intervention,  $n = 83$ ; control,  $n = 96$ ). For sleep macrostructure and qEEG only infants with a complete sleep cycle were included: intervention,  $n = 67$ ; control,  $n = 72$ . A total of 43093 spindles were recorded during the first cycle. Total sleep time, first cycle sleep stage durations and latencies to sleep and REM did not differ between groups. In the main analysis, the intervention group showed statistically higher spectral power in sleep spindles and overall higher EEG magnitudes (range EEG and spectral power) across different sleep stages and frequencies. Subgroup analysis confirmed main analysis observations and showed statistically lower inter-hemispherical coherence in the intervention group across various frequencies, predominantly during NREM sleep states.

**Conclusions:** Routine massage during the first four months of life does not alter cycle duration, and other sleep staging macrostructure features. However, this study showed that routine massage is associated with distinct changes in brain function that may suggest more advanced brain maturation, including sleep spindles, EEG magnitude and coherence.

**Acknowledgements:** To all participating families and the BabySMART team at the INFANT Research Centre.

#### EVALUATION OF A WOMB-LIKE SENSORY INTERVENTION TO IMPROVE INFANT SLEEP

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**Introduction:** Nearly half of parents (47%) report moderate to severe infant sleep problems during the first six months of their child's life. These sleep problems can trigger a cascade of negative effects among caregivers – including marital stress, postpartum depression and anxiety, obesity,

breastfeeding failure, unsafe sleeping practices, illness, and failure at work. Reducing infant sleep problems may significantly improve maternal mental health and functioning of the entire family, although interventions to improve infant sleep have demonstrated limited benefit. However, parents have often observed that baby sleep is immediately extended when the infant is rocked in a rocking chair or driven in a car. This observation has been buttressed by multiple studies showing that three womb-like stimuli – swaddling, white noise, and rhythmic motion – improve infant sleep, soothe fussing, and have an additive benefit when used in combination.

**Materials and Methods:** In this study, we compare infant sleep from birth to six months of age occurring in traditional cribs and bassinets relative to infant sleep in SNOO. The bed is a connected device and provides real-time, continual data on the movement of the bed's platform. Slow motion of the platform indicates sleep and rapid motion occurs during fussing. This study evaluates the aggregated, de-identified sleep logs across a cohort of 72,649 infants ages 0-6 months to compare the total sleep duration, longest sleep period, and number of sleep interruptions relative to a compilation of 14 peer-reviewed studies of normative infant sleep published over the past two decades.

The mean and standard deviation of each study was weighted by sample size and combined to calculate sleep metrics for the reference population. After filtering, mean and standard deviation of the three sleep metrics were calculated by age of the baby in months. Welch's T-test was used to calculate significance values by comparing the means of sleep metrics between SNOO babies and babies sleeping in traditional bassinets.

**Results:** For each month across the 6-month collection period, infants in SNOO experienced significant improvements in longest sleep period and total sleep duration ( $p < 0.0005$ ). Babies in SNOO also experienced significantly fewer night wakings at months 2-6. On average, SNOO adds 1+ hour of sleep per night during the first six months of life ( $p < 0.0005$ ).

**Conclusions:** These findings suggest that the responsive bassinet substantially improves infant sleep compared to babies sleeping in traditional cribs or bassinets. By improving infant sleep, this intervention may substantially reduce negative health outcomes associated with poor sleep quality among caregivers.

In the future, we must consider how technological advances can empower new parents, including through the use of digitally-enabled, thoughtfully designed tools to equip users with the most critical infant care skills and supports they need.

**Acknowledgements:** This study received financial and administrative support from Happiest Baby, Inc.

## EVALUATION OF THE NOVEL SITUATIONAL SLEEPINESS SCALE FOR CHILDREN WITH NARCOLEPSY

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**Introduction:** Monitoring of narcolepsy treatment response requires regular self-report of hypersomnolence. The Epworth Sleepiness Scale adapted to children (ESS-CHAD), is widely used for this purpose. The novel Situational Sleepiness Scale (nSSS) was designed to address limitations of the ESS-CHAD, specifically to:

1. Measure fluctuations of sleepiness across the day
2. Rate sleepiness according to the child's usual, rather than prescribed, activities
3. Improve intelligibility for children through a visual analogue scale.

### Aims:

- To gain structured feedback from children with narcolepsy, their parents and sleep centre clinicians on the strengths and weaknesses of the nSSS compared to the ESS-CHAD.

- To test children's ability to correctly interpret the visual analogue scale (VAS) and the language used in the scale to describe sleepiness.

**Methods:** The study was advertised by Narcolepsy UK and Sleep Disorders Australia. Parents and children took part in semi-structured interviews over Microsoft Teams. The nSSS design was assessed using a cognitive

interview approach. Children ranked the VAS and sleepiness language using an interactive whiteboard. Interviews were transcribed and analysed. Clinicians gave feedback through a structured Microsoft forms questionnaire. Semantic thematic qualitative analysis identified key observations and opinions.

**Results:** Seven parents and four children, (aged 12-14 years), were interviewed. Eight clinicians with a combined experience of treating over 400 children with narcolepsy, completed the questionnaire. There was a universal preference across both clinicians and families for the nSSS which was viewed as more child-friendly and easier to complete. For example, one parent stated: 'kids are more drawn to images than words; a picture says a thousand words.' The clinicians also preferred that the nSSS captured fluctuations in sleepiness across the day commenting: 'really useful to log a detailed record of the changes in sleepiness throughout the day. This is particularly useful to help with decisions about changes in treatment.' Minor formatting suggestions were made. The VAS and language used were understood by all children.

**Conclusions:** With minor adaptations, the scale has face validity. There was enthusiasm for this scale to be used clinically. Reliability and validity, compared with neurophysiological measures of sleepiness, should now be assessed.

**Acknowledgements:** We are grateful to the British Paediatric Sleep Society, Narcolepsy UK and Sleep Disorders Australia, in particular Nicola Rule and Michelle Chadwick, for their efforts in advertising the study and to all the families and clinicians for taking part.

## EXPOSURE TO SCREENS AND CHANGES IN TODDLERS' SLEEP DURING COVID ERA

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**Introduction:** The usage of electronic devices among very young children is common (Rideout et al., 2011). Exposure to small touch screens including tablets and smartphones, is rapidly growing in infants and toddlers (Ahearne et al., 2016). The diverse influences are a growing concern as multiple risks to young children behavior and development have been demonstrated (IBD,2021), including toddlers' sleep (Sonia et al., 2019). Coping with the Covid-19 has caused considerable disruption to families as parents were forced to stay at home and childcare settings were closed. One of the outcome of these circumstances is increased usage of digital devices (BMJ,2021) - a concern for child health and development (BMJ, 2020). Evidence from previous socio-historical events highlights that the young children are susceptible to severe and long lasting effects (Aprile & Rashmita, 2020). The objective of our study was to (a) address changes in screen-time and in sleep habits during the pandemic and (b) examine the link between changes in screen-time and sleep habits. We predicted that increase in exposure to screens will be associated with sleep disruption.

**Materials and Methods:** The sample comprised of 233 mothers and their children ages 2- to 4-years, with no known developmental or health problems; the sample was recruited, from the Arab sector in Israel, through announcements placed in social media groups. Mothers completed, online, 3 tools: *Demographic background*, *ISQ—Infant Sleep Questionnaire*, and *Children's screen-time* questionnaires. Data collection took place during June 2021, about 18 months after the outbreak of the coronavirus pandemic and following several periods of quarantines and other disruptions of nursery schools and small home-based daycare settings.

**Results:** In response to screen-related changes, 30% reported no change, 2% reported a decrease and the majority (68%) reported an increase (30% marked a large increase) in screen-time compared to the pre-pandemic period. As to sleep-habits, about half of the mothers (48%) reported changes (25% thought the changes were small, whereas 23% marked "moderate" to "major" changes. In examining the link between the increase in screen time and the co-related sleep changes, it was found that (a) even as small increase in screen-time was associated with a later sleep onset;(b) moderate increase was associated not only with later sleep onset but also with more naps. Finally, large increase in screen-time was associated with multiple changes in the child's nocturnal sleep habits ( $p < 0.001$ ).

**Conclusions:** It was found that two out of three toddlers had increased screen-time and that this increase was significantly associated with more screen time was significantly increase most of them also reported that the coronavirus period also affected their children's sleep routine, such as a later bedtime. Given the importance of good sleep to child development in general, and to learning and emotional regulation in particular, parents and clinicians should be aware of these risks. It is the task of professionals to develop intervention programs to support parents and their children during the present challenging era. More studies in diverse cultures and age groups are called for.

**Acknowledgements:**

#### GENDER AND RUMINATION AS PREDICTORS OF EMOTIONAL AROUSAL AFTER SLEEP RESTRICTION IN PRE-PUBERTAL CHILDREN

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**Introduction:** There is an abundance of evidence that poor sleep predicts negative behavioral, emotional, academic, and physical health outcomes in children. However, sleep loss is not universal in its negative effects and may look differently among individuals with different cognitive response styles including those who are more likely to ruminate. Little is known however about rumination among pre-pubertal children including whether a ruminatory cognitive response style predicts emotional responses to sleep loss. The current study examined these relationships including the potential moderational role of gender since females are known to ruminate more than males.

**Materials and Methods:** A sample of 53 healthy, pre-pubertal children (7–11 years) completed emotional assessments in the lab when rested and after two nights of sleep restriction (7h and 6h, respectively) monitored with objective sleep measures. At baseline, participants completed questionnaires including the Children's Response Styles Scale (CRSS) used to measure tendency for rumination. Subjective reports of arousal were measured using the Self-Assessment Manikin (SAM) in response to a series of positive, neutral, and negative images from the International Affective Picture System (IAPS). We conducted a moderation analysis using multiple linear regression to examine whether rumination scores predicted emotional arousal ratings and whether rumination and gender had an interaction effect.

**Results:** After sleep restriction, children with greater CRSS rumination scores showed significantly less arousal in response to neutral (Beta = -0.57,  $p < .001$ ) but not positive (Beta = -0.23, n.s) or negative (Beta = -0.17, n.s) IAPS images. There were no main or interaction effects based on gender.

**Conclusions:** Although previous research has found rumination to mediator the relationship between sleep problems and anxiety among teens, to our knowledge, there have been no studies examining rumination in relation to sleep in pre-pubertal children. Our findings suggest that rumination does not predict responses to 'emotional stimuli' (e.g., negative and positive IAPS images) after sleep loss among pre-pubertal children, but may serve to distract children from non-emotional stimuli.

**Acknowledgements:** N/A

#### HOW DO CHILDREN AND ADOLESCENTS OF SEPARATED PARENTS SLEEP? AN INVESTIGATION OF CUSTODY ARRANGEMENTS, SLEEP HABITS, SLEEP PROBLEMS, AND SLEEP DURATION IN SWEDEN

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**Introduction:** An increasing number of children and adolescents divide their time between their separated parents' homes. Although marital conflict is disadvantageous for children's sleep, little is known about how children of separated parents sleep. The objective was to investigate the association between children's custody arrangements and sleep habits and

sleep initiation difficulties.

**Materials and Methods:** Cross-sectional questionnaire data from the 2013 Health Behaviours of School-aged Children was used. The sample included over 7000 adolescents (50% girls), aged 11–15. Nuclear families were used as a reference in all analyses. The sleep issues were defined as follows: Less than 7 h of sleep = insufficient sleep; sleep initiation difficulties >1 per week = insomnia; bedtimes after 11 pm = late bedtimes; more than 2h variability between weekend and weekday bedtimes = jetlag. Short sleep duration, insomnia, late bedtimes and jetlag were respectively used as outcomes from regression analyses where custody forms, gender, and family affluence were used as predictors.

**Results:** The results show differences by custody arrangement, but they are not uniform across the dependent variables. Children and adolescents in sole maternal custody were less likely to sleep as much as recommended ( $P < .001$ ), more likely to have late bedtimes ( $P < .001$ ), report sleep initiation difficulties ( $P < .01$ ) and to report social jetlag between school mornings and weekends ( $P < .05$ ) compared to those in 2-parent families. Shared physical custody was associated with a higher likelihood of late bedtimes ( $P < .05$ ) and sleep initiation difficulties ( $P < .05$ ) compared to those in 2-parent families, but not of sleeping less than recommended or reporting social jetlag. Less-than-equal sharing was generally associated with worse sleep than in 2-parent families.

**Conclusions:** As custody arrangements seem to be associated with sleep, it is important to understand the mechanisms behind the findings.

**Acknowledgements:** This work was supported by Forte: the Swedish Research Council for Health, Working Life and Welfare (grant numbers: 2012–1736 & 2016-00511).

#### IMPACT OF COVID-19 PANDEMIC ON THE SLEEP OF HEALTHCARE WORKERS' OFFSPRING

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**Introduction:** The COVID-19 pandemic led to work overload in health care workers (HCW) either in the form of COVID-19 related or non-related work. COVID-19 related work is associated with increased anxiety levels and, in some cases, a shift in family dynamics. The aim of this study was to evaluate the impact of this supplementary work and, specifically, COVID-19 related supplementary work in the sleep of HCW offspring in our hospital.

**Materials and Methods:** A cross-sectional, anonymized, self-reported, online questionnaire survey regarding the period of January to March 2021 was conducted at a level 2 hospital. SPSS was used for statistical testing (Chi-square test or Fisher's exact test).

**Results:** 97 HCW were included, 160 offspring younger than 18y, of which 84% were male, with a median age of 7 years [0–17y].

As for parental perceptions regarding their offspring's sleep: 40.0% of the HCW offspring sleep less than desirable, 36.9% take longer to sleep than desirable, 21.9% wake up earlier than desirable and 18.9% wake up more often during the night than desirable.

The majority of all HCW offspring: watch 1–4h/day of screen time (57.5%), mainly before 8pm (82.5%); have their bedtime before 9pm (83.1%) with low bedtime resistance; lie in bed for 8h or more (93.3%) and practice physical exercise before 6pm (57.5%).

During the COVID-19 pandemic, HCW with supplementary work (n=97) managed to maintain their offspring's sleeping habits, namely lower bedtime resistance, physical exercise before 6pm and 1–4h/day of screen time. Specifically, in the COVID-19 supplementary work group (n=56), HCW managed to keep their offspring's bedtime consistent.

In the non supplementary work group (n=63) a difference was found between HCW with COVID-19 related work, when compared to HCW without COVID-19 related work. The group with COVID-19 related work (n=29) managed to keep their offspring's sleeping habits, namely lower bedtime resistance, physical exercise before 6pm; screen time 1–4h/day, and before 8pm. However, those who didn't work in COVID-19 areas (n=34) showed worse sleeping habits, with higher bedtime resistance, physical exercise after 6pm and screen time  $\geq 5$ h/day.

**Conclusions:** Globally, HCW perceive their offspring's sleep quality as

poor. Surprisingly, during the COVID-19 pandemic, HCW with supplementary work did not exhibit poorer sleep hygiene. Specifically, HCW with COVID-19 related supplementary work did not exhibit poorer sleep hygiene. Poorer sleep hygiene was observed in the offspring of HCW without supplementary work and without COVID-19 related work. A wider sample size could improve outcome reliability.

## IMPACT OF SLEEP DISTURBANCES IN JUVENILE FIBROMYALGIA SYNDROME

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**Introduction:** Sleep disturbances are a well-known part of the clinical spectrum of fibromyalgia (FM), a disabling condition characterized by musculoskeletal pain, fatigue, mood disturbances and many other symptoms that impact greatly the patients' quality of life. In contrast to adults, Juvenile Fibromyalgia Syndrome (JFS) has been investigated less extensively from the sleep viewpoint.

**Materials and methods:** Rheumatologic symptoms' severity, neuropsychiatric features, and sleep characteristics of a sample of 25 consecutive outpatients with JFS aged 12–19 years were assessed using both objective and subjective validated scores. Objective sleep parameters were evaluated using polysomnography. Moreover, we investigated the distribution of N3 during the night calculating the “N3 distribution index” defined as  $(\text{number of epochs of N3 in the first half of SPT} - \text{number of epochs of N3 in the second half of the SPT}) / \text{total number of N3 epochs}$ . All these variables were also extracted from a population of 27 age-matched control subjects. Mann-Whitney U test was used for comparison of quantitative data; non-parametric Spearman's correlation coefficient was used for correlations analysis; multiple regression models for different outcomes were finally performed.

**Results:** Nonrestorative sleep was reported by nearly all patients. Polysomnographic variables were compared between JFS patients and control group. JFS patients showed a significant longer Sleep Period Time ( $p=0.004$ ) and an increased wake time after sleep onset ( $p=0.026$ ) compared to healthy peers. No differences in sleep efficiency, number of arousals and sleep latency were found between the two populations. Although the time spent in N3 sleep stage did not differ between patients and control group, the N3 distribution index was significantly lower in JFS patients than in the control group ( $p=0.018$ ), indicating a more pronounced distribution of N3 sleep during the second part of the night. Subjective poor sleep quality and daytime sleepiness were related to bodily distribution of pain, increased symptom severity scale, depressive symptoms, fatigue and symptoms severity upon awakening. Reduced N3 sleep stage was related to symptoms' severity and depressive symptoms. Finally, the N3 distribution index correlated to depressive symptoms and irritability. Based on the results of multiple regression analyses, pain distribution was predicted by subjective poor sleep quality ( $\beta = -0.322$ ,  $p=0.035$ ), whereas depressive symptoms were predicted by both subjective poor sleep quality ( $\beta = -0.317$ ,  $p = 0.04$ ) and objective PSG measures (N3 min:  $\beta = -0.065$ ,  $p=0.032$ ).

**Conclusions:** This study confirms that sleep complaints and sleep alterations are a key hallmark of JFS and provides important insights on the impact of sleep disturbances on other relevant clinical domains of the disease, such as pain and depression. However, despite patients' poor subjective sleep assessment, objective sleep macrostructure is preserved when compared to healthy subjects and only few polysomnographic variables are significantly different; more specifically, N3 sleep distribution is significantly altered in JFS patients, with a higher representation during the second part of the night, thus suggesting an impairment in the

physiological release process of homeostatic drive to sleep. This last phenomenon may also explain the non-restorative sleep sensation complained by patients upon awakening.

## INTERACTIONS BETWEEN SLEEP AND GUT BACTERIA IN HEALTHY DEVELOPING INFANTS

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**Introduction:** Healthy infant development is driven by the maturation of different physiological processes. Two crucial processes are the establishment of sleep rhythms and the growth of a complex holobiotic ecosystem with gut bacteria. Studies have shown a bi-directional link between sleep and gut bacteria in animal models and human adults. However, no study has investigated how these two processes are linked in the first year of life nor how they contribute to healthy behavioral development.

**Materials and Methods:** We quantified habitual sleep (actigraphy-derived sleep composites Sleep Day, Sleep Night, Sleep Timing, Sleep Variability, and Sleep Activity), gut bacteria markers (16S rRNA gene profiling for computing bacterial diversity, enterotype, and bacterial maturation index), and behavioral development (Ages and Stages Questionnaire) in 162 infants at 3, 6 and 12 months of age. With multilevel and regression models we analyzed links between habitual sleep and gut bacteria, with random intercept cross-lagged panel models we evaluated interactions with behavioral developmental outcomes. Furthermore, in a subset of 32 6-months-old infants, we collected high-density EEG data during the first 2-h of nighttime sleep to quantify slow-wave activity, theta power, and sigma power.

**Results:** We found evidence of a sleep-gut link: daytime sleep (Sleep Day) was negatively linked to gut bacteria diversity ( $p = 0.02$ ), and nighttime sleep fragmentation (Sleep Activity) was positively linked to bacterial maturation index ( $p = 0.03$ ) and enterotype ( $p = 0.048$ ). Sleep Variability was linked to enterotype patterns ( $p = 0.02$ ). We also found evidence of a sleep-brain-gut link: The two enterotypes differed in slow-wave activity ( $p = 0.02$ ).

Lastly, we found associations between both gut bacteria and habitual sleep and behavioral development both at the same age and predictive for later ages. General patterns revealed that habitual sleep was associated more strongly with personal-social development, with daytime sleep showing most associations. Gut bacteria were associated mainly with gross motor development, with bacterial diversity showing most associations.

**Conclusions:** We find novel evidence for a sleep-brain-gut link in infants that is relevant for behavioral development. This research provides sleep and gut bacteria targets as fundamental anchors for non-invasive modification to promote healthy development. Considering that many adult diseases root in early childhood, early interventions can improve lifelong health.

**Acknowledgements:** This research was funded by the University of Zurich (Clinical Research Priority Program “Sleep and Health”, Forschungskredit FK-18-047, Faculty of Medicine), the Swiss National Science Foundation (PCEFP1-181279, POZHP1-178697), Foundation for Research in Science and the Humanities (STWF-17-008), and the Olga Mayenfisch Stiftung. We thank the parents and infants for participating in our study.

## LESSONS FROM THE COVID-19 SHUTDOWN: THE WAITLIST CHALLENGE & INSIGHTS IN OVERMEDICATION PATHWAYS

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**Introduction:** With exponentially increasing waitlists for sub-specialty services, the COVID-19 pandemic is magnifying existing gaps in service delivery and illuminating crucial challenges, which need to be revisited – one of the affected domains being sleep/wake-medicine. As such, we aimed to: (1) characterize patient load of a sleep/wake-behaviour clinic located in a child/adolescent psychiatry before and during the pandemic, (2) identify risk-factors, which could be targeted at the referral level, and (3) understand the needs of children and parents', and offer more individualized support.

**Materials and Methods:** In a quality improvement project, five 35+ hour weeks of ambulatory one-to-one service delivery for children and adolescents with neurodevelopmental and -psychiatric disorders (aged 2-19 years), prior to- and during the clinical shutdown were analyzed for: (a) the documented amount of time required for new and follow-up assessments, and (b) risk-factors requiring in-person/phone follow-up assessments. After implementing a restructured intake process with qualitative exploratory- and quantitative validated questionnaires, we revisited clinical care via virtual home visits, and assessed medication strategies implemented by sub-specialists in the community.

**Results:** Before COVID-19, 81 patient encounters scheduled over five weeks required on average 2.4 hours (165 hours in 24 workdays; without time allocation for breaks, additional administrative tasks and CME events). 18/81 patients were 'red-flagged' (defined as 911-call eligible at any clinical worsening, needing on average 2-3x more allocated time per patient). After implementing the revised intake and triage: (a) The number of red-flagged patients increased by 79%; (b) 108 patient encounters (+33%) were conducted via Telehealth (incl. short follow-ups by ad hoc phone calls); (c) preparation and assessment time was reduced by a third; new patient encounters increased by 60% and follow-ups were reduced by 32%. Further, we analyzed medication strategies in 41 consecutive patients. 81% had been medicated for disorders of initiating and maintaining sleep (39/41) and sleep/wake-transition disorders (37/41). In 17/41 (41%) patients, medications for initiating sleep (e.g. melatonin) were often used in combination with other sleep medications (e.g., clonidine; with up to a maximum of 6 medications) and psychotropics (stimulants: 24%; SSRIs: 22%; antipsychotics: 15%). 24/41 (59%) patients were subject to polypharmacy. Among symptomatic patients, only 3/40 and 1/22 patients with symptoms of RLS-induced insomnia and SDB were on iron supplementation and a nasal spray, respectively.

**Conclusions:** Regarding patient care, the QIQA-project helped us to revisit service delivery and change clinical processes, which resulted in a reduction of preparation/assessment time and allowed for the timely identification of at-risk patients. The new triage concept also allowed us to make evidence-based first line treatment recommendations during the wait time, before the assessment. Further, several main themes were identified and extracted in this QIQA-project: (1) *unsuccessful treatment of intractable chronic insomnia*, despite multiple therapeutic attempts that often build on off-label medication trials, (2) *lacking implementation of first line therapeutic measures*, and (3) *compromised family coping skills*, affecting adherence to suggested non-pharmacological interventions, ultimately resulting in further medication trials.

#### LINKS BETWEEN PARENTAL EDUCATION, INFANT NIGHTTIME SLEEP DURATION, AND PARENTAL CONFIDENCE IN MANAGING INFANT SLEEP

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**Introduction:** Parental confidence has been linked to improved child outcomes, as well as better overall parental health and wellbeing. The determinants of parental confidence in the context of their infants' sleep are not well understood. This study aimed to examine the associations between parental confidence and sleep among parents of infants who use a commercially available video sleep monitor and an associated mobile sleep health application.

**Materials and Methods:** This study was approved by the Institutional Review Board of New York State Psychiatric Institute (NYSPI). Parents of 576 US infants (age 9.13±1.8 months, 49.6% male) were recruited for this

study from the active customer base of Nanit sleep monitoring system. The Nanit system, a commercially available auto-videosomnographic device, includes a personalized, data-driven app that assists parents in understanding their infant's sleep health and offers tips and recommendations for improved sleep health. Parents were asked to complete the The Brief Infant Sleep Questionnaire-Revised (BISQ-R) and demographic questions via RedCap (75.8% mothers, 23.6% fathers, 0.5% other). The BISQ-R includes parent-reported sleep metrics, a Likert-scale question about the parent's self-reported confidence in dealing with their infant's sleep as well as a question asking whether they perceive their infant's sleep as a problem.

**Results:** The majority (87%) of parents reported that they were very confident or somewhat confident in managing their infant's sleep and only 17.2% reported they perceived their infant as having a sleep problem. Parents reported their infant's average nighttime total sleep time (nighttime TST) was 10.68±1.26 hrs and their infant's average bedtime was 7:30pm±0.86 hr. Infants' nighttime TST differed by parents' education level, wherein infants of parents with a high school education slept significantly less (10.1±1.7hrs) than infants of parents with some college or a college degree (10.7±1.7 hrs, p=0.003) and infants of parents with a graduate level education (10.7±1.7 hrs, p=0.001). There were no significant differences in parental confidence or parental perception of their infants having a sleep problem among parents with different education levels.

**Conclusions:** Our findings demonstrate that parents with access to the personalized sleep health information provided by the Nanit sleep system reported being confident in managing their infants' sleep. Infants of parents with college or graduate level education had longer nighttime TST than infants of parents with a high school education. Parental education was not significantly associated with their confidence in managing their infant's sleep. Future studies should include additional socio ecological factors to further examine influences on infants' sleep health. Additionally, further work will aim to determine the influence of the Nanit system on parental confidence considering the higher levels reported in this sample than have been reported previously in a similar sample.

**Acknowledgements:** This study was conducted in collaboration between Nanit and NYSPI.

#### LONGITUDINAL ASSESSMENT OF SLEEP STRUCTURE AND EXECUTIVE FUNCTIONS IN TYPICALLY DEVELOPING CHILDREN AND DRUG-NAÏVE CHILDREN DIAGNOSED WITH ADHD

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**Introduction:** Sleep problems, sleep-wake instability and impaired cognitive functioning are common in children diagnosed with attention deficit hyperactivity disorder (ADHD). Research findings, primarily from cross-sectional studies, are inconclusive regarding ADHD-related differences in sleep macrostructure. The age-related changes in sleep organization in children with ADHD, as well as longitudinal association of sleep and executive functioning, have not yet been investigated. Here we present data from the longitudinal study of the maturational trajectories of sleep architecture and cognitive functions in drug-naïve children diagnosed with ADHD and typically developing children followed from about 12 to 14 years, age range of most rapid developmental electroencephalogram changes.

**Materials and Methods:** Nine ADHD children (combined presentation, DSM-V criteria, mean age 12.39±0.61 years at the first measurement) without any additional comorbid condition or sleep-disordered breathing problem, and nine typically developing controls (12.07±0.35 years) were recruited. There were no major differences in overall cognitive performance between the two groups. All subjects underwent an adaptation night and all night polysomnography (PSG) twice yearly at the Laboratory. Actigraphy devices/sleep diaries documented sleep-wake schedules. Executive functioning was assessed by the Comprehensive Executive Function Inventory (CEFI, parent form). Data from 4 recording time-points were

analysed with mixed effects analysis for the PSG data and with repeated measures ANOVA for the executive functioning data.

**Results:** Comparison of the PSG between the ADHD and control groups showed that the ADHD group had significantly ( $p < 0.01$  for all) lower time in bed (mean ADHD vs. control, 518.2 vs. 552.3 min), total sleep time (TST, 481.1 vs. 523.0 min), and stage N2 duration (242.2 vs. 277.0 min). Expressed as percent of TST, stage N2 duration was lower and stage N3 duration was higher in the ADHD group ( $p < 0.05$  for both). Latency to REM sleep was shorter in the ADHD group (68.8 vs. 78.8 min,  $p < 0.05$ ). Sleep efficiency, wake after sleep onset, N1 duration, N3 duration, REM sleep duration, and the number of awakenings did not differ between groups ( $p > 0.1$  for all). N3 duration and N3 as a percent of TST decreased with age ( $p < 0.001$  for both) and N2 as a percent of TST increased with age ( $p < 0.001$ ). There were no group differences in the age-related changes in any sleep structure measure (age by group interaction  $p > 0.2$  for all). Children with ADHD had poorer executive functions. CEFI full scale and all subscales were significantly lower in the ADHD group, without significant recording by group interaction for any scale. The correlation between CEFI full scale and sleep structure variables were not significant for any recording session.

**Conclusions:** Sleep duration is shorter in drug-naïve children with ADHD due to the shorter stage N2 duration. Other than sleep duration and REM latency, sleep macrostructure is basically similar between groups and age-related changes do not differ between groups. Children with ADHD exhibit similar developmental trajectories but constantly poorer executive functioning compared to the typically developing children, suggesting a developmental lag.

**Acknowledgements:** The study was supported by Shota Rustaveli National Science Foundation Research Grant - FR17\_94

#### MAXILLARY EXPANSION AS TREATMENT OF NASAL OBSTRUCTION RESISTANT TO OTHER TREATMENTS IN CHILDREN

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**Objective:** maxillary constriction is both cause and consequence of nasal obstruction. Consequently, pediatric patients in otolaryngology consultation often suffer from nasal obstruction persistent after common causes of nasal obstruction such as rhinitis or adenoid enlargement have been treated. Maxillary expansion has demonstrated to diminish the nasal resistance in non-selected patients. Therefore, it could be a treatment of resistant nasal obstruction in children.

**Methods:** a consecutive case series of 16 pediatric patients with oral breathing and confirmed nasal obstruction, without any other cause of nasal obstruction apart from maxillary constriction were selected. These children performed maxillary expansion with different devices and protocols.

**Results:** there was a statistically significant reduction in nasal resistance, increase in nasal airflow, and improvement in quality of life through validated questionnaires.

**Discussion:** In conclusion, based on previous reports performing ME for orthodontic reasons, and the case series herein presented performing ME for nasal breathing, it seems that ME could be used with this objective. Future controlled studies should corroborate these results before performing a general recommendation.

#### MODALITIES OF PEDIATRIC APPROPRIATE PR MELATONIN (PEDPRM) PRESCRIPTION IN CHILDREN WITH ASD AND INSOMNIA - A CASE STUDIES

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**Introduction:** Despite high rates of comorbid insomnia among children and adolescents with autism spectrum disorder (ASD), and its negative impact on child development, health and quality of life, there is limited awareness among primary care physicians of evaluation and treatment of insomnia in this population. Pediatric appropriate Prolonged-release melatonin (PedPRM, available commercially as Slenyto®) is the first authorized drug for the management of insomnia in children and adolescents with ASD or Smith Magenis Syndrome (SMS) where sleep hygiene measures have been insufficient, but there is little evidence on how this new medicinal product performs in real life treatment.

**Materials and Methods:** This case series describes the decision-making process involved in PedPRM selection and treatment optimization in children and adolescents with ASD and insomnia. Since PedPRM was recently introduced to market, all patients were initially given behavioral treatment and off label pharmacological products for their insomnia (e.g. iron supplementation, antihistamines, immediate-release melatonin) with no or partial success and subsequently prescribed PedPRM.

**Results:** Following PedPRM dose optimization, patients obtained treatment success. Their sleep maintenance improved (longest sleep episode >6 hours), sleep initiation shortened (sleep onset latency < 30 minutes) and sleep duration increased up to recommended range for their age. Significant positive effects on daytime behavior and parent satisfaction were noted in these cases.

**Conclusions:** Pediatric appropriate prolonged release melatonin was swallowed whole without any difficulty. Upon dose optimization, it effectively resolves sleep initiation (SOL), maintenance (LSE) and duration (TST) problems as well as early morning awakenings to achieve sleep patterns within the norms for the children's age. No safety issues were observed and subsequent improvements in child behavior (mainly due to longer uninterrupted sleep) and in parent satisfaction and quality of life were reported.

**Acknowledgements:**

#### OBSTRUCTIVE SLEEP APNEA IN DOWN SYNDROME: A META-ANALYSIS AND NARRATIVE REVIEW OF SURGICAL AND NON-SURGICAL TREATMENT OUTCOMES

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**Introduction:** Obstructive sleep apnea (OSA) affects 31–97% of children with Down syndrome (DS). These children are more vulnerable to OSA related impairments than their neurotypical peers due to their limited cognitive reserve and high rates of pulmonary hypertension.

European guidelines recommend that intervention is considered at lower apnea/hypopnea index (AHI) thresholds in children with DS. In practice, uncertainty persists about when and how to treat. Adenotonsillectomy (AT) remains the first line approach in many centres where adeno-tonsillar hypertrophy is identified. Meanwhile, novel approaches, such as hypoglossal nerve stimulation (HNS), are being trialled. There has been no prior data synthesis of studies reporting alternative surgical approaches or non-invasive ventilation in this population.

The aim of this review was to systematically examine the literature reporting both surgical and non-surgical approaches used to treat OSA in these children, to inform current practice and set the agenda for future research.

**Materials and Methods:** Preferred Reporting Items for Systematic Reviews and Meta-Analyses (www.prisma-statement.org) guidelines were followed. Two separate protocols were registered in PROSPERO. One for surgical interventions (registration number CRD 42019133842) and one for non-surgical intervention (CRD 42019159588). Screening of abstracts and full papers was completed for 1485 and 170 papers respectively. Quality assessment was undertaken using the Newcastle-Ottawa Scale (NOS). This abstract will focus on AT in surgically naïve children. Eighteen papers were included. Meta-analysis focused on change in the commonest variables reported in the publications namely AHI, central apnoea index (CAI),

minimum oxygen saturation (SpO<sub>2</sub>) and EEG arousal both pre and post-intervention.

**Results:** Out of the 18 studies, there were 17 studies which were retrospective reviews of clinical cohorts, and one study which was done prospectively. NOS quality ratings were poor-fair. Within the 18 studies there were a total of 646 children under 18 years of age. Not all data were suitable for meta-analysis.

**Regarding the principal outcome of interest (AHI),** there were 10 studies of 341 participants (pre and post AT) which were analysed. The Results showed an overall effect in favour of the intervention, with the AHI being 6.77 points lower (95% CI –8.49, –5.04) after surgery. The heterogeneity was low at I<sup>2</sup>=0% and the chi-squared test for heterogeneity was not significant (p=0.745). Data will be presented for CAI, minimum SpO<sub>2</sub> and EEG arousals.

**Outcomes of surgical intervention** While most studies reported AHI as a continuous variable 7 studies provided data on OSA severity category before and after surgery, offering insights into residual post-operative OSA. Across the studies which included a total of 335 children 77.9% had moderate to severe OSA pre-operatively compared to 43.85% post-operatively.

**Conclusions:** Meta-analysis of surgically naïve children with Down Syndrome showed an improvement in AHI in all studies of surgically naïve children. However, 43.9% of children still had residual moderate to severe disease. Randomised controlled trials of AT are urgently needed to clarify the cost-benefits of surgical outcomes in this population.

**Acknowledgements:** Special thanks to the Down's Syndrome Research Foundation, UK for funding this study.

#### PACIFIER ERGONOMICS THAT CAN ENHANCE AIRWAY COMPETENCE IN INFANTS AND TODDLERS

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The Craniofacial Respiratory Complex (CFRC) is often overlooked in the process of designing a pacifier and it often results in mis-statement of the packaging claims of the brand. The use of pacifiers may be controversial but their significance as an adjunct for premature infants and other phenotypic micrognathic newborns is well established. The pacifier bulb design has commanded the most attention, but the function and design of the pacifier shield (mostly overlooked), plays an equally important role. Free mandibular movement, feeding competence, soothing, breathing, oral myofunction, palatal support and craniofacial growth and development co-exist with the need for 'proper' pacifier "fit". New biometric sizing algorithms incorporating facial anthropometrics, and other physical parameters, allow for development of new ergonomic pacifier designs that are based in science. Dynamic computational FEA models allow us to study oral myo-function and the biometrics of the pacifier "fit". Chronological age recommendations, that are based only on product SKUs, always vary from one brand to another and are rarely supported by peer reviewed research; they provide no consistent recommendations. This chronological age method of pacifier sizing can no longer be trusted; biometrics must be presented as the new gold standard. A new, simple smartphone app (Pacified®) is the screening tool needed by both parents and clinicians for early assessment.

Can this thought pathway, be the missing link to understanding the puzzle of the role of pacifiers in reducing the incidence of ALTE, BRUE and SIDS?

#### PARENTAL REPORT VERSUS AUTO-VIDEOSOMNOGRAPHY ASSESSMENT OF CHILDREN'S SLEEP

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**Introduction:** The discrepancy between self-report and objective assessments of sleep is common. Under-estimating sleep time and over-

estimating wake time have been proposed to contribute to the maintenance of insomnia. However, the discrepancy between parents' perceived and objectively assessed sleep of their child, and correlates of this discrepancy have not been previously explored. This study aims to explore 1) the differences between parent-reported vs auto-videosomnography assessed child's sleep; and 2) variables associated with differences of these two measures.

**Materials and Methods:** Participants were 1,420 English-speaking caregivers of children 6 to 36 months old. Objective sleep measures (obtained by NANIT auto-videosomnography) on average 12.00 nights (SD=3.14) were collected from all participants. Objective child sleep measurements used in this study include Total Sleep Time (TST), Wake After Sleep Onset (WASO), and Sleep Onset Latency (SOL). In addition to auto-videosomnography data, participants reported their child's sleep parameters. All participants also completed Maternal Cognition about Infant Sleep Questionnaire (MCISQ), and Brief Infant Sleep Questionnaire-Revised (BISQ-R). The sleep Discrepancy Index (DI) for each sleep index was calculated using the following formula: DI of TST = (objective TST (oTST) – parent-reported subjective TST (sTST)) / oTST. DI of WASO and SOL were calculated. Descriptive statistics and Pearson's correlation were conducted.

**Results:** The majority of the sample were mothers (68.0%), and 88.5% of the participants were between the ages of 25 and 40. Children consisted of 53.0% male and 46.8% female. The child's age ranged from 6 to 26 months, with a mean of 12.34 (SD=5.55). Mean (SD) parental DI of child sleep was -17.76 (78.10) for SOL, -0.06 (0.16) for TST, and 0.45 (1.32) for WASO. Greater DI of child TST was related to lower BISQ-R scores ( $r=-.250, p<.01$ ) and higher MCISQ scores ( $r=.144, p<.01$ ) among parents who under-estimated their child's TST and overestimated WASO and SOL. Also, greater DI of child SOL was associated with lower BISQ-R scores ( $r=.269, p<.01$ ) and higher MCISQ scores ( $r=-.131, p<.01$ ). Furthermore, DI of SOL was associated with greater perceived severity of their child's sleep ( $r=-.144, p<.01$ ), and confidence of parenting skills during bedtime ( $r=-.156, p<.01$ ) using BISQ-R. Parental DI of child WASO was not related to any of the variables in our sample.

**Conclusions:** The results showed that higher levels of parental discrepancy about their child's sleep are associated with parental cognition about child's sleep. Additionally, greater perceived severity of child's sleep and lower parental confidence during bedtime were associated with greater discrepancy of SOL. The results from this study imply that parental discrepancy about child sleep could be an important factor to consider for the intervention of pediatric sleep problems.

**Acknowledgments:** This work was supported by the National Research Foundation of Korea (NFK 2021S1A5A2A03061721).

#### PARENT-CHILD RELATIONSHIP QUALITY AND BOUNDARIES DURING EARLY CHILDHOOD AND ACTIGRAPHY-MEASURED SLEEP IN MIDDLE CHILDHOOD

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**Introduction:** In developmental and evolutionary theory, the parent-child interactive context is proposed to play a critical role in shaping sleep behaviors of children. However, most research in this area has relied on parental reports of child sleep and cross-sectional data. We examined correlations between observed parent-child relational variables (i.e., quality, cohesion, disengagement, enmeshment) during early childhood and actigraphy-measured sleep parameters during middle childhood in an ethnically diverse sample.

**Materials and Methods:** Participants included 21 preschoolers (mean age=3.96 years, standard deviation=0.86) who were 47.6% female, 31.6% Non-Hispanic White, 10.5% Non-Hispanic Black, and 52.6% Hispanic. A novel observational rating system was used to code parent-child relational

quality and boundaries (i.e., cohesion, disengagement, enmeshment) from a video-recorded free-play task between children and their primary caregivers. Adversity information was gathered from child protection records, parental report questionnaires, and semi-structured interviews. During a follow-up study when participants were ages 8–11, wrist-worn actigraphs measured one week of the following sleep parameters: sleep time in clock time (ST), wake time in clock time (WT), time in bed in minutes (TIB), total sleep time in minutes (TST), sleep efficiency in percent (SE), wake after sleep onset in minutes (WASO), and number of awakenings (NWAK). Pearson correlations were used to examine links among parent-child relational quality and boundaries, adversity, and sleep. Semi-partial correlations were used to examine associations between parent-child variables and sleep, adjusting for adversity.

**Results:** Stronger parent-child relationship quality was correlated with less TST variability ( $r=-0.45$ ,  $p=0.038$ ), shorter average TIB ( $r=-0.48$ ,  $p=0.029$ ), less TIB variability ( $r=-0.61$ ,  $p=0.003$ ), greater average SE ( $r=0.53$ ,  $p=0.013$ ), and shorter ( $r=-.64$ ,  $p=0.002$ ) and less variable ( $r=-.53$ ,  $p=0.013$ ) WASO. Parent-child cohesion was correlated with less TIB variability ( $r=-0.63$ ,  $p=0.002$ ), less TST variability ( $r=-0.49$ ,  $p=0.025$ ), greater average SE ( $r=0.47$ ,  $p=0.031$ ), less SE variability ( $r=-0.47$ ,  $p=0.030$ ), and shorter ( $r=-0.56$ ,  $p=0.008$ ) and less variable ( $r=-0.57$ ,  $p=0.007$ ) WASO. Parent-child disengagement was correlated with greater TIB variability ( $r=0.44$ ,  $p=0.049$ ), greater TST variability ( $r=0.60$ ,  $p=0.004$ ), lower average SE ( $r=-0.74$ ,  $p<0.001$ ), more SE variability ( $r=0.66$ ,  $p=0.001$ ), and longer ( $r=0.72$ ,  $p<0.001$ ) and more variable ( $r=0.50$ ,  $p=0.022$ ) WASO. Parent-child enmeshment was uncorrelated with sleep, and adversity was correlated with a greater number of average NWAK ( $r=0.39$ ,  $p=0.045$ ), but no other sleep variables. Links between parent-child variables and sleep held when adjusting for adversity.

**Conclusions:** Stronger parent-child relationship quality and cohesion and less disengagement during early childhood were correlated with better sleep outcomes in middle childhood, even when accounting for adversity. Findings support targeting parent-child relationships in pediatric behavioral sleep interventions.

**Acknowledgements:** This research was supported by NIMH R01 MH083704 (PI: Tyrka), NICHD R01 HD086487 (PI: Tyrka), NICHD, R01 HD095837 (PI: Parade), the Society for Research in Child Development Small Grant for Early Career Scholars (PI: Coe). DR, JC and TD received support from NICHD T32HD101392 (PI: Stroud & Tyrka).

## PARENTS' VALUES SHAPE PARENTING PRACTICES AND BELIEFS THAT IMPACT INFANT SLEEP

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**Introduction:** Parents' expectations about development influence parenting practices, which, in turn, shape child development. For example, expectations about motor development predict when infants achieve key motor milestones, like sitting or walking (Adolph, et al., 2010). Parents' expectations about sleep are stronger predictors of childhood sleep problems than child factors (Johnson & McMahon, 2008). Beliefs that are not specifically child-related also influence parents' decisions. For example, parents' values shape opportunities for preschoolers' play (Horger, et al. 2017) and how parents work together to manage parenting responsibilities (Pisauro, et al., 2021). This study asked whether parents' values impacted parenting expectations related to infant sleep.

**Materials and Methods:** 1863 parents (1425 mothers) with children 3- to 18-months old (mean=8.83 mos) completed an online survey. Families used *Nanit*, a home video baby monitoring system that uses computer vision technology to calculate nightly summary sleep characteristics (e.g., quality of night sleep, parent visits, night wakings).

The survey comprised the *maternal cognitions about infant sleep questionnaire* (MCISQ; Morrell, 1999) with 4 subscales on beliefs about setting limits around infants' sleep, *anger* at infants' sleep-related demands, *doubts* about parenting competence, and concerns about infant feeding during the night; and the *portrait values questionnaire* (PVQ; Schwartz, 1992) with 10 subscales related to personal vs. social foci and openness to change vs. tradition.

**Results:** Pearson correlations showed that the higher parents' scores on

the MCISQ subscales (more concerns about setting limits, more doubts about parenting competence, angrier about infants' demands, more concerns about infant feeding), the worse infants' night sleep quality, the greater the frequency of parent visits, and the more infant night wakings (all  $p's \leq .001$ ).

A cluster analysis of the value subscales revealed 4 profiles: weak endorsement of growth ( $n=429$ ), resistance to change ( $n=520$ ), openness to change ( $n=484$ ), and strong endorsement of growth ( $n=446$ ). A series of 2 (parent)  $\times$  4 (PVQ profile) ANOVAs on infants' sleep characteristics and the MCISQ subscales revealed that infants of parents who were resistant to change (took more time to fall asleep than infants of parents who were open to change. Moreover, parents open to change were significantly **less** likely to be concerned about setting sleep-related limits; have doubts about sleep-related parenting abilities; and have concerns related to feeding during the night. Parents with a weak endorsement of growth reported that they were significantly angrier about sleep-related demands than the other profiles. In addition, mothers had significantly more concerns about setting limits, doubts about parenting competence, and concerns about safety than fathers and fathers were significantly angrier about infants' sleep-related demands than were mothers.

**Conclusions:** This study may be the first to link value systems with parenting practices that infant development. Individuals who value personal growth may approach learning to parent with less anxiety and stress than those who resist change. This may have implications for parents' value systems on the development of infant sleep.

**Acknowledgements:** This work was supported by the NSF, Division of Behavioral and Cognitive Science [1941122] to S.E.B.

## PEDIATRIC POLYSOMNOGRAPHY: CROSS-SECTIONAL STUDY

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**Introduction:** Polysomnography (PSG) is the gold standard exam to evaluate sleep-disordered breathing (SDB) and other sleep disorders. Indications for PSG, diagnostic criteria, and therapeutic approach in pediatric age are specific, differing from adults.

This study aimed to review the sample of PSG performed in a tertiary pediatric hospital.

**Materials and Methods:** A cross-sectional study was performed in pediatric patients submitted for laboratory-based PSG from June/2018 to December/2021. Demographic patient data, PSG indications, results, and subsequent treatment were collected from clinical records.

**Results:** The initial sample included 291 PSG (patient mean age 10.0 $\pm$ 5.1 years, 60.3% male).

PSG indications were: suspected SDB in 252 (associated obesity in 95 cases, previous otolaryngology surgery in 79, genetic/dysmorphic syndromes in 67 and neuromuscular disorders (ND) in 27); suspected periodic limb movements of sleep (PLMS) in 36; excessive daytime sleepiness in 24 and complex parasomnias in 8.

PSG with total sleep time under 360 minutes and sleep efficiency under 60.0% were excluded, remaining a final sample of 252 PSG. In these, mild, moderate, and severe OSA was identified in 113 (44.8%), 46 (18.3%), and 43 (17.1%) cases, respectively. Of 81 patients over 13 years old, in 66 (81.5%) OSA severity changed when adult criteria were considered. Capnometry was performed in 119 patients with ND and/or obesity, and hypoventilation was identified in 24 (20.2%).

Regarding treatment in the moderate-severe OSA group ( $n=89$ ): 36 (40.4%) patients started non-invasive ventilation (NIV), 15 (16.9%) underwent otolaryngology surgery, 10 are awaiting surgery and 5 NIV start. Of 38 patients over 13 years with moderate-severe OSA, 25 (65.8%) had none or mild OSA according to adult criteria, which changed the therapeutic approach.

A significant PLMS index (>5/hour) was found in 60 (23.8%) of the 252 PSG, 53 (88.3%) of them with OSA. In 3 (9.1%) of the 33 with suspicion, a significant PLMS index was confirmed.

The 21 PSG performed before multiple sleep latency tests (diagnostic of narcolepsy in 8 and hypersomnia in 4) identified 15 cases of OSA (6 with narcolepsy) and 5 of PLMS>5/hour (1 with narcolepsy).

Globally, parasomnias were reported in 10(4.0%) of the 252 exams. In the group of 8 cases with complex parasomnias motivating the exam, 6 had OSA, 2 epileptiform activity, and 1 significant PLMS index.

**Conclusions:** Moderate-severe OSA was identified in approximately one-third of the sample and a significant percentage needed NIV. This is probably due to the complexity of the patients with PSG indications, who have obesity and genetic/dysmorphic syndromes as frequent comorbidities. We believe it's necessary to establish more defined criteria for OSA treatment in patients over 13 years old. Contrary to expectations, hypoventilation was found in only 20% of patients with higher risk.

PLMS were largely associated with OSA and SDB was frequent in narcoleptic patients.

Although parasomnias are common in children, only the atypical or frequent require PSG, which explains the fewer exams performed by this motive.

In our perspective, this study contributed to a better characterization of the broad indications and applications of PSG in the pediatric age.

### PERIODIC LIMB MOVEMENTS DURING WAKEFULNESS IN CHILDREN WITH RLS AND PLMD

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**Introduction:** Periodic limb movements (PLM) are a polysomnographic finding typically described as a brief extension of the toe and dorsiflexion of the ankle which can be associated with autonomic changes as well as arousals or awakenings<sup>1</sup>. PLM in sleep (PLMS) are seen in 80% of adults and 63–74% of children with Restless Leg Syndrome (RLS)<sup>2</sup>. Periodic Limb Movement Disorder (PLMD) is defined by the presence of PLMS associated with sleep or daytime dysfunction. PLMD and RLS are closely related in children as several studies have observed that a significant proportion of pediatric RLS were initially diagnosed with PLMD<sup>3,4</sup>. Adult studies have demonstrated that PLM during wakefulness (PLMW) are common in patients with RLS<sup>5</sup>, however, there are no available data in pediatric population. Therefore, this study examined PLMW and its association to PSG parameters and biomarkers in children with RLS and PLMD.

**Materials and Methods:** Video polysomnography of children with RLS and PLMD in our center were retrospectively reviewed from February 2019 to May 2021. The PSG was rescored for the presence of PLMW. Scoring of PLMW was done during the period preceding sleep onset while the patient was seated or supine in bed. A significant PLMW was defined by the presence of PLMW index (PLMWI) more than 20 per hour. The diagnosis of PLMD and RLS was assessed according to ICSD 3<sup>rd</sup> Edition and international RLS study group (IRLSSG) guidelines. Data examined included PSG characteristics, ferritin, and associated comorbidities. Statistical analysis were performed using unpaired non-parametric t-tests and non-parametric Spearman's correlation coefficients.

**Results:** 53 children met the criteria; 19 children with PLMD, 16 children with RLS (RLS/PLMS) and elevated PLMSI (PLMS  $\geq$  5/hr of sleep), and 18 children with RLS without elevated PLMS (RLS/no-PLMS). The mean age was 9, 10, and 10 years respectively. Analysis of PLMW revealed that there were no statistical differences in proportion of significant PLMW among children with PLMD (17.4%), RLS/PLMS (29.4%) and RLS/no-PLMS (28.6%) ( $P>0.05$ ). Similarly, there were no significant differences in the mean PLMWI among all 3 groups ( $12.75 \pm 21.57$ /hr (SD) [PLMD];  $18.78 \pm 18.07$ /hr [RLS/PLMS];  $13.66 \pm 17.19$  [RLS/no-PLMS]) ( $p=0.57$ ). Further analysis of relationship between PLMW and PSG and biomarkers demonstrated no significant correlations between PLMWI and PLMS index ( $r=0.22$ ) or PLMWI and ferritin level ( $r=0.02$ ).

**Conclusions:** This is the first study to examine PLMW in children with sleep related movement disorders. We observed that PLMW was relatively common in our cohort of children with RLS and PLMD with no significant differences in the number or frequency of significant PLMW between children with RLS and PLMD. In addition, we did not find a strong

correlation between PLMW and PLMS or between PLMW and ferritin level in our cohort. We speculate that the presence of significant PLMW in children with PLMD may be due to the early manifestation of RLS phenotype in significant proportion of children with PLMD.

**Acknowledgements:**

### PREVALENCE, PATTERNS AND SOCIO-DEMOGRAPHIC CORRELATES OF SLEEP DURATION IN ADOLESCENTS: RESULTS FROM THE LABMED STUDY

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**Introduction:** Adolescence is a period that affects health and behaviour, including sleep quantity. Despite the premise that sleep is a cornerstone in this vital phase of human development, a considerable number of adolescents worldwide have insufficient sleep, especially on weekdays, which has become a serious worldwide public health issue. Therefore, the aim of this study was to report the prevalence of adequate sleep and the correlates of sleep duration in adolescents.

**Materials and Methods:** This is a cross-sectional analysis with 1017 adolescents (471 girls) aged  $14.6 \pm 1.8$  years. Habitual total sleep duration on a weekday and on weekends was self-reported. Participants' sleep duration was categorized according to their age recommendations from the American National Sleep Foundation guidelines and recoded into 3 categories: adolescents meeting guidelines; short sleepers (those sleeping less than the recommended) and long sleepers (those sleeping more than the recommended).

**Results:** The percentage of adolescents meeting the guidelines was 72.7%, 60.7% and 51.3%, during a whole week, on weekdays and on weekends, respectively. Boys were always more compliant with the guidelines than girls, for all week categories. A significant difference was found on sleep duration on weekends, between boys and girls ( $p<0.001$ ). During weekdays, more adolescents were classified as short sleepers when compared to long sleepers. Younger adolescents were more likely to meet the guidelines over the whole week and on weekdays (OR=2.23, OR=2.13, respectively;  $p<0.05$ ) and being long sleepers on weekends (OR=1.49,  $p<0.05$ ). Those of medium and low SES were less likely to meet the sleep guidelines for all week categories ( $p_{\text{trend}}<0.001$ ). Girls were more likely than boys to meet the guidelines or being long sleepers on weekends (OR=1.78, OR=2.85, respectively;  $p<0.05$ ).

**Conclusions:** During weekends, the percentage of girls sleeping more than recommended is high, indicating a clear compensation of low sleep duration during weekdays. Those of low SES and older adolescents were less likely to meet the sleep guidelines. Policy makers and researchers should consider the potential effects that SES, gender and age might have on sleep duration, when designing targeted interventions to promote adequate sleep duration.

**Acknowledgements:** Rute Santos is supported by the Portuguese Foundation for Science and Technology (CEECIND/01069/2017 and FCT/UIDB/00617/2020). Luís Lopes is supported by the Portuguese Foundation for Science and Technology (CEECIND/01089/2017 and FCT/UIDB/00617/2020). Bruno Rodrigues is supported by the Portuguese Foundation for Science and Technology (UI/BD/150675/2020).

### RUNNING A PAEDIATRIC AMBULATORY SLEEP SERVICE IN A PANDEMIC AND BEYOND

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**Introduction:** In response to COVID-19, re-establishing safe elective services was prioritised in the UK. Here we assess the impact on face-to-face hospital attendance, cost, and efficiency of implementing a virtual sleep clinic (intervention one) to screen for children requiring level 3 ambulatory sleep studies, using newly implemented ENT-UK guidelines (intervention two) for investigation of obstructive sleep apnoea (OSA). The objectives are (1) to compare the proportion of children attending sleep clinic for investigation of OSA symptoms undertaking a sleep study before and after implementation of the interventions; (2) to compare clinic cancellations and first-time success rates of sleep studies before and after intervention.

**Materials and Methods:** We compared retrospective data from children aged 3 months to 16 years referred to sleep clinic by ENT for the investigation of OSA over the 3-months immediately following intervention (1<sup>st</sup> June 2020 - 1<sup>st</sup> September 2020) to the same period in the previous year before intervention (1<sup>st</sup> June 2019 - 1<sup>st</sup> September 2019). Data was collected on the following parameters: Patient demographics, number of children attending sleep clinic, number of children undergoing sleep studies, diagnostic outcomes, number of appointment cancellations and number of first-time sleep study failures.

**Results:** The proportion of children seen by the paediatric sleep-disordered-breathing service was less post-intervention; 49% (29/59) of patients had ambulatory sleep studies post-intervention, compared to 88% (73/83) pre-intervention ( $P < 0.001$ ). The trends in diagnosed OSA severity were similar pre- and post-intervention ( $P = 0.002$ ), with the exception of an increase in the proportion of children diagnosed with moderate OSA post-intervention (most diagnosed clinically). The mean age of children in the pre- and post-intervention groups was similar. The mean age of children having a sleep study to diagnose OSA was lower than those diagnosed clinically in both groups.

The proportion of children whose sleep clinic appointments were cancelled by parents was greater before intervention (13% [12/95]) than after intervention (5% [3/62]).

The first-time failure rate of ambulatory sleep studies was lower after intervention (7% [2/29]) compared to before intervention (10% [7/73]).

Overall, implementing a virtual sleep clinic to screen for children requiring a sleep study for the diagnosis of OSA using ENT-UK guidance led to a reduction of 39% in the proportion of children requiring face-to-face attendance for a sleep study.

**Conclusions:** The similar spread of diagnosed OSA severity before and after intervention and the higher proportion of children diagnosed clinically post-intervention across all diagnostic severities suggests clinical diagnosis of OSA is accurate in eligible children. As well as improved patient safety during the COVID-19 pandemic, there are cost-efficiency benefits of reduced face-to-face attendance. We evidenced further cost-efficiency benefits with reduced clinic cancellations and sleep study failure rates. These results have implications for the wider sleep community and other diagnostic services in the era of the COVID-19 pandemic and beyond.

**Acknowledgements:** Simone Millership, ESNEFT, assisted in data collection

#### SLEEP ALTERATIONS IN PORTUGUESE CHILDREN DURING THE FIRST COVID-19 LOCKDOWN: A DESCRIPTIVE ANALYSIS

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**Introduction:** It is well known that changes in a child's routine have a powerful influence in sleep. Naps can be reduced, bedtime may diverge, as well as sleep latency and total sleep time.

In Portugal, the first lockdown due to Covid-19 happened in between March and May 2020.

**Materials and Methods:** A questionnaire was randomly applied to Portuguese parents (615 valid surveys) of children of ages between 6 months and 12 years. We used SPSS for data analysis.

**Results:** At the time of the questionnaire, the children were in lockdown for approximately 31 days. The sample comprehended 615 children, 52% female gender and 48% male gender, with an average age of 3 years.

About 74% of the inquired parents referred child sleep alterations since the beginning of the lockdown.

Most of the children spent their days only with their mother and described their main activity to be "playing", followed by "ludic activities" and "watching television (TV)". The television also appeared in third place as the last thing that children did before going to sleep, preceded by "reading a story" and "eating".

The main difference in child sleep noticed by the parents was the increase in sleep latency. "Multiple differences" was the second response given by the parents, followed by changes in sleep schedules. Children with ages between 2 and 5 years showed more difficulties concerning nap time.

Upon 30.9% of the parents attributed the difference in their children's sleep to routine modifications, followed by the great number of hours spent at home. Bedtime also suffered a change in about 1-2hours, being that 69.8% of the children went to bed later. The wake up hour was also altered: 73.5% started waking up later.

More than half of the children slept about 10 to 12 hours per night and most of them fell asleep between 10pm and 11pm, and woke up between 8 and 9am. Nap schedules also changed during the lockdown.

Parents related their children's sleep alterations with a crescent irritability.

**Conclusions:** The Covid-19 lockdown in Portugal carried a marked change in children's sleep, concerning, in particular, bedtime, wake time and nap schedules and an increase in sleep latency. These changes were enhanced, for the most part, by a change in the routine and a augmented time spent at home.

**Acknowledgements:** To all the parents who contributed, thank you.

#### SLEEP DISORDERED BREATHING SINCE CHILDHOOD ASSOCIATED WITH ATHEROSCLEROSIS IN ADULTHOOD

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**Introduction:** We have previously shown that a cumulative exposure to sleep disordered breathing (SDB) since childhood is associated with endothelial dysfunction in young adulthood independent of obesity. Limited longitudinal cohort studies have examined the association of SDB with atherosclerosis using such a developmental targeted approach. The present study aimed to determine if exposure to SDB since childhood is associated with long-term increased carotid intima-media thickness (CIMT) in young adulthood.

**Materials and Methods:** We studied a subsample of 204 subjects (53% female, 23% racial/ethnic minority) from the Penn State Child Cohort who underwent 9-hour in-lab polysomnography in childhood at median age 9, about 7 years later in adolescence at median age 16, and about 15 years later in young adulthood at median age 24. Based on the apnea/hypopnea index (AHI) truncated at 5 events or more per hour of sleep, including participants on positive airway pressure therapy, we calculated the averaged exposure to AHI over the three time points (cAHI). Participants underwent B-mode ultrasound in young adulthood to assess total CIMT from right and left carotids. Linear regression models first controlled for sex, age, race/ethnicity, and length of follow-up and, thereafter, for body mass index (BMI).

**Results:** Despite cAHI being associated with higher CIMT in adulthood ( $\beta = 0.015$ ; 95% CI = 0.005, 0.025;  $p = 0.003$ ), the association was significantly diminished after adjusting for BMI ( $\beta = 0.004$ ; 95% CI = -0.004, 0.014;  $p = 0.424$ ). The results were similar when using the squared-root of CIMT as a test of the robustness of the analysis ( $\beta = 0.010$ ; 95% CI = 0.004, 0.017;  $p = 0.002$  before BMI adjustment;  $\beta = 0.003$ ; 95% CI = -0.004, 0.010;  $p = 0.415$  after BMI adjustment).

**Conclusions:** The novel data in this ongoing longitudinal study indicates that obesity is a major contributor to atherosclerotic risk associated with SDB in youth, which does independently impact endothelial function. Targeting obesity is crucial in preventing early stage atherosclerotic burden.

**Acknowledgements:** National Institutes of Health (R01HL136587, UL1TR000127)

## SLEEP DISORDERS AND NEUROPSYCHIATRIC DISORDERS IN A PEDIATRIC SAMPLE OF TUBEROUS SCLEROSIS COMPLEX: A QUESTIONNAIRE-BASED STUDY

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**Introduction:** sleep disorders (SD) are known to significantly affect children, especially when neuropsychiatric conditions are present. Tuberos Sclerosis Complex (TSC) is a rare systemic disease with a very high risk of neuropsychiatric comorbidity (TSC-associated neuropsychiatric manifestations - TAND) including intellectual disability, autism spectrum disorder and attention deficit hyperactivity disorder. Furthermore, these children can frequently present early onset seizures. SD are known to represent a significant problem in this population, but very few data are available. The objective of this study was to assess the prevalence of SD in children with TSC, and to evaluate the relationship between sleep, epilepsy and TAND.

**Materials and Methods:** we administered the Sleep Disturbance Scale for Children (SDSC) to parents of children with TSC referring to different Italian centers. We also collected information on epilepsy and TAND.

**Results:** We analyzed 177 questionnaires (mean age 9.7 years). An epilepsy diagnosis was reported in 87.3% of cases, with persistent seizures in 71.4% of them. At least one TAND was reported by 75.7% of participants. An existing SD diagnosis was reported in 16.4% of children.

SDSC score was positive in 59.3% of patients. In particular, SDSC was positive in 7/23 patients without epilepsy (30.4%) and in 98/154 patients with epilepsy (63.6%) ( $p=0.05$ ). Analyzing the correlation with TAND, SDSC was positive in 67.9% of patients with TAND and in 32.5% of those without ( $p<<0.001$ ). A univariate logistic regression analysis, estimated that a comorbid neuropsychiatric condition increased the risk of having a positive SDSC score ( $p<<0.001$ , OR=1.48). After adding in a multivariate logistic model the independent variables of active epilepsy, age, and pharmacological treatments, TAND continued to be a significant risk factor for positive SDSC ( $p=0.01$ , OR=1.11).

The median SDSC score in patients with and without a TAND complain were respectively 43 and 35 (ranges: TAND 27-85; no TAND 28-68; means: TAND 47.0; no TAND 38.1) ( $p<<0.001$ ). Regarding specific neuropsychiatric conditions, the only diagnosis that appeared to be significantly associated with a positive SDSC were autism spectrum disorder ( $p=0.004$ ), intellectual disability/psychomotor delay ( $p=0.003$ ), and language disturbances ( $p=0.0005$ ).

**Conclusions:** our results revealed a high prevalence of SD in children with TSC, thus highlighting the need of a specific screening program. SD did not appear to be significantly related to the presence of epilepsy, while a very strong association was found with TAND. SD and TAND are both factors severely impacting the quality of life of children and their families. Therefore, it is of utmost importance an early detection of a SD in order to plan an individualized treatment, that in some cases might also impact the severity of TAND symptoms, ameliorating behavior and attention.

**Acknowledgements:** we thank the Italian TSC Association for supporting us in performing this study.

## SLEEP DISORDERS IN PEDIATRIC MIGRAINE: A QUESTIONNAIRE-BASED STUDY

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**Introduction:** There is a high comorbidity between migraine and sleep

disorders, with a mutual dependence between sleep and headache. This study aimed to analyze the relationship between headache features (migraine frequency and severity, presence of migraine equivalents, use and efficacy of medications) and sleep in pediatric migraine.

**Materials and Methods:** Parents of children and adolescents with migraine completed the Children's Sleep Habits Questionnaire (CSHQ) and the Epworth Sleepiness Scale for Children and Adolescents (ESS-CHAD) and answered questions about headache characteristics in their children. The presence of sleep disorders was defined according to CSHQ score.

**Results:** Sleep disorders were detected in 72.9% of 140 subjects, but only 5.0% had already received a diagnosis. We found statistically significant higher headache frequency ( $p=0.031$ ) and higher prevalence of migraine equivalents ( $p=0.007$ ) in patients with sleep disturbances. A higher CSHQ total score was associated with higher frequency of severe attacks ( $p=0.012$ ) and lower efficacy of acute medications ( $p=0.003$ ). Significant positive correlations of sleep onset delay, sleep duration and nightwakings subscales with migraine frequency also emerged.

**Conclusions:** Our findings indicate that sleep disorders are highly prevalent in pediatric migraine and frequently associated with higher headache severity and lower response to acute therapy, but often remain underdiagnosed. Given the relationship between sleep and migraine characteristics, improving sleep quality could help to reduce migraine intensity and disability and vice versa.

## SLEEP EFFICIENCY AS A NEW MEASURE OF PEDIATRIC OBSTRUCTIVE SLEEP APNEA (OSA)

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**Introduction:** Pediatric Obstructive sleep apnea (OSA) is a common disorder, which shows different aspects from adult OSA: etiology, clinical features (nocturnal and diurnal) and treatment. Polysomnography (PSG) is a useful tool and the gold standard. The most frequent measure used to define and assess the severity of OSA is the apnea-hypopnea index (AHI). The aim of this work is to suggest additional measures, such as sleep efficiency to assess the severity of OSA.

**Materials and methods:** We performed a retrospective and analytical study of 101 children diagnosed with OSA using PSG, in our Hospital (Ramón y Cajal Hospital, Madrid) between 2019-2020. We analyzed demographic data, diurnal clinical features and polysomnographic measures such as AHI and sleep efficiency. We used AASM diagnostic criteria to assess the severity of OSA.

**Results:** Children were classified into 3 groups according to severity of OSA: mild (47 patients), moderate (22 patients) and severe (32 patients). The average sleep efficiency was 84.52%. The percentage of sleep efficiency in mild, moderate and severe OSA were 86.34%, 82.85% and 82% respectively. Pearson's correlation coefficient showed a negative correlation between AHI and sleep efficiency. In addition, we analyzed the association between diurnal symptoms and sleep efficiency in patients in the mild OSA group: children with low efficiency are more likely to suffer from diurnal symptoms.

**Conclusion:** Sleep efficiency could be a useful tool to support OSA diagnosis. Our study showed a decrease in sleep efficiency correlates with higher severity of OSA. In mild OSA, which is an heterogeneous group, we observed that patients with low efficiency sleep have a higher tendency to develop diurnal symptoms. Therefore, sleep efficiency could be considered as a measure of severity in the diagnosis of Pediatric OSA.

## SLEEP HABITS AND SCREEN USE BY ADOLESCENTS DURING COVID-19 LOCKDOWN

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**Introduction:** Technology has improved our lives in many ways. However, adolescents tend to spend excessive amounts of time watching screens. This can have an impact on their lives, namely on sleep. The COVID-19 pandemic exacerbated these problems.

We intended to characterize adolescents' habits regarding sleep and screen use during the COVID-19 lockdown as they relate to sleep quality and quantity.

**Materials and Methods:** Multicentric transversal descriptive study. A survey with questions about screen use, sleep and the Portuguese version of the Pediatric Daytime Sleepiness Scale was completed by adolescents seen in consultation between January 25<sup>th</sup> and March 25<sup>th</sup> 2021. Variables were correlated using Chi-square and Mann-Whitney tests, significance if  $p < 0.05$ .

**Results:** Our sample included 131 adolescents (66.4% female) with a median age of 15.0 years. Most don't have chronic (70.2%) or sleep (85.3%) disorders. Median sleep time was 9h during the week ([3h-11.5h]) and 10h on the weekend ([4.5h-15.5h]). During the week 26% slept less than the recommended time, with 37.7% falling asleep after midnight. About one third (35.9%) said they slept worse since the pandemic. We identified 39.7% with onset insomnia and 13.7% of adolescents with excessive daytime sleepiness (EDS).

A majority (74.0%) had a daily screen time of over 6 hours, 45.0% over 10h and 16.8% over 12h. Most of this time was used to attend classes (87.0% <10h/day; 45.0% <6h/day), followed by talking to friends (39.0% ≥6h/day), watching videos and gaming. When it came screens available in their rooms, 83.2% had a smartphone at night, 61.1% a television, 57.3% a computer and 16.0% a gaming console. Fifty-five percent claimed to use screens every day in the hour prior to sleeping.

The frequency of bad sleep habits correlated with worse self-reported sleep quality ( $p=0.04$ ). Having a computer or a smartphone in the bedroom at night correlated with shorter sleep duration during the week ( $p=0.01$  and  $p<0.01$ , respectively). Association was found between screen time above 6h and the following variables: onset insomnia ( $p=0.03$ ), shorter sleep duration on weekdays ( $p=0.04$ ) and EDS ( $p=0.04$ ). There was a correlation between screen use in the hour prior to sleeping more than 4 times per week and: onset insomnia ( $p=0.01$ ), shorter sleep duration on weekdays ( $p=0.04$ ) and EDS ( $p=0.01$ ).

**Conclusions:** As expected, a correlation was found between sleep quality and worse sleeping habits. During this lockdown the high percentage of those using devices over 6h/day can be explained by online classes. We also found a very high percentage of adolescents with devices in the bedroom used at bedtime with a clear negative impact on sleep. It's urgent to implement strategies and change these habits, particularly during the COVID-19 pandemic.

#### SLEEPLESS ON THE ROAD: ARE MOTHERS OF INFANTS WITH PEDIATRIC INSOMNIA AT RISK FOR IMPAIRED DRIVING?

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**Introduction:** Infant insomnia is highly prevalent, tends to persist when untreated, and is associated with a myriad of adverse child outcomes. Negative consequences for parents have also been demonstrated, including increased maternal anxiety and depression, and poorer physical health. Yet, much less is known about the consequences of infant insomnia on parents' daytime functioning, and specifically on their driving performance. One study has linked sleep problems with self-reported near miss accidents in parents of infants (Malish et al., 2015). However, it has yet to be examined whether objectively assessed driving is associated with infant insomnia. This study used a simulated driving test to compare the driving performance of mothers seeking treatment for their infants' sleep problems to two control groups: mothers of infants without sleep problems and childless age-matched controls.

**Materials and Methods:** A total of 45 women participated in this study

( $Mage=31.2$   $SD=5.2$ ;  $n=13$  mothers of infants aged 6-24 months with insomnia,  $n=13$  mothers of infants aged 6-24 months with no perceived sleep problems; and  $n=19$  childless controls). Participants completed a 7-day sleep diary before performing an in-lab computerized simulated driving task. Self-reports of sleepiness (Epworth Sleepiness Scale), driving (Driving Behaviour Questionnaire) and a demographic questionnaire were completed in the lab. Subsequently, a 25-min monotonous highway driving task was performed. Primary outcome measures consisted of standard deviation of lateral position (SDLP), and the number of lane crossings. General linear modelling was used to assess the effects of group, while controlling for relevant covariates.

**Results:** Based on sleep diary data, mothers of infants with sleep problems had significantly shorter sleep duration, longer wake after sleep onset, and more nighttime awakenings compared to mothers of infants who were reported to sleep well and childless controls (all  $ps < 0.001$ ). Moreover, daytime sleepiness scores were greater in mothers of poor sleeping infants compared to both control groups ( $F(2,42)=7.05$ ,  $p=0.002$ ). As for driving metrics, SDLP was significantly higher in the clinical group compared to both control groups ( $F(2,42)=5.84$ ,  $p=0.006$ ), indicating that mothers of infants with insomnia deviated from their lane to a greater extent. Non-significant trends in this direction were observed for lane crossings, as well as for self-reported driving lapses and errors.

**Conclusions:** Mothers of infants with insomnia had significantly more lane deviations compared to controls. While these findings are preliminary, they indicate that these mothers may be at increased risk for motor vehicle accidents. This risk may be further exacerbated by the presence of an infant passenger in the vehicle (Maasalo et al., 2017). Future research is warranted to replicate these findings, examine these links in fathers of infants with insomnia, and develop prevention programs aimed at raising awareness and managing driving safety risks associated with infant sleep problems.

**Acknowledgements:** We wish to thank Flinders University for funding this study, Tahlia Cross, Josh Fitton, and Rebecca Fry for their help in data collection, and our participants for their contribution.

#### SLEEP MACROSTRUCTURE IN ADOLESCENTS WITH ANOREXIA NERVOSA: A PILOT CASE-CONTROL STUDY

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**Introduction:** Eating disorders are an emerging psychiatric problem with high rate of mortality. Specifically, Anorexia Nervosa (AN) is the most frequent condition eating disorder during developmental age starting from puberty and prevalent among females. AN tends to alter all the body functions, including the sleep patterns. Aim of the present study is assessing the sleep macrostructure in AN.

**Materials and methods:** 14 adolescents (mean age  $14.36 \pm 1.45$ ) with AN underwent reduced polysomnographic recording (PSG) with neural network device and then compared with 14 neurotypical subjects. The following parameters were evaluated: Time in bed (TIB), Sleep period (SPT), Total sleep time (TST), Sleep latency (SOL), REM first phase latency (FRL), stage Shifting (SS/h), Number of awakenings/hour (AWN / h), Sleep efficiency% (SE%), N1%; N2%; N3%; REM%, N1, N2, N3, and REM duration and total sleep time for (N1, N2, N3, and REM. Statistical analyzes were performed with STATISTICA 8.0 software.

**Results:** Subjects with AN compared to controls showed a significant reduction in sleep duration parameters (TIB, SPT, TST;  $p \leq 0.001$ ), in stage duration of N2 ( $p=0.002$ ) and N3 ( $p=0.001$ ). On the other hand, an increase in AWN/h ( $p \leq 0.001$ ) and in REM-tst ( $p=0.04$ ) was found.

**Conclusions:** The data in the literature concerning sleep alterations in AN are few and dated and such as not to allow unequivocal conclusions. This pilot study supports the hypothesis of a dysregulation in the NREM/REM sleep balancing that could be linked to the alteration of the orexinergic and serotonergic neurochemical pathways. These statistical evidences tend to objectify the macrostructural alteration of sleep in patients with AN and suggest the need for PSG as a further examination to integrate and refine the psychodiagnostic evaluation.

## SLEEP TIMING AND DURATION IN ADOLESCENTS WITH DEBILITATING CHRONIC ORTHOSTATIC INTOLERANCE

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**Introduction:** Lack of adequate quality and quantity of sleep impacts neurocognition, mood, immunity and cardiometabolic functioning. Patients with orthostatic intolerance (OI) frequently report problems with sleep and fatigue. A study of adults with chronic OI reported more subjective complaints of daytime sleepiness, fatigue, worse sleep, and health related quality of life compared to controls. To our knowledge, there are no studies looking at objective measures of sleep timing and duration in adolescents with OI. The goal of this study was to gain a better understanding of sleep and fatigue complaints in adolescents with chronic OI by objectively measuring sleep duration and timing with actigraphy to correlate with subjectively reported sleep complaints.

**Materials/Methods** Adolescents with chronic OI and impaired functioning completed a sleep survey and wore an actigraph for two-weeks before starting an intensive treatment program. Actigraphy data assessed bedtime, rise time and total sleep time. A six-question survey to assess perceived sleep quality was completed upon device return. Charts were reviewed for demographic and clinical data including autonomic reflex screen and diagnoses of OI. Statistical analyses were performed on the actigraphy data, data extracted from chart review, and patient questionnaire.

**Results:** Among 28 subjects with chronic OI, the median age was 16 years, majority were female (86%) and identified their race as white (89%). The majority (68%) were not attending school (in person or virtually) at the time of their evaluation. Almost all (96%) had symptom duration greater than 12 months. Comorbid diagnoses included chronic pain (86%), headaches (64%), and chronic fatigue (32%). Per patient questionnaire, 75% of patients reported being “often” or “always” tired, 43% reported sleep being “rarely” or “not at all” refreshing, and 43% reported their sleep was “always” or “often” restless.

Consistent bedtimes were noted in 64%, consistent rise times in 57%. Average bedtime (95% CI) was 00:54 (00:23–1:25); average rise time was 9:32 (8:45–10:09), with an average sleep duration of 7.6 hours (7.2–8.1). Sleep duration, bed/rise times, activity level, and consistency of sleep times were not statistically related to vital sign changes during postural challenge. Of the 27 individuals with tilt table testing, 12(44%) had excessive postural tachycardia (>40 beat per minute change).

**Conclusions:** The majority of subjects demonstrated delayed sleep phase tendencies and borderline sufficient sleep. A third to half had inconsistent sleep schedules. Debilitated patients with chronic orthostatic intolerance frequently report tiredness, unrefreshing sleep, and restless sleep. Sleep assessment should be considered for patients presenting for an evaluation or treatment of OI.

**Acknowledgements:** Dysautonomia Youth Network of America, Greg and Beth Wahl, Mayo Clinic Small Grants Award, Mayo Clinic Children’s Center.

## SLEEP VERSUS SCHOOL TIMINGS OF PRESCHOOL AND SCHOOL-AGE CHILDREN

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**Introduction:** The circadian rhythms of children have received little attention when compared to circadian biology in adolescents, perhaps due to the assumption that children are essentially oriented towards morningness. However, sparse studies have suggested the sleep-wake rhythm

delay assumed to occur drastically around adolescence might start earlier. Although the delay in sleep-wake patterns and its conflict with school start-times is well studied on adolescents, there are fewer studies focusing on younger children. We aimed to investigate the sleep-wake patterns of school-age, non-pubertal children.

**Materials and Methods:** In this cross-sectional school-based survey, we collected data from 3155 children aged 4-to-11 years at Portuguese kindergarten and primary schools. All children were assessed through the Children’s ChronoType Questionnaire, a parent-report questionnaire. Children from the age nine attending fourth grade or above answered to the Self-Rating Scale for Pubertal Development.

**Results:** In our epidemiological study (Clara & Gomes, 2020), we found the delay of bed and wake times for later hours on free days started at an early age. On school days, we found later bedtimes as children grew older, but earlier wake times, imposed by school start times. This resulted in a progressive reduction of sleep duration on school nights and a behavioral sleep rebound on free-days, suggesting children are accumulating a sleep debt during the week for which they try to compensate on free-days by extending their sleep duration. Restriction-extension patterns and social jetlag increased gradually across age groups.

**Conclusions:** Changes in sleep-wake cycles assumed to occur around adolescence can be detected among preschool and school-age children. The delay of sleep-wake patterns starts at an early age, years before adolescence, and increases gradually with age and grade level, as children develop. Our study suggests the advance of school start times across school grade level, from preschool to the second study cycle, in the Portuguese school system is inappropriate, as it follows the inverse tendency of children’s biological rhythms. Delaying school start times could adjust the school rhythms to the biological rhythms of elementary age children. It is urgent to design and implement studies on pediatric chronobiology that further ascertain circadian regulation and individual differences in sleep need among younger children.

**Acknowledgements:** This study made use of research data from a national project (PTDC/PSI-EDD/120003/2010, hosted at the Department of Education and Psychology of the University of Aveiro, Portugal, funded by the Portuguese Foundation for Science and Technology) coordinated by Professor Ana Allen Gomes, who is currently coordinating the related research project True Times: Morningness-eveningness and time-of-day effects on cognitive performances and emotional states (PTDC/PSI-ESP/32581/2017 and CENTRO-01-0145-FEDER-032581, hosted at the Faculty of Psychology and Educational Sciences of the University of Coimbra).

## “SOMETHING IS WRONG!” A QUALITATIVE STUDY OF RACIAL DISPARITIES IN PARENTAL EXPERIENCES OF OSA DETECTION IN THEIR CHILD

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**Introduction:** African Americans are 4-6 times more likely to have obstructive sleep apnea (OSA) than white children, yet disparities in detection, diagnosis, and treatment persist. Our study objective was to examine parent perceptions and experiences with OSA detection for their child with sleep-disordered breathing.

**Materials and Methods:** Semi-structured phone interviews were conducted with n=30 parents of children (ages 2-12 years) who were referred for overnight polysomnography due to sleep-disordered breathing. Parents who identified as Black non-Hispanic (n=19) or White non-Hispanic (n=8) were included in the current analysis. Qualitative thematic analysis was conducted using a grounded theory approach, with themes organized in NVivo 12 software. Twenty-one themes falling into five categories were identified. To examine racial differences in parental experiences, themes were classified as convergent (presented by Black and White parents) or divergent (presented by one racial group but not the other).

**Results:** Participating parents were primarily mothers (92.59%). Children were 51.90% female aged 3-14 years old (M=7.93 years, SD=3.08). Delayed OSA detection was observed in Black children (M=9.00 years) compared to white children (M=5.78 years). Analysis of themes by race identified both

shared experiences and perspectives, as well as those that were specific to or more salient for parents of one race. Convergent themes that overlapped among both groups included “Wanting to Know, Worries, and Child Daytime Symptoms.” Divergent themes experienced by White mothers included “Low threshold for raising concerns with provider, Institutional delays, and Trust in provider,” Misplaced blame, Whatever it Takes, Something is wrong and Missing the day-night connection were divergent themes named by Black mothers/caregivers.

**Discussion:** Racial disparities and commonalities in OSA detection were identified for parents of children at-risk for OSA. Black mothers expressed a strong sense of advocacy for their child during the detection process and reported experiences of misplaced blame from teachers related to their child’s daytime sleepiness in school. White mothers reported overall positive experiences with their healthcare providers in areas related to communication and trust. Delayed OSA detection in Black children may be overcome with targeted education for caregivers and ongoing unconscious bias training for providers. Divergent themes among parents who underwent similar processes for an OSA diagnosis are a potential indication of racism and health disparities.

**Conclusions:** Black and white parents experience different paths to detection and diagnosis for their child’s sleep-disordered breathing, that are affected by individual awareness, education, patient-provider interactions, and experiences with the healthcare and education system.

**Acknowledgements:** We would like to thank the parents and caregivers who participated in this study.

#### SUVOREXANT IS SAFE AND EFFECTIVE IN A PEDIATRIC POPULATION: A SINGLE-CENTER, RETROSPECTIVE STUDY

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**Introduction:** Sleep-wake disorders are highly prevalent in children and adolescents. To treat certain sleep-wake disorders in children and adolescents, including insomnia and circadian rhythm sleep-wake disorders, a wide range of non-prescription and prescription somnogenic agents are used[1]. Evidence-based recommendations in this population are limited, however, in part because the literature on their safety and efficacy is lacking. Suvorexant is a very promising new medication which suppresses wakefulness through the reversible antagonism of the OX1R and OX2R receptors. These receptors bind wake-promoting neuropeptides orexin A and orexin B. Suvorexant was approved for the treatment of chronic insomnia in adults[2] in November 2014 in Japan and in February 2015 in the U.S. Its safety and efficacy in children has not been studied. Here, we report findings from a retrospective analysis of suvorexant use in pediatric populations.

**Methods:** A retrospective analysis was performed in pediatric patients (age < 18) who were prescribed suvorexant between 2015 and 2021 and were treated in the Departments of Psychiatry, Psychology, Pulmonary and Sleep Medicine, Developmental-Behavioral Pediatrics or Neurology at Cincinnati Children’s Hospital Medical Center. Primary sleep diagnoses, neurologic diagnoses, psychiatric diagnoses, and demographic information were identified. The starting suvorexant dose was recorded, as were titration ranges. Adverse effects and caregiver statements of efficacy were catalogued and discontinuation rates calculated. Normally distributed data were reported as mean[standard deviation] while non-normally

distributed data were reported as median[Q<sub>1</sub>,Q<sub>3</sub>].

**Results:** 129 unique individuals were prescribed suvorexant during the referenced time period. The mean[SD] age was 10.3 [± 4.5] years, 45% were female, and the median[Q<sub>1</sub>,Q<sub>3</sub>] weight was 21.4 [14.8,32.8] kg at initiation of suvorexant. Median weights by age group were: 2-5 years: 10.2 [9.3,12.5] kg, 5-12 years 21.1 [17.1 – 25.1] kg, and 12-18 years: 40.4 [32.6 – 56.0] kg. By age group, median [Q<sub>1</sub>,Q<sub>3</sub>] starting doses were as follows: 2-5 years: 5 [2.5,5] mg, 5-12 years: 7.5 [5,10] mg, and 12-18 years: 10 [5,10] mg. The dose was increased for 48% (n = 62) of patients. The median increase was 10 [5,15] mg. Suvorexant was well-tolerated and efficacious, with patients continuing on the medications months after initiation. No significant adverse effects were recorded that required an in-patient hospitalization or prolongation of an existing hospitalization, that resulted in significant disability/incapacity, that was life-threatening, or that resulted in death.

**Conclusions:** The use of an orexin-receptor antagonist, suvorexant, is safe, well-tolerated and efficacious in the treatment of insomnia and circadian rhythm sleep-wake disorders in pediatric populations.

**Acknowledgements:** This work was supported by the Cincinnati Children’s Research Foundation.

#### THE EFFECT OF MELATONIN TREATMENT ON CHRONIC INSOMNIA IN CHILDREN ONE TO THREE YEARS OLD

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**Introduction:** Melatonin is mainly produced by the pineal gland and is often called the sleep hormone. It is an endogenous and natural substance that causes sleep in the body and in addition, it has been used only in limited and short-term studies to treat insomnia in children. It is known to have a range of different effects when taken as a medication. This research was designed to investigate the effect of melatonin on sleep onset time, total sleep duration, sleep quality and finally, daily function in a population of healthy children with insomnia (IRCT code: IRCT20180719040526N1).

**Materials and Methods:** This study will be performed by clinical trial method on 60 children (1-3 years old boys and girls) referred to the sleep clinic of Qazvin Children’s hospital in 2019 due to complaints of poor sleep. Children are examined by a physician and defined by ICSD-3 as patients with insomnia. They were randomly divided into placebo and interventional groups. Pediatric sleep clinic questioner and sleep diary were filled out by parents by recording the sleep time before and after the drug taking medication. For 30 children, melatonin was prescribed at a dose of 0.1 mg/kg up to a maximum of 1 mg for one month. Analysis was performed using SPSS 21 software, Chi-square and paired t-test (p<0.05).

**Results:** Comparison of the two groups showed that, after taking melatonin in the intervention group, sleep habits improved in children; nocturnal awakenings were decreased (p = 0.004), stay up the night (p = 0.001) and medium night’s sleep (p=0.030). Also, psychological counseling treatments had a significant relationship with sleep improvement in children (p = 0.030).

**Conclusion:** Melatonin administration combined with psychological and nutritional therapies was effective in improving children’s sleep. Therefore, melatonin therapy can be used to improve children’s sleep. More research needs to be done in this area.

**Keywords:** Melatonin Treatment, Chronic Insomnia, Children

#### THE EFFECT OF SCREEN EXPOSURE ON SLEEP IN ADOLESCENTS: BOTH TIMING AND DURATION ARE IMPORTANT

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**Introduction:** Studies suggest a decline in sleep duration in adolescents over the last 30 years. The duration of screen use has been identified as a risk factor, but the impact of the timing (evening vs night-time) has not

been studied.

**Materials and Methods:** Cross sectional online questionnaire survey of adolescents performed in school. Sleep habits on school nights and weekends, symptoms of insomnia and daytime repercussions were recorded. Sleep deprivation (<7 hours in bed /night), school night sleep restriction ( $\geq 2$  hours difference in sleep duration on school nights vs weekends), excessive sleepiness (score >6 on a visual analogue scale), duration of screen use and timing of screen use (evening vs after bedtime) were determined. Screen use was divided into light (<1 hour), moderate (1–2 hours) and intense (>2 hours).

**Results:** 2513 students (53.4% female) mean age 14.3 years were included. 20% were sleep deprived and 41% sleep restricted. A clear dose effect relationship in a model controlling for age, sex, and sociodemographic class was seen with all levels of night-time screen use on sleep deprivation and sleep restriction (intense use: sleep deprivation OR 5.23[3.03–9.00], sleep restriction OR 2.05[1.23–3.42]) and with intense evening use (intense use sleep deprivation OR 2.72[2.15–3.44] sleep restriction OR 1.69[1.36–2.11]) but not moderate evening use. All night-time use and intense evening use were associated with an increased risk of insomnia, non refreshing sleep, daytime sleepiness, lack of energy and irritability

**Conclusions:** This study allows the definition of clear guidelines concerning screen use in adolescents for physicians and parents. Both duration of screen use and timing are important in determining adverse effects on sleep and daytime functioning. Intense (>2 hours) evening use and all night-time use should be avoided.

**Acknowledgements:** The study was supported via the Paris region health authority (ARS Ile de France) and the Paris region (Conseil Régional Ile de France).

#### THE IMPACT OF EXPERIMENTAL SLEEP RESTRICTION ON ENDOTHELIAL FUNCTION IN HEALTHY ADOLESCENTS

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**Introduction:** Despite clinical recommendations of 8 to 10 hours of sleep each night, 60% of adolescents report 7 hours or less of sleep each night. Sleep restriction (SR) impacts key performance indicators of physical and mental health. Previous studies have significantly linked SR to adverse impacts on cognitive outcomes including attention, executive function, memory and learning that lead to poor academic performance. Additionally, studies in adults have found that SR increases sympathetic activity, oxidative stress and pro-inflammatory markers leading to endothelial dysfunction. Endothelial dysfunction is a modifiable risk factor for disease and can be improved with a healthy lifestyle of adequate sleep, exercise and diet. Novel non-invasive measures of BOLD cerebrovascular reactivity (CVR), provide an imaging biomarker of endothelial function and new opportunities to study cerebrovascular health in adolescents. The purpose of this study was to investigate whether experimental sleep restriction, relative to ideal sleep, is associated with vascular endothelial dysfunction, as measured by CVR in healthy adolescents.

**Materials and Methods:** This was a counter-balanced crossover study. Healthy 15- to 18- year old neurotypical adolescents from the community without history of neurological, psychiatric or sleep disorder were recruited for this study. Participants underwent a 2-week at-home sleep manipulation protocol, including 5-nights of ideal sleep (IS; 9 hours in bed), and 5-nights of sleep restriction (SR; maximum 6 hours in bed). Objective measures of sleep were evaluated using a validated accelerometer to record sleep duration across multiple nights. At the end of each sleep manipulation condition, participants underwent a BOLD MRI with controlled carbon dioxide challenge to assess cerebrovascular reactivity. Images were reviewed for motion and quality. Cortical and subcortical regions of interests related to cognition were determined, and calculated mean CVR values were used for statistical analysis.

**Results:** Seventeen participants (mean age 16.9 years, 29% male) were

included in this study. The mean sleep duration was 5.44±0.68 hours for the SR condition, and 7.07±0.74 hours for the IS condition in this sample. Reduced CVR in cognitive regions of interest, including the cuneal cortex ( $p=0.006$ ), temporal occipital fusiform cortex ( $p=0.05$ ) and right lingual gyrus ( $p=0.04$ ) was seen with acute SR compared with IS.

**Conclusions:** Reduced CVR was seen in specific regions of cognitive function with sleep restriction compared to ideal sleep. This study provides novel data to demonstrate that acute sleep restriction is linked to adverse cerebrovascular health, particularly endothelial dysfunction, and may be the underpinning mechanism for adverse cognitive outcomes in sleep-restricted adolescents. Modifying sleep behaviours in adolescents may provide unique opportunity to promote endothelial function and prevent related diseases. Knowledge from this study may offer early insights into the mechanisms of cognitive impairment associated with sleep restriction and will inform health professionals, parents, and teachers.

**Acknowledgements:** No acknowledgements to declare.

#### THE IMPACT OF EXPERIMENTAL SLEEP RESTRICTION ON NEUROCOGNITION IN HEALTHY ADOLESCENTS

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**Introduction:** Despite clinical recommendations of 8 to 10 hours of sleep each night, 60% of adolescents report 7 hours or less of sleep each night. The etiology of sleep restriction (SR) is multifactorial and includes psychosocial pressures such as academic achievement, extra-curricular activities, electronic use, and societal obligations. SR impacts key performance indicators of physical and mental health. Previous cross-sectional studies have significantly linked SR to adverse impacts on cognitive outcomes including attention, executive function, memory and learning, that leads to poor academic performance. Further, SR has been associated with greater risk-taking behaviours and increased accidental injuries in adolescents. The purpose of this study was to investigate whether experimental sleep restriction, relative to ideal sleep, is associated with a change in healthy adolescents' cognitive and behavioral outcomes.

**Materials and Methods:** This was a counter-balanced crossover study. Healthy 15- to 18- year old neurotypical adolescents from the community without history of neurological, psychiatric or sleep disorder were recruited for this study. Participants underwent a 2-week at-home sleep manipulation protocol, including 5-nights of ideal sleep (IS; 9 hours in bed), and 5-nights of sleep restriction (SR; maximum 6 hours in bed). Objective measures of sleep were evaluated using a validated accelerometer to record sleep duration across multiple nights. At the end of each sleep condition, participants were assessed using standard neuropsychological assessments and the NIH-Toolbox, a computerized neuropsychological test, for cognitive and behavioural outcomes. Measures of interest included assessments of executive function and behavioral function. Age- and gender-corrected T-scores were used for statistical analysis.

**Results:** Thirty-three participants (mean age 16.7 years, 36% male) were included in this study. The mean sleep duration was 5.44±0.68 hours for the SR condition, and 7.1±0.74 hours for the IS condition in this sample. With SR compared to IS, participants had significantly greater scores of inattentiveness ( $p=0.05$ ) and impulsivity ( $p=0.05$ ), and significantly lower scores of overall fluid cognition ( $p=0.01$ ) and global cognition ( $p<0.01$ ). Additionally, participants with SR compared to IS had significantly higher scores for sleepiness ( $p=0.01$ ), fatigue ( $p=0.05$ ), and negative affect ( $p=0.01$ ). No significant differences were seen on assessments of working memory ( $p=0.43$ ), episodic memory ( $p=0.27$ ) or processing speed ( $p=0.49$ ).

**Conclusions:** This study provides data that acute sleep restriction is associated with adverse cognitive outcomes, specifically to areas of attention and executive function, and poorer behavioral function after less than one week of SR when compared to 5-nights of well-rested sleep.

Knowledge from this study may offer early insights for health professionals, clinicians, parents, and teachers on the impact of acute sleep restriction on cognitive ability, and behavioural function in the adolescent population.

**Acknowledgements:** No acknowledgements to declare.

### USING AUTO-VIDEOSOMNOGRAPHY TO STUDY THE RELATION BETWEEN SLEEP AND NIGHTWAKING IN INFANCY

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**Introduction:** The onset of motor milestones, such as crawling and walking disrupts infants' sleep. For example, as measured via actigraphy, crawling infants woke more frequently during the night than age-matched controls who had not yet begun to crawl (Scher, 2005). Intensive longitudinal analysis of prospective parent diaries showed that the first day infants performed a motor skill, as well as the day they demonstrated mastery, predicted increased night wakings and shorter sleep durations (Berger & Moore, 2021). These traditional methods of collecting sleep and motor data are too intrusive, costly, and/or effortful to feasibly collect data on a large scale. However, because infant sleep is so variable from night-to-night, large-scale data collection is necessary to describe periods of stable sleep and identify deviations from stability. Thus, the aim of this study was to test whether auto-videosomnography, which has been shown to be as accurate as actigraphy for documenting infants' sleep characteristics (Horger, et al., 2021), could efficiently capture the relation between infants' sleep and motor development.

**Materials and Methods:** 1302 parents of infants between the ages of 9 and 14 months completed the Survey of Well-being of Young Children (SWYC) on-line. The SWYC is a 40-question screening instrument for children under 5 years old that includes cognitive, language, motor and social-emotional subscales. All participants were users of *Nanit*, a commercial, home video baby monitoring system that video-records infants in their cribs. A sophisticated machine learning algorithm uses computer vision technology to calculate and report sleep characteristics including nightly *wake episodes*. For the purposes of this abstract, only data from the motor subscale and from families who reported their infant's walking experience (*not yet, somewhat, very much*; n=279) are reported.

**Results:** A 6 (age; 9, 10, 11, 12, 13, 14 mos) x 3 (experience) ANOVA on the number of night wakings revealed a significant main effect of walk experience,  $F(5, 261)=4.05$ ,  $p=.02$ . Across ages, but especially for younger infants, those whose parents reported that they walk *very much* woke more frequently than those with less experience.

**Conclusions:** These findings replicate previous work on the onset of crawling and pulling-to-stand showing that infants' sleep was most disrupted for those who achieved their motor milestones earlier than average (Atun-Einy & Scher, 2016; Scher & Cohen, 2015) and extends it to the new milestone context of walking. This study demonstrates the feasibility of using auto-videosomnography to study the relation between sleep and motor development in infancy. Thus, this new method has the potential to collect data more efficiently and on a larger scale than has been done to date. This creates opportunities for researchers to track individual developmental trajectories and, in turn, the power to predict change rather than just document it.

**Acknowledgements:** This work was supported by the National Science Foundation, Division of Behavioral and Cognitive Science [1941122] to S.E.B.

### VALIDATION OF THE WEARABLE DEVICE KRONOWISE™ (KW) FOR THE ASSESSMENT OF SLEEP IN CHILDREN BY COMPARISON WITH PSG

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Spain; <sup>6</sup> Ciber Fragilidad y Envejecimiento Saludable (CIBERFES), Madrid, Spain

**Introduction:** Wearable devices are increasingly useful tools in the clinical practice, enabling clinical assessments under normal-living conditions with minimal disturbances, and therefore facilitating progress towards effective telemedicine. However, there is a lack of validation studies designed to quantify device performance against accepted gold standards, especially across different populations. In this study, we aimed to test, by comparison with PSG, the validity of the wearable device Kronowise™ (KW) for estimating sleep parameters in a paediatric population.

**Materials and Methods:** The sleep of 48 patients (19 girls, mean age = 4.9; SD = 1.9), attending to the Sleep Unit of the University Hospital FJD (Madrid, Spain), was simultaneously assessed overnight by KW and PSG. KW registered 15 raw variables leading to measures of distal temperature, motor activity, tilt and light (total visible, blue and infrared), recorded at 10 Hz and stored in 30" epochs. TAPL algorithm (Madrid-Navarro et al., 2019), normalizing and integrating temperature, acceleration, position and visible light, was used to identify the main sleep periods. Then, epochs scored as sleep were rescored by the *Keywake*® algorithm, based on TIM (time in movement), to detect awakenings  $\geq 30$ . These algorithms are implemented on the *Kronowizard* platform (<https://kronowizard.um.es/>, UM). Time in bed (TIB), sleep latency (SL), total sleep time (TST), sleep efficiency (SE), no. awakenings (NA), and wake after sleep onset (WASO) were estimated from KW and PSG and agreement between both procedures was analysed by Pearson correlation and 1-factor ANOVAs for every sleep parameter. Further, the KW method was validated through the indexes of sensibility, accuracy, specificity and F1score.

**Results:** The analyses showed significant positive correlation ( $p<.05$ ) between PSG and KW estimations for every sleep parameter. According to the ANOVAs, PSG and KW did not differ in the estimation of TIB, SL, TST, SE or NA ( $p>0.1$ ); however, they differed in WASO ( $p<.05$ ). Sleep estimation by KW showed remarkably high rates of sensibility, accuracy, and F1score (all of them  $> 0.9$ ) and acceptable specificity ( $>0.6$ ).

**Conclusions:** Our results support the reliability of KW as an accurate device to measure sleep duration and quality in children, as previously demonstrated in adult population (Madrid-Navarro et al., 2019). This entails great possibilities for telemedicine and, together with big data analyses, allows epidemiological studies and clinical screenings in large paediatric populations.

**Acknowledgements:** Ministry of Economy and Competitiveness, Instituto de Salud Carlos III through CIBERFES (CB16/10/00239), Ministry of Science Innovation and Universities RTI2018-093528-B-I00 (co-financed by FEDER), Call H2020-sc1-BHC-2018-2020 (Grant agreement 825546, Diabfrail-Latam) and Spanish Sleep Society (SES), Ministry of Economy and Competitiveness through 2017 Torres-Quevedo Aids for the Recruitment of PhD Researchers, granted to Kronohealth SL.

### Pharmacology

#### EFFECTS OF SUVOREXANT ON SLEEP-EEG POWER SPECTRUM IN PATIENTS UNDERGOING BUPRENORPHINE TAPERED OPIOID WITHDRAWAL

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**Introduction:** Patients undergoing opioid withdrawal experience sleep disruption during the acute withdrawal period, manifesting in reduced sleep duration and continuity, as well as changes in sleep architecture. Previous data suggests that Suvorexant may hold promise as an adjunctive treatment to treat sleep disturbance during opioid withdrawal, due to its capacity to increase sleep duration and continuity with limited abuse liability. However, little is understood about whether Suvorexant is associated with changes in the sleep EEG power spectrum in this context, which provide a more nuanced and sensitive approach to shed further light on the neurophysiological actions of Suvorexant and their downstream outcomes in relation to opioid withdrawal. As part of a randomized placebo-controlled trial set in an inpatient treatment unit, we investigated

the effects of Suvorexant on spectral power during sleep whilst undergoing supervised opioid withdrawal.

**Materials and Methods:** We performed secondary analyses on a clinical trial dataset (clinicaltrials.gov [NCT03789214]) in which participants were randomly allocated (stratified by: baseline sleep quality, withdrawal severity, severity and buprenorphine dose, and gender at baseline) to receive either placebo, 20mg or 40mg Suvorexant. Following randomization, participants underwent an open-label four-day buprenorphine/naloxone taper and four-day post-taper observation period, during which Suvorexant or placebo were administered in the evening between 20:00 and 22:00. We measured the spectral densities (PSD) across the whole night, obtained from eight nights of wireless sleep-EEG recordings, during the taper and post-taper periods, and derived relative power across the delta (1–3.5Hz), alpha (8–12Hz), beta (18–28Hz), sigma (12–16Hz) and theta (4–6.5Hz) power bands. Analyses tested for the effects of drug allocation (placebo vs 20mg vs 40mg), and study phase (taper vs post-taper) in each of the spectral power bands using ANOVA.

**Results:** 38 participants were randomized to the three conditions (Placebo: n=12, 20mg: n=14, 40mg: n=14). ANOVA indicated a significant main effect of drug allocation on beta ( $F [1,37] = 5.618, p = 0.0041$ ) and sigma ( $F [1, 37] = 3.075, p = 0.0479$ ) band activity, with no significant main effect of study phase. *Post-hoc* Tukey HSD tests indicated a significant increase in beta power between placebo and 40mg (adjusted  $p$  value = 0.00657), but not 20mg Suvorexant (adjusted  $p$  value = 0.858), as well as a significant increase in beta power between 20mg and 40mg doses (adjusted  $p$  value = 0.0204). Data also indicated a significant increase in sigma power between placebo and 40mg groups (adjusted  $p$  value = 0.037), but not 20mg (adjusted  $p$  value = 0.462). There were no significant differences between placebo and Suvorexant in the other spectral powerbands.

**Conclusions:** Results suggest that suvorexant is associated with increased power in the beta and sigma power bands, during the opioid withdrawal period. Further work is required to resolve the clinical implications of these spectral changes in a withdrawal setting, particularly in relation to findings of increased beta power from suvorexant administration, which typically are explained as a function of disturbed or hyperaroused sleep.

## SOMNOLOGICS - MEDICINES FOR THE TREATMENT OF SLEEP DISORDERS

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**Introduction:** Sleep disorders can impair quality of life, contribute to morbidity and increase mortality. A range of pharmaceutical and phytotherapeutic substances from various substance classes are used to treat sleep disorders. However, the heterogeneity of these substances means selecting an appropriate agent for an individual patient is challenging. Until now, a taxonomy that classifies the clinical properties of such substances is lacking. To fill this gap, we propose a novel taxonomy that classifies medications for sleep disorders, which we term Somnologics (lat. somnologia). The intention of this new classification system is to assist clinicians in choosing the right pharmacological agent for the individual patient.

**Materials and Methods:** The Somnologics taxonomy is the first attempt at a unified classification of medications for the treatment of sleep disorders. For insomnia disorders, we review substances that promote sleep (anti-insomnics) by either increasing sleep pressure (somnics) or reducing wake pressure (antivigilants). For circadian rhythm disorders, we discuss medicines that realign an individual's sleep phase (chronotherapeutics). For hypersomnia disorders, we consider treatments associated with an increased need for sleep (antihypersomnics). And finally, we classify medications that reduce a patient's sleep drive (vigilants), and treat cataplexy (anticataplectics).

**Results:** The Somnologics classification system presented herein is a novel and comprehensive taxonomy of medications for sleep disorders. It

classifies the most common pharmaceutical and phytotherapeutic substances according to clinical use and physiological mechanisms.

**Conclusions:** The Somnologics taxonomy provides an effective reference for clinicians looking to treat patients with sleep disorders. It is intended as a tool to support clinical decision-making, which is frequently challenged by the large range of heterogeneous substances that treat sleep disorder and should be helpful support for clinicians facing the question of how to treat certain sleep disorders.

**Acknowledgements:** The authors would like to thank Prof. Dr. Peter Riederer and Springer Nature Switzerland for publication of the in-depth chapter in the most recent edition of Neuropsychopharmacotherapy 2021.

## Psychiatric Disorders Affecting Sleep/Wake

### ASSOCIATIONS BETWEEN PRE-SLEEP INTRUSIVE THOUGHTS, SLEEP DIFFICULTIES, AND BODY TEMPERATURE IN YOUTH WITH MOOD DISORDERS

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**Introduction:** The circadian phase delay characteristic of the adolescent developmental period may be amplified in youth with mood disorders. These individuals have lower circadian amplitudes, delayed circadian phase, and higher levels of pre-sleep arousal when compared to healthy controls. Previous research has established a relationship between pre-sleep arousal, sleep difficulties and mood disorders. However, little is known about how the circadian rhythms of body temperature may relate to these factors considering the physiological effects of body temperature on pre-sleep arousal. The main objective of this study was to assess the relationship between sleep difficulties, pre-sleep intrusive thoughts, and alterations in body temperature in adolescents with mood disorders.

**Methods:** Fourty-nine participants who experience at least mild depressive symptoms (score >6 on the QIDS A17-SR) were recruited from a tertiary psychiatric facility and surrounding areas. Actigraphy was used to monitor sleep and a dermal sensor on the abdomen was used to measure skin temperature for seven days in the participant's natural environment. Participants also completed the Leeds Sleep Evaluation Questionnaire (LSEQ) and the Glasgow Content of Thoughts Inventory (GCTI) to document subjective sleep and pre-sleep intrusive thoughts.

**Results:** Results indicate that increased pre-sleep intrusive thoughts significantly correlate with lower subjective ease of getting to sleep ( $r = -.30, p = .038$ ), later sleep onset ( $r = .36, p = .011$ ), lower subjective sleep quality ( $r = -.49, p < .001$ ), and higher instability in sleep efficiency ( $r = .31, p = .030$ ). A delayed circadian phase of skin temperature was significantly correlated with higher instability of wake after sleep onset as measured by actigraphy ( $r = .42, p = .022$ ). Sleep disturbances were significantly correlated with poorer rhythmicity of the circadian rhythm of skin temperature ( $|r| \geq .347, p \leq .045$ ), but not with amplitude ( $|r| < .081, p > .675$ ).

**Conclusion:** These results deepen our understanding of the potential influence that pre-sleep intrusive thoughts and dysregulation of the circadian rhythm of skin temperature, especially physiological arousal at sleep onset, may have on sleep difficulties experienced by youth with mood disorders. More research is needed to fully understand the mechanisms at play and whether these factors may be amenable to targeted interventions for youth with mood disorders.

### CHILD AND ADOLESCENT SLEEP DISTURBANCES AND PSYCHOPATHOLOGY IN A MENTAL HEALTH CLINIC SAMPLE

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**Introduction:** Children and adolescents (henceforth children) being

treated in specialty mental health services are more likely to have sleep disturbances than community samples. However, few studies have investigated the relationship between sleep and psychopathology in a broad sample of children seen at mental health agencies. This study aimed to fill this gap by examining sleep disturbances in relation to internalizing (e.g., depression, anxiety) and externalizing (e.g., attention-deficit/hyperactivity, conduct disorder) symptoms.

**Materials and Methods:** Secondary data analyses were completed on a sample of children (aged 4 to 18; 56.2% male) who completed the interRAI ChYMH- a semi-structured assessment tool- as a part of standard care in residential or outpatient settings from 39 mental health agencies in Ontario, Canada (N = 13, 472). A split-half sample approach was used to control for error and determine if results were reproducible (Sample 1 n = 6,773, Sample 2 n = 6,699). Hierarchical regressions examined the effects of child (i.e., age, sex, sensory sensitivity, pain), family (i.e., family functioning, caregiver distress, lack of parenting strengths), sleep disturbances (i.e., difficulty falling asleep and staying asleep, night waking, bedtime resistance and falling asleep during the day), and age as a moderator for sleep disturbances on both outcome variables: internalizing and externalizing symptoms.

**Results:** In both samples, sleep disturbances predicted both internalizing (Sample 1  $\Delta R^2 = 8.6\%$ , Sample 2  $\Delta R^2 = 10.0\%$ ) and externalizing (Sample 1  $\Delta R^2 = 1.5\%$ , Sample 2  $\Delta R^2 = 1.3\%$ ) above and beyond child and family variables. Age moderated the relationship between sleep disturbances and internalizing symptoms (Sample 1  $\beta = 0.06$ ,  $p < .001$ , Sample 2  $\beta = 0.08$ ,  $p < .001$ ), but not externalizing symptoms (Sample 1  $\beta = -0.01$ ,  $p > .05$ , Sample 2  $\beta = -0.01$ ,  $p > .05$ ).

**Conclusions:** The relationship between sleep and psychopathology may change as children move through developmental phases marked by structural and organizational changes in sleep-wake patterns and psychopathology prevalence.

#### CHILDREN WITH AUTISM AND INSOMNIA UTILIZE TWICE THE AMOUNT OF HEALTH SERVICES THAN THEIR COUNTERPARTS

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**Introduction:** Sleep disturbances consistent with a diagnosis of insomnia are commonly reported in 40-80% of children with autism spectrum disorders (ASD) in contrast to 20% of typically developing children. Previous studies have reported that sleep disturbances in the general population are associated with higher loads of comorbidities and health service utilization. Here we examined whether there is a similar association between insomnia and the utilization of health services specifically in children with ASD.

**Materials and Methods:** We conducted a retrospective, cross-sectional study of 541 children with ASD, between 1-11 years of age, registered in the National Autism Database of Israel. Children were included in the current study if they were members of Clalit Health Maintenance Organization, and their parents completed the Children's Sleep Habits Questionnaire (CSHQ). Pediatric insomnia was defined as a total CSHQ score >48. Sociodemographic and ASD diagnostic measures including the Autism Diagnostic Observation Schedule, 2nd edition (ADOS-2) calibrated severity scores, DSM-5 levels of required support, and cognitive scores of the children were extracted from the National Autism Database. Data about medication use, hospitalizations, visits to the emergency room, and visits to specialists were obtained from the Clalit electronic patient record system. The association between insomnia, comorbidities, and health utilization data were tested using standard univariate and multivariate statistical tests.

**Results:** Of the 541 children with ASD, 257 (47.5%) had insomnia. ASD children with insomnia were more likely to be prescribed medications (excluding sleep medications) for the management of chronic diseases (OR 1.50, 95% CI [1.02, 2.21],  $P = 0.0415$ ). In addition, children with insomnia had 50% more visits to the emergency room (mean[SD] = 0.63[1.19] vs. 0.42[1.01];  $p = 0.0153$ ) and had 2.7 times higher rate of hospitalizations

(mean[SD] = 0.19[0.60] vs. 0.07[1.30];  $p = 0.0042$ ) when compared to ASD children without insomnia. Consequently, children with ASD and insomnia spent, on average, twice the time at the hospital compared to children with ASD without insomnia (mean[SD] = 0.32[1.08] vs. 0.16[1.06] days per child respectively;  $p = 0.004$ ). No significant differences were found in the total number of outpatient visits, including visits to primary care physicians and specialists, between children with and without insomnia.

**Conclusions:** These findings suggest that children with ASD and insomnia utilize health services significantly more than children with ASD who do not have insomnia and are more likely to be prescribed medications for the management of chronic diseases. Thus, treating sleeping problems in children with ASD may have a broad clinical and economic impact that extends beyond the expected improvement in the sleep quality of these children and their parents.

**Acknowledgements:** This study was supported by Neurim Pharmaceuticals Ltd. who also assisted in the study design.

#### CHRONOTYPE PREDICTS PHENOTYPIC DIFFERENCES IN PSYCHIATRIC SYMPTOMS ACROSS THE DAY

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**Introduction:** Daily rhythms of physiology and behaviour are an integral part of human physiology. There are, however, large inter-individual differences in the phenotypic expression of circadian-regulated output, and individuals typically function and feel better at different times of day. In the current pre-registered study we wanted to determine how well an individual's psychiatric profile and chronotype can predict when psychiatric symptoms will be worse.

**Materials and Methods:** We recruited a sample of 500 individuals that rated psychiatric symptoms 5 to 6 times across the day. Self-reported measures of psychiatric traits (13 scales) and chronotype (rMEQ) were completed during a baseline session. Factor analysis was performed to obtain underlying latent constructs.

**Results:** Results revealed three psychiatric constructs: depression-anxiety, downregulatory problems, and social dysfunction. Key findings included the expected diurnal patterns of symptoms for fatigue (greatest in the early morning and evening) and proactiveness (most proactivity in the afternoon), while emotional and attentional problems showed only minor diurnal variation across the whole sample. Morning types showed low levels of fatigue (lower than evening types) in the morning (~8:00-10:00), but this relationship reversed in the evening (~21:00 and later). Morning types that were also high in depression-anxiety construct reported more ADHD-like symptoms in the evening (~19:00 and later) compared to evening types. For those high in social dysfunction construct, evening types were most vulnerable for emotional problems in the morning (~8:00), while by the afternoon (~15:00) this had reversed so that morning types were most likely to report worse emotional problems.

**Conclusions:** A person's chronotype did not only predict the expected diurnal pattern of fatigue, but also a parallel worsening of psychiatric symptoms in those who also had higher levels of subclinical psychiatric traits. While the present study was limited to individuals with subclinical levels of psychiatric traits, the results clearly indicate that an individual's chronotype contributes to phenotypic differences in when psychiatric problems are most likely. In all, chronotype should be considered in personalized medicine, diagnosis, and when tailoring treatments in psychiatry.

**Acknowledgements:** N/A

#### COMPARISON OF RTMS OF 1HZ, 5HZ AND 10HZ ON SLEEP ACTIGRAPHY IN PATIENTS WITH DEPRESSION

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**Introduction:** Repetitive Transcranial Magnetic Stimulation (rTMS) is an approved neurophysiological tool for the treatment of major depression (MD), and has been proposed as a tool that may have positive results in the treatment of sleep disorders (SD). However, clinical practice recommendations of rTMS protocols for the treatment of sleep disturbances in MD patients are inconsistent. In this regard, inhibitory rTMS ( $\leq 1$ Hz) and excitatory rTMS (5Hz and 10Hz) protocols in the dorsolateral prefrontal cortex (DLPC), approved for depression, activate different neural mechanisms, which may have a different clinical effect on sleep in MD patients.

**Objective:** To know the effect of 1Hz rTMS in the DLPC-left, 5Hz and 10 Hz in the DLPC-right on sleep actigraphic parameters in MD patients.

**Method:** Thirty adults (mean age =  $45.43 \pm 13.02$  years old, 77% women), with a diagnosis of major depression (MD), referred by psychiatrists, were divided into three treatment groups, each with 10 patients. Each group received one of the following treatments with rTMS: 1hz in DLPC-I, 5hz in DLPC-D or 10hz in DLPC-D. The treatments included 15 sessions at 80% of the motor threshold. Objective sleep data were obtained using an actigraphy device placed on the wrist 24 hours a day through seven days before treatment and during seven days after treatment.

**Result:** Using the related samples t-test analysis, no significant differences were found in sleep before and after the intervention in any of the three treatment groups ( $p > 0.05$ ), but, effect size analyses (Cohen's d), showed a different effect in each treatment group. The rTMS-1Hz, had a moderate effect, improving four sleep parameters: wake minutes (WMIN), sleep efficiency (SEFF), awakenings after sleep onset (WASO) and activity index (ACTX), (Cohen's d = .59, .60, .63 and .53, respectively). Treatment with rTMS-5Hz only improved the SEFF parameter with a small effect (Cohen's d = .44). Treatment with rTMS-10 Hz had a moderate effect on SEFF (Cohen's d = .52) and sleep minutes (SMIN, Cohen's d = .64), but they worsened after the intervention.

**Conclusions:** Inhibitory rTMS treatment has a better effect than excitatory rTMS on sleep disorders in MD patients.

#### CORRELATIONS BETWEEN SLEEP ARCHITECTURE AND EMOTIONAL INHIBITION PROCESSING DURING A SUICIDAL CRISIS: PRELIMINARY FINDINGS IN HOSPITALIZED ADOLESCENTS

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**Introduction:** Worldwide, suicide is the second most common cause of death for adolescents. Adolescent suicide is influenced by many factors, including difficulties with inhibitory control that may contribute to increased risk of future suicidal behaviour. In previous studies, we observed that adolescents in suicidal crisis have more light sleep and lower neural resources mobilized during inhibition processing compared to healthy adolescents. Their inhibitory control may be modulated by the emotional valence of surrounding stimuli. The current study aimed to determine how sleep architecture in suicidal adolescents may relate to inhibition processing in response to stimuli with neutral, positive and negative emotional valence.

**Materials and Methods:** Nine adolescents between 12 and 17 years of age (77.8% females, Mean $\pm$ SD =  $15.0\pm 1.7$  years old) who attempted suicide were recruited while hospitalized for a suicidal crisis in a psychiatric inpatient unit. Of those, all had a clinical diagnosis of depression based on DSM-V criteria. Polysomnography and event-related potentials were recorded in Patients' bedrooms. Event-related potentials were recorded during a Go/NoGo task involving pictures of emotionally neutral, sad, and happy faces. Pearson correlations were conducted to evaluate potential associations between sleep architecture parameters and the P3d, a brain response thought to reflect inhibition processing (i.e. difference waveform calculated as NoGo minus Go trials).

**Results:** All participants had significant suicidal symptoms on the adolescent version of the Suicidal Ideation Questionnaire (range: 32-82, Mean $\pm$ SD =  $46.3\pm 16.6$ ), and 88.9% were taking psychotropic medications.

Higher amounts of NREM2 sleep ( $r = -.82$ ,  $p = .007$ ) and lower amounts of NREM3 sleep ( $r = .68$ ,  $p = .043$ ) significantly correlated with lower amplitude of the P3d in response to sad stimuli. No such association was found for happy or neutral stimuli.

**Conclusions:** Our findings suggest that adolescents experiencing acute suicidal risk have shallower sleep and that this is associated with fewer neural resources mobilized by inhibitory processes, especially in context of negatively valenced stimuli. Thus, addressing sleep disturbances while managing suicidal crises in adolescents is vital and may help alleviate emotional inhibition processing difficulties in this vulnerable population.

**Acknowledgements:** The authors wish to thank the participants who volunteered their time for research during a very difficult period, as well as the staff of the Psychiatric Inpatient Unit at the Children's Hospital of Eastern Ontario.

#### EFFECTIVENESS OF TARGETING INSOMNIA AND NIGHTMARES IN POST-TRAUMATIC STRESS DISORDER: A TRANSDIAGNOSTIC INTERVENTION

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**Introduction:** Insomnia and nightmares are pervasive symptoms of post-traumatic stress disorder (PTSD) that have been associated with worse PTSD severity, distress level, daily functioning, and overall health. These nighttime difficulties often persist following improvements in PTSD symptoms, highlighting the need for sleep-focused care in the treatment of PTSD. Sleep interventions such as cognitive behavioral therapy for insomnia (CBT-I) and imagery rehearsal therapy (IRT) are showing promising results for the treatment of insomnia and nightmares in PTSD. Individuals with PTSD may benefit from interventions targeting insomnia and nightmares simultaneously. The current study aimed to evaluate the effectiveness of a sleep intervention program combining CBT-I with IRT (CBT-I+IRT) in a PTSD sample and to examine whether changes in sleep following this intervention are associated with changes in PTSD and related symptoms.

**Materials and Methods:** Sixty military veterans or law enforcement personnel with a clinician-based diagnosis of PTSD according to DSM-5 criteria (78% male, mean age =  $50.7 \pm 7.3$  years, range 29 to 64 years) underwent 10 weekly 2-hour group sessions of CBT-I+IRT. Participants were instructed to complete pre-, mid-, and post-intervention questionnaires including the Insomnia Severity Index (ISI), Post-traumatic Stress Disorder Checklist for DSM-5 (PCL-5), the Nightmare Distress Questionnaire (NDQ), the Brief Pain Inventory - Short Form (BPI-SF), and the Satisfaction with Life Scale (SWLS).

**Results:** Insomnia symptoms severity decreased significantly and progressively from pre-, to mid-, to post- intervention (ISI:  $F = 28.9$ ,  $p < .001$ ,  $\eta_p^2 = .58$ ). Nightmare-related distress also decreased significantly from pre- to post-intervention (NDQ:  $F = 23.4$ ,  $p < .001$ ,  $\eta_p^2 = .32$ ). This was accompanied by a significant decrease in PTSD symptoms severity (PCL-5:  $F = 16.2$ ,  $p < .001$ ,  $\eta_p^2 = .24$ ) and increase in life satisfaction (SWLS:  $F = 23.0$ ,  $p < .001$ ,  $\eta_p^2 = .31$ ) from pre- to post-treatment. When controlling for comorbid diagnoses of depression and substance use disorder, changes in PTSD symptoms and life satisfaction were no longer significant ( $F = 0.6$ ,  $p = .453$ ,  $\eta_p^2 = .01$ ;  $F = 0.4$ ,  $p = .520$ ,  $\eta_p^2 = .01$ ). The reduction in insomnia symptoms from pre- to post-treatment positively correlated with reductions in nightmare-related distress ( $r = .42$ ,  $p = .002$ ), PTSD symptoms ( $r = .43$ ,  $p = .002$ ), and pain (BPI-SF:  $r = .60$ ,  $p < .001$ ).

**Conclusions:** The current findings add to previous evidence supporting the use of CBT-I augmented by IRT to concomitantly address insomnia and nightmares in people with PTSD. We observed significant improvements in both insomnia severity and nightmare-related distress, with a parallel alleviation of PTSD symptoms and improvements in life satisfaction from pre- to post-treatment. The moderate correlations between sleep improvements and PTSD symptoms along the course of treatment reinforces the notion that sleep restoration plays an active role in mental health. This also seemed to positively affect other outcomes relevant for PTSD such as subjective pain and global life satisfaction. Further studies are needed to better understand the underlying mechanisms of change between improvements in sleep and improvements in PTSD symptomatology.

## BECOME YOUR OWN SLEEP EXPERT: DESIGN, DEVELOPMENT AND EVALUATION OF A PRAGMATIC BEHAVIORAL TREATMENT PROGRAM FOR INSOMNIA IN INPATIENT PSYCHIATRIC CARE

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**Introduction:** Mental disorders are among the leading causes for reduced quality of life due to illness worldwide. The majority of patients with mental disorders suffer from insomnia (disrupted sleep), and insomnia is associated with adverse health outcomes. Current guidelines identify cognitive behavioral therapy for insomnia (CBT-I) as the first-line treatment. However, CBT-I is too complex for patients with severe mental disorders and not systematically implemented in clinical care. Rather, insomnia often remains untreated or treated with hypnotics, related to the risk of adverse effects and dependency. The current project aims to empower patients with mental disorders to take care of their own sleep health based on a pragmatic behavioral treatment program.

**Materials and Methods:** We adapted CBT-I in a treatment development phase in collaboration with 24 patients (13F, 8M, age 36.2 ± 13.8 (19; 59) years) across diagnostic entities (transdiagnostic approach) and 30 health care providers (20F, 10M, 40.6 ± 14.5 (18; 64) years) on psychiatric wards ('Become your own SLEEP expert'). The program was implemented and evaluated by 15 patients (9F, 6M, age 41.7 ± 12.6 (19; 59) years) and 22 health care providers based on interviews and questionnaires before participation and prior to discharge.

**Results:** Implementation research resulted in the SLEEP expert intervention centering on the sleep/circadian science- and evidence-based treatment components bedtime restriction and circadian adaptation and consists of three phases (therapist-guided treatment initiation, self-management with nurse support, and self-management). Evaluative pre-post assessments in 15 patients demonstrated feasibility. An improvement of insomnia severity as indexed by the Insomnia Severity Index (ISI; 18.3 ± 4.6 vs. 11.4 ± 4.4,  $p < 0.001$ ,  $d = 1.2$ ) and sleep quality, indexed by the Pittsburgh Sleep Quality Index (PSQI; 12.9 ± 3.8 vs. 10.3 ± 3.3,  $p = 0.031$ ,  $d = 0.6$ ) was observed with a decreased self-reported time in bed (520 minutes ± 105.3 vs. 460 ± 78.1,  $p = 0.031$ ,  $d = 0.6$ ) and increased total sleep time (331 minutes ± 110.6 vs. 375 ± 74.6,  $p = 0.09$ ,  $d = 0.5$ ), resulting in increased sleep efficiency (65.3% ± 21.8 vs. 81.9 ± 11.2%,  $p = 0.011$ ,  $d = 0.8$ ).

**Conclusions:** We present a novel sleep-centered intervention that has the potential to be implemented and disseminated in routine clinical care for patients with severe mental disorders and comorbid insomnia. A control comparison is needed to further test for efficacy. Given the substantive burden of insomnia and mental disorders, the proposed developments are expected to be of high public health relevance.

**Acknowledgements:** Intramural funds.

## EVENINGNESS AND RUMINATIONS ARE INDEPENDENTLY ASSOCIATED WITH POOR SLEEP QUALITY IN HEALTHY YOUTHS

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**Introduction:** Evening chronotype has been associated with poor sleep quality, mood disturbances, and a greater tendency to rumination. Moreover, ruminations may mediate the association between chronotype and depression and may predict reduced sleep quality in both healthy youths and young adults with depressive symptoms. A recent study exploring the role of chronotype, depressive symptoms, and cognitive emotion regulation strategies in response to stressful events or threats (including ruminations, putting into perspective, among others) as predictors of sleep

quality found that eveningness, depressive symptoms, less capability of 'putting into perspective' and smoking were independently associated with poorer subjective sleep quality in university students. Considering the relevance of exploring specific depressive-related ruminations, the present study aims to evaluate whether ruminations, as measured through the Ruminative Response Scale, may modify the association between chronotype and sleep quality. This study focuses on youths since the transition from adolescence to adulthood involves biological changes that increase the tendency to eveningness and the vulnerability to disturbed sleep quality and mental health disturbances.

**Materials and methods:** A sample of 213 healthy subjects aged 22.13 ± 2.3 (range 15–25, 76 males) was assessed through the reduced version of the Morningness-Eveningness Questionnaire (rMEQ), the Pittsburgh Sleep Quality Index (PSQI), and the Ruminative Response Scale (RRS). Correlations between variables of interest were estimated. Linear regression models were used to explore the effect of ruminations on the associations between chronotype and sleep quality, adjusting for age, gender, and BMI.

**Results:** Negative correlations were found between the rMEQ and the PSQI total score (Spearman  $r = -0.269$ ,  $p$ -value  $< 0.001$ ); positive correlations were found between the RRS and the PSQI total score (Spearman  $r = 0.391$ ,  $p$ -value  $< 0.001$ ). No significant correlations emerged between the rMEQ and the RRS (Spearman  $r = -0.076$ ,  $p$ -value = 0.267). Regression analysis with the PSQI as outcome and the rMEQ and RRS as predictors adjusted for age, gender, and BMI, showed that both rMEQ ( $\beta = -0.2$ ,  $p$ -value  $< 0.001$ ) and RRS ( $\beta = 0.094$ ,  $p$ -value  $< 0.001$ ) were associated with the PSQI. In models including both rMEQ and RRS, significant associations were found (rMEQ  $\beta = -0.18$ ,  $p$ -value = 0.002 and RRS  $\beta = 0.09$ ,  $p$ -value  $< 0.001$ ), while in models evaluating interactions between rMEQ and RRS no significant effect was observed ( $\beta = -0.001$ ,  $p$ -value = 0.732).

**Conclusion:** Eveningness and ruminations were associated with poor sleep quality in a sample of healthy youths. Ruminations did not significantly modify the association between chronotype and sleep quality. No interaction between chronotype and ruminations was observed. Goodness-of-fit measures suggest that depressive-related ruminations, as measured through the RRS, may explain subjective sleep quality to a greater extent than chronotype. These results suggest that repetitive thoughts with negative content may negatively impact the perceived sleep quality in the young population. Further research is required to explore if these findings may be replicated in studies using objective measurements of sleep quality and in other samples.

**Acknowledgements:** We thank G. Peretto, E. Scardina, and M. di Galante for their support in data collection.

## INCIDENCE AND RELATIVE RISK OF SLEEP PROBLEMS AMONG CHILDREN AND ADOLESCENTS WITH NEWLY DIAGNOSED NEURODEVELOPMENTAL DISORDERS. A NATION-WIDE REGISTER-BASED STUDY

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**Introduction:** Sleep problems in children with neurodevelopmental disorders are among the most common parental complaints to mental healthcare professionals. Sleep problems mainly include difficulty falling asleep, night awakenings and reduced sleep duration. Such difficulties are associated with a poor health-related quality of life in the child and the family and may contribute to aggravation of symptoms of neurodevelopmental disorders. These disorders include attention deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), oppositional defiant disorder/conduct disorder (ODD/CD) and epilepsy. Studies focusing on a single disorder have found that sleep problems are common in children with ADHD, where prevalence rates range from 25% to 66%, and in ASD, where prevalence rates of sleep problems range from 40% to 80%. Other studies have found sleep problems in very young children to be associated with higher ODD/CD symptom scores. In addition, sleep problems are prevalent in children with epilepsy. However, these problems may be related to epilepsy itself or be associated with the use of antiepileptic medications.

**Materials and Methods:** We estimated the absolute and relative risk of

sleep problems in children and adolescents with newly diagnosed neurodevelopmental disorders.

This was a population-based cohort study of individuals born in Denmark 1993–2014 and followed in nationwide registers 2011–2016. We estimated the 5-year cumulative incidence of sleep problems in incident cases of attention deficit/hyperactivity disorder (ADHD;  $n=12,844$ ), autism spectrum disorder (ASD;  $n=8,073$ ), oppositional defiant disorder/conduct disorder (ODD/CD;  $n=2,234$ ) and epilepsy ( $n=3,709$ ). Hazard ratios (HRs) for sleep problems were estimated by Cox regression.

**Results:** The 5-year risk of sleep problems was highest in ADHD (29.2%; 95% CI: 28.4–30.1), ASD (24.2%; 95% CI: 23.1–25.3) and ODD/CD 27.1% (95% CI: 25.0–29.2%) and lowest in epilepsy (11.3%; 95% CI: 10.2–12.6%). For ADHD and ASD, sleep problems were more common in females than in males. Furthermore, sleep problems were predicted by high parental socioeconomic status and varied with the geographical region of residence, suggesting that different clinical practices exist across Denmark and that sleep problems may be more likely to go undetected in families of lower socioeconomic position. Compared with individuals without these disorders, the likelihood of sleep problems was increased in individuals with ADHD (HR 33.81; 95% CI: 32.78–34.87), ASD (HR 16.77; 95% CI: 16.15–17.41), ODD/CD (HR 14.73; 95% CI: 13.88–15.64) and epilepsy (HR 6.01; 95% CI: 5.67–6.37). After mutual adjustment for comorbidity, HRs were attenuated, especially in ASD, ODD/CD and epilepsy when adjusted for ADHD.

**Conclusions:** The result suggest that the increased risk of sleep problems in individuals with ASD, ODD/CD and epilepsy is driven largely by comorbid ADHD.

**Acknowledgements:**

#### INSOMNIA AND EVENINGNESS ARE INDEPENDENT TRANS-DIAGNOSTIC MARKERS OF POOR MENTAL HEALTH ACROSS THE LIFESPAN

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**Introduction:** Insomnia and an evening circadian preference are associated with numerous psychiatric disorders. Mapping overlap and differences of distinct sleep profiles across different types of psychiatric problems in men and women of different ages may aid more precise diagnostics, prevention, and treatment of common psychiatric conditions. Our exploratory study aimed to establish whether persons can be classified into specific sleep profiles based on their insomnia symptoms and circadian preferences and if such sleep profiles would be related to specific mental health problems.

**Materials and methods:** We used cross-sectional data from 37,716 Dutch individuals aged 4–91 years from the Comorbid Conditions of ADHD study, performed in a subsample of the general population cohort from the Lifelines study. Each participant or their parent completed a digital survey about sleep habits and mental health. To account for qualitative differences between males and females and between different age groups, analyses were conducted within specific age/sex-subgroups. We performed latent class analyses to identify subgroups of persons based on their severity of three insomnia symptoms and three dimensions of circadian preferences, i.e. “sleep profiles”. Next, these sleep profiles were linked to different dimensions of psychopathology (depression, anxiety, aggression, autism, ADHD, smoking, drug use, and alcohol intake) using linear regression. We described the sex and age differences in the association between sleep profiles and dimensions of psychopathology.

**Results:** We derived three sleep profiles comparable among all age groups and sexes. The first profile included persons with low eveningness and low insomnia, and two others with higher eveningness with and without insomnia. The evening profiles were significantly related to higher scores on all dimensions of psychopathology. This association was even stronger for the evening profile with insomnia. Outcomes related to substance use, however, showed slightly different association patterns. Insomnia but not eveningness was linked to higher drug use and frequency of smoking, while the opposite held for alcohol use and the number of smoked cigarettes per day. Overall, we found that younger persons had stronger associations with all dimensions of psychopathology than adults. There were no conclusive patterns in sex differences.

**Conclusions:** Individuals in the general population can be classified according to the combination of their circadian preference and insomnia symptoms. However, there are no substantial differences related to individual symptoms of insomnia and dimensions of circadian preference. These profiles are stable across all ages and sexes. Evening profiles strongly relate to more severe mental health problems, and even more so for younger persons. The presence of insomnia strengthens this relationship even further. Therefore, we showed that sleep problems constitute a transdiagnostic problem in mental healthcare, with a more specific relation in case of substance use. These similarities and differences are important for improving mental health care at both clinical and population levels.

**Acknowledgments:** This research received funding from the European Community's Horizon 2020 Programme (H2020/2014–2020) under grant agreement n° 667302 (CoCA).

#### INTERVENTIONS TO IMPROVE SLEEP QUALITY FOR MENTAL HEALTH INPATIENTS IN SECURE SETTINGS: A SYSTEMATIC REVIEW & META-ANALYSIS

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**Introduction:** Despite the bidirectional relationship between mental health and sleep, no systematic review or meta-analysis, as yet, has examined the effect of interventions to improve sleep quality for mental health inpatients in secure settings.

The aim of the current work is to identify the effect of interventions for improving sleep quality in mental health inpatients in secure settings and identify moderating factors.

**Materials & Methods:** Eligible studies involved adults from secure inpatient mental health settings, included a quantitative measure of sleep as primary outcome, and were published in or after 2007. The Cochrane Library, Scopus, PubMed and ProQuest were searched; last search conducted October 2021. 12,409 abstracts were screened for inclusion from the databases. Thirty-eight studies were included in the systematic review.

**Results:** The meta-analysis included 22 studies (36 individual trials), with Sleep Quality, Insomnia Severity, Total Sleep Time and Sleep Efficiency as outcomes. The total pooled effect size for all interventions (random-effects model) was  $d=0.54$ , ( $p<0.0001$ , 95% CI: 0.30, 0.77). Subset-analyses indicated the pooled effect sizes for behavioural interventions as  $d=0.65$ , ( $p<0.01$ , 95% CI: 0.16, 1.14), medical interventions as  $d=0.58$ , ( $p<0.001$ , 95% CI: 0.25, 0.91) and environmental interventions as  $d=0.19$ , ( $p=0.38$ , 95% CI: 0.24, 0.62). Based upon duration, interventions conducted over a five-to-ten-week period were most effective,  $d=0.92$ , ( $p<0.005$ , 95% CI: 0.29, 1.55). Interventions with predominately (50%+) male samples reported a pooled effect of  $d=0.80$ , ( $p<0.005$ , 95% CI: 0.30, 1.30); greater than those with predominantly female samples,  $d=0.39$ , ( $p<0.005$ , 95% CI: 0.12, 0.66).

**Conclusions:** Interventions to improve sleep quality in this population are effective. Behavioural interventions, including Cognitive Behavioural Therapy and physical activity, are most impactful. Clinical practitioners should consider implementing behavioural interventions, incorporated over a five-to-ten-week period.

#### INVESTIGATING THE NOSOLOGICAL STATUS OF UNIPOLAR MANIA WITHIN UK BIOBANK USING OBJECTIVE AND SUBJECTIVE MEASURES OF REST AND ACTIVITY

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**Introduction:** There is uncertainty whether unipolar (hypo)mania is best viewed as a distinct mood disorder or a sub-type of bipolar disorder. Disrupted rhythms of rest/activity rhythms are key features of bipolar disorder but have not been well characterised in unipolar (hypo)mania. We

aimed to compare subjective and objective rest/activity patterns – as well as demographic, lifestyle and mental health outcomes – across three groups (bipolar disorder, unipolar (hypo)mania and controls) to assess whether unipolar (hypo)mania should be viewed as nosologically distinct from bipolar disorder.

**Materials and Methods:** UK residents aged 37–73 years were recruited into the UK Biobank general population cohort from 2006 to 2010. Probable cases of bipolar disorder and unipolar (hypo)mania were identified based on answers to a self-report mental health questionnaire, as were a healthy control group. Demographic, lifestyle, mental health and self-reported sleep outcomes were reported by participants in questionnaires. Accelerometers were provided to a subset of participants for 7 days and objective measures of sleep and activity were derived from this. Bipolar disorder and unipolar (hypo)mania were each compared to the control group, and then compared against each other. Binary logistic regression models were adjusted for age, sex, ethnicity, educational attainment, Townsend score, body-mass index, smoking status, alcohol status, psychotropic medication and season of accelerometer wear.

**Results:** There was some evidence of demographic differences between bipolar disorder and unipolar (hypo)mania: unipolar (hypo)mania had a greater proportion of males and bipolar disorder had a greater proportion of females. Both bipolar disorder and unipolar (hypo)mania had poor mental health outcomes compared to controls (worse in the bipolar disorder group). For objectively measured rest/activity rhythmicity, the bipolar disorder group had lower relative amplitude, lower sleep efficiency and longer sleep duration compared to controls. Average activity levels were different between all three groups: unipolar (hypo)mania had highest levels of activity and bipolar disorder lowest. For subjectively measured rest/activity rhythms, both mood disorder groups had late chronotype preference, more disturbed sleep and increased difficulty compared to controls. The unipolar (hypo)mania group were more likely to report an early chronotype compared to the bipolar disorder and control groups.

**Conclusions:** Bipolar disorder and unipolar (hypo)mania share features in common but some key differences support the proposition that unipolar (hypo)mania could be viewed as a distinct and more homogenous disorder. Specifically, unipolar (hypo)mania was characterised by increased activity levels, early chronotype and shorter sleep duration.

**Acknowledgements:** Medical Research Council (MRC)

## MELATONIN – PRODUCTION AND RELEASE IN CHILDREN AND ADOLESCENTS WITH ADHD AND CHRONIC SLEEP PROBLEMS - GENETIC VARIATION ? A NEW STUDY IS PRESENTED

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**Introduction:** Attention Deficit Hyperactivity Disorder (ADHD) is a common neuropsychiatric disorder, affecting an estimated 5.3% of children and adolescents worldwide and persisting into adulthood in approx. 2/3 of patients. Although the diagnosis is based on observations while the patient is awake, there is a prevalence of sleep disturbances of 25-55% in persons with ADHD

There is a growing evidence that a number of sleep traits in humans are heritable, such as timing of sleep and sleep requirement.

The timing of sleep is determined by the circadian clock and is generated by transcriptional-translational feed-back loops. There is a growing list of core clock genes that have been discovered participating in this feedback loop.

This complex mechanism of circadian regulation and its downstream regulatory processes were hypothesized to play an important role as etiological factors for, among other psychiatric disorders, ADHD.

Several genetic mutation including Casein kinase 1 delta (CK1d), T44A and H46R, Period” (PER2), period3 (PER3) P415A7H417R and cytochrome2 (CRY2) A260T is found in families suffering from familial advance sleep phase.

**Materials and Methods:** Genotype analysis:

A single saliva swap sample from each participant will be collected for genomic DNA extraction. After DNA purification, real-time qPCR analysis

for SNP rs1801260 will be performed. This SNP is located in the 3UTR part of the CLOCK gene harbouring a T or C in position 3111. Saliva samples will be analysed immediately after sampling, and then destroyed.

**Results:** In this study we will look into the complex mechanisms underlying circadian regulation as e.g., the timing of sleep, are cell autonomous transcription-translation feedback loops where the transcription factors CLOCK and BMAL1 drive the expression of *Period* (*Per1/2*) and *Cryptochrome* (*Cry1/2*), whose protein products in turn feed-back to inhibit CLOCK and BMAL1. Correlation between ADHD, circadian rhythmicity and sleep disturbances have been demonstrated for ADHD patients, and circadian regulation and its downstream regulatory processes have been suggested to play an important role as etiological factor for, among other psychiatric disorders, ADHD.

**Conclusions:** CLOCK is considered as the master gene the circadian rhythm, and understanding the relationship between ADHD and CLOCK may provide additional information to understand the correlation between ADHD and sleep problems. This has only been explored in few studies. As can be seen, it is important to gain more knowledge about the normal release of melatonin, and the release of melatonin in a group of children and adolescents with a variety of psychiatric diagnoses. It is essential to investigate whether there are any differences in the release of melatonin in children and adolescents with chronic sleep onset problem and children and adolescents who do not have sleep problems.

Also, if there is a genetic component or explanation in the different DLMO and whether there is a further relation to ADHD.

**Acknowledgements:**

## PERCEIVED SLEEP QUALITY AND OBJECTIVE SLEEP CHARACTERISTICS IN PATIENTS WITH ANOREXIA AND BULIMIA NERVOSA

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**Introduction:** Eating disorders (ED) are highly prevalent disorders characterized by negative beliefs regarding body shape and weight, irregular eating habits, and associated with a high level of anxiety and depression. Clinical observations and few controlled studies seem to indicate that individuals with ED often complain about their sleep. However, the literature on sleep and ED is scarce, and often ED focused on self-report instruments. Here, we investigate subjective (questionnaire) and objective (actigraphy) sleep characteristics, and the relationship with psychological distress, in a cohort of consecutive patients with a diagnosis of anorexia nervosa (AN) and bulimia nervosa (BN) admitted to an ED inpatient treatment ward.

**Methods:** A total of 66 patients were enrolled in this study. Forty-five patients had a diagnosis of AN (Mean=21.6±8.3, 2M) whereas 21 had a diagnosis of BN (Mean=24.1±9.2, all females) based on the DMS-5 criteria. Psychological and self-reported sleep evaluation was conducted at the beginning of their inpatient treatment (the first week after their admission), whereas during the second week they were asked to wear an actigraphy for 7 days.

**Results:** AN and BN patients did not show differences in the level of ED symptomatology (as assessed by the Eating Disorder Examination Questionnaire) and general psychiatric symptoms and psychological distress, including anxiety and depression (as assessed by the Symptom Checklist-90-Revised), chronotype (as assessed by the Morningness-Eveningness questionnaire) and subjective sleep quality (as assessed by the Pittsburgh Sleep Quality Index, PSQI) were similar between AN and BN. The majority of AN (86.7%) and BN (76.2%) patients reported poor sleep quality (PSQI>5), and a morning (45.5%) or intermediate (50%) chronotype. Actigraphy data showed that BN patients slept less and had a higher wake after sleep onset, resulting in lower sleep efficiency (86.8vs89.3%) compared to AN. Poorer perceived sleep quality was mildly associated with higher psychological distress and ED symptomatology in both groups, whereas no clear associations were observed for objective sleep parameters.

**Conclusions:** Our study showed a high prevalence of self-reported sleep difficulties in individuals with ED, with no differences between AN and BN patients, consistent with the literature suggesting that sleep can be a

clinical marker in ED patients. Moreover, these difficulties were greater in individuals with higher psychological distress. Actigraphic sleep assessment showed a more fragmented sleep in BN compared to AN, suggesting that different ED diagnoses may be characterized by different sleep patterns and difficulties.

### PREFRONTAL THETA CORDANCE IN RAPID-EYE MOVEMENT SLEEP AS BIOMARKER FOR PRECISE GUIDANCE OF ANTIDEPRESSANT THERAPY OF MAJOR DEPRESSION TO HIGHER RESPONSE RATE

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**Introduction:** Prefrontal theta cordance in rapid-eye movement (REM) sleep (PTC-R) is a quantitative EEG measure computed from prefrontal absolute and relative theta power in tonic REM-sleep. PTC-R correlates with frontocingulate brain activity, and it has been acknowledged as reliable predictor of antidepressant treatment response in major depression. The aim of this prospective clinical study were to examine if providing the prediction of PTC-R prospectively at week one and changing the antidepressant medication in case of predicted non-response immediately would increase the final response rate. Further, we wanted to compare the reliability of the biomarker PTC-R with the clinical finding of “early response”.

**Materials and methods:** At treatment onset with antidepressants, 37 inpatients with major depressive episode were randomly assigned either to the intervention condition (IG, N = 22, mean age: 39.5 years; 45.5 % females) or the control condition (CG, N = 15, mean age: 45.4 years; 50 % females). The biomarker PTC-R was computed from a 19-electrodes sleep-EEG recording at week 1. Only in the IG, the PTC-R was provided prospectively so that physicians were able to maintain or adapt antidepressant treatment depending on predicted response or non-response. Experts rated the depression severity with the Hamilton Depression Rating Scale (HAMD) at baseline, at week one after treatment onset, and at week five. Early response was defined as a  $\geq 20\%$  reduction of baseline HAMD at week 1, and final response as a  $\geq 50\%$  reduction of the score at week 5. For comparison of the predictive values of PTC-R with early response 7 non-responders of the IG were excluded from the analysis because of a possible bias in final response through treatment change.

**Results:** When PTC-R predicted non-response at week one, and antidepressant treatment was modified immediately (IG), the PTC-R predicted non-responder had an 85.7% chance of response at week five instead of 20% in the CG where antidepressant treatment was maintained unchanged ( $F = 4.18$ ,  $p = .03$ ,  $\eta^2 = .29$ ). There was no significant difference between IG and CG response rates in the PTC-R predicted responders when medication was maintained unchanged in both, IG and CG ( $F = .26$ ,  $p = .77$ ). The predictive power of PTC-R was similar to that of early response at week one, though PTC-R was better in predicting non-response.

**Conclusions:** These preliminary data suggest that PTC-R is suitable for biomarker guided antidepressant treatment. While PTC-R is similarly predictive than the clinical observation of early response at week one, the first is better in predicting non-response, which would allowed prevention of poor treatment outcomes.

### PREVALENCE OF SLEEP COMPLAINTS AMONG ARMY SERVICEMEN AFTER WAR EXPERIENCE

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**Introduction:** Neuropsychological problems are common among patients after acute stress events. The relationship between traumatic event related

to war and sleep disturbances are well-known to medical science. The latter are subject to adequate assessment and therapeutic approaches and through time the sleep symptoms can change their quantity, quality, and intensity. Our study was aimed at identifying sleep-related complaints among Armenian servicemen in early and late posttraumatic periods after the recent war in Artsakh (2020).

**Materials and Methods:** Overall 99 male servicemen being treated at a mental health rehabilitation center participated in our study, mean age  $19.9 \pm 3.17$  years. All participants passed psychiatric consultation. We developed a form assessing different complaints related to sleep such as insomnia in general and its phenotypes - sleep-onset insomnia (SOI) and sleep-maintenance insomnia (SMI), nightmares, excessive daytime sleepiness (EDS), circadian rhythm abnormalities (CRA), as well as subjective sleep latency (SL), total sleep time (TST). We assessed sleep quality by the validated Armenian version of the Pittsburgh Sleep Quality Index (PSQI). It is a widely used questionnaire with a cutoff of  $>5$  meaning poor sleep quality. We divided the participants into two groups based on the post-war admission time period: early (EPWP) and late (LPWP) post-war periods. In the EPWP group, we involved servicemen less than two months after the traumatic event ( $n=66$ ). The LPWP group consisted of the participants admitted later - two to four months after the war ( $n=33$ ). We administered the sleep form and PSQI before the interventions (psychotherapy and/or medications). Chi-square test was used for statistical analysis.

**Results:** The participants had insomnia in 99.1% of cases, while 97% showed poor sleep quality by PSQI. For the total sample the PSQI mean score was  $12.6 \pm 3.7$ , the SL was  $120.6 \pm 98$  minutes, the TST was  $5.8 \pm 2$  hours, 83.5% had SOI, 48.5 % had SMI, 59.1% - CRA, 26.5% had EDS, 83% complained of nightmares. Within groups EPWP/LPWP: insomnia - 90.9%/93.8% ( $p>0.05$ ), SOI - 83.1%/84.4% ( $p>0.05$ ), SMI - 32.3%/81.25% ( $p<0.01$ ), CRA - 60.6%/56.3% ( $p>0.05$ ), EDS - 21.2%/37.5% ( $p>0.05$ ), nightmares - 80.3%/90.3% ( $p>0.05$ ), PSQI - 95.45%/100% ( $p>0.05$ ). In summary, between the two groups we obtained significant difference only for SMI.

**Conclusions:** The results of our study suggest that sleep complaints were very common among Armenian servicemen, which corresponds to data from other studies in this field. Most of the studied sleep complaints, including insomnia in general, SOI, EDS, and nightmares, did not differ in the early or late periods after the war. Interestingly, we found that SMI can even increase over time, being the most significant finding of this study.

### PSYCHOLOGICAL AND BEHAVIOURAL INTERVENTIONS IN BIPOLAR DISORDER THAT TARGET SLEEP AND CIRCADIAN RHYTHMS: A SYSTEMATIC REVIEW OF RANDOMISED CONTROLLED TRIALS

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**Background:** Sleep and circadian rhythm disruptions are prominent symptoms of bipolar disorder (BD) and potential targets for adjunctive interventions. The aim of this systematic review was to appraise evidence from randomised controlled trials on the effects of psychological and behavioural interventions in BD that target sleep and circadian rhythms.

**Methods:** The review included records from inception until January 3rd, 2021 (PROSPERO registration: CRD42019156782; Open Data, Materials, and Source: <https://osf.io/gv3pe/>). All included trials were summarised via narrative synthesis and meta-analytic models were applied when appropriate.

**Findings:** Nineteen studies met the inclusion/exclusion criteria. Out of these studies, six delivered bright therapy, five delivered interpersonal and social rhythm therapy, two used blue-light blocking glasses, one delivered cognitive behavioural therapy for insomnia, one delivered total sleep deprivation, and four delivered bespoke combination treatments. Quality assessment produced mixed results but there was a general trend towards improvement in the last five years. Acceptability of the interventions was 89.2%, no serious adverse events were reported, and side-effects were rare.

However, more than half of the included studies (N=10, 52%) did not measure sleep or circadian rhythms despite being the principal target of the intervention. The evidence base for the effectiveness of these interventions was limited. There was a small number of trials for each intervention type, and a lack of consistency in treatment protocols and assessed outcomes. Meta-analysis was possible for the effect of bright light therapy on depression severity, revealing a medium-to-large post-treatment effect (Nc=6;  $g=-0.74$  [95% CI=-1.05 to -0.42],  $p<0.001$ ). Findings for blue-light blocking glasses and cognitive behavioural therapy for insomnia were mostly positive for sleep, morningness, and mood. Only mood symptoms were assessed in interpersonal and social rhythm therapy trials, and results were conflicting. No individual trial containing a total sleep deprivation element showed any significant effects on any domain examined. This finding is contrary to recent claims in support of the effectiveness of total sleep deprivation for bipolar depression. However, those claims were based on a literature dominated by non-controlled studies or RCTs that compare total sleep deprivation plus medication against total sleep deprivation alone.

**Conclusions:** There is a clear need for larger, adequately powered trials that incorporate comprehensive measures of sleep, circadian rhythms, mood, and functioning. Nevertheless, the psychological and behavioural treatments included in this review offer a promising avenue as adjustment interventions in BD given their minimal side effect burden.

**Funding:** Nuffield Department of Clinical Neurosciences, University of Oxford; UK Medical Research Council; National Institute for Health Research Oxford Biomedical Research Centre

#### PTSD AND SLEEP ARCHITECTURE IN ACTIVE DUTY SERVICE MEMBERS

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**Introduction:** Sleep is increasingly recognized as a marker of overall psychological health and resilience. Sleep complaints are also a hallmark of post-traumatic stress disorder (PTSD). Additionally, sleep disorders may be implicated in the underlying pathophysiology of PTSD and not just a consequence of the disease. Military personnel can be at high risk for developing sleep disorders, which can negatively impact health, resilience and operational readiness. Further, active duty military personnel are at high risk for developing PTSD given the nature of deployments, war and other factors. The majority of published studies have shown a correlation between sleep relating breathing disorders and PTSD. To our knowledge, none of these studies have focused solely on active duty military members.

**Materials and Methods:** This is a case-controlled observational cohort from the Sleep Disorders Center of an academic military medical center. Sleep-related questionnaires (Epworth Sleepiness Scale, Insomnia Severity Index, Pittsburgh Sleep Quality Index) and polysomnographic (PSG) data were obtained. We excluded patients with history of traumatic brain injury, use of psychoactive medications and abnormal neuroimaging.

**Results:** 169 active duty service members underwent sleep evaluations. Of these, 43 (25.4%) had PTSD compared to 126 (74.6%) without PTSD. The majority of the population was predominately male (80.5%) with a mean age of 37.1 and a BMI of 28.6. In patients with PTSD vs no PTSD, there was no significant difference in the rate of obstructive sleep apnea, mean total sleep time, sleep efficiency, mean apnea-hypopnea index, rapid eye movement (REM) sleep percentage, or any other objective sleep variable on PSG that was analyzed. Subjective sleepiness was similar between those with PTSD and no PTSD. However, subjective insomnia symptoms and perceived sleep quality were worse in those with PTSD vs no PTSD.

**Conclusions:** In a relatively young active duty service member cohort, we found that patients with PTSD had more subjective complaints about sleep compared to those without PTSD. However, objective sleep parameters did not statistically differ between these two groups. Previously published research has identified an association between PTSD and sleep disorders that our data did not confirm. These studies did not exclude patient's with history of traumatic brain injury, use of psychoactive medications or abnormal neuroimaging. It is known that these factors can cause abnormalities seen on PSG and/or lead to the development of sleep disorders, which may explain the objective sleep abnormalities documented in prior

studies. Our findings suggests that there is a sleep-state misperception in patients with PTSD that is present at a relatively young age. These findings have profound implications and could provide insight into early treatment with cognitive behavioral therapy for PTSD patients to prevent onset of sleep disorders.

**Acknowledgements:** None

#### SLEEP DISTURBANCE AND CHANGES IN OSCILLATORY ACTIVITY IN A MOUSE MODEL OF DEPRESSION: EFFECTS OF SLEEP DEPRIVATION, KETAMINE AND CIRCADIAN CLOCK MODULATION

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**Introduction:** Sleep disturbance is increasingly recognised as an important feature of affective disorders. Assessment of sleep disturbances and subsequent response to different treatment is an important consideration for any model of these disorders. The chronic despair model (CDM) is a recently established mouse model for depressive-like symptoms in which repetitive forced swim stress produces long-lasting anhedonia- and despair-like phenotypes. In the current pilot study, sleep was assessed in the CDM model in respect to architecture and oscillatory activity, compared to non-depressive controls. Sleep measures were then assessed after treatment with known rapid acting anti-depressants, sleep deprivation and ketamine, and after treatment with an agonist of circadian clock gene *ROR $\alpha$* , which has been recently suggested to produce anti-depressant effects via modulation of the activity of the circadian clock.

**Materials and Methods:** C57BL/6 mice were surgically implanted with electrodes for recording electrocorticography (ECoG) and electromyography (EMG) in order to assess sleep, as well as a deep electrode in the medial pre-frontal cortex (mPFC) for the recording of local field potentials (LFP). Each electrophysiological recording session was conducted over a period of 48h. After recovery from surgery, recordings were conducted before and after the CDM protocol, consisting of five consecutive days of 10-minute forced swim test. After induction of the model, CDM mice underwent recordings before and after three anti-depressant treatments: 6h sleep deprivation (conducted from the onset of the light cycle); IP injection of *ROR* agonist SR1078 (10mg/kg); IP injection of ketamine (3mg/kg); and IP vehicle injection as a control. ECoG and EMG data from recording sessions were manually analysed to calculate the time spent in states of wake, slow wave sleep (SWS) and REM sleep. Within these episodes, spectral analysis was performed to assess oscillatory activity in ECoG and mPFC signal.

**Results:** The CDM protocol caused changes to the architecture and spectral content of sleep. CDM mice exhibited more fragmented sleep, with a reduction in theta band oscillations during REM sleep. Sleep deprivation resulted in selective increase of REM sleep in the period immediately following treatment, alongside a reduction in the fragmentation of SWS. CDM mice did not exhibit a rebound in slow wave activity (SWA) after sleep deprivation, as would be expected, but did exhibit a suppression of wake and REM sleep gamma activity during the light cycle immediately following treatment. Treatment with *ROR* agonist SR1078 resulted in suppression of mPFC gamma activity in wake, SWS and REM sleep, without affecting sleep architecture. Similarly, ketamine produced suppression of mPFC gamma activity in wake and REM sleep, alongside increased SWA during SWS.

**Conclusions:** The initial results of the current study indicate fragmentation of sleep after the CDM paradigm, without classical hallmarks of affective disorders such as decreased latency to REM sleep, suggesting mixed validity of the model in regard to sleep disturbance. Response after sleep deprivation suggests a possible blunted SWA response in the CDM mouse. All treatment modalities appeared to suppress gamma activity in the mPFC, suggesting a potential common mechanism or marker of anti-depressant response.

## SLEEP DISTURBANCES AND MENTAL HEALTH: A TRANSDIAGNOSTIC VIEW OF SLEEP DISORDERS SYMPTOMS IN A REPRESENTATIVE CANADIAN SAMPLE

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**Introduction:** Sleep problems can actively contribute to the onset, maintenance and worsening of mental disorders. Beyond insomnia, several other sleep pathologies may be associated with adverse mental health outcomes, and having multiple sleep disorders may be an aggravating factor. This study aimed to delineate the current landscape of sleep difficulties and symptoms of sleep disorders linked to poor mental health, investigate associations between the age at onset of sleep problems and subsequent mental health, and assess the perceived impacts of sleep problems.

**Materials and Methods:** A representative sample of 1,200 Canadians (16 to 88 years old, 53% females) completed an online survey on sleep and mental health between 21 and 24 September 2021 (i.e. after the acute phase of the COVID-19 pandemic in Canada). The survey included questions inspired from the Sleep Disorders Questionnaire, Sleep Disorders Symptom Checklist-25, Pittsburgh Sleep Quality Index, STOP-Bang, and Insomnia Severity Index. The sample was stratified in two groups based on self-reported current mental disorder diagnosis: mental disorder diagnoses [219 (18.2%)] vs no diagnosis [960 (80.0%)]. Total scores on the General Anxiety Disorder-7 and Patient Health Questionnaire were used to determine anxiety and depression symptoms severity.

**Results:** Of those with mental disorder diagnoses, 80.4% (176/219) endorsed symptoms of at least one sleep disorder, a proportion significantly higher compared to the 42.7% observed in the rest of the sample ( $p < .001$ ,  $V = .29$ ). The mental disorder diagnoses group included higher proportions of respondents endorsing symptoms of insomnia disorder, sleep apnea, bruxism, restless legs syndrome, nightmare disorder, hypersomnia and somnambulism. After adjusting for age, sex, income level and total sleep time, having a mental disorder diagnosis was associated with: insomnia (OR=3.52,  $p < .001$ ), obstructive sleep apnea (OR=1.95,  $p = .006$ ) and bruxism (OR=2.77,  $p < .001$ ). Half of those with mental disorders diagnoses endorsed symptoms of multiple sleep disorders, a proportion significantly higher than what was observed in the rest of the sample ( $p < .001$ ,  $V = .35$ ). Endorsing symptoms of insomnia, sleep apnea, bruxism, restless legs syndrome, and hypersomnia were associated with more severe anxiety and depression symptoms after adjusting for age, sex, income level, total sleep time, and mental disorders diagnoses ( $B > .98$ ,  $p \leq .012$ ). Younger age at onset of sleep problems was a significant independent predictor for current self-reported diagnosis of mental disorders (OR=.96,  $p < .001$ ). Compared to the rest of the sample, the mental disorder group reported significantly worse impacts of sleep problems on mental health, family relationships, physical health, cognitive functioning, productivity level, and global daily functioning.

**Conclusions:** These results reinforce the transdiagnostic nature and cumulative impacts of the various profiles of sleep problems associated with mental health issues. These findings also suggest that the relationship between sleep and mental health is not solely driven by short sleep duration or insomnia. There is a need to enhance awareness about the diverse profiles of sleep issues linked to poor mental health and the relevance of early intervention, notably during youth. Should future longitudinal studies based on objective measures confirm these observations, this may inform further development of transdiagnostic sleep interventions for people with mental disorders.

## SLEEP DISTURBANCES, MENTAL AND COGNITIVE HEALTH IN JOURNALISTS, HUMAN RIGHTS DEFENDERS AND RELATIVES OF DISAPPEARED PERSONS VICTIMS OF VIOLENCE

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**Introduction:** In Mexico, violence index has increased dramatically during the last years. Within affected population sectors are journalists, human rights defenders and relatives of disappeared persons. The exposition to violence events increase the risk of development post traumatic stress disorder with high comorbidity of other psychiatric disorders such as depression and anxiety. Sleep disturbances are considered hallmark symptoms of diagnostic criteria for the psychiatric disorders mentioned and exacerbate the associated symptoms. Poor sleep quality due to sleep restriction or disturbances impact on cognitive performance. Our objective was to evaluate the efficiency of cognitive behavioral therapy for sleep disorders in this population.

**Materials and methods:** We evaluated 15 participants (age 22 – 60 years, 60% women) journalists (n=2), human right defenders (n= 8) and relatives of disappeared persons (n=5) whom had been exposure to violence directly (n=4), indirectly (n=8) or both of them (n=3). After providing informed consent, all participants completed neuropsychiatric (International Neuropsychiatry Interview, MINI), neuropsychological (Neuropsi Battery; Neuropsychological Battery of Executive Functions and Frontal Lobes, BANFE-2), sleep quality (Pittsburgh Sleep Quality Index, PSQI) and sleep pattern (polysomnographic study) evaluations, as well as clinic sleep interview to identify sleep disorders associated in this population, victim of violence. After diagnosis, we conducted six sessions of Cognitive Behavior Therapy (CBT) for sleep disorders. Two weeks after CBT conclusion, we evaluated sleep quality and mental health post-treatment.

**Results:** We identified mental disorders comorbidity, of which, depression (n=12), Post-Traumatic Stress Disorder (n=9) and anxiety (n=9) were the most common. Regarding to cognitive functions, people showed deficits in codification (n=10) and evocation (n=8) of memory, as well as in attention tasks (n=5). We observed alterations on orbitofrontal and ventromedial cortex function in four cases, as well as on dorsolateral cortex in two cases. All participants reported poor sleep quality and irregular sleep patterns. Increase in sleep stages N1 y N2 ( $M = 70\% \pm 0.7$ ) and decrease in N3 and REM ( $M = 16\% \pm 0.06$ , and  $M = 14\% \pm 0.05$ , respectively), as well decrease of sleep efficiency ( $M = 78\% \pm 0.13$ ). Symptoms of sleep disturbance, like, insomnia, nightmares, obstructive sleep apnea (OSA) and sleep restriction were the most frequent. After CBT treatment, we observed improvement in sleep quality. Most of the participants reported decrease in severity of the symptoms associated with depression, anxiety and post-traumatic stress disorders, and improvement in the performance of executive functions, which allow controlling, regulating and planning behavior.

**Conclusion:** The results show a particular trend in the psychological and psychiatric profile of this population sector subject to an experience of violence. The intervention through CBT therapy produced an impact on the improvement of sleep disorders, affective, cognitive and mental health disorders without the risk of produce re-victimization in this vulnerable population sector.

**Acknowledgments:** We are grateful with Sistema Integral de Derechos Humanos de la Ciudad de México (SIDH CDMX) y el Mecanismo de Protección Integral de Personas Defensoras de Derechos Humanos y Periodistas de la Ciudad de México (MPI CDMX). Scholarship support PRODEP 511-6/2020-9264.

## SLEEP HABITS IN PATIENTS WITH ANOREXIA NERVOSA ASSESSED IN THEIR NATURAL ENVIRONMENT

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**Introduction:** Anorexia nervosa is a mental health disorder characterized by abnormal eating patterns, severe self-induced weight loss, intense fear of weight gain and a disturbed body perception. Reduced sleep quality and fragmented sleep might be a part of the complex presentation of behaviors and complications of anorexia nervosa. To our knowledge, this study is the first examining sleep patterns in patients with anorexia nervosa in their natural environment using accelerometers. As most patients with anorexia nervosa receive outpatient treatment, knowledge about sleep patterns in their home environment is of importance, as behaviors in in-patient treatment to a larger degree might depend on department routines. The aim of this study was to compare sleep habits in patients with anorexia nervosa to healthy controls, and to assess associations between sleep habits in patients with anorexia nervosa and clinical symptoms.

**Materials and methods:** This study had a case-control design assessing patients prior to starting outpatient treatment. We included 20 female patients with anorexia nervosa (median: 19.5 years old and Body Mass Index (BMI) 16.7) and 23 age matched female healthy controls (median: 19 years old and BMI 22.9). Sleep patterns were measured objectively by accelerometer (Philips Actiwatch2) for seven consecutive days. Mean week results were used in non-parametric statistical analyses. The severity of eating disorder symptoms and psychosocial impairment associated with eating disorders were evaluated using the Eating Disorder Examination Questionnaire (EDE-Q) and the Clinical Impairment Assessment (CIA).

**Results:** There were no differences between patients and healthy controls (median (IQR)) regarding: sleep onset time (00:19 (2:07) vs 00:33 (1:38)), sleep offset time (07:59 (2:05) vs 08:16 (1:16)), mid-sleep time (04:04 (1:48) vs 04:23 (1:22)), sleep duration (409 (92) vs 452 (64) minutes per night) or number of wake up periods >5 minutes after sleep onset (0.93(1) vs 0.50(1) per night). However, patients with anorexia nervosa had a larger variability in sleep habits than healthy controls as shown by larger IQR, more wake-nights (in total 6 nights within 4 patients vs 0 nights in healthy controls) and longer wake-up periods after sleep onset (9 (32) vs 6 (1) minutes per wake-up lasting over 5 minutes,  $p=0.012$ ). In patients with anorexia nervosa, EDE-Q global score was positively correlated with mean duration of wake periods >5 minutes after sleep onset ( $\rho=0.484$ ,  $p=0.036$ ). CIA was positively correlated with sleep onset ( $\rho=0.487$ ,  $p=0.029$ ), sleep offset ( $\rho=0.448$ ,  $p=0.048$ ) and mid-sleep time ( $\rho=0.524$ ,  $p=0.018$ ).

**Conclusion:** This study finds sleep duration and timing in patients with anorexia nervosa living at home and healthy controls to be similar. However, the patients show more variability in sleep patterns and longer wake periods during the night. The severity of eating disorder (symptoms and psychosocial impairment) is associated with later sleep onset and offset time and longer wake up periods after sleep onset. Due to a small sample size findings need to be interpreted with caution.

**Acknowledgements:** Supported by grant from the Norwegian Competence Center for Sleep Disorders (SOVno) and from the Health Authorities in Western Norway (Helse Vest), Grant/Award Number 912177; Haukeland University Hospital.

## SLEEP IN PEOPLE WITH CURRENT AND PAST EATING DISORDERS DURING THE COVID-19 PANDEMIC

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**Introduction:** The COVID-19 pandemic and related containment measures impacted several domains of individuals' functioning – one of them was sleep patterns. While difficulties were present in the general population, individuals with current or past psychological disorders were particularly vulnerable. Individuals with eating disorders are prone to experiencing sleep disturbances; however, no studies have investigated how the pandemic affected their sleep. The objective of this study was to compare

subjective sleep disturbances before and during the COVID-19 pandemic among three groups: current eating disorder, history of an eating disorder, and no history of psychiatric diagnoses.

**Materials and Methods:** Between April 3 and June 23, 2020, Canadians completed an online survey (subsample in present study:  $n = 1042$ , mean age =  $42.34 \pm 15.63$ , range: 17–81, 92% female). Two clinical groups were included: individuals reporting a current eating disorder (ED;  $n = 69$ ) and individuals reporting a history of an ED ( $n=129$ ). ED diagnoses included AN, BN and BED. A third (control) group comprised those without current or previous psychiatric diagnoses ( $n = 844$ ). Participants completed the PSQI (sleep), GAD-7 (anxiety) and QIDS-SR16 (depression) for two time references: (1) retrospectively for the month before the pandemic started, and (2) during the pandemic. To assess changes in sleep disturbances (total PSQI score), a 2 (time: before and during the pandemic) X 3 (groups: current ED, history of ED, control) ANOVA was conducted. A second adjusted ANCOVA model was computed, with age, sex, anxiety, and depression symptoms as covariates.

**Results:** A significant interaction between time and group status ( $F(2, 1039) = 4.58$ ,  $p = .010$ ) was found in the unadjusted model. All three groups reported a worsening in sleep disturbances from before to during the pandemic, but this worsening was more pronounced in the current ED group, followed by those with a history of ED and those without any psychiatric history (+1.51, +1.02, +.58, respectively; all  $p < .001$ ). A significant interaction was also found in the adjusted model ( $F(2, 971) = 6.87$ ,  $p = .011$ ) and a similar profile was observed. Again, all three groups reported a worsening of sleep disturbance from before to during the pandemic ( $p < .001$ ). In the adjusted model, those with a current ED reported a higher relative change (+1.72) than those with a history of an ED (+1.20) and those with no ED (+.52).

**Conclusions:** Whether individuals had a current ED, history of an ED, or no psychiatric history, subjective sleep patterns were negatively impacted by the onset of the pandemic. Even when controlling for anxiety and depression, individuals with a past ED reported a more notable worsening in sleep disturbance than those with no psychiatric history – suggesting that even after recovery, sleep patterns may not return to baseline. Whether these results can be explained by a specific sleep variable remains to be determined. Nonetheless, findings highlight the importance of identifying and treating sleep disturbances in contexts of potentially heightened stress for all individuals, but particularly for those with current or previous mental health disorders, such as EDs.

## SLEEP PROFILE AND CANNABIS USE IN WOMEN – AN ONLINE SURVEY

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**Introduction:** Women usually present more sleep complaints than men, which interfere with daily activities and decrease quality of life. A significant share of the female population routinely uses sleeping aids to overcome these problems. Recently, cannabis use has been proposed as an adjuvant therapy for sleep complaints, however recent literature is scarce and controversial. Some studies show a reduced sleep quality among cannabis users, while others demonstrate some sleep-inducing effects. Evaluating the effects of cannabis use on sleep could be important from a public health perspective. Thus, this project aimed to evaluate the association of cannabis use and sleep characteristics among women.

**Materials and Methods:** The initial sample comprised 2,055 women of reproductive age, from 18 to 40 years, who filled up an online questionnaire between 2016 and 2017, about sociodemographic data, drug use, and sleep characteristics. Insomnia symptoms were evaluated using the Insomnia Severity Index (ISI) and individuals were categorized according to symptoms severity (no, mild, moderate and severe). Excessive daytime sleepiness (EDS) was analyzed by the Epworth Sleepiness Scale (ESS). Sleep Efficiency (SE) was calculated based on self-reported bedtime, awakening time and total sleep time (TST). Cannabis use was considered according to the self-reported use pattern in the last 3 months and two groups were compared in this study: daily/almost daily use and no use. The effects of cannabis use on ISI and ESS score, TST and SE were compared

using the Mann-Whitney test, and the association with insomnia symptoms categories and presence of EDS was compared with the  $\chi^2$  test. Analyses were performed using Jamovi and significance level was established as  $p < 0.05$ .

**Results:** A total of 1,669 women were included in this study. Among those, 24 (1.4%) reported daily or almost daily cannabis use, while 1645 reported no use. The average ISI score was  $6.9 \pm 5.6$  among cannabis users and  $8.7 \pm 5.7$  among no users and no statistically significant differences were observed among groups ( $p = 0.09$ ). Insomnia symptoms were considered as normal in 768 participants (46.0%), mild in 631 (37.8%), moderate in 241 (14.4%) and severe in 29 (1.7%), with no significant association between cannabis use and insomnia severity ( $\chi^2 = 2.98$ ;  $p = 0.39$ ). The average ESS score was of  $8.5 \pm 3.7$  among cannabis users and  $10.0 \pm 4.7$  among no users ( $p = 0.06$ ). EDS was reported in 723 participants (43.3%) and no association was observed between cannabis users and no users ( $\chi^2 = 3.33$ ;  $p = 0.06$ ). Cannabis users had a mean TST of 445 minutes ( $\pm 67.8$ ) and SE of 88.3% ( $\pm 11.0$ ), while no users had a TST of 417 minutes ( $\pm 84.7$ ), and SE of 87.5% ( $\pm 12.4$ ). No differences between the groups were found in these variables (TTS:  $p = 0.05$ ; SE:  $p = 0.92$ ).

**Conclusions:** Insomnia symptoms, daytime sleepiness, self-reported total sleep time and sleep efficiency among women of reproductive age was not associated with cannabis use in our sample. In this sense, cannabis use does not seem to be related to any harmful effect on sleep.

**Acknowledgements:** AFIP, CAPES and CNPq

#### SLEEP-RELATED TREATMENT-EMERGENT ADVERSE EVENTS (TEAES) IN ADHD RANDOMIZED CONTROLLED TRIALS (RCTS) INVESTIGATING AMPHETAMINE-BASED STIMULANTS: A SCOPING REVIEW

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**Introduction:** ADHD and sleep are highly interconnected, illuminated by the high prevalence of individuals with ADHD exhibiting sleep disorders. The clinical implications of disturbed sleep include worsening ADHD symptoms. Given this intrinsic relationship, interventions aimed at ameliorating ADHD symptoms should consider effects on sleep. Of specific interest are amphetamine-based stimulants, which are commonly prescribed despite their known adverse effects on sleep. To further investigate the associations between ADHD and sleep-related TEAEs, this literature review was conducted. The goals of this review are: 1) identify the incidence of sleep-related TEAEs in treatment and placebo/control groups, and 2) evaluate medication timing and administration schedules.

**Methods:** A previous scoping review screened 2265 studies to identify 71 interventional ADHD RCTs that measured sleep as a primary or secondary outcome measure (DOI 10.17605/OSF.IO/VWRPT). The current review investigates the excluded studies of the aforementioned scoping review, employing the same search strategy and databases. Inclusion criteria for this review are: 1) Diagnosis of ADHD according to e.g. DSM, 2) Intervention was an amphetamine-based stimulant(s), 3) Reported sleep-related TEAEs but did not include sleep as an outcome, 4) Study design was an RCT.

**Results:** After screening 2194 excluded studies, 33 RCTs investigating amphetamine-based interventions that reported sleep-related TEAEs were identified. 11/33 were performed in adults ( $n = 2029$  participants), and 22/33 were performed in children and adolescents ( $n = 3917$  participants). Two major categories of sleep-related TEAEs were identified: insomnia/initial insomnia (Adult  $n = 11$ , Pediatric  $n = 22$ ) and fatigue/somnolence (Adult  $n = 5$ , Pediatric  $n = 5$ ). In adult studies, incidence rates of insomnia/initial insomnia TEAEs ranged from 5%-37% vs. 1%-13% in the treatment vs. placebo groups respectively, and ranges for fatigue/somnolence TEAEs

were 1%-7.60% vs. 3.70%-12% respectively. For pediatric studies, 15 studies contained placebo groups, 2 contained active control groups, and 3 contained both. The incidence rates of insomnia/initial insomnia TEAEs ranged from 2.10%-25.90% vs. 0%-19% in the treatment vs. placebo groups respectively, and ranges for fatigue/somnolence TEAEs were 0%-9.40% vs. 2.60%-3.70% respectively. Additionally, information regarding medication timing, dosage, administration schedule, and titration strategy were extracted and analyzed.

**Conclusion:** In amphetamine-based stimulant ADHD RCTs, the incidence of sleep-related TEAEs are higher in treatment groups. The paucity of sleep-related side effect assessment tools and criteria when reporting sleep-related TEAEs highlights the need for standardization. Furthermore, the total number of participants in studies reporting sleep-related TEAEs was nearly threefold greater than in studies reporting sleep as a primary/secondary outcome identified in our previous scoping review (McWilliams et al., SMRV, under revision). This disparity in participants underlines again the need for standardization of sleep-related outcome measures and more studies to include sleep as a primary/secondary outcome to further assess the effects of amphetamines on sleep.

**Acknowledgments:** BC Children's Hospital Research Institute

#### THE EFFECT OF SLEEP DEPRIVATION ON EARLY NEURAL (P1, N170, P2) RESPONSES TO TARGET/NON-TARGET STIMULI PROCESSING IN YOUNG ADULT MEN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD): AN ERP STUDY

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**Introduction:** The present study aimed to identify the effect of sleep deprivation on early neural (P1, N170, P2) responses to target and non-target stimuli in young adults with and without attention deficit hyperactivity disorder (ADHD) using scalp-recorded event-related potentials (ERPs).

**Materials and Methods:** Early ERP components P1, N170, and P2 were measured. Participants comprised twenty-seven young adult men ( $M = 25.2 \pm 5.5$ ) with ( $n = 13$ ) and without ( $n = 14$ ) ADHD, using a visual oddball task which combined facial and non-facial stimuli, before and after 26 hours of sleep deprivation. Neural responses to target and non-target stimuli were compared across groups of young adult men with or without ADHD.

**Results:** A significant time (before/after sleep deprivation)  $\times$  group (ADHD/control)  $\times$  target (target/non-target) interaction was found for P1 ( $F(1,25) = 4.39$ ,  $p < 0.05$ ), N170 ( $F(1,24) = 4.43$ ,  $p < 0.05$ ) and P2 ( $F(1,25) = 9.59$ ,  $p < 0.01$ ) at frontal electrodes. Follow-up analysis revealed that at P2 there was a significant time  $\times$  target interaction in the ADHD group ( $F(1,12) = 8.34$ ,  $p < 0.02$ ) (but not in the control group), with sleep deprivation inducing an increased response to the target stimuli but not to the non-target stimuli.

**Conclusions:** Among young men with ADHD, sleep deprivation may hinder the processing of target/non-target stimuli. Moreover, the current results suggest that the neuronal processes involved in the processing of target/non-target stimuli and their sensitivity to sleep deprivation differ between young adult men with ADHD and young adult men without ADHD.

#### THE ROLE OF MENTAL HEALTH IN THE SPANISH SLEEP DISORDERS UNITS

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**Introduction:** Sleep disorders units in Spain are made up of specialized multidisciplinary teams (technicians, nurses, and doctors) who generally belong to the pneumology, neurology and neurophysiology services. Insomnia is a very frequent reason for consultation in sleep disorders units, as well as a very prevalent pathology in the general population. It is estimated that 10-15% of the adult population suffers from chronic insomnia and that 25-35% have suffered insomnia at some stage in their life. In most

cases, insomnia is a symptom of an underlying disorder rather than a disease itself, and mental disorders are one of the main related causes.

**Materials and Methods:** A retrospective study is carried out using the “Savana Manager” tool. We analyse the database of the Spanish public health system corresponding to the area of the Infanta Leonor University Hospital, and target the period between the 1<sup>st</sup> of January 2020 and the 31<sup>st</sup> of December 2020. This analysis includes the adult population (over 18 years of age) who describe insomnia as a symptom collected in their medical history, and how many of these patients simultaneously present a diagnosis of mental disorder.

**Results:** A sample of 6360 patients presented insomnia as a symptom recorded in their clinical history. Out of these patients, 73% (N = 4653) have an associated diagnosis of mental disorder. The main associated mental disorders can be distributed as follows: 64% (N = 4089) anxiety disorders, 45% (N = 2881) depressive disorders, 15% (N = 996) psychotic disorders, and 9% (N = 606) personality disorders. It is noted that some persons may have comorbidity with two or more mental disorders.

**Conclusions:** The evaluation of the mental health of the patient with insomnia (and probably of many other sleep disorders) is essential for its correct diagnosis and treatment. Psychiatrists should be represented in sleep disorders units as part of the multidisciplinary approach.

### TRANSDIAGNOSTIC SLEEP THERAPY REDUCES SLEEP PROBLEMS IN PSYCHIATRIC PATIENTS

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**Introduction:** Patients with psychiatric diagnoses often suffer from a variety of sleep problems such as insomnia, delayed sleep phase or they spend too much time in bed. The relationship between sleep problems and e.g. depression has been described as bidirectional. Insomnia may double the risk of developing depression and insomnia has been associated with increased suicidal ideation and poorer treatment response. Yet, non-pharmacological sleep therapy for patients with psychiatric disorders is almost unavailable in Denmark. This led us to design a Transdiagnostic sleep therapy intervention based on a manual by A. Harvey and D. Buysse. Our intervention consists of six sessions and tailors’ treatment of sleep problems to the individual. The aim of this study was to examine changes in sleep quality and severity of sleep problems after participation in the intervention.

**Materials and Methods:** A Quality Improvement study including fifty-five out-patients with sleep problems (insomnia, delayed sleep phase, or hypersomnia) and a psychiatric diagnosis was conducted. The patients were included in *Psykiatriens Hus*, a regional health authority’s psychiatry centre in Aarhus, in 2019–2020. Patients had a broad variety of psychiatric diagnoses, and their sleep problems should have lasted for a minimum of one month prior to inclusion. They received a sleep intervention consisting of six weekly sessions of transdiagnostic therapy delivered by two nurses and a clinical psychologist. The six sessions had the following content: assessment and introducing a sleep diary, stimulus control therapy, sleep restriction, education on sleep and circadian rhythm, relaxation technique, cognitive behavioural therapy and relapse prevention. At the start and end of the intervention, the patients completed the questionnaires; *Insomnia Severity Index (ISI)* and *Pittsburgh Sleep Quality Index (PSQI)* to assess the severity of their sleep problems and the quality of their sleep.

**Results:** A data extract from the electronic health record of the first 55 patients showed that 46 completed the intervention, 30 were female and median age was 34 years. Bipolar disorder was the highest-incidence diagnosis followed by attention deficit disorder and depression. The median duration of treatment was 50 days. A significant and clinically relevant reduction was seen on ISI and PSQI. Mean ISI score decreased from 18.76 at baseline to 12 at endpoint ( $p < 0.05$ ) and the PSQI score from 13.48 to 8.68 ( $< 0.05$ ).

**Conclusions:** Analyses indicate that the patients achieved a clinically significant reduction in the severity of their sleep problems and attained significantly improved sleep quality. The therapy can be provided independently by educated and trained nurses. In 2022 a randomized controlled study will be initiated to investigate whether the positive results can be confirmed in a controlled design.

### VARIABILITY IN SLEEP DURATION AND SLEEP TIMING ARE ASSOCIATED WITH SUICIDAL IDEATION IN ADOLESCENTS AND COLLEGE STUDENTS ENROLLED IN AN INTENSIVE OUTPATIENT PROGRAM

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**Introduction:** Sleep is a consistent risk factor for suicidality, though longitudinal studies and those that employ objective sleep measurement are scant. We therefore examined variability in actigraphic measures of sleep duration and sleep timing across weeks in relation to suicidal ideation in an intensive longitudinal study in young people with serious affective disorders.

**Materials and Methods:** Participants included N=59 (75% female; 24% non-white) ultra-high-risk adolescents and college students ages 18–24 enrolled in an Intensive Outpatient Program, and they were studied for up to 12 weeks (M=8.3, SD=4.3 weeks). Daily ratings of suicidal ideation and its intensity were collected electronically. Wrist actigraphy was used to objectively measure sleep/wake patterns continuously. Variability was examined with the coefficient of variation across weeks in two sleep outcomes: sleep duration (total sleep time; TST-COV) and sleep timing (midsleep; MID-COV; midsleep calculation: sleep onset – sleep offset / 2). Logistic and negative binomial regression models examined whether individuals with high or low variability in sleep duration and timing were more likely to report any suicidal ideation, rates of suicidal ideation, and intensity of suicidal ideation within the concurrent week, as well as predicting suicidal ideation the following week, controlling for age, gender, and mean daily depression rating across the week.

**Results:** Greater TST-COV was associated with greater likelihood of having any day with suicidal ideation (OR=1.34, 95% CI: 1.06-1.70,  $p=0.02$ ), higher number of days with ideation endorsed (quadratic,  $p=0.03$ , linear,  $p=0.01$ , generally showing more days of suicidal ideation at higher levels of variability), and higher intensity ratings (5.9 points higher, 95% CI: 0.5-11.2,  $p=0.03$ ) within the same week. Greater COV-timing was linearly associated with greater likelihood of having any day with suicidal ideation (but not intensity) within the same week (OR=1.11 for 0.1 increase in COV, CI: 1.01-1.20,  $p=0.02$ ). Greater COV-timing also predicted the likelihood of having any day with suicidal ideation during the following week (OR=1.16 for 0.1 increase in COV, 95% CI: 1.04-1.30,  $p=0.01$ ), higher number of days endorsed (rate ratio=1.08 for 0.1 increase in COV, 95% CI: 1.02-1.14,  $p=0.01$ ), and intensity of suicidal ideation the following week (each 0.1 increase in COV-timing was associated with a 1.8-point increase in next week ideation intensity, 95% CI: 0.5-3.1,  $p=0.005$ ). Notably, compared to self-reported depression, COV-timing had a stronger and more significant effect on suicidality the following week.

**Conclusions:** High variability in the amount and timing of sleep were associated with suicidal ideation. Associations between variability in sleep duration were detected during concurrent weeks. Variability in sleep timing was particularly related to acute increases in suicidal ideation the following week, more so than daily self-reported depression. Behavioral sleep interventions are available to improve erratic sleep/wake patterns, and as such, these are modifiable risk factors. By understanding the temporal relationship between sleep and suicidality, new or refined interventions targeting variability in sleep duration and sleep timing may improve mental health and lessen suicidality.

**Acknowledgements:** Funded by American Foundation for Suicide Prevention and the University of Pittsburgh Clinical and Translational Science Institute

### WHY SLEEP SPECIALIST SHOULD GIVE MORE FOCUS TO FASD PATIENTS?

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Fetal alcohol spectrum disorders (FASD) are a group of developmental conditions that are caused when a pregnant mother consumes alcohol

during pregnancy. It affects the development of the fetus. The damage can range from mild to severe, from neurological brain damage to physical (facial) and developmental changes. An unusually high rate of abnormal melatonin secretion is observed in this population (Goril et al, 2016). The objective of this study was to investigate the sleep issues faced by FASD children and their care givers.

Subjective sleep problems are experienced by 58% of individuals with FASD (Goril et al., 2016). The main sleep issues include for example insomnia (16.8%) and parasomnia (27.9%). In addition there is an abnormal melatonin secretion in 79% of the population (Goril et al, 2016). Poor or insufficient sleep has far-reaching negative impacts on health, cognitive and psychological functioning, behavior and quality of life in children and youth (Baldassari et al., 2008). These negative impacts are then projected on to the families and their sleep. Very recently an Italian group Dylag et al (2021) have emphasized that sleep problems are important in FASD.

Thirty patients with a FASD diagnosis were consulted (Aged 4-21). They or a caregiver were asked to fill out a FASD sleep impact questionnaire, devised for the purpose of this study. It consists of 6 standard questionnaires such as the family assessment device, child's sleep habits questionnaire (CSHQ) and more. In order to gain better insight into their diagnoses and family background, patients/caregivers were also asked their child's age, when they were diagnosed with FASD, their relationship to the child, the living arrangement (biological family, adoptive, foster, guardianship or other) and age and sex of child.

The impact poor sleep has on a family with FASD children was substantial. The caregivers are suffering from PTSD, depression and poor sleep caused by the sleep problems of their children. Most children with FASD have abnormal melatonin secretions causing further problems in initiating for sound sleep, requiring dosed melatonin supplementation. During the assessment, families were asked to rate on a scale from 0-100, zero being no routine and 100 being in a regimented routine. The implication is that the higher the level of regimentation, the smoother the family functioned on a daily basis. Spontaneity is something these families can not cope with nor tolerate due to the lack of good sleep by the child and caregiver.

The clinical observation of the impact of sleep problems in children with FASD on their family as a whole is monumental. The ramifications are an inter-generational affect from a single diagnoses of FASD. Unfortunately there has been relatively little research on this subject. To the best of our knowledge this is the first study looking at the ramification of the sleep problems in this population and family function. The results indicate an urgent need to help children with FASD to optimise their sleep. This should be seen as a "bed rock" for improving the patient and families quality of life.

#### WHY WE MIGHT NEED PSYCHIATRIC DAY WARDS MORE THAN WE THINK? SLEEP PROBLEMS IN PATIENTS WITH SEVERE MENTAL DISORDERS

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**Introduction:** Individuals suffering from schizophrenia often report numerous sleep disturbances, which persist even during the period of remission and significantly hinder patients' daily activities and their quality of life. One of such is sleep-wake pattern disturbances. This poster aims to present and compare two clinical cases of patients with schizophrenia. Both of them reported ongoing sleep-wake cycle disturbances that negatively affected their mood and energy level, as well as their ability to attend daily activities.

**Materials and Methods:** Patient 1 was a male, aged 33, who initially reported insomnia. Patient 2 was a male, aged 40, who reported a delayed sleep phase. Patient 1 was treated in ambulatory care, while patient 2 was examined during the first month of therapy in a psychiatric day ward. Both patients voluntarily took part in an ongoing project aiming to assess sleep disturbances in patients with schizophrenia.

We used actigraphy as an objective tool to analyze the sleep-wake cycle, alongside sleep diaries filled in by the patients. Both patients were assessed for schizophrenia and depressive symptoms with the Positive and Negative Syndrome Scale (PANSS) and the Calgary Depression Scale for Schizophrenia (CDSS). They also completed self-report questionnaires

related to sleep and daytime functioning such as Insomnia Severity Index (ISI), Ford Insomnia Response to Stress Test (FIRST), Sleep Preoccupation Scale (SPS), Dysfunctional Beliefs and Attitudes about Sleep (DBAS-16) and Sleep Hygiene Questionnaire. Additionally, the WHOQOL-BREF questionnaire was used to measure the patients' perceived life quality.

**Results:** The actigraphy revealed a non-24-hour sleep-wake disorder in Patient 1 and only modest irregularities in the sleep-wake pattern in Patient 2. Interestingly Patient 1 scored slightly higher on Sleep Hygiene Questionnaire.

However, he exhibited more insomnia symptoms, showed greater vulnerability to sleep disruption, and more negative daytime cognitions and feelings about sleep. Patient 1 also showed lower results in the psychological health domain of quality of life.

**Conclusions:** Both patients reported poor sleep quality, obtained scores that are indicative of maladaptive attitudes and beliefs about sleep. Therefore, in both cases, treatment programs targeting these maladaptive cognitive processes may be valuable. At this point, it would be a far-reaching conclusion that attending psychiatric day wards, by itself, may positively impact the circadian rhythms of people with schizophrenia. However, psychiatric day wards can become a place where there is more time and effort dedicated to sleep health interventions.

#### REM Behavior Disorders

#### ALTERATIONS OF THE HUMAN K-COMPLEXES DURING NREM SLEEP IN ISOLATED REM SLEEP BEHAVIOUR DISORDER

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**Introduction:** REM sleep Behavior Disorder (RBD) represents a strong prodromal marker of  $\alpha$ -synucleinopathies. Albeit recent findings underlined the importance of NREM sleep in protecting the aging brain from neurodegeneration, only few studies assessed NREM sleep alterations in RBD and their possible role in cognitive decline. The human K-complex (KC) during NREM sleep exhibits alterations in patients with Alzheimer's disease, and a recent study highlighted a relation between KC density and cognitive functioning in isolated RBD (iRBD), particularly in specific domains known to be relevant in predicting conversion into neurodegenerative disorders. The aim of the present study was to assess for the first time the existence of KC alterations in iRBD compared to healthy controls (HC).

**Materials and Methods:** we assessed KC density in 31 patients with iRBD (27 M; age: 68.64±6.67 y) and 31 HC (23 M; age: 69.03±6.12 y). In both groups, KCs were detected during Stage 2 NREM sleep in frontal (F3, F4), central (C3, C4, Cz), and parietal (P3, P4) derivations. We performed a direct comparison of the KC density between iRBD and HC. Moreover, we assessed the correlation between midline central KC density, Mini-Mental State Examination (MMSE) scores (in the whole iRBD+HC sample) and performance in specific neuropsychological measures (in the iRBD group).

**Results:** iRBD patients exhibited a drastic reduction of KC density compared to HC in frontal, central, and parietal derivations. The midline central KC density in the whole sample was positively associated with MMSE scores. Finally, the midline central KC density in the iRBD group was also selectively and positively associated with performance in attention and executive functions (i.e., attentional matrices; Raven Colored Progressive Matrices).

**Conclusions:** our results describe for the first time a clear reduction of the KC density in iRBD patients compared to HC. Moreover, we confirmed the relation between KC density and cognitive functioning, particularly in specific domains considered relevant for the prediction of conversion into  $\alpha$ -synucleinopathies. These findings highlight the need of a further understanding of NREM sleep alterations (and particularly KC features) in iRBD, and their possible role in neurodegenerative processes.

**Acknowledgements:**

## ASSESSING BLINK REFLEX CIRCUITS IN PATIENTS WITH REM BEHAVIOUR DISORDER AND PATIENTS WITH PARKINSON'S DISEASE

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**Introduction:** Idiopathic/isolated REM sleep behavior disorder (iRBD) can represent an early manifestation of neurodegenerative alpha-synucleinopathies. It has been largely hypothesized that these neuropathological processes ascends from the brainstem, progressively involving the lower brainstem. The electric blink reflex (BR) is a technique that evokes trigemino-facial reflex by stimulation of the supraorbital nerve. BR can investigate the brainstem function, and it has been already hypothesized that BR may be altered in patients with neurodegenerative diseases, such as Parkinson's Disease (PD). BR consists of two components: R1, ipsilateral to the stimulated side, reflects operation of an oligosynaptic pathway; R2, is bilateral and polysynaptic, indicating an interneuronal control by both segmentary and heterosegmentary influences. BR recordings were previously described in patients with PD and Dementia with Lewy Bodies (DLB), but results are mixed; conversely, no study investigated BR in iRBD patients. The present study aimed at determining the neurophysiological brainstem function measured by BR in patients with iRBD compared to PD patients and controls.

**Materials and Methods:** In this cross-sectional observational study iRBD patients, PD patients and a group of healthy controls were enrolled. A BR was elicited by stimulation of the supraorbital nerve in all participants. Moreover, all patients underwent a clinical, neurological assessment, including the Unified Parkinson Disease Rating (UPDRS) scale – section III, the Non-Motor Symptoms Scale (NMSS) and the Mini-Mental State Examination (MMSE). Krusk-Wallis test was used to evaluate the differences in the BR, and Spearman correlations were conducted to assess the relations between the BR latencies and the motor and non-symptoms related to the disease.

**Results:** Eighteen iRBD patients (mean age 69.47±6.97; 100% male), 21 PD patients with or without RBD (mean age 61.85±9.21; 57.1% male) and 11 controls (mean age 56.30±5.48; 70% female) were included. From the 21 PD patients, 6 patients had RBD, while the remaining 14 did not have RBD. iRBD patients showed a delayed response in ipsilateral (35.71±3.05) and contralateral R2 response from the right stimulus (35.84 ± 3.91) than controls (30.53±2.63; 31.78±2.74, respectively). No latencies or amplitudes differences between PD patients and iRBD patients, as well between PD patients and controls were found. The latency of ipsilateral R2 response after left stimulus correlated negatively with UPDRS-III scores in iRBD patients ( $\rho=-0.63$ ), while the latency of R1 response after right stimulus correlated positively with UPDRS-III ( $\rho=0.56$ ) and negatively with miscellaneous subscale of the NMSS ( $\rho=-0.55$ ) in PD patients. No correlations were found between BR latencies and the subscales of NMS in iRBD patients and PD patients.

**Conclusions:** This electrophysiological study showed brainstem functional impairment in iRBD patients than controls possibly reflecting the early neurodegeneration occurring in those patients in critical brain areas for alpha-synucleinopathy. The lack of differences between PD patients and controls can reflect the fact that RBD can aggravate brainstem neurodegeneration (in the PD group only 6/21 patients were co-diagnosed by RBD). Further studies, with a larger sample, should be carried out in iRBD patients longitudinally followed to understand the implications of BR responses in the time to phenoconversion.

## BRAIN ATROPHY IN REM SLEEP BEHAVIOR DISORDER IS SHAPED BY GENE EXPRESSION AND STRUCTURAL CONNECTIVITY

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**Introduction:** Isolated rapid eye movement sleep behavior disorder (iRBD) is a parasomnia strongly associated with dementia with Lewy bodies (DLB) and Parkinson's disease (PD). Brain changes in iRBD are manifold and include brain atrophy. However, despite several immunohistochemical assays reporting high positivity rates to pathologic alpha-synuclein in iRBD, the mechanisms linking brain atrophy to the underlying alpha-synuclein pathophysiology are poorly understood.

In this study, we investigated how the prion-like and regional vulnerability hypotheses of alpha-synuclein might explain the brain atrophy in iRBD.

**Materials and Methods:** A multicentric cohort of 182 polysomnography-confirmed iRBD patients (67.8 years, 84% men) and 261 healthy controls (66.2 years, 75% men) underwent clinical assessment and MRI acquisition of T1-weighted images. Brain atrophy was characterized using vertex-based cortical surface and deformation-based morphometry. Region-wise measures of cortical thickness and surface area and grey matter tissue deformation corrected for age, sex, and site (and total intracranial volume for area) were generated as the measures of observed brain atrophy.

We next applied the agent-based Susceptible-Infected-Removed (SIR) model, a computational model that simulates in silico the spread of pathologic alpha-synuclein based on structural connectivity and gene expression, to create a simulated propagation of alpha-synuclein in the brain. We used correlation analyses to assess whether the pattern of simulated atrophy recreated the pattern of observed atrophy in iRBD patients. The impact of gene expression and brain connectivity was evaluated separately by comparing the model fit to the fit obtained in null models where either gene expression or connectivity was randomized. We also investigated if other network-based measurements could recreate the atrophy observed in iRBD as efficiently as the atrophy simulated by the SIR model.

**Results:** We found that the atrophy simulated based on connectivity and gene expression recreated cortical thinning ( $r=0.51$ ,  $p=0.0007$ ) and grey matter tissue deformation ( $r=0.52$ ,  $p=0.0005$ ) in iRBD, and that the connectome's architecture and gene expression of *SNCA* and *GBA* shaped atrophy in iRBD. We further demonstrated that unlike the atrophy measurement simulated by the SIR model, using network measures or gene expression alone in the absence of the agent-based model was not sufficient to recreate the atrophy found in iRBD.

**Conclusions:** We demonstrated that atrophy in iRBD is extensive and can be recreated using the dynamics of agent-based modelling, structural connectivity, and gene expression. These findings support the concepts that both prion-like spread and regional susceptibility account for the atrophy observed during prodromal synucleinopathies. The agent-based SIR model may therefore be a useful tool for testing hypotheses underlying neurodegenerative diseases and testing new therapies.

**Acknowledgements:** This work was supported by the Investissements d'Avenir, the Paris Institute of Neurosciences – IHU, Fondation EDF, Biogen, Fondation Thérèse and René Planiol, Energipole, and Société Française de Médecine Esthétique in France, by the CIHR, the FRQS, and the W. Garfield Weston Foundation in Canada, by the NMHRC Dementia Team Grant in Australia, and by the Lundbeck Foundation, the Danish Parkinson's Disease Association, and the Jascha Foundation in Denmark. Shady Rahayel received a fellowship from the FRQS.

## BRAIN-CLINICAL PERFUSION PATTERNS MAY PREDICT CONVERSION SUBTYPE IN REM SLEEP BEHAVIOR DISORDER

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**Introduction:** Isolated rapid eye movement sleep behavior disorder (iRBD) is a parasomnia and a risk factor for dementia with Lewy bodies (DLB) and Parkinson's disease (PD). Patients with iRBD show abnormal patterns of cerebral blood flow, but no study has yet identified a blood flow pattern that predicts DLB over PD. Being able to identify patients at risk of dementia is important for optimizing care and recruiting individuals for clinical trials. In this study, we identified brain-clinical perfusion patterns that predicted at the individual level the conversion trajectory of iRBD patients.

**Materials and Methods:** Fifty-two polysomnography-confirmed iRBD patients (67.9 years, 73% men) underwent annual clinical assessments for an average of  $4.5 \pm 2.0$  years, and 99mTc-HMPAO SPECT scan to quantify cerebral blood flow perfusion. Blood flow values were normalized by the mean for the scan.

Partial least squares correlation was applied on a matrix of 27 features of iRBD and an imaging matrix of the relative perfusion at each voxel. Singular value decomposition was applied to generate 27 latent variables, each of which was tested for significance using permutations.

Each patient's SPECT scan was projected back onto the brain pattern of the significant latent variables, and the patient-specific brain scores were then used in logistic regression analyses to assess if they predicted DLB over PD during follow-up, while controlling for age, sex, and education. A total of 22 healthy controls (67.0 years, 73% men) and 21 PD patients (66.8 years, 45% men) also underwent clinical assessment and were scanned with the same parameters for comparing the expression of the patterns.

**Results:** Of the 52 iRBD patients, 47 were followed longitudinally and 12 (26%) developed a synucleinopathy: 4 DLB and 8 PD.

Of the 27 latent variables, two were significant after permutation testing ( $p=0.002$  and  $p=0.037$ ), explaining 39.5% and 9.6% of the brain-clinical covariance. The first variable (LV1) predicted the development of an overt synucleinopathy in iRBD ( $p=0.043$ ); it linked relative hyperperfusion in the temporo-occipital cortex, hippocampus, putamen, and pallidum and relative hypoperfusion in the parieto-occipital cortex to worse motor and cognitive features. However, this latent variable did not predict DLB versus PD ( $p=0.49$ ). In contrast, the second variable (LV3) predicted conversion to DLB over PD ( $p=0.04$ ); it linked relative hyperperfusion of the insula and basal fore-brain to mild cognitive impairment and visuospatial deficits. Both controls ( $p=0.096$ ) and PD patients ( $p=0.026$ ) had a lower expression compared to iRBD patients converting to DLB, suggesting that the patterns represented prodromal markers of phenoconversion.

**Conclusions:** We identified a new biomarker that predicts DLB in iRBD. Since a brain score can easily be derived at the individual level, our approach may represent an elegant tool for identifying patients at risk of DLB early in the disease course, which may prove important for clinical trials and for testing potential neuroprotective therapies.

**Acknowledgements:** This work was supported by the Canadian Institutes of Health Research, the Fonds de recherche du Québec – Santé (FRQS), and the W. Garfield Weston Foundation. Shady Rahayel receives a fellowship from the FRQS.

## CEREBROSPINAL-FLUID BIOMARKERS AND BLOOD-BRAIN BARRIER ALTERATION MAY BE USEFUL TO PREDICT THE PHENOCONVERSION OF PATIENTS WITH IDIOPATHIC/ISOLATED REM SLEEP BEHAVIOUR DISORDER

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**Introduction:** Rapid eye movement (REM) sleep behaviour disorder (RBD) is a sleep disorder characterized by the loss of physiological muscle atonia during REM sleep and accompanied by dream-enacting behaviours. Several longitudinal studies have documented that patients with idiopathic/isolated RBD (iRBD) have an increased risk of developing neurodegenerative diseases, including Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA). Different predictive biomarkers for iRBD conversion have been investigated, however few cerebrospinal fluid (CSF) studies have been performed in iRBD patients, and some CSF markers have not yet been considered in these patients. Moreover, the dysfunction of the blood-brain barrier (BBB) has been demonstrated in previous studies investigating PD patients but not in iRBD patients. Hence, the present study aimed to assess CSF beta-amyloid and tau proteins biomarkers and BBB alteration in iRBD patients compared to controls and ascertain whether these biomarkers may represent a marker of phenoconversion to alpha-synucleinopathies disorder.

**Materials and Methods:** All patients and controls underwent a clinical, neurological assessment, including the Unified Parkinson Disease Rating (UPDRS) scale – section III and the Mini-Mental State Examination (MMSE), as well as a lumbar puncture for CSF analysis. CSF biomarkers ( $\beta$ -amyloid<sub>42</sub> – A $\beta$ <sub>42</sub>; total tau, and phosphorylated tau) and CSF albumin quotient (expression of BBB alteration) samples were collected in iRBD patients and age- and sex-matched healthy controls. All iRBD patients were followed for at least five years. RBD patients were then classified into patients who phenoconverted to alpha-synucleinopathies (RBD converters, cRBD) and remained alpha-synucleinopathies disease-free (RBD non-converters, ncRBD). Krusk-Wallis test was used to evaluate the differences in CSF biomarkers and CSF albumin quotient.

**Results:** Thirty-four iRBD patients (mean age  $67.12 \pm 8.14$  years; 82.4% male) and 38 controls (mean age  $65.37 \pm 9.28$  years; 65.8% male) were included. At follow-up, 12 patients were ncRBD and 22 patients were cRBD: 12 converted to PD, 8 to DLB and 2 to MSA. cRBD patients showed lower CSF A $\beta$ <sub>42</sub> levels ( $661.91 \pm 240.16$ ) and higher CSF albumin quotient ( $7.15 \pm 2.04$ ) than controls ( $800.0 \pm 254.66$ ;  $5.69 \pm 2.38$ , respectively). Considering the cRBD group, iRBD patients that converted to DLB had lower CSF A $\beta$ <sub>42</sub> levels than controls. Moreover, both cRBD to PD and DLB showed lower MMSE scores ( $26.16 \pm 2.03$ ;  $26.54 \pm 2.29$ , respectively) than controls ( $28.84 \pm 0.95$ ) at baseline.

**Conclusions:** This CSF-based study showed that CSF A $\beta$ <sub>42</sub> levels may be used for predicting the cognitive decline in patients affected by iRBD and possibly developing the DLB. Based on the BBB alteration, it seems that CSF albumin quotient may be a marker for predicting the conversion to alpha-synucleinopathies. Further studies, with a larger sample, should be carried out in iRBD patients to define the role of CSF biomarkers as predictors of conversion.

## CEREBROSPINAL FLUID TNF- $\alpha$ AND OREXIN IN PATIENTS WITH PARKINSON'S DISEASE AND RAPID EYE MOVEMENT SLEEP BEHAVIOR DISORDER

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**Introduction:** Parkinson's disease (PD) pathological changes begin before motor symptoms appear. Rapid eye movement sleep behavior disorder (RBD) has the highest specificity and predictive value of any marker of prodromal PD. Tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) plays a part in the pathology of PD and disease conversion in isolated RBD (iRBD). TNF can also directly impair the hypocretin system in mice *in vivo*. As a result, we intend to investigate the effect of TNF- $\alpha$  on orexin levels in PD patients with RBD.

**Materials and Methods:** Participants were recruited from the Department of Neurology of Xuanwu Hospital, Capital Medical University to engage in assessments on motor symptoms, sleep, cognition, etc. Then we collected blood and cerebrospinal fluid of all patients and ten controls' cerebrospinal fluid. The levels of TNF- $\alpha$  in the serum and cerebrospinal fluid, as well as

the level of orexin in the cerebrospinal fluid, were measured in the patients.

**Results:** The difference in TNF- levels in cerebrospinal fluid and serum between the three groups were not statistically significant. The levels of orexin in the three groups were not significantly lower than in the control group. UPDRS-III scores were significantly higher in the PD+RBD and PD-RBD groups than in the iRBD group. There was no statistically significant difference in H-Y stages, PSQI, or ESS scores between the PD+RBD and PD-RBD groups.

**Conclusions:** Our findings suggest that TNF- $\alpha$  may not have a significant effect on the orexinergic system in patients with Parkinson's disease and iRBD. As a result, it is necessary to investigate the changes in TNF- $\alpha$  and orexin levels in different disease stages and to enlarge the sample size to determine whether TNF- $\alpha$  affects the function of the orexin system, which may be related to the occurrence of RBD and disease progression in Parkinson's disease.

**Acknowledgements:** The authors thank Yi Zhai and Xin Zhao for their technical assistance.

### CLINICAL AND POLYSOMNOGRAPHIC CHARACTERIZATION OF REM SLEEP BEHAVIOR DISORDER: CASUISTIC OF A PORTUGUESE SLEEP MEDICINE CENTER

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**Introduction:** REM sleep behavior disorder (RBD) is characterized by clinical history of sleep-related complex motor behaviors presumed to occur during REM sleep or recorded during polysomnography and by polysomnographic evidence of REM sleep without atonia (RSWA). It is known that RBD is associated with neurodegenerative diseases, especially synucleinopathies such as Parkinson's disease (PD), dementia with Lewy bodies (DLB) and multiple system atrophy (MSA) and could precede them by many years, corresponding to a recognized premotor symptom. Accordingly, RBD may occur isolated (iRBD) or in association with neurodegenerative diseases. Thereby, our aim was to compare the clinical and video-polysomnography (vPSG) features of patients diagnosed with iRBD and RBD plus DP.

**Materials and Methods:** We designed a retrospective study of all patients with a clinical diagnosis of iRBD and RBD plus PD, with follow-up in our sleep center. We observed 66 patients but 18 were excluded due to lack of PSG recording, so a total of 48 patients were included and divided into two groups: iRBD (27 patients) and RBD plus PD (21 patients). We proceeded to a clinical, demographic and vPSG characterization and comparison of both groups.

**Results:** In iRBD group, 74,1% were male and the average age of RBD diagnosis was 65±12,3 years (y). The average duration time of RBD was 59±39,5 months (m). The most reported manifestation was violent sleep movements (40,7%) and 70,4% had another concomitant sleep pathology, with the most frequent being obstructive sleep apnea syndrome (OSAS). At examination, we found 5 patients (18,5%) with subtle motor signs with a mean motor UPDRS of 2,2±0,8 points. 51,9% were treated with clonazepam. About vPSG findings, the average percentage of REM sleep was 17±8,2% and of RSWA was 34,0±25%. 66,7% had clinical manifestations of RBD during the recording.

In RBD plus PD group, 71,4% were male, the average age of PD diagnosis was 67±11,7y and 81% had a previous diagnosis of RBD. The average age of RBD diagnosis was 64±11,7y and the most common clinical feature was the presence of vivid dreams with violent content (61,9%). The majority had another sleep pathology (76,2%), and 57,1% of these cases had OSAS. The average percentage of REM sleep was 13,4±6,1% and of RSWA was 28,9±20,4%. 57,1% had clinical features of RBD during vPSG.

We didn't find any statistically significant correlation between the two groups. However, we noticed that the percentage of RSWA in iRBD group was higher in patients with subtle motor signs and other premotor symptoms (34,2%) than in patients without any of those features (31,6%).

**Conclusions:** We presented the first study to describe the clinical and PSG features of a Portuguese cohort of iRBD vs RBD plus PD patients. Further

studies with larger samples are needed to better understand if any clinical or vPSG feature of RBD patients could predict a phenoconversion to a neurodegenerative disorder in order to identify these high-risk patients earlier in the disease course.

**Acknowledgements:** to medical teams involved in the approach of these patients.

### COMPUTERIZED ANALYSIS OF MUSCULAR ACTIVITY IN THE FLEXOR DIGITORUM SUPERFICIALIS MUSCLES AS SCREENING TOOL FOR REM SLEEP WITHOUT ATONIA

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**Introduction:** Quantification of rapid eye movement (REM) sleep without atonia (RWA) is required for diagnosis of REM sleep behavior disorder (RBD). RWA quantification with the Sleep Innsbruck Barcelona (SINBAR) index (i.e. % of 3-s mini-epochs with any activity in the chin and/or phasic activity in the bilateral flexor digitorum superficialis (FDS) muscles) has high sensitivity and specificity. A semi-automatic algorithm scoring RWA according to the SINBAR method has been validated, but its application is still time consuming due to the need of manually selecting 3-s mini-epochs and of correcting artefacts. Previous studies have shown that muscular activity in the FDS muscles is less affected by artifacts than the one in the chin. Here we aimed to evaluate whether phasic FDS activity automatically identified in whole REM sleep (i.e. without selection of 3-s mini-epochs) and without artifact correction could be a fast and reliable RWA quantification screening tool to either confirm or rule out RWA.

**Material and methods:** A total of 36 video-polysomnographies (v-PSGs) of isolated RBD (iRBD) patients and 35 v-PSGs of controls were included. RBD diagnosis was made according to the v-PSG guidelines of the International RBD Study Group, RBD behaviors and RWA were documented in v-PSG. Absence of technical artifacts from the electromyographic signals was visually checked. Using the automatically scored activity without artifact correction, we calculated the following RWA indices according to the SINBAR recommendations: 30-s phasic chin, 30-s any chin, 30-s phasic FDS, 30-s tonic chin and 30-s SINBAR. Using the previously published cut-offs, the sensitivity and specificity of the RWA indices for distinguishing iRBD from controls were calculated. The analysis was performed separately for v-PSGs with apnea-hypopnea index in REM sleep (AHI<sub>REM</sub>) <15/h and ≥15/h.

**Results:** Twenty-seven v-PSGs of iRBD patients and 20 v-PSGs of controls had AHI<sub>REM</sub><15/h. For those subjects, the values of sensitivity/specificity were: 85.2%/95.0% for 30-s phasic chin, 77.8%/95.0% for 30-s any chin, 100.0%/85.0% for 30-s phasic FDS, 37.0%/100.0% for 30-s tonic chin and 100.0%/40.0% for 30-s SINBAR. For the nine v-PSGs of iRBD patients and the 15 v-PSGs of the controls with AHI<sub>REM</sub>≥15/h the values of sensitivity/specificity were: 88.9%/6.7% for 30-s phasic chin, 88.9%/13.3% for 30-s any chin, 100.0%/60.0% for 30-s phasic FDS, 55.6%/66.7% for 30-s tonic chin and 100.0%/0.0% for 30-s SINBAR.

**Conclusions:** The automatic 30-s phasic FDS index without artifact correction showed 100.0% sensitivity and 85.0% specificity when AHI<sub>REM</sub><15/h. Therefore, it can be used as a screening tool to rule out RWA in subjects without relevant respiratory events during REM sleep. These results further support the usefulness of recording the FDS channels during routine v-PSG.

**Acknowledgements:** Thanks to Heinz Hackner for accurate v-PSG scoring.

### ELECTROCORTICAL OVERLAP BETWEEN ISOLATED RBD AND PARKINSON'S DISEASE WITH RBD: A PILOT TMS STUDY

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**Introduction:** Previous studies found an impairment of the short-interval intracortical inhibition (SICI) and the intracortical facilitation (ICF) to transcranial magnetic stimulation (TMS) in Parkinson's disease (PD), including the early stages, compatible with a disinhibition and hypofacilitation of the motor cortex, largely mediated by GABAergic and glutamatergic dysfunction, respectively. Conversely, little is known on the TMS correlates of isolated rapid eye movement (REM) sleep behavior disorder (iRBD), which can precede the onset of synucleinopathies. In a recent study in iRBD patients compared to age-matched healthy controls, we observed a significant decrease of ICF and, to a lesser extent, of SICI. Moreover, SICI correlated with muscle tone alteration, possibly supporting the RBD model of retrograde influence on the cortex from the brainstem. However, a direct comparison between iRBD and RBD in the context of an overt extrapyramidal syndrome, allowing to define not only a predictive but possibly a pathogenic role of RBD in neurodegeneration, is lacking.

**Materials and Methods:** The following single- and paired-pulse TMS measures, recorded from the right first dorsal interosseus muscle, were obtained from 10 *de novo* patients with iRBD (median age 66 years, range 60–69), 10 *de novo* patients with early PD and RBD (median 70 years, range 66–79), and 10 healthy controls (median 65 years, range 65–71): resting motor threshold, cortical silent period, latency and amplitude of the motor evoked potentials, SICI, and ICF. Mini Mental State Examination (MMSE), Epworth Sleepiness Scale (ESS), and Geriatric Depression Scale (GDS, short form) were also assessed. All participants were right-handed and drug-free.

**Results:** The three groups were comparable in terms of age, education, and RBD duration. Neurological examination, MMSE, ESS, and GDS were normal in all iRBD patients and controls, whereas PD subjects showed a mild-to-moderate motor impairment (MDS-Unified PD Rating Scale, part III <32). Compared to controls, the two patient groups exhibited a significant decrease of ICF (iRBD median 0.15, range 0.10–0.70; PD median 0.14, range 0.10–0.23; controls median 0.80, range 0.30–1.80;  $p = 0.007$ ) and a trend, though not significant, towards a reduction of SICI (iRBD median 0.10, range 0.01–0.30; PD median 0.07, range 0.05–0.11; controls median 0.25, range 0.10–0.30;  $p = 0.086$ ), without any difference between iRBD and PD with RBD groups. Correlation analyses by pooling the two groups of patients showed a significant negative correlation between SICI and both MMSE ( $r = -0.495$ ;  $p < 0.027$ ) and ESS ( $r = -0.602$ ;  $p < 0.005$ ).

**Conclusions:** iRBD and PD with RBD shared the same electrocortical profile to TMS, thus suggesting that RBD would not simply precede synucleinopathies but it could even “mark” their onset. In RBD patients, with or without PD, the disinhibition of the motor cortex inversely correlated with cognition, possibly hypothesizing its role as a marker of cognitive dysfunction, even at the pre-motor stage. This disinhibition might also enhance the level of cortical arousal, thus decreasing the daytime sleepiness. Translationally, glutamate and GABA activity might emerge as new therapeutic targets for both RBD and early PD.

**Acknowledgements:** None.

#### EPIGENETIC CLOCKS SUGGEST ACCELERATED AGEING IN ISOLATED REM SLEEP BEHAVIOR DISORDER PATIENTS

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**Introduction:** Isolated REM Sleep Behavior Disorder (iRBD) is a well-recognized prodromal state of an underlying  $\alpha$ -synucleinopathy, occurring several years before an overt neurodegenerative disorder can be fully manifest. Indeed, the presence of iRBD indicates already early ageing and

neurodegeneration of specific brainstem nuclei. Epigenetic clocks are mathematical models that, starting from DNA methylation profiles, return an estimate of the age of an individual. The discrepancy between predicted epigenetic age and chronological age (i.e., the epigenetic age acceleration –EAA) has proven to be informative of biological age in several pathological conditions, including neurodegenerative diseases. To date, epigenetic clocks have not been evaluated in Rapid eye movement sleep Behavior Disorder (RBD).

**Materials and Methods:** We compared epigenetic age between video-polysomnography (vPSG)-confirmed iRBD patients (iRBD\_pos) and vPSG-negative controls (CTR\_vPSG). We considered the following epigenetic clocks, based on distinct sets of CpG sites, which can be indicative of different aspects of biological age: 1) the pan-tissue Horvath's clock; 2) the blood-specific Hannum's clock; 3) the PhenoAge, developed considering clinical measures related to differences in healthspan and lifespan; 4) the GrimAge, developed considering plasma levels of 7 proteins and smoking pack-years, which is associated with mortality. We calculated EAA for each epigenetic age estimate, obtaining the following values: Horvath-EAA, Hannum-EAA, PhenoAge-EAA and GrimAge-EAA. We also calculated two additional EAA measures derived from Horvath's clock: the intrinsic-EAA, that is independent from changes in blood cell composition, and the extrinsic-EAA, that is indicative of immunosenescence.

**Results:** We compared 28 iRBD\_pos (23 males, age 67.92±7.20 years) and 57 CTR\_vPSG (32 males, age 66.56±9.56 years). Compared to CTR\_vPSG, iRBD\_pos patients showed higher Horvath-EAA and intrinsic-EAA values when correcting for experimental batch (CTR\_vPSG = 0.42±4.78 iRBD\_pos = 3.74±5.57  $p = 0.04$  and CTR\_vPSG = -0.90±5.92 iRBD\_pos = 3.78±6.77  $p = 0.03$  respectively). A similar trend was present also for most of the other EAA values, without reaching statistical significance. When sex was added as covariate, intrinsic-EAA values were confirmed as marginally significantly different between CTR\_vPSG and iRBD\_pos ( $p = 0.05$ ).

**Conclusions:** Our results suggest the presence of an accelerated ageing process in iRBD patients in respect to controls. As previously demonstrated by Horvath and collaborators in Parkinson's Disease, we suppose that the accelerated ageing in these patients reflects the neurodegenerative process already occurring in the brainstem. Bigger cohorts and longitudinal evaluations will allow us to strengthen these data and to evaluate their predictive value.

#### IDENTIFICATION AND VALIDATION OF A BRAIN GLUCOSE METABOLISM CONVERSION PATTERN IN IDIOPATHIC REM BEHAVIOUR DISORDER

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**Introduction:** Idiopathic REM Sleep Behaviour disorder (iRBD) is considered the prodromal phase of alpha-synucleinopathies, such as Parkinson's Disease (PD) and Dementia with Lewy Body (DLB). Nevertheless, robust biomarkers of phenoconversion in iRBD patients are still needed. Aim of this work was to identify and validate a brain glucose metabolism phenoconversion-related pattern of iRBD (RBDPRconv) in two centers, by using a Scaled Subprofile Model Principal Component Analysis (SSM-PCA) approach.

**Materials and Methods:** Polysomnography-confirmed iRBD patients were consecutively enrolled in Genoa and Rome Tor Vergata. Dementia and parkinsonism were ruled out by neurological examination and comprehensive neuropsychological assessment. Clinical conditions were evaluated prospectively every six months from baseline. Phenoconversion to overt synucleinopathy (i.e. PD or DLB) was assessed using current criteria. All patients underwent  $^{18}\text{F}$ -FDG-PET to investigate brain glucose metabolism within 12 months from diagnosis. The SSM-PCA approach was used to identify and validate the RBDRPconv in 30 iRBD converters patients ( $73\pm 6$  years, 23 males, 14 PD, 16 DLB) and 46 iRBD non-converters patients ( $69\pm 6$  years, 38 males).

**Results:** SSM-PCA was first applied in a training set (Group A) of 16 iRBD converters patients ( $74\pm 6$  years, 11 males) and 27 iRBD non-converters patients ( $70\pm 6$  years, 21 males), and the resulted pattern was applied to a validation set (Group B) of 14 iRBD converter patients ( $71\pm 6$  years, 12 males) and 19 iRBD non-converter patients ( $68\pm 5$  years, 17 males). Then, another SSM-PCA was performed using Group B as the training set and Group A as the validation one. The resulting patterns were comparable between the two analyses, thus a third SSM-PCA was applied to the whole set (Group A+B), identifying the final RBDRPconv. The RBDRPconv was formed by a linear combination of PC1 and PC2 (13.59% and 10.75% of variance, respectively). Stable regions of the RBDRPconv (95 CI threshold after bootstrap resampling) included relative hypermetabolism in cerebellum, brain stem, pons, right hippocampus, left superior frontal gyrus, medial globus pallidus, putamen, anterior cingulate, and medial frontal gyrus, while relative hypometabolism was found in the cingulate cortex, precuneus, cuneus, caudate nuclei, thalamus, calcarine cortex and parieto-occipital areas. A receiver operating characteristic (ROC) analysis was applied to discriminate converters from non-converters, showing an area under the curve (AUC) of 0.90 (sensitivity 0.73, specificity 0.92).

**Conclusions:** In this study we identified and validated a stable RBDRPconv, able to efficiently discriminate converters from non-converters iRBD patients, with high specificity. The SSM-PCA approach has been proved to be reliable, robust and highly reproducible in several neurodegenerative diseases, including PD. We suggest that the RBDRPconv expression may be a promising biomarker to identify iRBD patients to be enrolled in disease modifying clinical trials. The RBDRPconv should be further validated in independent cohorts. Longitudinal studies are needed to evaluate whether the CONVRP-RBD may be used also as a progression biomarker.

**Acknowledgements:** This work was developed within the framework of the DINOGMI Department of Excellence of MIUR 2018–2022 (legge 232 del 2016), and supported by an Italian Ministry of Health grant - Italian Neuroscience network (RIN).

## IDENTIFICATION OF EARLY AND PERIPHERAL BIOMARKERS PREDICTIVE OF PARKINSON'S DISEASE AND DEMENTIA WITH LEWY BODIES IN PATIENTS WITH ISOLATED REM SLEEP BEHAVIOR DISORDERS

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**Introduction:** Idiopathic rapid eye movement sleep behavior disorder (iRBD), olfactory impairment and gastrointestinal dysfunction are considered non-motor early manifestations of a group of pathologies known as  $\alpha$ -synucleinopathies, whose archetypes are Parkinson's disease (PD) and dementia with Lewy bodies (DLB). More than 80% of patients with PD develop olfactory impairment in their prodromal disease stage and the onset of olfactory impairment in iRBD subjects is associated with an increased risk of short-term conversion to PD or DLB. However, the lack of sensitive and measurable biomarkers hampers the possibility to accurately predict the progression from early phases to overt  $\alpha$ -synucleinopathies. With disease-modifying therapeutic options targeting  $\alpha$ -synuclein ( $\alpha$ Syn), we face the need for more specific biomarkers able to identify

those iRBD subjects who will progress to overt  $\alpha$ -synucleinopathy. Different  $\alpha$ -synucleinopathies are associated with distinct conformers of misfolded and disease-associated  $\alpha$ -synuclein ( $\alpha$ Syn<sup>D</sup> strains). The process of  $\alpha$ Syn misfolding begins many years before the onset of clinical signs, and several lines of evidence indicate that  $\alpha$ Syn<sup>D</sup> appears in peripheral tissues of patients in the early stage of the disease. By Real-Time Quaking-Induced Conversion (RT-QuIC) assay, traces of  $\alpha$ Syn<sup>D</sup> have been detected in the cerebrospinal fluid (CSF) and olfactory mucosa (OM) of patients with PD, DLB and other  $\alpha$ -synucleinopathies. Moreover, cytokines or proteins (even at subpicomolar levels) are differentially expressed in OM and blood samples of patients with  $\alpha$ -synucleinopathies. Additionally, alterations of the gut microbiota can promote  $\alpha$ Syn<sup>D</sup> formation by producing microbial amyloid proteins and by stimulating local inflammation. Also the nasal microbiota could contribute to  $\alpha$ Syn<sup>D</sup> formation. Our study aims at identifying novel disease-specific biomarkers in the OM, blood and urine of PD and DLB patients, potentially identifiable in iRBD subjects as early indicators of any of these pathologies.

**Materials and Methods:** Fifteen patients will be recruited for each disease group (iRBD, PD, and DLB) and 15 healthy controls (HC) over a 12 months' period. After the evaluation of olfactory functions, OM, blood and urine will be collected from patients with iRBD, PD, DLB, and HC and subjected to several multi-omics analyses. In particular, OM and blood will be subjected to Bio-Plex LUMINEX, Quantikine® HS ELISA, Ella Simple Plex™, and microbiota analyses. All samples will be analyzed by The RT-QuIC and the final reaction products will undergo biochemical, fluorescence spectroscopy and morphological evaluation.

**Results:** The study will characterize OM, blood and urine of PD and DLB patients and verify whether samples collected from iRBD subjects contain early and measurable biomarkers that can be linked to the progression of  $\alpha$ -synuclein-associated pathology. The preliminary results of the first recruited patients will be presented.

**Conclusions:** Our translational approach could have a major impact on counseling and prevention strategies for patients in the prodromal stages of  $\alpha$ -synucleinopathies, representing a key goal on the path to disease-modifying and neuroprotective therapies before full-blown phenotypes have manifested.

**Acknowledgements:** Italian Ministry of Health – Current Research to FM

## NEUROPSYCHIATRIC, NEUROPSYCHOLOGICAL, AND NEUROIMAGING FEATURES IN ISOLATED REM SLEEP BEHAVIOR DISORDER: DOES MCI MATTER?

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**Introduction:** Mild cognitive impairment (MCI) can be a very early sign of neurodegeneration in idiopathic REM sleep behavior disorder (iRBD), although the extent of neuropathology has not yet been quantified. The present study investigated the markers of neurodegeneration in patients with iRBD distributed on the basis of MCI through a comprehensive neuropsychiatric, neuropsychological and neuroimaging evaluation useful to predict neurodegenerative outcomes.

**Materials and Methods:** Sixty-one patients with iRBD were included in the study, with 30 iRBD patients included in the MCI (RBD-MCI) subgroup and 31 iRBD patients presenting normal cognition (RBD-NC). Both the groups underwent a neuropsychiatric and neuropsychological assessment to evaluate psychopathological symptoms, executive dysfunction, and nonverbal/verbal memory patterns. Brain  $^{18}\text{F}$ -FDG-PET and [ $^{123}\text{I}$ ]-ioflupane SPECT (123I-FP-CIT-SPECT) were performed in convenience subgroups of patients to evaluate in a pilot model brain metabolism and nigrostriatal dopaminergic functioning, respectively.

**Results:** Neuropsychological measures generally confirmed an overall cognitive decline in iRBD-MCI patients. Immediate long-term verbal memory and visuospatial functions as well as attentional-executive impairment were more impaired in patients with MCI as compared to

those with NC. Neuroimaging results indicated a reduced brain glucose uptake consumption in the bilateral posterior cingulate cortex and a more evident nigrostriatal deafferentation in RBD-MCI group, confirming the well-known central role of this subregion in cognitive deterioration. Controversially, there is no overall noticeable trend evident in the frequency and severity of psychopathological symptoms reported by the two groups.

**Conclusions:** These findings highlight the diffuse neurodegenerative process affecting brain of iRBD patients and thus reflecting not only the risk of future motor symptoms, but also the non-motor burden of the disease with the predominant cognitive and psychopathological symptoms. The clinical implications suggest the importance of submitting cognitive tests in patients with iRBD to identify MCI and possibly targeting early those patients to neuroprotective strategies.

#### PERCENTAGE TONIC REM SLEEP IS MOST PREDICTIVE OF PHENOCONVERSION TO NEURODEGENERATIVE DISEASE IN IRBD

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**Introduction:** Previous studies have shown that REM sleep without atonia (RSWA) during polysomnography (PSG) can predict the risk of phenoconversion to neurodegenerative disease in patients with idiopathic REM sleep behaviour disorder (iRBD). Despite this, discrepancy remains with regards to the morphology of RSWA that best predicts phenoconversion risk. This study aimed to ascertain the predictive value of tonic, phasic and mixed RSWA in patients with iRBD, at time of diagnosis.

**Materials and Methods:** 64 patients with PSG-confirmed iRBD, including those that phenoconverted during follow-up after diagnosis and those that remained free from neurodegeneration, were identified from an existing database. Tonic, phasic, mixed and "any" RSWA activity from the mentalis, tibialis anterior and flexor digitorum superficialis muscles was analysed. RSWA variables were compared between converters and non-converters; standard statistical analysis was undertaken. A Bonferroni correction for multiple comparisons was applied to results. Additionally, RSWA cut-offs predicting phenoconversion were established using receiver operating characteristic analysis to determine the predictive value of the different RSWA morphologies.

**Results:** Of the patients in total, 18 (28.3%) converted to neurodegenerative disease during follow-up. Phenoconverters had significantly higher amounts of tonic ( $p = 0.00010$ ), mixed ( $p = 0.00024$ ) and "any" RSWA solely derived from the mentalis muscle ( $p = 0.00003$ ) at iRBD diagnosis than non-converters. Optimal RSWA cut-off values to predict phenoconversion were 5.8% for tonic (78% sensitivity; 76% specificity), 8.4% for mixed (72% sensitivity; 78% specificity) and 45.0% for "any" RSWA solely derived from the mentalis muscle (72% sensitivity; 83% specificity). Area under the curve values, with their corresponding 95% confidence intervals, were 0.84 (0.73 - 0.95) for "any" RSWA solely derived from the mentalis muscle, 0.81 (0.68 - 0.95) for tonic RSWA, 0.81 (0.68 - 0.94) for "any" RSWA solely derived from the mentalis muscle without the mixed RSWA component and 0.80 (0.67 - 0.93) for mixed RSWA.

**Conclusions:** Patients with greater amounts of tonic, mixed and "any" RSWA solely derived from the mentalis muscle at iRBD diagnosis have an increased risk of developing subsequent neurodegenerative disease. Thus tonic, mixed and "any" RSWA solely derived from the mentalis could be used in conjunction with other biomarkers to establish an individual iRBD patient's phenoconversion risk.

**Acknowledgements:** The authors thank the staff at the Department of Sleep Medicine, Royal Infirmary of Edinburgh, United Kingdom for their assistance throughout the duration of the study.

#### PROGNOSTIC MODEL FOR THE DEVELOPMENT OF PARKINSON'S DISEASE IN PATIENTS WITH REM-SLEEP BEHAVIOR DISORDER

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**Introduction:** The presence of REM-sleep without atonia (RSWA) and REM-sleep behavior disorder (RBD) are well-demonstrated to increase the risk of developing  $\alpha$ -synucleinopathies, including Parkinson's disease (PD). Other than RSWA and RBD, olfactory dysfunction, impaired color vision, depression and constipation were also established as the prodromal features of PD, preceding the disabling motor symptoms. Here we analyzed the predictive value of these prodromal features in patients with RBD for the development of PD.

**Materials and Methods:** We have prospectively investigated the patients with idiopathic RBD diagnosed by a full-night polysomnography. The other sleep disorders that might be associated with the RSWA and/or RBD were excluded. All patients had a detailed neurologic examination, and those with any parkinsonian symptoms and/or signs of neurodegeneration were also excluded. Olfactory function was tested by using the Sniffin' Sticks kit, the color vision was tested by using the FM-100 Hue Test, depressive symptomatology was evaluated by using the Beck Depression Inventory (BDI), and the presence of constipation was evaluated by using the Rome III Criteria. The patients were followed-up for eight years regularly at every six months (with some exceptions, having a maximum of one-year interval).

**Results:** Forty-five Patients were included in this study; the mean age of the patients was 57.9±10.0 years, and 26 of them (57.8%) were men. The olfactory dysfunction was present in 88.9% of the patients (24.4% were anosmic), and a decrease in color discrimination was observed in 73.3% of the patients. Depressive symptomatology was found in 56.8% (varying from mild to severe). Constipation was reported in 56.8% of the patients. At the end of eight years, 17.8% of the patients (8 patients) developed PD following a mean of 38.5±12.3 months. In prognostic models for predicting the PD development in RBD patients, age ( $\geq 60$  years), male gender, and the other prodromal symptoms were used in different varying combinations. When all parameters were put into the equation, the Odd's ratio was not found to be significantly increased. The Odd's ratio was highest for the patients RBD >60 years of age with anosmia and constipation (44.8 [4.5-445.7]; kappa=4.291;  $p < 0.001$ ). The model with the second highest Odd's ratio was found in the patients with RBD >60 years of age with constipation (36.1 [3.7-350.1]; kappa=4.034;  $p < 0.001$ ). Male gender was also associated with a significant increase in the risk of the development of PD, though the Odd's ratio was lower in compared to other models. The depressive symptomatology defined by the BDI was not associated with the PD conversion in any model.

**Conclusions:** We observed that the conversion rate from RBD to PD was 17.8% following a mean of 38.5 months. The predictive value was highest in RBD patients being >60 years of age and having both anosmia and constipation. Between anosmia and constipation, the presence of constipation in addition to RBD and age showed a higher predictive value for the development of PD.

**Acknowledgement:** This study was founded by the Turkish Sleep Medicine Society.

#### ROLE OF REM SLEEP BEHAVIOR DISORDER IN ATYPICAL PARKINSONISM: A LOCUS COERULEUS-BASED NEUROMELANIN MRI STUDY

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**Introduction:** Locus coeruleus/subcoeruleus complex (LC/LsC) is a tiny structure comprising noradrenergic neurons that contain neuromelanin (NM) pigment. LC comprises neurons contributing to memory and cognition while the LsC comprises neurons contributing to muscle atonia during rapid eye movement (REM) sleep. Parkinson's disease (PD) and atypical parkinsonism such as multiple system atrophy (MSA) and progressive supranuclear palsy (PSP) demonstrate LC/LsC neurodegeneration that can be imaged using NM-sensitive MRI. LsC damage leads to REM sleep behavior disorder (RBD) and is associated with isolated RBD (iRBD), and the presence of RBD in PD. We studied LC/LsC damage in neurodegenerative parkinsonian disorders and its association with the manifestation of RBD.

**Methods:** Subjects were recruited in three prospective studies (Nuclei-park, Iceberg, Parkatypique) on a 3T Siemens MRI. RBD status was confirmed by video-polysomnography. We automatically segmented the LC/LsC area as 10 connected voxels with the brightest intensities to compute the signal intensity. Multivariate linear regression was used to explore the association between the signal intensity of the healthy volunteers (HV) and patients.

**Results:** We investigated 104 HV (mean age  $\pm$  SD:  $61.8 \pm 8.6$  years) and 310 patients comprising 47 iRBD ( $67.2 \pm 5.1$  years), 145 PD without RBD (age:  $61.3 \pm 9.9$  years, mean disease duration (DD):  $5.3 \pm 2.4$  years) and 77 with RBD (age:  $64.7 \pm 8.2$  years, DD:  $6.5 \pm 3.3$  years), 22 PSP (age:  $69.9 \pm 7.9$  years, DD:  $4.9 \pm 3.0$  years), and MSA (14 with the parkinsonian form, MSAp, age:  $62.7 \pm 8.5$  years, DD:  $4.0 \pm 1.7$  years and 5 with the cerebellar form, MSAc, age:  $57.6 \pm 5.1$  years, DD:  $2.4 \pm 1.5$  years; 12 MSA patients had RBD). Age was different between groups. HV were younger than iRBD and PSP. Participants with iRBD and PSP were older than PD without RBD. Sex ratio differed between groups, as there were more men in iRBD compared to HV, PSP and PD without RBD groups.

LC/LsC signal intensity was lower in the patient groups compared to HV. The signal intensity decreased linearly with age in all groups.

Signal intensity was higher in HV (LC signal intensity:  $127.3 \pm 5.4$ ) than in PSP ( $123.1 \pm 3.1$ ,  $p=0.04$ ), MSA ( $p<0.0001$ ,  $120.6 \pm 4.2$ ) and PD with RBD ( $123.6 \pm 4.7$ ,  $p<0.0001$ ) groups, but not in PD without RBD group ( $126.0 \pm 4.8$ ). The HV had the highest and MSA had the lowest signal intensity. Signal intensity was lower in MSA than in iRBD ( $p=0.02$ ) and than PD without RBD ( $p<0.001$ ). Signal intensity was lower in PD with RBD than without RBD ( $p=0.02$ ). There was no difference between MSAp ( $121.0 \pm 3.0$ ) and MSAc ( $119.7 \pm 4.7$ ) or between the other groups. There was no scanner effect in imaging measurements between HV groups.

**Conclusion:** NM-MRI signal was reduced in iRBD and in parkinsonian disorders as compared to the HV except in PD without RBD. Signal changes in PD were associated with the manifestation of RBD. The signal variations in the LC/LsC appeared associated with the manifestation of RBD in iRBD, PD with RBD, and MSA.

This insight could be used as a potential biomarker for clinical trials of disease-modifying therapies.

#### WHICH SHOULD BE A BEGINNING POINT FOR THE DISEASE DURATION OF IDIOPATHIC RAPID EYE MOVEMENT SLEEP BEHAVIOR DISORDER, THE ESTIMATED ONSET OF SYMPTOMS, OR THE DATE WHEN DIAGNOSED?

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**Introduction:** Idiopathic rapid eye movement sleep behavior disorder (iRBD) is a harbinger of neurodegenerative diseases. It is crucial to assess the disease duration of iRBD to consider the risk of progression to phenoconversion. However, previous studies have used two different onset points to define the disease duration of iRBD: the estimated onset of dream enactment behavior (DEB) and the date diagnosed with RBD. When discussing the duration of iRBD, which duration is more appropriate? In this study, we examined the relationship between the two disease durations and the clinical characteristics of iRBD patients.

**Materials and Methods:** Thirty-six iRBD patients (four females) were

included. The beginning point of "duration from estimated onset" was defined as the confirmed date of the first occurrence of DEB according to the statements of the patient's family members. The start of "duration from diagnosis" was defined as the date when a diagnosis was made through polysomnography. The following clinical features were evaluated. (1) cognitive function (Montreal cognitive assessment, MoCA; Brief Assessment of Cognition in Schizophrenia, BACS). (2) depressive symptoms (Geriatric depression scale-15, GDS), (3) autonomic dysfunction (Scale for Outcomes in Parkinson's disease-Autonomic, SCOPA-AUT). Only in GDS and SCOPA-AUT, there was missing data, and 35 patients were included. Correlations between age at the assessment of clinical features, duration from estimated onset, and duration from diagnosis were examined. Then the relationship between the two disease durations and clinical characteristics was examined using Spearman's correlation coefficient ( $r$ ). This study was approved by the Shiga University of Medical Science Research Ethics Committee (R2017-027)

**Results:** The mean ( $\pm$  standard deviation) age was  $73.7 \pm 6.2$  years, duration from estimated onset was  $9.9 \pm 6.4$  (range: 1.7–32.6) years, and duration from diagnosis was  $3.1 \pm 3.1$  (range: 0.2–13.0) years. Age was correlated with the duration from estimated onset ( $r = 0.503$ ,  $p = 0.002$ ) and not significantly associated with the duration from diagnosis. Duration from estimated onset was correlated with duration from diagnosis ( $r = 0.338$ ,  $p = 0.044$ ). The duration from estimated onset was significantly correlated with the following scores: (1) MoCA ( $r = -0.351$ ,  $p = 0.036$ ), z-score of Token motor task on BACS ( $r = -0.348$ ,  $p = 0.038$ ), (2) GDS ( $r = 0.404$ ,  $p = 0.016$ ), (3) SCOPA-AUT total score ( $r = 0.461$ ,  $p = 0.005$ ). On the other hand, duration from diagnosis was correlated with (1) z-score of digit sequencing task on BACS ( $r = -0.408$ ,  $p = 0.014$ ), but no other significant association was observed.

**Conclusions:** In this study, duration from estimated onset was associated with more clinical characteristics than duration from diagnosis. The definition of estimated onset could involve recall bias. In contrast, although the definition of duration from diagnosis is evident, we need to pay attention to selection bias, such as patients' knowledge level or ease of access to medical care. It will be necessary to accumulate knowledge on the relationship between disease duration and symptoms and the risk of phenoconversion. It will be essential to describe the disease duration in both ways, considering their biases.

#### Restless Legs Syndrome (RLS)

#### A REVIEW OF IRON DEFICIENCY GUIDELINES IN THE CONTEXT OF IRON DEFICIENCY-ASSOCIATED SLEEP/WAKE BEHAVIOURS

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**Introduction:** Iron deficiency (ID) is the most common micronutrient deficiency in the world, disproportionately affecting children and women. Beside iron's essential role in hemoglobin synthesis and hematopoiesis, iron has numerous functions within the brain. In this context, iron deficiency must be viewed not only from a hematological perspective, but also from the perspective of neurological, developmental, and behavioural morbidities. Despite high level evidence of an association between ID and restless legs syndrome (RLS) and attention deficit hyperactivity disorder (ADHD), ID and iron supplementation are not routinely considered in the diagnostic work-up and as a treatment option in clinical practice.

The goals of this scoping literature review are to (1) review whether RLS and ADHD have been included (e.g., as signs/symptoms or comorbid conditions) in ID guidelines, (2) compare recommended biomarkers and cutoff values in general, as well as disease-specific ID guidelines, and (3) identify whether specific cutoff values (e.g., serum ferritin; SF) for RLS and ADHD were included in ID guidelines.

**Materials and Methods:** A search was conducted in June 2020 (updated May, 2021) in Medline, CINAHL, and Embase. Search terms included: "iron deficiency" or "anemia" and "guideline". Websites of national medical

affiliations were also searched. Guidelines were included if they were: 1) general ID guidelines, defined as those targeting a general population, pregnancy-specific ID guidelines, and/or if they included a variety of disease states and/or medical diagnoses that could be associated with ID (e.g., chronic kidney disease), and 2) if the guideline or consensus paper was created by/on behalf of a larger governing body (e.g., national/regional organizations). Opinion papers or reviews of guidelines were excluded.

**Results:** ID guidelines: n=47, including 25 general ID guidelines, eight pregnancy-specific, and 14 disease-specific ID guidelines. Guidelines were published between 1989 and 2021, with the majority (n=33) published in the 2010's. 42 ID guidelines included SF cutoff values ranging from 10 ug/L to 800 ug/L. The highest SF cutoff values were found in disease-specific guidelines. 17 guidelines recommended concomitant measurement of CRP with SF. Other common iron-specific biomarkers included transferrin saturation (n=34), total iron binding capacity (n=18), and sTfR (n=16). Common hematologic markers (e.g., to detect anemia) were hemoglobin (n=46), MCV (n=32), and MCH (n=16).

Two general and one disease-specific ID guidelines included both RLS and ADHD as conditions that could present as signs/symptoms of ID. RLS and ADHD were included in four and one additional guidelines, respectively. Only one guideline included a specific SF cutoff value for RLS, while no guideline provided a SF cutoff value for ADHD.

**Conclusions:** ID-associated restlessness, affecting day- and nighttime behaviours, has not yet been implemented in ID guidelines. Despite the widespread use of SF for the diagnosis of ID, its role as an acute phase reactant, inability to reflect brain iron levels, and heterogeneity in cutoff values limit its clinical utility. Nonetheless, as iron supplementation should be considered a first line measure to alleviate symptoms of restlessness-associated conditions, harmonization and review of ID guidelines is needed.

#### EFFECTS OF ACUTE EXPOSURE TO ALTITUDE ON RESTLESS LEGS SYNDROME

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**Introduction:** Genetic factors, brain iron dysregulation and dopaminergic dysfunction play an important role in the pathogenesis of restless legs syndrome (RLS). Previous studies suggested also a role of hypoxia in RLS pathogenesis: vascular endothelial growth factor is upregulated in the skeletal muscles of the legs in RLS; peripheral tissue hypoxia has been demonstrated in patients with RLS, strongly correlating with RLS severity; a higher prevalence of RLS was found in high-altitude regions; RLS was associated with reduced oxygen saturation in individuals living at high altitudes. Aim of this study was to investigate the effect of acute exposure to high-altitude on periodic leg movements during wakefulness (PLMW) and RLS symptoms during a suggested immobilization test (SIT) in RLS patients.

**Methods:** Twenty-eight RLS individuals (diagnosed according to the IRLSSG criteria) underwent 1-hour SIT twice on two separate days: in randomized order, double-blinded, in a simulated high-altitude environment with normobaric hypoxia corresponding to 3000m above sea level, and at the Innsbruck local altitude (574m). Both SITs were performed in the same setting. PLMW and subjective discomfort as well as urge to move the legs were recorded. PLMW scoring was performed using a validated algorithm. Subjective discomfort and urge to move were assessed at baseline and every 15 minutes using a visual analogue scale from 0 to 10.

**Results:** Twenty-eight RLS patients aged 45.1±10.8 years were included, 53.6% female. Ten patients were untreated, 10 under dopaminergic treatment and eight under non-dopaminergic treatment or polytherapy. PLMW index at 574m was 26.5±33.6, compared to 33.3±48.6 at 3000m (p=0.289). Subjective discomfort and urge to move the legs both increased with time during SIT, and were worse at 3000m. This difference reached statistically significance only for urge to move the legs at 30 minutes (16.4±20 vs 24.5±28.2, p=0.043) and at 45 minutes (21.4±24.1 vs 29.4±30.5, p=0.039) after SIT onset. When analysing both sex separately, a statistically significant difference was still present only in males: I. both subjective discomfort and urge to move were higher at 3000m compared to 574m 30 minutes after SIT onset (8.5±16.8 vs 11.8±19.3, p=0.045, and 7.1±12.5 vs 14.9±19, p=0.006, respectively); II. urge to move the legs was stronger at high altitude after 45 minutes from SIT onset (13.3±22.6 vs 21.8±25.6, p=0.019); III. PLMW index during SIT was 20.8±30.9 at 574m vs 28±37.1 at 3000m, p=0.029.

**Conclusions:** In patients with RLS, urge to move the legs is stronger at high-altitude. The effect of altitude on RLS symptoms was present only in male RLS patients. In this group both sensory and motor subjective symptoms, as well as PLMW index worsened at high altitude. These data support the role of peripheral hypoxia in RLS. Further studies assessing influence of RLS treatment on altitude related changes, studies including a control group, as well as studies investigating pathophysiological mechanisms underlying the interaction between sex and hypoxia are needed.

**Acknowledgements:** We are thankful to Mr. Heinz Hackner for accurate PSG scoring and technical support.

#### METHYLGLYOXAL – A CENTRAL METABOLIC FACTOR IN RESTLESS LEGS SYNDROME?

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**Introduction:** The glyoxalase system consists of the enzymes glyoxalase 1 (GLO1), glyoxalase 2 (GLO2), and the co-factor glutathione. Its central task is to detoxify methylglyoxal (MG) and related reactive dicarbonyls such as glyoxal (GO) into the non-toxic lactate. Dysfunction of this system can increase or decrease levels of dicarbonyl compounds. Altered MG levels have been linked to various diseases. For restless legs syndrome (RLS) genome-wide association studies have identified significant association signals in and close to *GLO1*, suggesting an involvement of the glyoxalase system in RLS. Therefore, we analyzed the metabolites of the glyoxalase system in sera of idiopathic RLS cases and healthy controls from a population-based cohort (KORA) to expand the phenotypic correlations of MG.

**Methods:** The concentrations of the reactive dicarbonyl compounds MG, GO and 3-deoxyglucosone (3-DG) were measured in serum samples of 246 idiopathic RLS patients (median age of 68 [23 - 96]; 167 [67.9%] female; 79 [32.1%] male) and 482 KORA controls (median age of 57 [32 - 81]; 243 [50.4%] female; 239 [49.6%] male) using liquid chromatography mass spectrometry (LC-MS).

**Results:** Regarding the comorbidities in the KORA cohort, nearly all known phenotype associations of the measured dicarbonyls were replicated (i.e., cardiovascular diseases, diabetes, age, obesity, impaired liver and renal function). Accordingly, associations were found for waist-hip ratio, glomerular filtration rate, blood pressure, HDL, AST, ALT, GGT, HbA1c, and blood glucose levels. Comparing RLS cases to KORA controls MG had significantly lower concentrations in RLS. This was true across all age and gender groups (p = 4.12×10<sup>-23</sup>).

**Conclusion:** Decreased concentrations of MG in RLS patients could be due to an increased activity of the glyoxalase system. MG is known to be a competitive partial agonist at GABA<sub>A</sub> receptors (Distler et al., 2012). Decreased levels of MG in RLS could therefore decrease GABAergic activity. Lower GABAergic activity has been linked to anxiety, restlessness and an impairment of sleep. The enhancement of arousal mechanisms in RLS may also be favored by insufficient GABA-mediated inhibitory control (Lanza et al., 2019). Taken together, these properties point to a potential role of the observed changes in dicarbonyl concentrations in RLS, revealing a new potential target for treatment.

#### NONINVASIVE PERONEAL NERVE STIMULATION REDUCES SYMPTOMS OF RESTLESS LEGS SYNDROME

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**Introduction:** Restless Legs Syndrome (RLS) is a prevalent sleep disorder associated with an irresistible urge to move the legs that interferes with sleep initiation and maintenance. The most common first-line treatments for RLS are dopamine agonist medications that often lead to augmentation and other debilitating side-effects. Here, we investigated a device-based alternative to medications for RLS treatment, noninvasive bilateral electrical stimulation of the common peroneal nerve (NPNS).

**Materials and Methods:** We conducted a multi-site randomized crossover study comparing NPNS to sham control. RLS patients with moderate-to-severe RLS ( $n=37$ ) self-administered NPNS and sham nightly for 14 days per treatment in randomized order. The Patient-rated clinical Global Impressions of Improvement scale (PGI-I) and International RLS Rating Scale (IRLS) were employed as outcome measures. To assess the acute effects of NPNS, a 60-minute suggested immobilization test (SIT) was performed at baseline, and with sham and NPNS in randomized order, and both leg movements and subjective measures of RLS severity were assessed. Additionally, to investigate NPNS mechanism of action, surface electromyography (sEMG) was collected on the tibialis anterior muscle during stimulation ( $n=20$ ).

**Results:** NPNS resulted in a reduction in RLS severity of 6.81 points on the IRLS relative to 3.38 for sham ( $P<0.01$ ) and a 66% clinically significant responder rate on the PGI-I scale compared to 17% for sham ( $P<0.01$ ). Subgroup analysis indicated that medication-resistant and medication-naïve participants both exhibited similarly robust responses. There were no serious device-related adverse events, >95% of subjects reported that NPNS was compatible with sleep onset, and 87% of subjects used NPNS on 5 or more nights/wk. Results from the SIT procedure indicated that NPNS resulted in acute relief of RLS symptoms, as measured by a subjective numerical rating scale (NRS), as well as acute suppression of leg movements, as measured by a 3-axis accelerometer placed at the lateral malleolus. NPNS resulted in tonic sEMG activity in the tibialis anterior muscle in 87% of subjects, which was predictive of efficacy; subjects with higher levels of evoked sEMG activity and lower thresholds for inducing sEMG activity reported greater reduction in IRLS score in response to NPNS relative to sham control.

**Conclusions:** These results suggest that NPNS has the potential to be a safe and efficacious approach to relieve RLS symptoms when administered acutely or when patient-administered in the home environment. NPNS shows promise for both medication-resistant RLS patients and medication-naïve RLS patients. Notably, both exercise and NPNS provide acute relief for RLS symptoms and are associated with leg muscle activation, suggesting potential mechanistic similarities. In contrast to exercise, however, NPNS appears to be compatible with sleep, thus conferring advantages for the majority of individuals with RLS symptoms during the sleep period.

#### PERIODIC LIMB MOVEMENTS AMONG PERSONS WITH EPILEPSY – A RETROSPECTIVE POLYSOMNOGRAPHY STUDY

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**Introduction:** Sleep-wake disturbances, common among persons with epilepsy (PWE), can be attributed to seizures, epilepsy etiology, psychiatric comorbidities, medication side effects, as well as primary sleep disorders like insomnia, obstructive sleep apnea (OSA), and restless legs syndrome (RLS). Sleep fragmentation resulting from these is associated with poorer quality of life and seizure control.

While sleep apnea and insomnia have been studied more closely in the epilepsy population, RLS and periodic limb movements (PLMs), which also significantly disturb sleep, remain far less investigated. There are only a limited number of studies on epilepsy populations reporting PLM details, which are potentially important contributors to overall sleep efficiency. The aim of this study is to evaluate prevalence and characteristics of PLMs among PWE and their association with other objective sleep parameters.

**Materials and methods:** This is a retrospective chart-review-based study. The study population consisted of consecutive adult patients with a diagnosis of epilepsy who had undergone polysomnography (PSG) at the sleep lab of this tertiary care referral center, over a 10-year period. The control group included patients referred for possible diagnosis of OSA. The

groups were matched according to age, sex, and OSA severity.

The university hospital sleep lab database was interrogated for patients carrying a diagnosis of “epilepsy” or “seizures”. The charts of the epilepsy group were reviewed to confirm the ‘epilepsy’ diagnosis and extract other details of epilepsy characteristics like duration, focal versus generalised onset, anti-seizure medications (ASMs), etc. Key PSG parameters including sleep efficiency, spontaneous arousal index; periodic limb movement index (PLMI), periodic limb movement with arousal index (PLMAI) and apnea-hypopnea index (AHI) were extracted from archived reports of included subjects in both groups.

Data was analysed using descriptive statistical tools.

**Results:** Among a total of 152 patients identified from the database, 61 PWE (mean age  $41.4 \pm 17.2$ , 31 females) could be included and matched with 61 OSA patients. Forty-three patients had focal onset and 16 had generalized epilepsy; 25 were on  $\geq 2$  anti-seizure medications and 12 patients were medically refractory. Prevalence of PLM activity was found to be similar in both groups (14/61 [23%] in PWE, 16/61 [26%] in OSA) with mean PLMI of  $6.1 \pm 16.8$  among PWE vs  $8.8 \pm 20.7$  in the OSA group. PLMAI was also similar in both groups ( $0.5 \pm 1.0$  vs  $1.1 \pm 2.4$ ). RLS was diagnosed in 4 PWE and 3 OSA patients. No significant difference was detected between the two groups in other sleep parameters either. Mean AHI was  $16.0 \pm 20.0$  in the epilepsy group vs  $19.7 \pm 19.4$  in the OSA group. Among PWE, only older age (and not epilepsy type, responsiveness to or number of ASMs) was associated with presence of PLMs.

**Conclusions:** Periodic limb movements are commonly detected in PSG studies of PWE, and are significantly associated with older age. The observations of similar PLM indices among PWE and an age-and-sex-matched OSA population and of lower prevalence of RLS, indicate that OSA itself likely accounts for most PLMs in epilepsy.

#### RLS PREVALENCE AND IMPACT ON SLEEP QUALITY IN A GROUP OF RELAPSING-REMITTENT MULTIPLE SCLEROSIS PATIENTS

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**Introduction:** Multiple sclerosis (MS) is a risk factor for Restless Legs Syndrome (RLS). Patients with MS (PwMS) have a mean higher prevalence of RLS compared to general population, with different rates across studies. Inconsistent correlations were found between RLS and demographic as well as MS related and sleep related parameters.

**Materials and Methods:** In this monocentric cross-sectional study we aimed at assessing the prevalence of RLS in particular in patients with relapsing-remitting MS (PwRRMS) and assessing possible differences between PwRRMS with and without RLS.

We recruited 92 consecutive PwRRMS. Either these patients were in no chronic treatment or they were with a 1<sup>st</sup> or 2<sup>nd</sup> line disease modifying therapy. Patients underwent a clinical interview to diagnose RLS and were asked to complete a series of questionnaires about MS related disability (Expanded Disability Status Scale (EDSS)), sleep quality and disorders screening (among which: Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), Restless Legs Syndrome Rating Scale (RLSRS)), and mood disorders screening questionnaires (Beck's Depression Inventory (BDI), State-Trait Anxiety Inventory (STAI-Y)).

**Results:** Our population was made of PwRRMS with a median age of  $47 \pm 19$ , 68.5% (63/92) of them females, with  $9 \pm 13$  years since MS diagnosis. Both infratentorial and supratentorial lesions were present in 91.1% of PwRRMS (84/92). The majority of patients was in treatment with a 1st or 2nd line disease modifying therapy (respectively 48.9%, 45/92 and 40.2%, 37/92). Patients' median EDSS scores were  $2 \pm 2$  indicating mild disability. Sleep quality was borderline with a median PSQI score of  $5 \pm 4$  and 45.7% PwRRMS (42/92) had poor sleep quality, with 9.8% of patients (9/92) requiring therapy with hypnotic drugs. BDI median score was  $6 \pm 11$  and STAI-Y1 and STAI-Y2 had a median score of  $45 \pm 7$  and  $45 \pm 8$  respectively. Prevalence of RLS was 47.8% (44/92) and positive familiarity for RLS was found in 25% of patients (11/44). Out of PwRRMS and RLS, 63.6% (28/44) had pRLS whereas 36.4% (16/44) had iRLS. Overall severity was moderate, considering that RLSRS median score was  $11 \pm 20$ . Comparing rates of pathological PSQI, PwRRMS with RLS had worse sleep quality than those

without (56.6%, 25/44 vs 35.4%, 17/48,  $p=0.04$ ). However, comparing PSQI scores we found only a tendency to significance with patients with RLS having a median PSQI score of  $6\pm 4$  vs  $5\pm 4$  in those without RLS ( $p=0.09$ ). Although other parameters did not reach statistical significance, patients with RLS also had higher hypnotic drug intake (15.9%, 7/44 vs 4.2%, 2/48,  $p=0.1$ ) and slightly worse MS related disability (EDSS median scores  $2\pm 2$  vs  $1.5\pm 1.4$ ,  $p=0.2$ ).

**Conclusions:** Our study confirms higher prevalence of RLS in MS patients compared to general population. We only found a tendency to worse sleep quality and few patients reported hypnotic drugs intake. There were no correlations with MS duration, lesions localization, line of treatment, nor with mood alteration. Future aim will be to assess possible correlations between cervical lesion and RLS presence and severity as well as including fatigue assessment in our analysis.

### SPECTRAL ELECTROENCEPHALOGRAPHIC CHANGES AND HEART RATE VARIABILITY ACCOMPANYING LEG MOVEMENTS DURING SUGGESTED IMMOBILIZATION TEST IN PATIENTS WITH RESTLESS LEGS SYNDROME

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**Introduction:** Restless Legs Syndrome/Willis-Ekbom disease (RLS/WED) is commonly associated with the periodic leg movements during sleep (PLMS). Studies have shown that PLMS are associated with the electroencephalographic (EEG) activation with prominent changes in delta and other EEG bands. Moreover, an increase in sympathetic autonomic nervous system associated with PLMS was shown in the heart rate variability (HRV) analysis. Nevertheless, RLS/WED is a sleep-related movement disorder characterized by the symptoms occurring in wakefulness, especially at nighttime before sleep. In this study, we aimed to evaluate the leg movements in the patients with RLS/WED in wakefulness during the suggested immobilization test (SIT).

**Materials and Methods:** The SIT was performed before polysomnography (PSG) recordings in 78 patients with RLS/WED during one-year study period. Both periodic (PLM) and isolated (ILM) leg movements were scored in the SIT, and the spectral EEG changes 20 seconds before and after the leg movements were analyzed. The heart rate analysis was also performed accompanying the leg movements. The PSG recordings were scored; sleep efficiency, awakenings and the sleep stage transitions, apnea-hypopnea index (AHI) and PLMS were noted. The HRV analysis was made in wakefulness during the SIT and in sleep during the PSG.

**Results:** A total 65 Patients were included in the study; 35 were females (53.8%) and 30 were males (46.2%). The mean age of the study population was  $52.0\pm 12.6$  years. Sixteen patients (24.6%) had  $PLMS\geq 15/hr$  (mean,  $32.4\pm 19.6/hr$ ). AHI was  $\geq 5/hr$  in 43 patients (66.2%; mean,  $19.4\pm 12.9/hr$ ). In the SIT, 49 patients (75.4%) had PLM index  $\geq 40/hr$  (mean,  $60.7\pm 18.0/hr$ ). The index of ILM was  $9.4\pm 4.2/hr$ . The EEG spectral analysis revealed that the EEG activation was associated with both PLM and ILM in the SIT. The increase in the delta band 7–8 seconds after the PLM was higher than those following the ILM, though not significantly ( $p=0.062$ ). The increase in theta band (2–3 seconds after the movement), alpha band (2–7 seconds after the movement), and beta band (3–10 seconds after the movement) was significantly higher following PLM than ILM ( $p<0.001$ ). The increase in heart rate was higher following PLM in compared to that of following ILM, but not significantly ( $p=0.771$ ). The HRV analysis in wakefulness during SIT revealed that the LF ( $p=0.010$ ) and LF/HF ( $p=0.004$ ) were significantly higher, and HF ( $p=0.009$ ) was significantly lower in patients with a PLM index  $\geq 40/hr$  than those in patients with a PLM index  $< 40/hr$ .

**Conclusions:** Our study showed that the leg movements during wakefulness in the Patients with RLS/WED are accompanied by the EEG activity, especially in the theta, alpha and beta bands. They were also associated with an increase in the heart rate, though the difference between the PLM and ILM was not significant. These findings suggest the role of the cortical and subcortical mechanisms associated with the cyclic alternating pattern generators in the leg movements during wakefulness. The increase in the LF/HF ratio in patients with a PLM index  $\geq 40/hr$  in SIT demonstrates the presence of sympathetic activation during wakefulness in patients with RLS/WED, which may explain the increased risk of cardiovascular complications.

### TWO CASES OF PEDIATRIC RLS AND ELEVATED CK – AN ASSOCIATION OR A COINCIDENCE?

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**Introduction:** Restless Leg Syndrome (RLS) is a sleep disorder with a clinical diagnosis that is not always straightforward, particularly in pediatric age. Elevated creatine kinase (CK) can either be present in physiological or pathological conditions. The authors present two case reports of RLS with elevated CK in pediatric age.

**Case report 1:** A 5-year-old black male with no relevant medical history referred for lower limb pain since 1.5-years-old. Initially located on the dorsum of the right foot, it progressed to the contralateral foot, knees, sometimes affecting the hands. The pain occurred 1–2 times/week, predominantly during the night, causing awakening, and occasionally in the evening and morning. It worsened in bed and was relieved through massage and acetaminophen/ibuprofen. The mother reported increased feet movement during such episodes. There were no inflammatory signs or complaints referred to the diaphysis, limitation of physical activity, lower limbs muscle hypertrophy, muscle weakness or sensory anomalies. The mother had similar complaints as a teenager. Laboratory testing showed ferritin below 50ng/mL (25ng/mL) and persistent increased CK (maximum 431U/L). Sickle cell disease, osteoid osteoma, Pompe, MacArdle and Fabry diseases were excluded after laboratory tests, bone scintigraphy and magnetic resonance imaging. He begun a 6-month iron supplementation, with an unsatisfactory response. A polysomnography (performed after iron supplementation) didn't detect periodic limb movements of sleep (PLMS). Gabapentin was started and successfully controlled the symptoms and CK level. Currently he is 9-years-old and is asymptomatic with normal CK under treatment with gabapentin.

**Case report 2:** A 14-year-old boy referred for insomnia since childhood. He reported difficulty in falling asleep, taking 1–3 hours, and a strong urge to move when in bed. He also mentioned nonrestorative sleep and inability to concentrate and staying still in school. Reported sleep duration was about 6 hours, with no nocturnal awakenings. He also suffered from migraine and asthma, treated with flunarizine and budesonide. The father also had insomnia. Physical examination, including neurological and musculoskeletal examination, was normal. Laboratory testing showed ferritin above 50ng/mL (57ng/mL) and increased CK (606U/L). He mentioned he had been exercising more than usual that day and complained about myalgia. He started treatment with gabapentin, with partial improvement of the symptoms, (leading to dose increase) and normalization of CK (maintaining low intensity physical activity).

**Discussion:** Mild CK elevation can be found in 20% of healthy individuals, and serum levels are strongly affected by race, sex and physical activity. When a mild CK elevation is detected, it is important to consider both physiological and pathological causes. In the first case, the diagnosis of RLS was hindered by atypical manifestations, which led to a broader investigation to exclude other causes of limb pain and CK elevation. CK elevation could be explained by black race in the first case and intense physical activity in the second case. However, elevated CK has also been described in cases of RLS, possibly related to excessive leg movement and muscular distress, which leads to the question whether elevated CK in the aforementioned cases is a coincidence or an association.

### Sleep Breathing Disorders

#### ABSOLUTE GAMMA POWER OF EEG AROUSAL IS MODULATED BY RESPIRATORY EVENT TYPE AND SEVERITY IN OSA

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**Introduction:** Obstructive sleep apnea (OSA) is a sleep disorder characterized by complete (apnea) or partial (hypopnea) obstructions of the upper airway during sleep. Many of these respiratory events are terminated by arousals from sleep, noticeable in the electroencephalogram (EEG). It remains unclear whether different respiratory events affect the EEG during arousals differently. As EEG gamma band (30–40 Hz) has been associated with wakefulness<sup>1</sup>, this study aimed to compare EEG gamma power between arousals caused by different respiratory events, and between sleep stages.

**Materials and Methods:** Power spectral densities were computed from EEGs recorded during Type I polysomnographies of 869 patients with clinically suspected OSA. Absolute EEG gamma power during respiratory arousals was compared between the type (obstructive apnea and hypopnea), and duration (short 10–20 s, moderate 20–30 s, and long >30 s) of the respiratory event causing the arousal. In addition, absolute gamma power was compared between groups based on whether the respiratory event was accompanied by a  $\geq 3\%$  blood oxygen desaturation. Gamma power of arousals was also investigated in different sleep stages (rapid eye movement REM, and non-REM stages N1, N2, and N3), by comparing the arousals to 3-second epochs of steady sleep in the corresponding stages.

**Results:** As opposed to steady sleep, where gamma power decreased towards deeper stages (i.e., from N1 towards N3), arousal gamma power was higher when the arousal occurred in deeper sleep. Gamma power was the lowest in REM stage both during steady sleep and arousals. Moreover, gamma power was significantly higher in arousals related to obstructive apneas compared to hypopneas. Gamma power was also higher related to longer obstructive apneas compared to shorter ones. However, this increase was significant only between short and long, and short and moderate duration groups, but not between moderate and long groups. Moreover, hypopnea duration was not related to arousal gamma power. Yet, arousal gamma power was significantly higher when the obstructive apnea or hypopnea was accompanied by a  $\geq 3\%$  desaturation.

**Conclusion:** Gamma power was higher when the arousal occurred in deeper sleep and when the related respiratory event was more severe. As EEG gamma activity could indicate a shift towards wakefulness<sup>1</sup>, these findings illustrate that the degree of sleep disturbance may vary depending on the type and severity of respiratory event. These results reinforce the importance of developing more comprehensive methods for the clinical assessment of OSA severity.

**Acknowledgements:** This work was supported by the European Union (Horizon 2020 programme 965417), the Academy of Finland (323536), NordForsk (NordSleep Project 90458) via Business Finland (5133/31/2018), the Research Committee of the Kuopio University Hospital Catchment Area for the State Research Funding (5041767, 5041794, 5041797, 5041804, 5041803), Finnish Cultural Foundation – North Savo Regional Fund, the Research Foundation of the Pulmonary Diseases, Päivikki and Sakari Sohlberg Foundation, Maud Kuistila Memorial Foundation, Foundation of the Finnish Anti-Tuberculosis Association, Tampere Tuberculosis Foundation, Seinäjoki Central Hospital, and the Competitive State Research Financing of Expert Responsibility Area of Tampere University Hospital (VTR3242, VTR3249, EVO2089).

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#### ACHIEVING REDUCED TREATMENT TIME FOR OBSTRUCTIVE SLEEP APNEA UTILIZING SURGERY FIRST APPROACH: A COMPARISON OF TRADITIONAL VERSUS NOVEL TECHNIQUES

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**Introduction:** The concept of surgery-first (SF) orthognathic surgery was first described in the early 2000s and was attractive due to its ability to eliminate lengthy pre-operative orthodontic treatment. While the approach requires meticulous virtual pre-surgical planning, it has significant potential for being the preferred approach for patients with obstructive sleep apnea (OSA) requiring maxillomandibular advancement (MMA). On average, the date of initial surgical evaluation to date of surgery

is 18–24 months, during which patients undergo extensive pre-surgical orthodontic treatment without addressing the underlying disease. Thus, a SF approach can reduce the burden of disease by providing immediate treatment to an active chronic disease and reduce total treatment time while maintaining excellent surgical results. The objective of this paper is to compare the safety and efficacy of SF approach with the conventional approach and to evaluate duration of time required for each.

**Methods/Materials:** This retrospective cohort study examined adult patients who presented to a single center for surgical evaluation of OSA from January 2017 - 2021. Inclusion criteria included patients undergoing MMA for treatment of OSA with concurrent orthodontic treatment. 41 patients were enrolled in the study, of which 21 underwent surgery-first (SF) and 20 underwent traditional orthodontic decompensation first. Virtual surgical planning was utilized for all patients. Patients in the SF cohort were treated by a single orthodontist to control for variability. Objective measures include pre and post operative AHI, ODI, and lowest oxygen saturations (LOS) obtained from polysomnography. The Epworth Sleepiness Scale (ESS), and Nasal Obstruction and Symptom Evaluation (NOSE) questionnaires were utilized to measure subjective outcomes. The duration of time from initial surgical consultation visit to date of surgery was recorded for each group respectively.

**Results:** 20 patients met inclusion criteria, of which 10 underwent SF approach and 10 underwent traditional orthodontic treatment followed by MMA. The average age of the SF cohort was  $39.7 \pm 6.35$  with average AHI decreasing from  $56.2 \pm 31.0$  to  $10.2 \pm 6.3$  ( $p=0.02$ ). The average age of the traditional cohort was  $34.8 \pm 12.2$  with AHI decreasing from  $52.7 \pm 29.5$  to  $13.8 \pm 9.6$  ( $p=0.01$ ). An independent t test assessing differences between the surgical outcome of SF vs traditional cohort (utilizing pre/post AHI), revealed  $p=0.67$ . The average duration between initial visit and date of surgery was  $8.16 \pm 2.6$  months for SF group and  $19.8 \pm 5.15$  for traditional group ( $p=0.0005$ ). No significant differences in complication rates between the two cohorts.

**Conclusions:** There is no difference between the surgical success rate of SF versus the traditional approach in terms of AHI reduction nor in the complication rates. There is however, a significant difference in the time between initial visit and date of surgery between the two cohorts. The results of this study reveal a significant advantage in the SF approach which can help reduce total treatment time and reduce the burden of disease for this patient population. While more research is needed to outline a standardized approach for SF treatment of OSA, it is a technique well worth perfecting and normalizing over the next decade.

**Acknowledgements:** Nil

#### A COMPREHENSIVE STRATEGY FOR IMPROVING NASAL OUTCOMES AFTER LARGE MAXILLOMANDIBULAR ADVANCEMENT FOR OBSTRUCTIVE SLEEP APNEA

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**Introduction:** Rate of corrective nasal surgery after maxillomandibular advancement (MMA) for obstructive sleep apnea (OSA) has been reported to be 18.7% for functional and aesthetic indications. The goal is to describe a comprehensive strategy to optimize nasal outcomes with MMA for OSA.

**Materials and Methods:** A retrospective review of patients undergoing MMA for OSA in a tertiary referral center was performed, with a comprehensive perioperative intervention to optimize nasal outcomes from January 2014 to February 2018. Outcomes included the Apnea–Hypopnea Index (AHI), oxygen saturation (SpO<sub>2</sub>) nadir, corrective nasal surgery needed after MMA, and Nasal Obstruction Symptom Evaluation (NOSE) scores.

**Results:** AHI after MMA showed significant reduction ( $34.65$ ,  $p < 0.001$ ), SpO<sub>2</sub> nadir increased ( $+6.08$ ,  $p < 0.001$ ), and NOSE scores decreased ( $5.96$ ,  $p < 0.001$ ). Corrective nasal surgery needed after MMA was reported in 6.5% (8 of 122) subjects at a mean of 8.5 months, ranging from 1 to 24.7 months. Six subjects underwent either septoplasty and/or valve stenosis repair, and two subjects underwent functional and aesthetic rhinoplasty.

**Conclusions:** A perioperative strategy was applied since 2014 that showed

effectiveness in reducing post-MMA corrective nasal surgery to 6.5%.

#### Acknowledgements:

#### A CURIOUS CASE OF REPETITIVE LOSS OF CONSCIOUSNESS

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**Introduction:** Emergency department (ED) professionals deal very frequently with patients with episodes of loss of consciousness, especially in neurological clinical practice, with seizures leading the list of suspected diagnosis. It is essential to characterize the episode and discriminate between differential diagnosis. For patients with higher risk for seizures it becomes even more difficult to confirm if an episode of loss of consciousness associated with involuntary limb movements is not of epileptic origin. Then we describe a representative case of a patient with the uncommon Wolfram syndrome.

**Clinical case:** Patient was a male, 23 years old, diagnosed with Wolfram syndrome type 1, with diabetes mellitus and insipidus, bilateral optic nerve atrophy, primary hypogonadism and cognitive handicap. He was admitted in ED with history of several episodes of loss of consciousness with lip cyanosis and involuntary limb movements, with spontaneous recovery after approximately 3 minutes. Diagnostic workup with blood analysis and electrocardiogram was normal and brain CT scan revealed brainstem and cerebellar atrophy. When the neurologist was asked to observe the patient with suspected seizures, another episode was registered. Sequentially, he presented absence of respiratory movements, lip and mucosal cyanosis, significant hypoxemia, loss of consciousness and short-lasting distal limb myoclonias, with complete recovery after 2 minutes. Shortly after this episode, he was studied with electroencephalogram, which was normal (without paroxysmal activity). Then study proceeded with polysomnography that registered frequent central and obstructive apnea. With mechanic noninvasive ventilation, the patient improved considerably.

**Conclusion:** Wolfram syndrome is a multisystemic progressive and genetic disease characterized for diabetes mellitus and insipidus, optic nerve atrophy, deafness and other neurological signs. It manifests early in life, progressing inevitably with severe bulbar dysfunction and respiratory failure, in course of brainstem atrophy. Even though seizures can be a feature of the disease, it more frequently gives rise to bulbar dysfunction and central and obstructive apnea. Clinicians must be aware of this to guarantee the best care and treatment of these patients, preventing further complications.

#### ADENOID FACIES AS A RISK FACTOR IN PEDIATRIC OBSTRUCTIVE SLEEP APNEA SYNDROME (OSAS)

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**Introduction:** The aim of this investigation is to evaluate the usefulness of identification of facial phenotype in children, as an easy and rapid screening tool assessing the risk of pediatric obstructive sleep apnea syndrome (OSAS).

**Materials and Methods:** Parents/guardians of 713 children, aged from 4 to 17 years old, completed a survey (Pediatric Sleep Questionnaire) to assess the risk of them having OSAS. 64 children who were found to be at risk of OSAS and 66 children as a control group, underwent physical examination which included identification of their facial phenotype – either adenoid, normal or adult facies.

**Results:** The risk of having pediatric OSAS was identified in 13,18% of the examined children. Adenoid facies phenotype was found to be present only in children at risk of OSAS. Among children without the risk of OSAS, mainly normal facial phenotype was identified. There was a statistically significant difference in the distribution of facial phenotypes between

every control and at-risk subgroup ( $\chi^2 = 31,36$ ;  $p < 0,001$ ).

**Conclusions:** Identification of adenoid facies in children should bring attention of a doctor to the possibility of a patient being at risk of OSAS and arrive at appropriate diagnostic and therapeutic decisions.

**Acknowledgements:** None

#### ADJUNCT PHARMACOTHERAPY AFTER UPPER AIRWAY SURGERY FOR OBSTRUCTIVE SLEEP APNEA: PRELIMINARY RESULTS OF A PARALLEL-GROUP, DOUBLE-BLIND, RANDOMIZED TRIAL.

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**Introduction:** Upper airway surgery is often recommended in patients with obstructive sleep apnea (OSA) who cannot tolerate or adhere to positive airway pressure therapy. However, response to surgery is variable, being determined by anatomical and physiological factors. Specifically, an unstable ventilatory control, i.e. elevated loop gain, is considered to be a negative predictor for surgery. Acetazolamide, a carbonic anhydrase inhibitor, stabilizes breathing and reduces loop gain by producing metabolic acidosis. This mechanism of action may prove beneficial in surgically treated patients with OSA.

**Materials and Methods:** We conducted a double-blind, parallel-group, randomized trial comparing acetazolamide with placebo in adults who underwent barbed reposition pharyngoplasty for moderate to severe OSA. Treatment with acetazolamide (250 mg twice a day) or placebo was initiated three weeks post-surgery for a period of 16 weeks. The reduction in apnea-hypopnea index (AHI), the primary outcome parameter, was determined by in-laboratory polysomnography. The Mann-Whitney U test was used for intergroup comparisons. All reported values are median (Q1–Q3) unless otherwise specified.

**Results:** This interim analysis included 11 participants, (9 [81.8 %] males; age 51.7 [44.1–57.5] years; body mass index 28.0 [26.0–30.3] kg/m<sup>2</sup>), of which 10 completed the trial. One patient with placebo dropped out due to general discomforts. The AHI was 22.6 (19.0–37.2) events/h at baseline and 9.1 (6.1–17.7) events/h at follow-up in the acetazolamide group ( $P = .02$ ) and 22.4 (16.5–32.7) events/h at baseline and 17.3 (9.0–29.6) events/h at follow-up in the placebo group ( $P = .13$ ). One patient with placebo developed predominant central sleep apnea after surgery. Acetazolamide caused a greater improvement in AHI than placebo (65.0% [49.7–73.1] vs. 23.7% [9.8 to 46.3];  $P = .04$ ). The oxygen desaturation index decreased by 48.7% (18.8–71.9) and 21.5% (-1.6 to 38.4) in the acetazolamide and placebo group, respectively ( $P = .17$ ). Four out of six participants were compliant to acetazolamide therapy; the two others discontinued the therapy near the end of the study due to side effects. The mean visual analogue scale for side effects was 4.0 in the acetazolamide group and 0.3 in the placebo group. The most common side effects were paresthesia ( $n = 2$ ), nausea ( $n = 2$ ) and nocturia ( $n = 2$ ).

**Conclusions:** Based on our preliminary data, adjunct therapy with acetazolamide may improve the outcome of velopharyngeal surgery for OSA. However, side effects may hamper long-term adherence.

**Acknowledgements:** None.

#### ALTERATIONS OF OCULAR SURFACE AND TEAR FILM IN PATIENTS WITH OBSTRUCTIVE SLEEP APNEA/HYPOPNEA SYNDROME

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**Introduction:** To investigate the alterations of ocular surface and tear film in patients with obstructive sleep apnea/hypopnea syndrome (OSA) and further compare the ocular surface parameters between different severities of OSA and normal control subjects.

**Materials and Methods:** Participants who had snoring and daytime

sleepiness consecutively underwent a full-night polysomnography to determine OSA occurrence and severity. Simple snores (with AHI less than 5/hr.) were as controls. All participants subsequently received Ocular Surface Disease Index questionnaire evaluation and ocular exams, including floppy eyelid syndrome (FES), Oculus Scan of tear meniscus height, tear film break-up time (TFBUT), and ocular surface redness, central corneal thickness and endothelial cell density, basic Schirmer test, and corneal fluorescein staining.

**Results:** A total of 181 participants were prospectively enrolled in the study. FES was found in 11.5% of the normal control group, 45.3% of the mild OSA group, 45.2% of the moderate OSA group, and 60.0% of the severe OSA group ( $p=0.0005$ ). There were significant differences in the first-TFBUT (T-TFBUT) ( $p<0.0001$ ), average-TFBUT (A-TFBUT) ( $p=0.0007$ ), and redness scores over the nasal bulbar ( $p=0.032$ ), temporal bulbar ( $p<0.0001$ ), nasal limbal ( $p=0.014$ ), and temporal limbal ( $p<0.0001$ ) areas among 4 groups. When the participants were divided into two groups: normal/mild OSA ( $AHI<15$ ), and moderate/severe OSA ( $AHI\geq 15$ ), we found the F-TFBUT and A-TFBUT were significantly shorter in the moderate/severe OSA group than in the normal/mild OSA group (both  $p<0.0001$ ). The redness scores over the temporal bulbar ( $p<0.0001$ ) and temporal limbal ( $p<0.0001$ ) areas were significantly different between normal/mild OSA and moderate/severe OSA groups. Furthermore, F-TFBUT ( $r=-0.282$ ,  $p=0.0004$ ) and A-TFBUT ( $r=-0.226$ ,  $p=0.0046$ ) inversely correlated with AHI. Nasal bulbar redness ( $r=0.225$ ,  $p=0.0049$ ), temporal bulbar redness ( $r=0.259$ ,  $p=0.0011$ ), nasal limbal redness ( $r=0.215$ ,  $p=0.0073$ ), and temporal limbal redness ( $r=0.202$ ,  $p=0.0117$ ) positively correlated with AHI.

**Conclusions:** OSA patients had higher occurrence of FES. The TFBUT was significantly shorter and the temporal conjunctival redness scores over bulbar and limbal areas were significantly higher in patients with moderate/severe OSA than normal/mild OSA group.

**Acknowledgements:** N/A.

#### A NOVEL PHYSIOLOGICAL-BASED MODEL TO PREDICT TREATMENT OUTCOMES IN CHILDREN WITH OBSTRUCTIVE SLEEP APNOEA

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**Introduction:** Although adenotonsillectomy (AT) is the first-line treatment of childhood obstructive sleep apnoea (OSA), the decision to treat is clinically challenging due to variable and currently unpredictable treatment efficacy. The possibility of spontaneous resolution with time as observed in a high proportion of children diagnosed with OSA in previous longitudinal studies and randomised controlled trials (RCTs) is also an important consideration. Recent studies have suggested that estimation of the four key endotypes that contribute to OSA pathophysiology (i.e. pharyngeal collapsibility, loop gain, arousal threshold, and pharyngeal muscle responsiveness) may help predict treatment responses to different OSA therapies in adults. This study aimed to develop a physiological-based model to predict treatment responses to adenotonsillectomy (AT) and watchful waiting (WW) in children with OSA.

**Methods:** Data from our recently completed RCT was used for prediction model development. The RCT involved a total of 104 children with moderate-to-severe OSA (obstructive apnoea hypopnoea index,  $OAIH\geq 3$ /hour), of whom 58 underwent AT and 46 did not receive any active treatment (WW). Standard sleep study parameters and clinical data at the baseline visit were used to predict the improvement/resolution of OSA defined by the  $OAIH$  at follow-up ( $OAIH<1$ /hour or  $<3$ /hour) with or without the change in  $OAIH$  following treatment ( $OAIH$  dropped by  $\geq 50\%$ ). Separate models were developed to predict the treatment responses to AT and WW. Eighty-five percent of the available data (49 and 39 participants from the AT and WW group, respectively) were used for machine learning training and 10-fold internal cross-validation. The remaining 15% was used for independent, blinded validation.

**Results:** In the 10-fold cross-validation, the accuracy of the AT and WW models to predict improvement/resolution of OSA ranged from 73% to 100% and from 62% to 100%, respectively, depending on the definition of

treatment success. Similarly, the performance of the AT and WW model obtained from the blinded validation was also satisfactory, with accuracies ranging from 33% to 78% and from 71% to 86%, respectively depending on the definition of treatment success.

**Conclusions:** While further validation in larger clinical datasets is needed, these findings highlight a new approach to help predict treatment outcomes of AT and WW for childhood OSA using readily available data collected from standard sleep study and clinical measurements. The prediction model is a potentially useful tool to identify who should be treated with AT and who should wait for spontaneous resolution.

**Acknowledgements:** We thank to the International Sleep Research Training Program (IS RTP) organised by World Sleep Society which has linked up Dr. C.T. Au (mentee) and Prof. D. Eckert (mentor) who initiated this study. The RCT involved in the study was supported by General Research Fund provided by Research Grants Council of the Hong Kong SAR, China (Grant number: CUHK 14110614).

#### A PROSPECTIVE RANDOMISED STUDY TO EVALUATE THE EFFICACY OF PROPOFOL-KETAMINE (KETOFOL ) AND DEXMEDETOMIDINE FOR PERFORMING DRUG INDUCED SLEEP ENDOSCOPY (DISE) IN PATIENTS OF OBSTRUCTIVE SLEEP APNEA

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**Introduction:** Drug- Induced Sleep Endoscopy (DISE) currently is the most acceptable method of identifying the exact site and severity of upper airway obstruction in real time and planning surgical intervention for OSA patients. The choice of sedative agent for conducting DISE is extremely crucial in OSA patients as there is a risk of exaggerating airway compromise. Our study is the first to use the combination of Ketamine and Propofol for conducting DISE in adult patients of OSA and has compared its efficacy with the current gold standard i.e. Dexmedetomidine.

**Materials and Methods:** The diagnosis and severity of OSA was made on the basis of clinical history, physical examination and overnight polysomnography. Subjects with mild and moderate OSA were included. DISE was performed in the Operation Theatre under Monitored Anaesthetic Care. Baseline HR, BP and SPO2 were recorded and monitored. Group PK received sedation via propofol and ketamine. Group D received sedation via dexmedetomidine. Time at which the drug infusion was started was noted. HR, ECG, SPO2, NIBP and BIS was recorded at every 5 minute after induction to assess the haemodynamic and respiratory stability of the patient. The endoscope was placed at different levels of the upper airway, to visualise the site of collapse in real time. The grading and the severity of the airway collapse was done using the VOTE classification. After the completion of the procedure, time taken for eye opening to verbal commands was noted.

**Results:** A total of 76 (53 males and 23 females) patients in the age group of 18-65years were included in this study. Statistical analysis was done using SPSS version 16. The time taken to complete the procedure was less with SPSS (10.7minutes) as compared to Dexmedetomidine(15.5minutes)( $P<0.001$ ). Intra-Operative Parameters noted include:

1. Heart Rate – Ketofol showed tachycardia and with dexmedetomidine bradycardia was observed. ( $P<0.001$ )
2. BP – No significant difference was noted when intra-operative SBP and DBP were compared to baseline SBP and DBP in both the groups.
3. SPO2-When compared to the baseline SPO2 values, desaturations were noted in both the groups, although this difference was not statistically significant.
4. Level of Upper airway obstruction- VOTE Classification- In both the groups, the most common site of obstruction was Velum followed by tongue base and finally Oropharyngeal lateral walls. Multiple sites of airway collapse was noticed in patients with severe OSA.
5. Recovery Time – Time to recover was significantly more with Ketofol (14.16 minutes) than with Dexmedetomidine(8.29minutes) ( $p<0.001$ ).
6. Adverse effects- No adverse effects were noticed in the intra-operative and recovery period.

**Conclusions:** Ketofol, when used as a sedative agent in adult patients of

OSA proved to be as efficacious as dexmedetomidine. With respect to the Heart Rate, it was noticed that dexmedetomidine caused bradycardia whereas normocardia was observed with Ketofol. Both the drugs maintained normotension. Both the drugs produced desaturations but the fall in SPO<sub>2</sub> was not severe and was more physiologically acceptable with dexmedetomidine than with ketofol. Therefore, both the drugs can be used safely for performing DISE.

**Acknowledgements:** TATA MOTORS HOSPITAL

#### A RANDOMIZED CONTROLLED TRIAL EXPLORING SAFETY AND TOLERABILITY OF SULTHIAME IN SLEEP APNEA

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**Introduction:** Obstructive sleep apnea (OSA) is highly prevalent. Current therapies are limited by insufficient efficacy, compliance or tolerability. An effective and well-tolerated pharmacological treatment in OSA is warranted. Carbonic anhydrase (CA) inhibition is known to ameliorate sleep disordered breathing. The current study was designed to explore safety and tolerability of the CA inhibitor sulthiame (STM) in patients with OSA. **Materials and Methods:** A four-week double-blind, randomized, placebo-controlled dose guiding trial in patients with moderate/severe OSA and not tolerating CPAP. STM was titrated to 200 and 400 mg during the first two weeks in the study and the dose was maintained thereafter. A conventional polysomnography recording was performed twice at baseline and at day 28 and 29, respectively. Recordings were scored in accordance with the American Academy of Sleep Medicine (AASM) rules. Vital signs including blood pressure were repeatedly monitored in association with visits to the study site. Samples for safety biochemistry and therapeutic monitoring of drug plasma concentration were obtained. The study was approved by the regional research ethics committee (Dnr: 045-18, 2018-02-07) and posted in the EU Clinical Trials Register (EudraCT N<sup>o</sup>: 2017-004767-13).

**Results:** Intermittent paresthesia was reported by 79, 67 and 18 % of patients receiving 400 mg (N=25), 200 mg (N=12) or placebo (N=22), respectively. Dyspnea was reported only in the 400 mg STM group (21 %). There were no serious adverse events. STM reduced the Apnea-Hypopnea Index (AHI) from 55.3 to 33.1 events/h (-41.0 %) in the 400 mg group and from 61.2 to 40.7 events/h (-32.1 %) after 200 mg (p<0.01, respectively). Corresponding placebo values were 53.8 and 50.9 events/h (-5.4 %). The AHI reduction threshold of ≥ 50 % was reached in 40 % after 400 mg, 25 % after 200 mg and 5 % following placebo. Mean overnight oxygen saturation improved by 1.1 % after 400 mg and 200 mg (p<0.01 respectively). Measures of daytime function and vigilance appeared to improve in patients receiving 200 mg or 400 mg STM and with > 2 reported side effects in this short-term study.

**Conclusions:** STM showed a satisfactory safety profile in moderate to severe OSA. STM reduced OSA, on average, by more than 20 events/h, one of the strongest reductions reported in a drug trial in OSA. Larger scale clinical studies of STM in OSA are justified.

**Acknowledgements:**

#### A REAL-WORLD STUDY ASSESSING THE RELATIONSHIP BETWEEN POSITIVE AIRWAY PRESSURE TREATMENT, EXCESSIVE DAYTIME SLEEPINESS, AND PATIENT SATISFACTION IN OBSTRUCTIVE SLEEP APNOEA

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**Introduction:** Excessive daytime sleepiness (EDS) persists in some positive airway pressure (PAP)-treated patients with obstructive sleep apnoea (OSA). This study examined prevalence and severity of EDS in a real-world

population with OSA to understand how EDS, PAP adherence, and patient satisfaction with care relate.

**Materials and Methods:** US residents (aged ≥18 years, self-reported clinician diagnosis of OSA [from 1/1/2015 to 31/3/2020]) completed a survey in Evidation Health's Achievement app assessing the Epworth Sleepiness Scale (ESS), PAP usage, and satisfaction with healthcare providers (HCPs) and overall OSA care. Patients were categorised by self-reported PAP use (nonuse [no PAP use], nonadherent [ $<4$  h/night or  $<5$  d/wk], intermediate [ $4-6$  h/night,  $\geq 5$  d/wk], or highly adherent [ $\geq 6$  h/night,  $\geq 5$  d/wk]); PAP-adherent refers to the intermediate and highly adherent groups). ESS  $>10$  defined EDS. A linear model assessed relationship between PAP use and ESS score; a logistic regression model assessed the impact of PAP use and EDS on satisfaction with HCPs and overall OSA care. P-values are uncontrolled for multiplicity (nominal).

**Results:** In total, 2289 participants completed the survey (50.3% female; 82.5% White; mean±standard deviation [SD] age, 44.8±11.1 years; body mass index, 35.4±8.7 kg/m<sup>2</sup>). PAP use was: nonuse (n=700), nonadherent (n=153), or adherent (n=1436; intermediate n=225, high n=1211). Overall, 42.5% had EDS (ESS $>10$ ); mean (95% confidence interval [CI]) ESS scores were 14.1 (13.9, 14.3) in those with EDS and 6.7 (6.5, 6.8) in those without. The proportion (95% CI) with EDS per group were: nonuse (47% [43.7, 51.1]), nonadherent (52% [44.4, 60.2]), intermediate (53% [46.4, 59.4]), and highly adherent (36% [33.7, 39.1]). In a linear model (PAP users; n=1589), an additional h/night of PAP use was associated with lower ESS scores ( $\beta=-0.28$ ; 95% CI=-0.40, -0.16; P<0.001). Overall, 72% were satisfied with HCPs and 65% with OSA care. Logistic regression (PAP users; n=1589) identified a positive association between PAP adherence (non-adherence=0, adherence=1) and satisfaction with HCPs (adjusted odds ratio [adjOR]=2.37; 95% CI=1.64, 3.43; P<0.001) and satisfaction with overall OSA care (adjOR=2.91; 95% CI=2.03, 4.17; P<0.001). EDS was associated with lower satisfaction with HCPs (adjOR=0.62; 95% CI=0.48, 0.80; P<0.001) and overall OSA care (adjOR=0.50; 95% CI=0.39, 0.64; P<0.001).

**Conclusions:** In this real-world study, ESS scores decreased as PAP use increased, but EDS remained highly prevalent even among highly adherent patients. Adherence was associated with greater patient satisfaction with HCPs and overall care, whereas persistent EDS was associated with lower patient satisfaction with HCPs and overall OSA care. Strategies to improve patient satisfaction with OSA care should focus equally on PAP adherence and monitoring and resolution of residual EDS.

**Acknowledgements:** This study was supported by Jazz Pharmaceuticals.

#### ARTERIAL BICARBONATE IS ASSOCIATED WITH HYPOXIC BURDEN AND HYPERTENSION IN OBSTRUCTIVE SLEEP APNEA - THE ESADA COHORT

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**Introduction:** Renal bicarbonate retention acts as an important compensatory mechanism for obstructive sleep apnea (OSA) patients to maintain acid-base balance. We investigated the association between arterial standard bicarbonate ([HCO<sub>3</sub><sup>-</sup>]) and nocturnal hypoxia as well as comorbid hypertension in patients with suspected OSA.

**Materials and Methods:** A retrospective analysis of 3329 patients in the European Sleep Apnea Database (ESADA) was performed. Arterial blood gas analysis and lung function test were performed in conjunction with polysomnographic sleep studies. The 4% oxygen desaturation index (ODI), mean and minimum oxygen saturation (SpO<sub>2</sub>), and percentage of time with SpO<sub>2</sub> below 90% (T90%) were used to reflect nocturnal hypoxic burden. Arterial hypertension was defined as a physician diagnosis of hypertension with ongoing antihypertensive medication.

**Results:** Mean [HCO<sub>3</sub><sup>-</sup>] was 24.0±2.5 mmol/L in the cohort. ODI, T90% increased whereas mean and minimum SpO<sub>2</sub> decreased across [HCO<sub>3</sub><sup>-</sup>] tertiles (ANOVA, p=0.030, <0.001, <0.001, and <0.001, respectively). [HCO<sub>3</sub><sup>-</sup>] did not differ across OSA severities (p=0.41). [HCO<sub>3</sub><sup>-</sup>] was independently associated with ODI, mean SpO<sub>2</sub>, minimum SpO<sub>2</sub>, and T90% after adjusting for confounders (β value [95%CI]: 1.21 [0.88 - 1.54], -0.16 [-0.20 - -0.11], -0.51 [-0.64 - -0.37], 1.76 [1.48 - 2.04], respectively, all p<0.001). 1 mmol/L elevation of [HCO<sub>3</sub><sup>-</sup>] was associated with a 4% increased risk of arterial hypertension (OR: 1.04 [1.00 - 1.08], p=0.038).

**Conclusions:** We identified an independent association between [HCO<sub>3</sub><sup>-</sup>] and nocturnal hypoxic burden as well as comorbid hypertension in OSA patients. Future studies are needed to determine if increased bicarbonate can be used as a novel pathophysiological trait in OSA phenotyping.

**Acknowledgements:** The ESADA network has received support from the European Union COST action B26 (2005–2009) and the European Respiratory Society funded Clinical Research Collaboration (CRC; 2015–2020). Unrestricted seeding grants from the ResMed Foundation and the Philips Respiration Foundation for establishment of the database are gratefully acknowledged. The ESADA has a scientific collaboration with Bayer AG. Nonfinancial support was provided by the European Sleep Research Society and the European Respiratory Society in terms of logistics for communication, meetings and data presentations for the ESADA collaborators. The current study was supported by the Swedish Heart and Lung Foundation (project 20180585) and partially supported by MIAI @ Grenoble Alpes, (ANR-19-P3IA-0003).

#### ASSESSMENT OF PLEURAL PRESSURES DURING SLEEP IN MARFAN SYNDROME

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**Introduction:** Patients with Marfan syndrome (MFS) have a high risk for aortic aneurysms. They are also susceptible to sleep-disordered breathing that may expose them to highly negative intrathoracic pressures known to increase aortic transmural pressure which may accelerate aortic dilatation. We hypothesize that sleep causes highly negative intrathoracic pressure in snoring patients with MFS, even during periods without overt apneas/hypopneas. Our objective was to quantify overnight inspiratory intrathoracic pressure changes during sleep in snoring patients with MFS, and the therapeutic effect of continuous positive airway pressure (CPAP).

**Materials and methods:** We used a questionnaire to identify self-reported snoring patients with MFS. In these patients, we monitored intrathoracic pressure using esophageal pressure (Pes) during overnight baseline and CPAP sleep studies. We defined a peak inspiratory Pes (Pes<sub>peak-insp</sub>) < -5 cmH<sub>2</sub>O as greater than normal, and examined the distribution of Pes<sub>peak-insp</sub> during baseline and CPAP studies.

**Results:** In our sample of 23 MFS snorers, we found that 70% of sleep breaths exhibited Pes<sub>peak-insp</sub> < -5 cmH<sub>2</sub>O, with apneas/hypopneas accounting for only 12%, suggesting prevalent stable flow-limited breathing and snoring. In a subset (n=12) with Pes monitoring during CPAP night, CPAP lowered the mean proportion of breaths with Pes<sub>peak-insp</sub> < -5 cmH<sub>2</sub>O from 83.7±14.9% to 3.6±3.0% (p<0.001).

**Conclusions:** The sleep state in MFS revealed prolonged exposure to exaggerated negative inspiratory Pes, which was reversible with CPAP. Since negative intrathoracic pressure can contribute to thoracic aortic stress and aortic dilatation, snoring may be a reversible risk factor for progression of aortic pathology in MFS.

**Acknowledgement:** We acknowledge the Johns Hopkins Vascular Connective Tissue Disorders Clinic and the Marfan Foundation for their support and providing access for participant recruitment.

#### ASSESSMENT OF UPPER AIRWAY COLLAPSE IN OBSTRUCTIVE SLEEP APNEA - COMPUTED TOMOGRAPHY VERSUS DRUG INDUCED SLEEP ENDOSCOPY - PILOT STUDY

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**Introduction:** Anatomic, mechanical, and neuromuscular factors play an important role in the pathophysiology of obstructive sleep apnea (OSA). The medical and/or surgical treatment are ideally directed to the structures with the greatest narrowing. Two exams are available to identify these structures: drug induced sleep endoscopy (DISE) and neck and sinuses computed tomography (CT). The aim of this pilot study was to test and identify possible relations between the results of these exams.

**Materials and Methods:** This study was carried out with 5 patients (all male; 40.6±10.8 years; body mass index 25.5 ± 2 kg/m<sup>2</sup>; apnea-hypopnea index (AHI) of 22.2±8.31 /h) with OSA, diagnosed with a home sleep polygraphic level II study who underwent concomitant DISE and neck CT to assess the therapeutic decisions on the presence and level(s) of upper airway collapse at Hospital CUF Tejo. DISE and CT findings were characterized according to the VOTE classification. This pilot study was carried out in accordance with ethical and legal principles, in particular with recommendations of the Declaration of Helsinki. According to the institutional guidelines of the ethical committee, all patients signed an informed consent form.

**Results:** 2 patients had multilevel collapse and 3 patients in a single location of the upper airway, in both exams. The most frequent location of collapse was the velum (80%) and the least frequent were the epiglottis and the tongue base, both in DISE and Neck CT. In DISE, the upper airways showed a greater degree of collapse when compared to neck CT (complete vs. partial), however the locations of collapse were identical.

**Conclusions:** In this study, no differences were observed between DISE and neck CT in relation to upper airway collapse locations, however the degrees of collapse were more accentuated in DISE. This can be explained due to the drug used in the DISE (Propofol).

**Acknowledgements:** We would like to acknowledge Dr. Sérgio Cardoso (Radiologist, CUF Tejo Hospital), Dr. Teresa Cardoso (anesthesiologist, CUF Tejo hospital) and all the CUF Tejo hospital ENT operating room nurse team.

#### ASSOCIATION BETWEEN THE SUBJECTIVE SYMPTOMS OF OBSTRUCTIVE SLEEP APNEA AND VARIOUS POLYSOMNOGRAPHIC PARAMETERS

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**Introduction:** Obstructive sleep apnea (OSA) is a common sleep disorder characterized by recurrent episodes of upper airway collapse during sleep, causing intermittent hypoxemia and sleep fragmentation leading to unrefreshing sleep and excessive daytime sleepiness (EDS). Although EDS is a commonly reported symptom of OSA, it has a weak correlation with Apnea-Hypopnea Index and OSA severity. Hence, in this study we have attempted to find the association of symptoms of OSA with polysomnographic indices other than the conventionally used Apnea-Hypopnea Index (AHI) and Respiratory Distress Index (RDI).

**Materials and Methods:** All adult subjects diagnosed with OSA on Level 1 Polysomnography over the last 4 years (2017–2021) were included in this retrospective record analysis after Ethical Committee approval. Clinical and polysomnographic data were anonymized and compiled. Association between symptoms (snoring, EDS, witnessed apneas) and PSG parameters (T90-% of time spent at <90% oxygen saturation, AHI, RDI, REM (Rapid eye movement) and Supine AHI) was analyzed using IBM SPSS Software 25.0. As data collection is ongoing, interim results of analysis of 49 patients is

being presented here.

**Results:** Forty-nine polysomnographically proven OSA subjects were included in this retrospective observational study. Mean age of included patients was  $50.67 \pm 12.88$  with male preponderance ( $n=33$ , 67.3%). Snoring was the most reported symptom (93.9 %) with 64.5% of the snorers being men. EDS was experienced by 63.3% of subjects while 55.1% reported witnessed apneas. Epworth sleepiness scale (ESS) score was  $\geq 10$  in 19 (38.6%).

On PSG, 12 (24.5%) patients had mild OSA, 10 (20.4%) had moderate and 27 (55.1%) had severe OSA. On analysis of the association between symptoms and PSG indices, it was found that while ESS score  $\geq 10$  was not significantly associated with AHI, there was a statistically significant association between ESS score and REM AHI ( $p=0.041$ ), Supine AHI ( $p=0.028$ ), REM RDI ( $p=0.030$ ) and Supine RDI ( $p=0.027$ ).

Out of the 46 snorers 56.5% had severe OSA, 23.9% had mild OSA and 19.6% had moderate OSA but there was no significant association between snoring and OSA severity. However, there was a significant association between snoring and T90 as % of TST (Total sleep time) ( $p=0.000$ ).

Out of the 27 subjects who reported witnessed apneas, 59.3% were diagnosed with severe OSA, 14.8% with moderate OSA and 25.9% with mild OSA. Witnessed apneas also showed statistically significant association with T90 as % of TST ( $p=0.028$ ).

**Conclusions:** This study has reiterated the fact AHI cannot be used as the sole PSG indicator of OSA and exploring other PSG parameters related to desaturation, sleep architecture positional and sleep stage related events is essential for studying the association of clinical presentation with PSG parameters as well as for better understanding of systemic consequences of OSA.

Besides, mining the rich physiological data available in the overnight PSG recording can help in the better understanding of pathophysiological consequences and aid in customized management of OSA.

**Acknowledgement:** Sleep clinic, St. John's National Academy of Health Sciences, Bengaluru

**Keywords:** Obstructive sleep apnoea, ESS, T90%, AHI, RDI

## A SYSTEMATIC REVIEW ON ADHERENCE TO CONTINUOUS POSITIVE AIRWAY PRESSURE (CPAP) TREATMENT FOR OBSTRUCTIVE SLEEP APNOEA (OSA) IN INDIVIDUALS WITH MILD COGNITIVE IMPAIRMENT AND ALZHEIMER'S DISEASE DEMENTIA

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**Introduction:** Obstructive sleep apnoea (OSA) is a sleep disorder involving complete or partial collapse of the airway causing breathing to stop and start during sleep. The prevalence of OSA in people with Alzheimer's disease (AD) and mild cognitive impairment (MCI) has been reported from 42% to 91% and 11% to 71% respectively. OSA is most commonly treated with continuous positive airway pressure (CPAP). Exploratory studies have suggested that CPAP treatment for OSA can slow cognitive deterioration in patients with AD and improve psychomotor/cognitive processing speed in MCI patients. However, long-term, well-powered efficacy trials are required to understand if OSA treatment in MCI/AD could slow decline. To design a trial, we need to understand adherence to CPAP and this is currently unclear. In this review we investigate CPAP adherence amongst individuals with OSA and AD or MCI.

**Materials and Methods:** Electronic searches were performed on Embase, MEDLINE, Scopus, British Nursing Index, PsycInfo, CINAHL, EMCARE and AMED. These databases were searched for studies including individuals with either AD dementia or MCI co-morbid with OSA. 1456 studies were identified in the search. Following screening of titles/abstracts and full texts completed by a group of reviewers, 6 independent studies and 3 secondary analyses were included in the review. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed, and the protocol was registered on PROSPERO (CRD42021292782).

**Results:** Three of the studies included are secondary analyses of two larger trials which are included in the review; additional information was used from these secondary analyses, but no data was repeated. There were 288 participants in the studies with a mean age of 74.2 years and, of the studies which recorded BMI, a mean BMI of 28.3. Adherence was defined as  $> 4$  hours of CPAP use overnight.

Differences in reporting methods made synthesis of the results challenging; some papers reported binary adherence outcomes (the number of individuals adherent vs. non-adherent) and others reported adherence using the mean number of hours of CPAP usage. In the studies with binary adherence outcomes, around half of participants (56% of AD patients,  $N = 39$  and 47% of MCI patients,  $N = 158$ ) were adherent to CPAP. Two studies ( $N = 91$  patients) reported mean averages of CPAP adherence per night as 4.9 to 6.4 hours. One of these studies ( $N = 39$  patients) also recorded a range of 0.37 to 8.34 hours of CPAP adherence per night.

**Conclusions:** CPAP adherence in AD patients and MCI patients seems to fit within the range seen in CPAP adherence in individuals with OSA and no MCI/AD, which have previously reported adherence ranging from 33% to 64%. These data will help with planning of interventional studies of CPAP in MCI and AD dementia.

**Acknowledgements:** Thanks to Sarah Rudd at the North Bristol NHS Trust Library for conducting the search.

## AUTOMATIC DETECTION OF OBSTRUCTIVE APNEA ON AN INDIVIDUAL BREATH BASIS

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**Introduction:** The current literature on the automatic detection of respiratory events is performed largely on fixed-length signal segments. This rigid signal segmentation effectively ignores the physiology that the signal is measuring. We propose that the respiratory system can be more effectively examined when the signal segments capture the respiratory cycle more closely, and we demonstrate this by training machine learning classifiers to classify breaths as either apneic or non-apneic.

**Materials and Methods:** Using signal segments containing individual breaths, a set of features were extracted from the airflow, thorax, and abdomen signals.

The features were then evaluated for their ability to separate apneic from non-apneic breaths, and the feature list was narrowed down to 5 features. The resulting feature-set was then used to train a collection of different machine learning models to classify breaths as either non-apneic or apneic.

The data used for this work came from the VSN-14-080 dataset. The dataset contained 31 polysomnographies from participants ranging from healthy breathing to snoring and obstructive sleep apnea. Of the participants, 13 were female and 18 were male. The mean age of the subjects was 47.1, in the range of 20 - 69 years, and the range of body-mass-indexes was 21.6 - 49.3 kg/m<sup>2</sup> (with the mean BMI of 29.9 kg/m<sup>2</sup>). The range of apnea-hypopnea indexes (AHI) was 0.0 to 34.8 h<sup>-1</sup>, with a mean of 9.3h<sup>-1</sup>.

**Results:** The different classifiers achieved variable performance, ranging from 75% to 95% accuracy. The highest accuracy of 95% was achieved by a pair of hidden Markov models, while a convolutional neural network achieved an accuracy of 85%, a long short-term memory model achieved an accuracy of 83%, and a deep neural network achieved an accuracy of 83%.

**Conclusions:** The detection of respiratory events (apneas and hypopneas) is possible on an individual breath basis with high accuracy. We present an algorithm that can detect the presence of apnea using a very limited set of non-invasive respiratory signals in individual breaths.

Our results also indicated that approaches that model the change in features over time have a greater chance to achieve better results than those that model only whole breaths.

**Acknowledgments:** This work was supported by Nox Medical, Íslensker erfðagreining (deCODE Genetics), and Rannís (Icelandic Research Fund Rannís grant #175256-0611)

## CAN OXYGEN DESATURATION MEASURED BY WEARABLE OPTICAL SENSOR AT THE ARM BE USED TO MEASURE OBSTRUCTIVE SLEEP APNEA?

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**Introduction:** Obstructive sleep apnea (OSA) is the most prevalent respiratory sleep disorder and continuous positive airways pressure (CPAP) is the most effective treatment. However, most patients with suspected OSA remain undiagnosed due to the lack of sleep laboratories or the high cost of in-lab polysomnography, and poor adherence to CPAP is also a significant limiting factor in OSA treatment. Wearable sleep trackers like smartwatches and armbands are booming, creating a hope for cost-efficient at-home OSA diagnosis and assessment of CPAP treatment effectiveness. However, such products are still not available. The major challenge is probably to detect sleep hypopnea defined by  $\geq 30\%$  drop in breathing and an at least 3% drop in peripheral capillary oxygen saturation (SpO<sub>2</sub>) measured by fingertip pulse oximetry. Whether the measures of oxygen desaturation (OD) at the fingertip and at the arm or wrist are identical, is essentially unknown. We aim to compare event-by-event arm OD (arm\_OD) with fingertip OD (finger\_OD) in sleep hypopneas during both naïve sleep and CPAP titration.

**Materials and Methods:** Thirty OSA patients underwent 1-h baseline sleep without CPAP followed by stepwise increments of 1 cmH<sub>2</sub>O CPAP pressure per hour starting from 5 to 8 cmH<sub>2</sub>O during all-night in-lab video-polysomnography. Arm\_OD of the left biceps muscle and finger\_OD of the left index fingertip were simultaneously measured by frequency-domain multi-distance near-infrared spectroscopy and video-polysomnography photoplethysmography, respectively. Bland-Altman plots were used to illustrate the agreements between arm\_OD and finger\_OD during baseline sleep and under CPAP. Linear mixed-effects model (LMM) with a random intercept by patients was used to predict the arm\_OD and finger\_OD caused by the respiratory events, respectively. Explanatory variables were demographic variables, types of respiratory events, durations of event, sleep stages, mean HR during the events, per-hour AHI under each pressure, and CPAP pressures. Stepwise regression using backward elimination was performed to automatically select the best predictors.

**Results:** In total, 534 obstructive apneas and 2185 hypopneas were recorded. The mean difference between finger\_OD and arm\_OD was 2.86% [95% confidence interval (CI) 2.67%–3.06%] and the 95% limits of agreement (LoA) were (–2.27%, 8.00%) during baseline sleep. These values were 1.83% (95% CI 1.72%–1.94%) and (–2.54%, 6.19%) during CPAP titration. Using the standard criterion of at least 3% saturation drop, arm\_OD only recognized 16.32% (109/668) and 14.90% (226/1517) of hypopneas at baseline and during CPAP, respectively. LMM suggested that CPAP pressure was only a significant predictor associated with changes in finger\_OD (P-value < 0.0001) but not in arm\_OD.

**Conclusions:** Arm\_OD is 2% to 3% lower than standard finger\_OD in sleep hypopnea, probably because the measured arm\_OD originates physiologically from arterioles, venules, and capillaries; thus, the venous blood adversely affects its value. Our findings demonstrate that the standard criterion of  $\geq 3\%$  OD drop at the arm is not suitable to define hypopnea because it could provide large false-negative results in diagnosing OSA. Arm\_OD measured by near-infrared optical sensors may not be a suitable indicator of the effectiveness of CPAP titration either.

**Acknowledgements:** This work was supported by Clinic Barmelweid Scientific Foundation and the Swiss Lung Association (No. 2014–22).

## CARDIAC ARRHYTHMIAS IN PATIENTS WITH COMORBID CONDITIONS AND OBSTRUCTIVE SLEEP APNEA SYNDROME ACCORDING TO TYPE 3 PORTABLE MONITOR

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**Introduction:** Portable monitors of type 3 register at least four channels. 12-lead ECG recording allows for a complete analysis of cardiac arrhythmias, including the differentiation of ventricular and atrial tachycardia, a full analysis of the P wave, PR (PQ) interval and other issues. If the patient

did not indicate information about the onset of sleep in his report, then the analysis of the actigram data and body position helps to determine the period of sleep (or rest). The aim of this study was to analyze the frequency and circadian distribution of supraventricular and ventricular arrhythmias, sinoatrial (SA) and atrioventricular (AV) blockades in patients with moderate and severe obstructive sleep apnea syndrome (OSAS).

**Materials and Methods:** Observational study. 370 patients (men) with OSAS (apnea-hypopnea index 15 and more) aged 25–75 years (mean age 46±7.9 years). Diagnosis of OSAS was performed according to clinical data and the results of a portable 24-hour monitor ‘Kardiotekhnika-07’ (Inkart, St. Petersburg, Russia). We recorded: electrocardiogram (12 leads), reopneumogram (2 leads from the upper and lower parts of the chest), aktigram, as well as during sleep blood oxygen saturation, oronasal airflow and sound phenomenon during breathing. The duration of sleep was determined from the set of data dynamics: actigrams, respiratory pattern, 24-hour heart rate trend. Automatic detection of apnea and hypopnea was supplemented by a manual analysis according to the criteria of AASM (2012). Patients with a permanent form of atrial fibrillation were not included.

**Results:** Clinical characteristics of patients: snore and arterial hypertension (100%), abdominal obesity (90%), dyslipidemia (70%), hypertriglyceridemia (8%), hyperuricemia (10%), stable angina pectoris and myocardial infarction in the past (40%), chronic obstructive pulmonary disease (10%), diabetes mellitus (6%), chronic heart failure I (36%), II (56%) and III (8%) functional class (NYHA). Ventricular extrasystole (VE) was registered in 60% (n=222) patients, with a frequency of >10/h - in 39% cases. The circadian distribution VE is as follows: mixed type 49%, over night 26%, daytime 25%. The following grades were determined (Ryan, 1975): I (51.5%), II (5.4%), III (19%), IVA (11%), IVB (7.2%). Unstable paroxysms of monomorphic ventricular tachycardia were observed in 5.9% (n=13) patients with VE. Supraventricular ectopic (SE) activity (extrasystole and tachycardia paroxysms) was registered in 89% (n=330). The frequency of single SE exceeded the value of 30/h in a relatively smaller number of patients (n=48; 14.5%). The circadian distribution SE is as follows: daytime 50%, over night 29%, mixed type 21%. SA blockade 2-nd degree with pauses duration from 1500 to 3000 ms was registered in 7.3%; arrest of the sinus node - from 3000 to 7035 ms in 1.1% of patients. AV blockade 2-nd degree Mobitz 1 was registered in 6.5%; Mobitz 2 - 0.54%; fixed 2:1 - 0.27%. In all cases of SA and AV blockades, the pauses occurred during sleep and were registered in the apnea phase.

**Conclusions:** The portable 24-hour monitor makes it possible to diagnose cardiac arrhythmias associated with disorders of breathing regulation during sleep in the usual conditions for patients.

**Acknowledgements:** Nil.

## CARDIORESPIRATORY RESPONSE TO TRANSCUTANEOUS ELECTRICAL STIMULATION IN HEALTHY VOLUNTEERS

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**Introduction:** Electrical stimulation has been explored in the context of non-CPAP therapy of patients with Obstructive Sleep Apnoea (OSA). Hypoglossal nerve stimulation (HNS) and, more recently, transcutaneous electrical stimulation (TESLA) have been used in clinical trials and established in clinical practice in some healthcare systems. Transcutaneous electrical stimulation of the submental area may potentially affect chemo- and baroreceptor sensitivity in human subjects. It is important to understand the short-term consequences of such methods on cardiorespiratory function. We sought to test the baro- and chemoreceptor response to electrical stimulation while seated, supine, and head-down-tilt (HDT) under hypercapnic and hypoxic conditions.

**Method and Subjects:** Healthy adult volunteers were recruited into an interventional, physiological cohort study. The study was approved by

King's College London ethics committee (RESCM-20/21-8487), and written, informed consent obtained. Subjects attended for a baseline study and a follow up visit at least one week later during which TESLA (Premier Combo Plus, the TENS+ Company Lets, Stockport, UK) was applied using two 4×4 cm patches (Med-Fit Plus Ltd, Stockport, UK). Subjects breathed room air, hypoxic (FiO<sub>2</sub> 12%), or hypercapnic (FiCO<sub>2</sub> 5%) gas mixtures in random order in seated, supine, and HDT (50°) position. Subjects were studied under each gas condition for 5 mins seated and supine, and for 10 mins in HDT. We measured respiratory (respiratory rate, tidal volume, airflow/minute ventilation, oxygen saturation, end-tidal CO<sub>2</sub>/O<sub>2</sub> concentration) and cardiovascular (heart rate, mean/systolic/diastolic blood pressure, ECG) parameters. Blood pressure was measured beat-by-beat using a Finapres device (Ohmeda 2300, BOC Health Care, Crawley, Sussex UK). Submental electrical stimulation (TESLA) was delivered individually titrated to skin sensation 8(1) mA, with a frequency of 30Hz, pulse width of 250µs, and bipolar current.

**Results:** 10 healthy and young volunteers were studied (age 28 (12.29) years, 6 male: 4 female, body mass index, BMI 23.70 (1.6) kg/m<sup>2</sup>, neck circumference 38 (2.1) cm, waist: hip ratio 0.87 (0.06) a.u.), all subjects completed the two visits. During electrical stimulation, minute ventilation increased significantly when on room air when seated ( $\Delta+2.0$  (1.3) L/min,  $p=0.006$ ) and with hypercapnoea in all postures (seated  $\Delta+2.8$  (2.2) L/min,  $p=0.018$ ; supine  $\Delta+3.7$  (3.1) L/min,  $p=0.022$ ; HDT  $\Delta+2.8$  (2.6) L/min,  $p=0.041$ ) compared to baseline. The increase in minute ventilation during electrical stimulation was due to increases in tidal volume and respiratory rate. The cardiovascular response indicated a significant decrease in the mean blood pressure with electrical stimulation in supine and HDT posture when hypercapnia (supine  $\Delta-11.3$  (11.1),  $p=0.047$ ; HDT  $\Delta-15.6$  (15.2),  $p=0.045$ ), and hypoxic (supine  $\Delta-18.4$  (10.4),  $p=0.003$ ; HDT  $\Delta-20.2$  (12.2),  $p=0.004$ ). The heart rate did not significantly change with electrical stimulation, independent of any posture. No participant reported any adverse events due to electrical stimulation, or required electrical stimulation to be halted.

**Conclusion:** These data suggest that TESLA sensitises the chemo- and baroreceptor response in normal healthy volunteers resulting in increased neural respiratory drive and minute ventilation during hypercapnoea, and decreased levels of blood pressure, particularly during exposure to CO<sub>2</sub> and hypoxia in supine and HDT position.

#### CENTRAL SLEEP APNEA IN A TREATMENT-RESISTANT MIGRAINE PATIENT: A CASE REPORT

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**Introduction:** Patients with migraine who suffer from sleep apnea, whether obstructive or central, might lead to treatment-resistant headaches. In this study we have reported a 42-year-old man with a confirmed treatment-resistant migraine headaches and hemiplegic attacks, who was referred to our sleep clinic for evaluation of sleep breathing problems.

**Materials and Methods, results:** The patient had recurrent attacks of migraine headaches with hemiplegic attacks. The patient had headache in the past 15 years that based on ICHD-3 criteria classified as hemiplegic migraine. The severity and recurrences of headache and hemiplegic attacks gradually increased for 1 year, before he referred to our sleep clinic that led to several hospital admissions. He had been evaluated for other causes of headache; it seems that other headache causes have been ruled out. Treatment with medication wasn't effective to abolish symptoms. He had a history of occasional snoring and his wife had witnessed multiple episodes of apnea and frequent awakening by feeling suffocation at sleep. The patient abused methadone since 2 years ago. Based on the findings in polysomnography, the patient was diagnosed with central sleep apneas. After titration, bilevel positive airway pressure- spontaneous timed mode (BiPAP-ST) was prescribed for the patient. In one year of using BiPAP-ST the central apneas events were controlled, while the frequency of migraine headache decreased remarkably to one attack per month and the hemiplegic attacks resolved without any other change in his medical treatment

or methadone use.

**Conclusions:** It is important to screen high-risk patients for possible sleep disorders such as apnea, especially in treatment resistant migraine cases. Also, we should assess analgesics or opioids abuses and a complete history for other risk factors of central sleep apnea.

**Acknowledgements:** All authors need to thank the Sleep Sciences Department of Isfahan University of Medical Sciences Pediatrics Clinic.

#### CHANGES IN TONGUE MORPHOLOGY PREDICT RESPONSES IN PHARYNGEAL PATENCY TO SELECTIVE HYPOGLOSSAL NERVE STIMULATION

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**Introduction:** Obstructive sleep apnea (OSA) is a prevalent disorder characterized by recurrent upper airway (UA) obstruction. Reductions in genioglossus (GG) muscle tone, the main UA dilator, play a critical role in the pathogenesis. Nevertheless, several lingual muscles work in concert to stabilize tongue shape and position and maintain UA patency, leading us to hypothesize that responses in tongue morphology to lingual muscle stimulation will predict changes in UA patency during sleep.

**Materials and Methods:** Twelve apneic patients implanted with a multi-channel targeted hypoglossal nerve stimulating system underwent mid-sagittal ultrasound tongue imaging during wakefulness. Changes in tongue shape were characterized by measuring its vertical height and polar dimensions between tongue surface and genioglossi origin in the mandible. Changes in patency were characterized by comparing airflow responses between stimulated and adjacent unstimulated breaths during NREM sleep.

**Results:** Two distinct morphologic responses were observed. Anterior tongue base and hyoid-bone movement (5.4(0.4) to 4.1(1.0)cm (median, IQR)) with concomitant increases in tongue height (5.0(0.9) to 5.6(0.7)cm) was associated with decreases in airflow during stimulation. In contrast, comparable anterior hyoid movement (tongue protrusion from 5.8(0.5) to 4.5(0.9)cm) without significant increases in height (5.2(1.6) to 4.6(0.8)cm) was associated with marked increases in airflow during sleep.

**Conclusions:** Tongue protrusion with preservation of tongue shape predicted increases in patency, whereas anterior movement with concomitant increases in height were associated with decreased pharyngeal patency. These findings suggest that pharyngeal patency can be best stabilized by stimulating lingual muscles that maintain the shape and position of the tongue, thereby preventing it from prolapsing posteriorly during sleep.

**Acknowledgements:** TFC would like the American Heart Association grant AHA 19CDA34660245 that enabled this research.

#### CLINICIAN AWARENESS OF OBSTRUCTIVE SLEEP APNOEA RISK FACTORS AND CONFIDENCE IN REFERRAL

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**Introduction:** Obstructive Sleep Apnea (OSA) is a highly prevalent disorder with an increase in prevalence across the globe. This increase has been parallel to the increase in obesity, which is recognized as a major risk factor.

OSA is an important health problem due to its contribution as a risk factor for metabolic, cardiovascular, and psychiatric disorders such as diabetes, hypertension, stroke, and depression.

Patients with symptoms of OSA present to nearly all physicians, which requires a basic level of knowledge to identify those patients and provide an appropriate referral. From a dental perspective, this includes appropriate risk assessment for dental treatment under general anaesthesia or

intra-venous sedation.

**Materials and Methods:** A questionnaire utilising open and close-ended questions based on the knowledge and confidence of diagnosis and referral of OSA was delivered to dental clinicians at Guy's Dental Hospital. Clinicians from various dental specialties including oral surgery, periodontology, paediatrics, restorative, and special care with varying levels of expertise, were included.

Data was inputted into an excel spreadsheet, and the average score on the "knowledge" component and "confidence" component were calculated according to three categories; Risk Awareness, Symptom awareness, Confidence in referral/signposting.

This was compared to a set gold standard, which was 100% of clinicians should be aware of risk factors, symptoms and be confident in referring/signposting.

**Results:** Of 50 dental clinicians, none scored 100% on the knowledge component of the questionnaire. The highest score was 70%, and the lowest 40%. The departments with the highest scores were Oral Surgery and Restorative Dentistry. Only 32% of clinicians opted for the correct referral pathway for patients with suspected OSA.

An increased level of clinical experience resulted in higher scores in the "knowledge" component as well as increased levels of confidence in assessment and referral.

**Conclusions:** Dental clinician awareness of OSA is limited and below the expected standard. There is scope for improvement for all dental clinicians to increase awareness of obstructive sleep apnea to provide holistic care for patients and better risk assessment for dental treatment.

**Acknowledgements:** No conflict of interest

#### COGNITIVE DYSFUNCTION IN 'PURE' OSA PATIENTS WITHOUT ANY OTHER COMORBIDITIES

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**Introduction:** Patients with Obstructive Sleep Apnoea (OSA) complain of a variety of cognitive deficits. Several studies have shown impairment in executive functions, attention, memory, visuospatial abilities and psychomotor functions. However, despite numerous studies over the years, there is still lack of agreement on the cognitive domains that are mostly compromised in patients with OSA. Discordant results may be due to the different tools used, different study populations as well as the presence of other comorbidities. The aim of this study was to investigate cognitive function in a (rare) group of patients with different OSA severity and without any other comorbidities.

**Methods:** Male patients  $\geq 35$  years old newly diagnosed with OSA were recruited from a tertiary sleep centre (Guy's Hospital, NHS GUST UK). A control group of healthy individuals, age-matched to OSA patients, were recruited from volunteers. Exclusion criteria included the presence of any other sleep disorders, psychiatric, neurological and medical conditions, BMI  $> 32$  Kg/m<sup>2</sup>, use of drugs affecting Central Nervous System and sleep structure, history of alcohol or recreational drug-abuse, cigarette smoking, professional drivers/shift workers. All patients and controls completed Cambridge Neuropsychological Test Automated Battery (CANTAB). A two-way ANOVA, corrected for multiple comparisons was performed. The study was part of the multimodal clinical study InCOSA (IRAS-Project-ID-170912; REC-REF16/L0/0893).

**Results:** Eleven mild, eleven severe OSA, eleven controls (mean age was 43.7  $\pm$  7.5 years, 46.7  $\pm$  10.1 years and 42.3  $\pm$  5.4 years respectively) were recruited and completed CANTAB tests. No statistically significant differences were found between OSA patients and controls for BMI, education, age. Comparison between the three groups (mild OSA, severe OSA,

controls) demonstrated statistical differences in three cognitive domains. A statistically significant delayed latency of response in the Attention Switching Task was found in severe OSA compared with controls ( $p < 0.0379$ ): in severe the median latency of response was 840.55ms  $\pm$  164.51ms and in controls was 553.07ms  $\pm$  111.74ms. Statistically significant differences were found in the median latency of the Delayed Matching to Sample Test between severe OSA and controls ( $p < 0.0001$ ) and between severe and mild OSA ( $p < 0.0001$ ): median latency was 2930.21ms  $\pm$  870.90ms in controls, 3096.28ms  $\pm$  781.35ms in mild OSA, and 4000.59ms  $\pm$  1206.6ms in severe OSA. Statistically significant differences in the Emotion Recognition Task were found between severe group and controls ( $p < 0.0033$ ) and between mild group and controls ( $p < 0.0024$ ): in severe OSA the median latency was 1692.59ms  $\pm$  686.67ms, in mild OSA was 1322.38ms  $\pm$  329.9ms and in controls was 1135.0ms  $\pm$  157.63ms.

**Conclusion:** Preliminary results showed that patients with OSA and with no co-morbidities demonstrated a distinct pattern of cognitive deficits that included impairment in three cognitive domains: attention switching task, social cognition and a short-term visual recognition memory. Future multi-centre multi-modal longitudinal studies should confirm these findings, as well as decipher how these cognitive deficits may interplay in time and in function with other co-morbidities-driven impairments over time.

**Acknowledgements:** Wellcome Trust 103952/Z/14/Z

#### COMBINATION OF ATOMOXETINE WITH THE NOVEL ANTIMUSCARINIC AROXYBUTYNIN IMPROVES MILD TO MODERATE OSA

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**Introduction:** OSA remains a common and serious sleep disorder worldwide. Despite advances in CPAP therapy acceptance and adherence rates continue to be challenging.

Muscle hypotonia is a major contributor to OSA pathogenesis. Loss of pharyngeal muscle activity during NREM sleep is believed to be secondary to loss of norepinephrine (NE) stimulation and during REM sleep secondary to muscarinic inhibition. Combining drugs that increase NE activation and minimize muscarinic inhibition has [rf1] shown some efficacy in treating OSA. This study assessed atomoxetine plus a novel anti-muscarinic drug, aroxybutynin, on OSA severity.

Previous pharmacological treatment studies of OSA suggested that the combination of atomoxetine and oxybutynin is safe and effective. The current study is with aroxybutynin (combination designated AD-109), a new enantiomerically pure form of oxybutynin which is proposed to have an improved safety and efficacy profile in OSA compared to racemic oxybutynin.

**Materials and Method:** This was a randomized, double-blind, placebo-controlled, multisite, crossover design study of 30 patients who met eligibility criteria for mild to moderate OSA. Each received low-dose AD109, high dose AD109, and placebo at bedtime across three overnight periods in a randomized order. Subjects who met all enrollment criteria were randomized to receive the following experimental treatments, one treatment on each of 3 PSG nights, separated by at least a one-week washout period:

- Atomoxetine 75 mg + aroxybutynin 2.5 mg (i.e. 75/2.5)
- Atomoxetine 37.5 mg + aroxybutynin 2.5 mg (i.e. 37.5/2.5)
- Placebo

Dosing occurred immediately prior to lights out. The morning following each PSG, in the crossover period, the DSST, KSS, and sleep quality VAS were administered. Each PSG night was followed by a 1-week washout period. AE/SAEs were collected at each visit and by telephone with participants. The primary endpoint was change in Hypoxic Burden (HB) and key secondary endpoints included Apnea Hypopnea Index (AHI) and oxygen desaturation index (ODI).

Safety endpoints included: physical exam, vital signs, clinical laboratory assessment, spontaneous adverse events including the post-dosing period, DSST and PSG parameters.

**Results:** Patients treated with both the high and low doses of AD109 had a large, statistically significant, and clinically meaningful difference from placebo in their Hypoxic Burden (HB), which was the study's primary

endpoint. The median HB for participants on placebo was 13.9 (%min)/h as compared to a median of 2.3 (%min)/h for patients on the high dose ( $p < 0.001$ ) and to a median of 7.3 (%min)/h on the low dose ( $p < 0.01$ ). HB measures the total amount of respiratory event-related hypoxemia during sleep. Additionally, the data showed a statistically significant and clinically meaningful median reduction in Apnea-Hypopnea Index (AHI) [Median AHI of 13.2 events/h on placebo reduced to a median of 5.5 events/h on the high dose ( $p < 0.001$ ) and to a median of 7.8 on the low dose ( $p < 0.05$ )]. AD109 also demonstrated a highly favorable safety profile.

**Conclusions:** This study provides further support that a pharmacological intervention for OSA, namely the combination of atomoxetine and aroxbutymin offers promising results. Additional development of this compound and others is warranted.

This study was funded by Apnimed.

#### COMPARISON BETWEEN AUTO-CPAP VERSUS MANUAL TITRATION OF FIXED PRESSURE CPAP IN ATTENDED POLYSOMNOGRAPHY IN PATIENTS WITH OBSTRUCTIVE SLEEP APNOEA

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**Introduction:** After a patient is diagnosed with obstructive sleep apnoea (OSA), a current standard of practice involves performing attended polysomnography (PSG), during which positive airway pressure is adjusted throughout the recording period to determine the optimal pressure for maintaining upper airway patency. The aim of this study is to compare the auto CPAP use versus manual titration of fixed pressure CPAP during an attended PSG study in patients with obstructive sleep apnoea.

**Materials and Methods:** 50 patients with OSA participated in our study. Participants were randomly divided in two groups of 25 patients. The group A underwent a manual titration of fixed pressure CPAP and for the group B an auto-CPAP was used. For patients in group A the mean age was 50,31 ± 14,6 years, mean BMI: 30,5 ± 6,1 kg/m<sup>2</sup> and mean Apnea Hypopnea Index (AHI) was 65,74 ± 21,2 per hour. For patients in group B the mean age was 50,9 ± 13,1 years, mean BMI: 32,9 ± 5,9 kg/m<sup>2</sup> and mean Apnea Hypopnea Index (AHI) 68,9 ± 20,5 per hour.

**Results:** Wilcoxon signed-rank test was used. A comparison of Total Sleep Time between groups A and B revealed no significant difference (215,4 ± 78,5 vs 233,1 ± 81,6,  $p > 0.742$ ). A comparison of sleep efficiency (%) between groups A and B revealed no significant difference (97,7 ± 53,0 vs 99,2 ± 46,3,  $p > 0.884$ ). A comparison of AHI between groups A and B revealed no significant difference (14,2 ± 78,5 vs 13,3 ± 4,9,  $p > 0.884$ ). The CPAP pressure for group A was 8,2 ± 2,7 and Pmean for group B was 8,6 ± 2,1.

**Conclusions:** Although our study showed that there is no difference between auto CPAP and fixed pressure CPAP use throughout a PSG study to determine the optimal pressure for maintaining upper airway patency more studies are required to clarify it.

#### COMPARISON OF SIX SCREENING SCORES FOR SLEEP-DISORDERED-BREATHING IN AN AFRICAN POPULATION: RESULTS FROM THE BENIN SOCIETY AND SLEEP (BESAS) STUDY

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**Introduction:** Little is known about the best clinical score to screen for sleep-disordered-breathing (SDB) in African Populations. The objective of the study was to assess the performance of six screening scores compared to objective sleep recording in an African general population sample.

**Methods:** This study was conducted in the population-based (Benin Society and Sleep) cohort from Benin, West Africa from April 2018 and January 2021. Respiratory polygraphies were performed using a type III device. Sleep questionnaires (STOP, STOP-Bang, Berlin) were administered to participants via Kobocollect software using digital tablets. Morphometric components of NoSAS (Neck-Obesity-Sex-Age-Snoring), No-Apnea (Neck-Age) and GOAL (Gender-Obesity-Age-Loud snoring) scores were collected by trained investigators. NoSAS score was evaluated using two thresholds ( $\geq 8$  and  $\geq 5$  points). SDB severity categories were defined according to apnoea-hypopnoea index (AHI): mild ( $5 < \text{AHI} < 15/\text{h}$ ), moderate ( $15 \leq \text{AHI} < 30/\text{h}$ ) or severe ( $\text{AHI} \geq 30/\text{h}$ ).

**Results:** Overall, 1810 subjects with valid polygraphy data were included in the analysis. Participants were predominantly females (57.3%) and with a mean (+/- SD) age of 45.5 +/- 14.6 and a BMI of 24.7 +/- 5.9. The prevalence of mild, moderate, and severe SDB was: 31.6%, 8.9% and 2.7% respectively. Mean Age and mean neck circumference increased with SDB severity. For mild, moderate and severe SDB respectively, the highest to lowest score performance for the following parameters were:

- **Area under ROC curve (AUC):** NoSAS<sub>5</sub> (0.67, 0.69, 0.75); GOAL (0.65, 0.70, 0.79); No-apnea (0.64, 0.70, 0.73); STOP BANG (0.64, 0.67, 0.73); Berlin (0.57, 0.61, 0.73); STOP (0.60, 0.62, 0.70); NoSAS<sub>8</sub> (0.59, 0.66, 0.74);
- **Specificity:** NoSAS<sub>8</sub> (0.95, 0.91, 0.89), Berlin (0.92, 0.88, 0.87), GOAL (0.80, 0.71, 0.68), STOP-Bang (0.78, 0.70, 0.67), No-apnea (0.76, 0.69, 0.65); STOP (0.72, 0.66, 0.64); NoSAS<sub>5</sub> (0.75, 0.65, 0.62);
- **Sensitivity:** NoSAS<sub>5</sub> (0.59, 0.73, 0.87); No-Apnea (0.52, 0.72, 0.81); GOAL (0.51, 0.69, 0.75); STOP-Bang (0.50, 0.65, 0.79), STOP (0.48, 0.57, 0.75); NoSAS<sub>8</sub> (0.23, 0.40, 0.58); Berlin (0.22, 0.33, 0.58);
- **Positive predictive value (PPV):** NoSAS<sub>8</sub> (0.79, 0.38, 0.13); Berlin (0.67, 0.27, 0.11); NoSAS<sub>5</sub> (0.65, 0.21, 0.06); GOAL (0.65, 0.24, 0.07); STOP-Bang (0.63, 0.22, 0.06); No-Apnea (0.63, 0.23, 0.06); STOP (0.56, 0.18, 0.05);
- **Negative predictive value (NPV):** NoSAS<sub>5</sub> (0.71, 0.95, 0.99); GOAL (0.68, 0.95, 1.00); No-Apnea (0.68, 0.95, 0.99); STOP-Bang (0.67, 0.94, 0.99); STOP (0.64, 0.92, 0.99); NoSAS<sub>8</sub> (0.62, 0.92, 0.99); Berlin (0.61, 0.91, 0.99).

**Conclusion:** This study provides the first comparison of the performance of various screening scores for SDB in an African Population. NoSAS<sub>8</sub> score showed the highest PPV and specificity and could be a useful support for SDB diagnosis in resource-constrained settings where polygraphy or polysomnography are not accessible for objective assessments.

**Acknowledgement:** Ligue Pulmonaire Vaudoise, Lausanne, Switzerland for funding.

#### CONSUMER WRIST-WORN SMARTBANDS AND OSAS SCREENING: PERFORMANCE OF SUPERVISED MACHINE-LEARNING ALGORITHMS

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**Introduction:** Notwithstanding the high prevalence of Obstructive Sleep Apnoea Syndrome (OSAS) in adults, OSAS is still largely underdiagnosed in the general population. Polysomnography and Cardiorespiratory Monitoring (CRM), the two diagnostic techniques included in the guidelines of both the American Academy of Sleep Medicine and the European Respiratory Society, are unfit for large-scale screenings given their invasiveness, expensiveness, and the lengthy process of sleep scoring. In this prospective, questionnaires are a simpler and more convenient approach to polysomnography and CRM, but they intrinsically lack objectivity, and they require to be actively addressed to the population of interest. Instead, commercially available wrist-worn smartbands are popular devices capable of objectively collecting physiological data such as accelerometric measures and heart rate. We questioned whether machine-learning algorithms trained on data collected through wrist-worn smartbands could possibly screen for the severity of OSAS in an adult population, thereby serving as screening tools for OSAS.

**Materials and Methods:** Seventy-eight (78) patients (mean age  $\pm$  SD: 57.2  $\pm$  12.9 years; 30 females and 48 males) undergoing CRM for diagnostic purposes wrist-wore a Fitbit Inc.'s device during the CRM's monitoring period. CRM traces were scored by a trained professional according to the Apnoea Hypopnea Index (AHI), which was used as the ground-truth for estimating the performance of the trained algorithms. We trained three pairs of algorithms: for AHI<5 vs AHI $\geq$ 5 (Healthy vs OSAS-suffering) prediction we used two multi-layer perceptron placed in series. For AHI<15 vs AHI $\geq$ 15 (Mild vs Moderate-Severe) prediction we used a multi-layer perceptron and a random-forest classifier placed in series, while for AHI<30 vs AHI $\geq$ 30 (Moderate vs Severe) prediction we used two random-forest classifiers placed in series. In each pair of classifiers, the second algorithm had as an additional descriptor the result of the classification of the first algorithm. A Leave-One-Out procedure was adopted to train the pairs of algorithms. Performance was assessed through the following metrics: Matthews Correlation Coefficient (MCC), sensitivity, specificity, positive predictive values, negative predictive values, and diagnostic odds ratio.

**Results:** According to the MCC, the proposed algorithms reached an overall good correlation with CRM in Healthy vs OSAS-suffering (MCC: 0.4), Mild vs Moderate-Severe (MCC: 0.3) and Moderate vs Severe (MCC: 0.6) classification. AHI<5 vs AHI $\geq$ 5 and AHI<30 vs AHI $\geq$ 30 classifiers' sensitivity, specificity, positive predictive values, negative predictive values, and diagnostic odds ratio were found in line with those of the STOP-Bang questionnaire, valued as the most sensible self-reported questionnaire for screening OSAS.

**Conclusions:** Machine learning algorithms showed a comparable performance to the performance of already available OSAS screening questionnaires. Unlike self-reported questionnaires, these algorithms do not suffer from subjectivity since they were trained on physiological data objectively collected by a wrist-worn device. Furthermore, these devices are widely distributed in the general population, that adopts them as everyday self-monitoring tools. The aforementioned advantages of machine-learning algorithms applied to smartbands' data over questionnaires lead to the conclusion that they could guide a population-scale screening for OSAS.

**Acknowledgements:** We thank Arpa Foundation for funding this research.

## CRANIOFACIAL GROWTH MODIFICATION PROTOCOL FOR PEDIATRIC OSA

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### Craniofacial Growth Modification Protocol for Pediatric OSA

Audrey Yoon, Jasmine Faldu, Christine Hong

**Introduction:** As our professions strive to bridge the gap between sleep medicine and orthodontics, it is imperative that providers have a guideline to follow as patients grow and develop. Orthodontists can play an important role in the team for interdisciplinary care for pediatric patients with obstructive sleep apnea (OSA). OSA presents with four major pathophysiologic traits and anatomy is the one etiology orthodontists can influence with targeted therapy. The literature supporting this team approach to sleep medicine and orthodontics is very limited.

**Objectives:** Healthcare providers would benefit from knowing an orthodontist's ability to manipulate and guide craniofacial growth patterns depending on a patient's age and craniofacial maturity. It could be valuable to understand which strategies can be used in conjunction with other providers to create a timely team approach for patients with pediatric obstructive sleep apnea.

**Materials and Methods:** Studies from PubMed, Scopus, and the Cochrane library database were selected for craniofacial growth and structure-targeted orthodontic treatments. An integrated craniofacial growth modification treatment protocol encompassing maximum skeletal growth potential and favorable airway anatomy was proposed.

**Results:** With an orthodontist's extensive knowledge of the craniofacial growth and development stages, providers can take advantage of the therapeutic appliances that can make a substantial change in a patient's

growth pattern during maturity. The goals are to maximize patient growth potential, achieve nasal breathing, and guide favorable growth. Up to 80% of cranial development occurs by age 6, anterior cranial base and nasal expansion should be targeted areas to develop for preschoolers. Naso-maxillary complex slow expansion appliances with or without facemask therapy advancement can be beneficial at this stage. The midpalatal suture can be optimally influenced with expansion before interdigitation occurs. As the patient's midpalatal suture calcifies throughout maturity, temporary anchorage devices (TADs) can be used to influence skeletal change after suture maturation. As the mandible develops, intervention can help guide mandibular growth and accelerate growth in favorable patterns and the ideal timing is pre-puberty. There is controversy regarding the impact of functional appliances and mandibular growth, but there are various avenues to help influence development. TADs can also be beneficial in mandibular autorotation to change growth direction from unfavorable to favorable. Keeping an interdisciplinary approach in mind, myofunctional therapy can be integrated into the patient's treatment plan, which can serve as a beneficial adjunct to craniofacial complex changes.

**Conclusions:** Appropriate targeted therapy can help maximize favorable growth potential based on well-established knowledge on growth and development of the cranium. Timely craniofacial growth modification would be valuable for pediatric sleep apnea patients.

## DEFINING THE HETEROGENEITY OF SLEEP APNEA SYNDROME: A CLUSTER ANALYSIS WITH IMPLICATIONS FOR PATIENT MANAGEMENT

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**Introduction:** Obstructive sleep apnea (OSA) is a complex pathology with heterogeneity that has not been fully characterized to date. Our objective is to identify groups of patients with common clinical characteristics through cluster analysis that could predict patient prognosis, the impact of comorbidities and/or the response to a common treatment.

**Materials and Methods:** Cluster analysis was performed using the hierarchical cluster method in 2025 Patients in the apnea-HUGU cohort. The variables used for building the clusters included general data, comorbidity, sleep symptoms, anthropometric data, physical exam and sleep study results.

**Results:** Four clusters were identified: 1) young male without comorbidity with moderate apnea and otorhinolaryngological malformations; 2) middle-aged male with very severe OSA with comorbidity without cardiovascular disease; 3) female with mood disorder; and 4) symptomatic male with established cardiovascular disease and severe OSA.

**Conclusions:** The characterization of these four clusters in OSA can be decisive when identifying groups of Patients who share a special risk or common therapeutic strategies, orienting us towards personalized medicine and facilitating the design of future clinical trials.

**Acknowledgements:** The authors thank the computer scientists of our hospital for their work on the data base.

## DESATURATION SEVERITY AFFECTS OSA-RELATED CHANGES IN SHORT-TERM HEART RATE VARIABILITY

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**Introduction:** Obstructive sleep apnea (OSA) patients suffer from

recurrent blood oxygen desaturations caused by nocturnal apneas and hypopneas [1]. Desaturations can further cause overactivation of the sympathetic nervous system (SNS) and decrease the long-term heart rate variability (HRV) [2,3]. HRV is a non-invasive, inexpensive tool for assessing the sympathovagal balance, and it could be determined routinely during the current OSA diagnostics as the electrocardiogram (ECG) is always recorded during the polysomnography. Yet, the effect of the severity of desaturations on short-term (~5min) HRV reflecting acute electrophysiological consequences has remained unclear. In this study, we tested our hypothesis that the more severe desaturations influence more strongly on neurocardiac regulation measured as higher short-term HRV.

**Materials and methods:** We retrospectively analysed the overnight ECG signals of 642 patients (349 men) referred to polysomnography due to OSA suspicion. R-peaks were detected automatically from ECGs with Kubios HRV Premium 3.4.1 (Kubios Oy, Kuopio, Finland) [4], and the time- and frequency-domain HRV parameters were determined from 5-minute RR interval segments during sleep. The median HRV was calculated in subgroups divided separately based on the desaturation severity ( $Des_{Sev}$ ) and the frequency of the respiratory events in the segment ( $Ev_{Freq}$ ). The HRV results were then compared separately between the  $Des_{Sev}$  groups and the  $Ev_{Freq}$  groups.

**Results:** The mean RR interval decreased from 915 ms to 869 ms, the low-frequency (LF) band power increased from 160.9  $ms^2$  to 536.3  $ms^2$ , and the ratio of low- and high-frequency band powers (LF/HF-ratio) increased from 0.924 to 1.745 as the  $Ev_{Freq}$  increased. Similarly, the mean RR interval decreased from 952 ms to 854 ms, the LF band power increased from 186.6  $ms^2$  to 479.7  $ms^2$ , and the LF/HF-ratio increased from 1.004 to 1.747 with increasing  $Des_{Sev}$ . All these differences in HRV parameter values were statistically significant ( $p < 0.01$ ).

**Conclusions:** This study provides valuable insight into the role of OSA in cardiac autonomic control. Shorter RR intervals, higher LF band power, and LF/HF-ratio values demonstrate higher SNS activity. Therefore, these short-term HRV results may illustrate SNS dominance due to the higher  $Des_{Sev}$  and  $Ev_{Freq}$ . The short-term HRV response, however, differs based on the desaturation severity and the number of respiratory events in OSA patients. Thus, considering HRV and both the desaturation and respiratory event characteristics could be useful when assessing the risk of developing OSA-related cardiac consequences in a more detailed manner.

**Acknowledgments:** This study was funded by the European Union's Horizon 2020 Research and Innovation Programme (965417), Kuopio University Hospital State Research Funding, the Academy of Finland (323536), Business Finland (5133/31/2018), the Finnish Cultural Foundation (Central Fund and North Savo Regional Fund), Foundation of the Finnish Anti-Tuberculosis Association, Instrumentarium Science Foundation, Päivikki and Sakari Sohlberg Foundation, Respiratory Foundation of Kuopio Region, Scientific Foundation of the Pulmonary Diseases, and Tampere Tuberculosis Foundation.

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## DESIGNER RECEPTORS EXCLUSIVELY ACTIVATED BY DESIGNER DRUGS TREATMENT OF SLEEP-DISORDERED BREATHING

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**Introduction:** Obstructive sleep apnea is recurrent upper airway obstruction caused by a loss of upper airway muscle tone during sleep. The main goal of our study was to determine if designer receptors exclusively activated by designer drugs (DREADD) could be used to activate the

genioglossus muscle as a potential novel treatment strategy for sleep apnea. We have previously shown that the prototypical DREADD ligand clozapine-N-oxide increased pharyngeal diameter in mice expressing DREADD in the hypoglossal nucleus. However, the need for direct brainstem viral injections and clozapine-N-oxide toxicity diminished translational potential of this approach, and breathing during sleep was not examined.

**Materials and Methods:** Here, we took advantage of our model of sleep-disordered breathing in diet-induced obese mice, retrograde properties of the adeno-associated virus serotype 9 (AAV9) viral vector, and the novel DREADD ligand J60. We administered AAV9-hSyn-hM3(Gq)-mCherry or control AAV9 into the genioglossus muscle of diet-induced obese mice and examined the effect of J60 on genioglossus activity, pharyngeal patency, and breathing during sleep.

**Results:** Compared with control, J60 increased genioglossus tonic activity by greater than sixfold and tongue uptake of 2-deoxy-2-[<sup>18</sup>F]fluoro-d-glucose by 1.5-fold. J60 increased pharyngeal patency and relieved upper airway obstruction during non-REM sleep.

**Conclusions:** We conclude that following intralingual administration of AAV9-DREADD, J60 can activate the genioglossus muscle and improve pharyngeal patency and breathing during sleep.

**Acknowledgments:** American Heart Association grant AHA 19CDA34660245 and an American Thoracic Society unrestricted award to T.F.C.

## DETERMINANTS OF ADHERENCE/PERSISTENCE TO POSITIVE AIRWAY PRESSURE THERAPY IN PATIENTS WITH OBSTRUCTIVE SLEEP APNOEA

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**Introduction:** Positive airway pressure (PAP) is the primary treatment for airway obstruction among patients with obstructive sleep apnoea (OSA). Nonadherence and high discontinuation rates of PAP therapy remain significant challenges in the real world. This study aimed to characterise the existing real-world evidence (RWE) regarding determinants of adherence/persistence of PAP in patients with OSA. A second aim was to characterise the use of alerting agents (AAs; ie, wake-promoting agents or traditional stimulants), and their association with PAP adherence or persistence.

**Methods:** A systematic literature review was conducted by searching Embase and MEDLINE® from inception to May 2021 and “grey literature” from relevant conferences (2019–2020). Title/abstract screening, full-text screening, quality appraisal, and data extraction were conducted by two independent investigators; a third reviewer adjudicated all disagreements within each step. Quality appraisal was performed using the National Institutes of Health and Joanna Briggs Institute critical appraisal tools. Determinants were categorised under 5 main headings: demographics, OSA, device/intervention, sleep, psychosocial.

**Results:** Of the 3,096 unique articles returned via the main database and grey literature searches, 136 passed title/abstract screening; 66 passed full-text screening and were included in the review. Among the 66 included articles, most had a prospective (35%) or retrospective (33%) cohort study design. Approximately half of the included studies were published in North America (49%), followed by Asia (24%) and Europe (21%). Sample sizes ranged from 29 to 789,260 (median=153). Follow-up periods (reported in 57 studies) also varied, from 1 week to 10 years, with most studies (70%) collecting  $\leq 6$  months of data. The median proportion of female participants across included studies was 23%, while the mean age reported was 54 years. Epworth Sleepiness Scale scores were reported in 29 studies and ranged from 8 to 15, with a mean score of 11. Disease severity measures by the apnoea-hypopnoea index were reported in 36 studies and ranged from 11 to 78, with a mean score of 42. In total, 404 assessments of determinants were conducted across the 66 studies. The most frequently investigated determinant category was demographics (39%), followed by the sleep (19%), device/intervention (15%), psychosocial (14%), and OSA (13%) categories. Of all determinants assessed, 43% showed a statistically significant association with PAP use. Within the sleep

category, 32% of determinants assessed were significantly associated with continuous PAP use, including measures of daytime sleepiness (12%). No studies reported the use of AAs or measured their association with adherence or discontinuation of airway therapy.

**Conclusions:** Determinants of PAP adherence/persistence are complex and multifaceted, with ~40% of assessed determinants being significantly associated with adherence/persistence. Although a secondary aim of this review was to understand the relationship between AAs and airway therapy, no compelling RWE data on this association exist. However, sleep-related measures, including presence of excessive sleepiness and improvements in sleep symptoms, were, in some studies, positively correlated with adherence/persistence. Additional research to understand the effects of AAs on adherence/persistence with OSA therapy outcomes in the real world is needed.

**Acknowledgements:** Supported by Jazz Pharmaceuticals. Ana Howarth, PhD provided methodologic support.

#### DETERMINANTS OF HIGH CIRCULATING MYELOPEROXIDASE AND MATRIX METALLOPROTEINASE-9 LEVELS IN CORONARY ARTERY DISEASE PATIENTS WITH OBSTRUCTIVE SLEEP APNEA: A SECONDARY ANALYSIS OF THE RICCADSA STUDY

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**Introduction:** Obstructive sleep apnea (OSA) is common in patients with coronary artery disease (CAD), in which rupture of atherosclerotic plaques, endothelial dysfunction, and oxidative stress play role in initiation and progression of the disorder. Circulating levels of myeloperoxidase (MPO), as an oxidative stress marker, as well as matrix metalloproteinase-9 (MMP-9), as a destabilizer of plaques, are known to be elevated in patients with CAD, and associated with worse prognosis in those patients. Less is known regarding the effect of OSA on MPO and MMP-9 in cardiac cohorts.

**Materials and Methods:** The current study was a secondary analysis of the RICCADSA trial that was conducted in Sweden between 2005 and 2013. A total of 502 revascularized CAD patients with OSA (apnea-hypopnea-index [AHI]  $\geq 15$  events/h; n=391, or no-OSA (AHI <5 events/h; n=101), based on a home-sleep apnea test, and who had circulating blood samples at baseline, were included in the analysis. The patients were dichotomized into a high or low MPO and MMP-9 groups, based on the median cut-off values (116 ng/ml, and 270 ng/ml), respectively.

**Results:** The mean age of the participants was 63.9 ( $\pm 8.6$ ), and 84% of the study cohort were men. Median values of MPO and MMP-9 levels were similar between the OSA and no-OSA groups. In different multivariate linear and logistic regression models, neither OSA nor OSA severity in terms of AHI and oxygenation indices were associated with the high MPO and MMP-9 levels. Current smoking was significantly associated with both high MPO (odds ratio [OR] 1.83, 95% confidence interval [CI] 1.12 – 2.98;  $p=0.015$ ), and high MMP-9 levels (OR 2.48, 95% CI 1.49 – 4.11;  $p<0.001$ ), respectively. Other significant determinants were revealed as acute myocardial infarction at baseline (OR 1.49, 95% CI 1.04 – 2.15;  $p=0.030$ ) for high MPO, and male sex (OR 1.96, 95% CI 1.17 – 3.27;  $p=0.010$ ) for high MMP-9 levels.

**Conclusions:** Current smoking, but not OSA, was significantly associated with high MPO and MMP-9 levels in this revascularized CAD cohort. Smoking status should be seriously taken into consideration while evaluating the effects of OSA and its treatment on long-term adverse cardiovascular outcomes in adults with CAD.

**Clinical Trial Registration:** clinicaltrials.gov NCT00519597.

**Acknowledgements:** The study was funded by the Swedish Research Council, Swedish Heart and Lung Foundation, and ResMed Foundation.

#### DEVELOPMENT OF A NOVEL INTRA-ORAL SENSOR SYSTEM FOR MONITORING NIGHTLY EFFICACY AND COMPLIANCE WITH MANDIBULAR ADVANCEMENT SPLINT THERAPY FOR OBSTRUCTIVE SLEEP APNOEA

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**Introduction:** Effective management of obstructive sleep apnoea (OSA) requires an optimal combination of efficacy and compliance. Objective monitoring of efficacy and compliance is available for Positive Airway Pressure treatment, but to date only objective compliance has been available for Mandibular Advancement Splint (MAS) therapy. The overall aim of this project is to develop a novel sensor system with capabilities for monitoring nightly efficacy and compliance of MAS treatment. The specific aim of this research study was to develop and validate an algorithm for estimating adherence, head position and the Apnoea-Hypopnoea Index (AHI).

**Materials and Methods:** A novel sensor system was developed for insertion into the MAS during custom fabrication. The sensors include a magnetometer, accelerometer, thermometer and microphone. The signals from these sensors were used to develop algorithms for estimating Apnoea-Hypopnoea Index (AHI), nightly usage and head position. Patients underwent a level 2 home sleep test (HST; Nox Medical, Iceland) during which a MAS with the in-situ sensor system was worn. Scoring of respiratory events for the HST was conducted by an experienced sleep technologist according to AASM 2012 criteria. A statistical approach using medians and standard deviations on a single magnetometer signal was used to derive an algorithm for estimation of the AHI. Signal thresholds were used to derive algorithms for nightly usage and head position. Performance was assessed using RMS error and Bland-Altman analysis.

**Results:** 31 patients were studied using the sensor system and the HST. Based on the HST, 1 patient had no OSA (AHI <5/hr), 9 patients had mild OSA (AHI 5-15/hr), 10 patients had moderate OSA (AHI 15-30/hr), and 11 patients had severe OSA (AHI >30/hr). The overall R-value for the AHI algorithm was 0.76, with 18/31 patients having the equivalent OSA severity category using both methods. No patient was incorrectly classified by more than 1 category. Insertion and removal of the device was clearly identified using temperature (allowing calculation of usage), and head position was clearly identified using an accelerometer.

**Conclusions:** The study has shown the feasibility of using sensor technology embedded within a MAS to derive information about treatment efficacy and compliance. The algorithm to estimate AHI provided an excellent correlation with a level 2 HST, and further clinical validation of this algorithm is ongoing. This work has the potential to vastly improve treatment outcomes in OSA patients treated with MAS by providing physicians and dentists with nightly data on AHI, body position and usage.

**Acknowledgements:** Mel Madronio for scoring HSTs, and volunteer subjects for their participation.

#### DIFFERENCE BETWEEN SIMULTANEOUS EAR-LOBE AND FINGER OXIMETRY VALUES INCREASES WITH AGE

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**Introduction:** Measurement of blood oxygen saturation by an oximeter may vary according to measurement site, device used, sensor used, and software used. We systematically used the following two oximeters: Nox with finger sensor and Sentec with ear-lobe sensor. Our clinical experience indicated that significant differences may exist between these two

simultaneous measurements.

**Materials and Methods:** We reviewed 393 in-lab polysomnographies. We excluded recordings with <1 hour of valid oximetry data. Oximetry mean SpO<sub>2</sub> values and patient characteristics were collected.

**Results:** SpO<sub>2</sub> mean values measured by ear-lobe oximetry were 0.67% higher than those measured by finger oximetry. Differences between two oximetry values increased significantly with age. BMI and gender did not affect these measurement differences.

**Conclusions:** The difference between Nox finger oximetry mean values and that of Sentec ear-lobe oximetry increases with age. Oximetry values in advanced age should be interpreted with caution.

## DISE ASSESSMENT - ONE COMPREHENSIVE PRO-FORMA

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**Introduction:** Drug Induced Sedation Endoscopy (DISE) represents the most acknowledged evaluation of snoring and obstructive sleep apnoea hypopnea syndrome (OSAHS)

Usually, it is performed after diagnosing an obstructive sleep apnea by polysomnography. However, many debates exist about how to perform the sedation, the indication for DISE, how to report its findings and consequent surgical implications. DISE standardisation is critical in evaluating the outcome of different surgical modalities and to unify the treatment framework universally which would enhance improvements possible through scientific research. We carried out a trial of integration of the three common classification systems in one comprehensive evaluation.

**Materials and Methods:** A literature search was performed in Pubmed to find out studies in which contain DISE Classification as a title or abstract. An evaluation pro-forma was designed to assess OSA patients by clinical examination and DISE interpretations. Oral manoeuvres were performed during DISE. This Pro-forma was used prospectively over the last two years evaluating 70 patients.

**Results:** Of four published abstracts, Three systematic reviews about DISE classification were used to develop this evaluation pro-forma. The most widespread classifications; VOTE Classification, NOHL Classification and PTLTbE Classification were included in the pro-forma. Over the last two years, this pro-forma gave us a comprehensive understanding which was used with 70 patients to indicate the possible level of upper airway collapse. Additionally, it guided for a step wise treatment plan including conservative and surgical managements.

**Conclusions:** This Pro-forma emphasised the significant impact of unified system for DISE evaluation which can be obtained by integration of established classification systems rather than formulating a new one. We assume this trial get benefits of different classifications and avoid its pitfalls. Also, it could be a first step for a universal DISE that would be reflected on a research database.

## DIURNAL CORTISOL VARIABILITY IN APNEIC AND NON-APNEIC MALE OBESE YOUTHS

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**Introduction:** Obstructive sleep apnea (OSA) is a condition characterized by recurrent episodes of upper airway obstruction, arousals, and oxygen desaturations during sleep. That disease leads to changes in cortisol secretion and weight gain. So, we aimed to compare the salivary content of cortisol at four-time points in apneic and non-apneic male obese youths.

**Materials and Methods:** A cross-sectional design was used in order to study 30 male obese youths (18 - with OSA; 12 - without OSA – obese controls) and 15 healthy lean controls aged 15-17 years. All subjects underwent anthropometric measurements, polysomnography and collection of saliva samples at four-time points (at 7:00 am, 1:00 pm, 7:00 pm, and 11:00 pm.). Cortisol levels (ng/mL) were measured by enzyme-linked immunosorbent assay (ELISA) using a commercial kit on the absorbance microplate reader. Obesity was diagnostic if body mass index (BMI) ≥ 95th

percentile for age and sex. OSA was identified if apnea/hypopnea index (AHI) ≥ 2/hour. All differences were considered significant at p<0.05.

**Results:** There were significantly increased evening and night cortisol levels in OSA subjects (27.35± 17.57 ng/ml and 26.67 ng/ml) compared to obese (14.31 ± 9.23 ng/ml, p=0.016; and 9.12 ± 4.35 ng/ml ±19.45 ng/ml, p=0.006, respectively) and lean controls (13.26 ± 6.45 ng/ml, p=0.003; and 6.13 ± 3.66 ng/ml, p=0.000, respectively). Both morning and afternoon cortisol had an only tendency toward to be increased. Wherein, in non-apneic obese boys there is a significant increase of cortisol content at 1 p.m. than in lean subjects (33.45 ± 11.12 ng/ml vs 21.67 ± 13.03 ng/ml, p=0.035), but did not reach that level in OSA patients.

**Conclusions:** Obese apneic male youths had more pronounced diurnal cortisol alternations than their non-apneic obese peers. Wherein reported modulations of the circadian cortisol rhythmicity associated with OSA and obesity may underlie some negative health outcomes, i.e. hypertension, type 2 diabetes, etc.

## DOES PAP TREATMENT HAVE A PROTECTIVE ROLE ON OSAS PATIENTS FROM COVID-19 PNEUMONIA?

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**Introduction:** Obstructive sleep apnea syndrome (OSAS) is associated with major comorbidities overlap with Covid-19: cardiovascular diseases such as hypertension, diabetes mellitus and obesity. The aims of our study were to examine possible relationship between Covid-19 severity and OSAS on the patients under effective treatment (positive airway pressure treatment) and non-treatment.

**Materials and Methods:** Cases who diagnosed with covid-19 between May 1, 2020 and December 31, 2020 were selected from among the patients who underwent polysomnography before December 1, 2019. OSAS cases were divided into two groups: 1) PAP Group: Patients diagnosed with Covid-19 while using their device effectively for at least a month, 2) Non-PPAP Group: Patients diagnosed with Covid-19 who do not use their device or do not meet the effective use criteria. OSAS cases were further divided into two groups: 1) Pneumonia group: Covid-19 with pneumonia detected on HRCT. 2) Non-Pneumonia group: Covid-19 without pneumonia. In the OSAS group (n=64), there were 30 patients in the PAP group and 34 patients in the Non-PAP group.

**Results:** There were 21 patients in the Pneumonia group and 43 patients in the Non-Pneumonia group. The main finding of this study indicated that the Covid-19 pneumonia prevalence was higher in the OSAS patients who do not use PAP (95,2%) compared to the OSAS patients who use their PAP effectively (4,76%) (p<0,000).

**Conclusions:** Snoring and sleep apnea might increase aspiration of Covid-19 virus during sleep. Non treated OSAS could act as a trigger for a higher incidence of Covid-19 pneumonia, leading to an unfavorable clinical progression.

**Acknowledgements:**

## DRUG-INDUCED SLEEP ENDOSCOPY (DISE): A COMPARISON BETWEEN NOHL AND VOTE CLASSIFICATIONS

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**Introduction:** There is no standardized method to express DISE results. Several classifications have been proposed, but none are globally accepted. The objective of this study is to analyze the most used classifications: NOHL and VOTE to assess which of them provides more advantages.

**Materials and Methods:** a prospective cohort study of 100 patients who underwent DISE was carried out. Three otolaryngologists blindly evaluated the DISE videos and coded the results according to the NOHL and VOTE scales and at what level surgery was indicated.

**Results:** according to the main researcher, surgery of only one level was the most indicated (64%), being the palate the predominant level (58%), followed by multilevel surgery (26%), in 10% no surgery was indicated. The global agreement to express the DISE results according to the NOHL, VOTE scales regarding the degree of obstruction is moderate / regular at the level of the epiglottis ( $k = 0.467$ ) and low in the rest of the structures ( $k = 0.097$ ).

**Discussion:** Although the degree of interobserver agreement is similar in both scales, for VOTE it is slightly higher.

**Conclusions:** DISE is a safe, reproducible and easy to perform test. We recommend the use of the VOTE scale because it has been shown to have a higher degree of interobserver agreement, it is not only the most widely used scale, but also recommended in consensus documents.

**Acknowledgements:** Hospital Universitario Fuenlabrada

### EFFECTIVENESS OF MANDIBULAR ADVANCEMENT DEVICE IN COMPLEX SLEEP APNEA: A CASE REPORT

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**Introduction:** Complex sleep apnea syndrome (CompSAS) is a type of central sleep apnea (CSA) that develops in obstructive sleep apnea (OSA) patients during initial treatment with continuous positive airway pressure (CPAP) device. The mechanisms underlying CompSAS are not well understood.

**Report of Case:** 64-year-old male diagnosed with severe OSA (AHI = 52.3, 84.2% O<sub>2</sub>, and Central apnea index = 22) while subjectively reporting 14/24 on the Epworth Sleepiness Scale (ESS). Initially, he was prescribed and attempted PAP therapy as the first line of treatment for this level of severity. However, he was intolerant to the PAP machine and was consequently referred to Tufts Dental Sleep Clinic for assessment and therapy with a mandibular advancement device (MAD). Upon clinical history and physical examination, the patient had a BMI of 31.4 and a neck circumference measured 17", and cephalometric analysis depicted a low mandibular angle and reduced hyoid bone to mandible distance. Dental impressions and bite registration were completed, and a bilateral interlocking design MAD was fabricated with 80% of mandibular advancement as a starting point. The MAD sleep device and morning repositioning aligner were then delivered to the patient and properly fitted. The patient returned for follow up appointments to assess changes in symptoms; no additional titration of the oral device was needed based on subjective assessment, and patient reported no side effects from the use of MAD. After completion of the MAD clinical protocol, he was referred to his sleep physician for a follow up sleep study which objectively revealed a significant reduction of respiratory events (AHI = 8.8, 90% O<sub>2</sub>, and Central apnea index = 6) while subjectively reporting 5/24 on the Epworth Sleepiness Scale (ESS)

**Discussion:** Patients with CompSAS have a poor initial experience with CPAP and may be non-adherent to continued therapy. MAD are indicated for mild to moderate OSA and in selected patients with severe OSA who are non-adherent to PAP therapy. This case report showed successful management of CompSAS with MAD. Assessment of patient characteristics, predictors of MAD success, and therapeutic mandibular position must be assessed by the sleep dentist to optimize patient selection and improve treatment outcomes.

**Support:** Authors declared no conflict of interest and no financial support provided for this case report.

### EFFECT OF MULTILEVEL SURGERY ON POST SURGICAL PAIN, IN PATIENTS WITH OBSTRUCTIVE SLEEP APNOEA

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**Introduction:** Sleep apnoea is associated with complete or partial obstruction of the upper airway. one of the primary option for treatment of this disease, is opening upper airway with surgery. one of the challenges at post operation is the severe pain. type of surgery, its duration, the patient's age, the type of opioid prescribed after surgery and other factors, affect different amounts of postoperative pain that have been reported in different studies. In many cases, one stage surgery would not be complete and they need multilevel surgery for opening the airway therefor, the aim of this study was to investigate effect of multilevel surgery on post operative pain and comparison with single level surgery in patients with obstructive sleep apnoea.

**Materials and Methods:** This descriptive cross-sectional study was performed on patients referred to the hospital to determine the factors affecting postoperative pain for patients with obstructive sleep apnoea (OSA). Patients' information was recorded: age, sex, weight, height, body mass index, duration of surgery, type of surgery, single level or multilevel surgery, possible complications, and anaesthesia. Patients were evaluated for pain according to VAS criteria. The first time a patient requested a drug was recorded in 24 hours after surgery and data was then analysed.

**Results:** A total of 40 patients were enrolled in the study, including 14 women (35%) and 26 men (65%). The mean age of patients was  $41.55 \pm 7.43$  years. Examination of the relationships between other variables with patients' pain intensity showed a statistically significant difference between patients' pain intensity with other variables such as history of stroke ( $P = 0.005$ ), history of cardiovascular disease ( $P = 0.048$ ), history of drug abuse ( $P = 0.046$ ) and type of analgesia received after surgery ( $P = 0.032$ ). In multivariate analysis of the studied data, no statistically significant relationship was found between any of the variables with the intensity of patients' postoperative pain. The variances of height, weight, body mass index, duration of surgery and the first time of application of analgesic after surgery, being single level or multilevel surgery did not differ in different groups of pain intensity variables. But a significant difference was found between the two variables of age and pain intensity of patients ( $P < 0.05$ ).

**Conclusions:** The results of this study showed a statistically significant difference in pain intensity with a history of stroke, cardiovascular disease, history of drug abuse and also the type of analgesia received after surgery. The serious complications caused by tolerating acute postoperative pain, especially the long-term effects of experiencing severe pain, necessitates more attention to pain control

**Acknowledgements:** no conflicts of interest

### EFFECT OF SURGICAL THERAPY OF OBSTRUCTIVE SLEEP APNEA SYNDROM IN PATIENT TREATED BY POSITIVE AIRWAY PRESSURE

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**Introduction:** The method of choice in patients with sleep apnea syndrome is Positive Airway Pressure (PAP - CPAP / BPAP), surgical intervention is usually a last resort. Some patients with PAP, who are treated suboptimally, may also benefit from concomitant surgery.

**Material and methods:** The study included 25 patients with severe obstructive sleep apnea syndrome (age 17 - 72, baseline AHI 31 - 120, av. 66, baseline pressure on PAP 8-20 mbar) who were indicated for PAP therapy and whose treatment for various reasons was suboptimal. All patients underwent oropharyngeal surgery (tonsillectomy, uvulopalatopharyngoplasty, radiofrequency-assisted uvuloplasty, or a combination thereof). Two months after the operation, a controlled limited polygraphy and off-line retitration of the ventilation device were performed. Monitored parameters: 1. subjective difficulties, preventing further use of PAP treatment. 2. AHI before and after surgery. 3. The level of pressure on the PAP device before and after surgery.

**Results:** 1. None of the patients in our group had problems preventing

further use of the ventilation device. 2. In all patients there was a statistically significant reduction in AHI after surgery ( $p$  0,000012). The mean reduction in AHI was  $45 (\pm 26,68)$ . Five patients did not continue treatment with CPAP / BPAP because it reached the limit of the indicative criteria for PAP (AHI 15), so their treatment can be considered successful. In eighteen of the remaining 20 patients, it was possible to reduce the pressure on the device after retitration, in two it was left at the original level. The mean pressure drop on the PAP device after retitration was  $3,3 \text{ mBar} (\pm 3,3)$ , the average percentage reduction was 20%. The difference between the values before and after surgery is statistically significant ( $p$  0,00294)

**Conclusion:** The results of our study show that patients with OSAS, who are treated with non-invasive ventilation and whose treatment is suboptimal, can benefit from concomitant surgical therapy. None of the patients in our cohort had problems with postoperative use of PAP therapy, while all had a decrease in AHI and most had a decrease in pressure on the PAP device.

### EFFECTS OF SACUBITRIL-VALSARTAN INITIATION ON SLEEP APNEA IN CHRONIC HEART FAILURE

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**Introduction:** Patients with chronic heart failure (CHF) often develop central sleep apnea with cheyne-stokes respiration (CSA-CSR) during sleep with worse prognosis. The sacubitril/valsartan, angiotensin receptor neprilysin inhibitor (ARNI) has been shown to can improve HF, however, the relationship between treatment with ARNI and CSA-CSR has not yet been reported. We studied the effect of ARNI on CSA-CSR in CHF patients.

**Materials and Methods:** 18 HF patients were enrolled. We titrated the starting dose of sacubitril and valsartan to the highest tolerated dose, and performed cardiopulmonary exercise testing (CPET), transthoracic echocardiography and ApleaLink at baseline and 3 months later.

**Results:** ApleaLink results showed that the apnea-hypopnea index (AHI) was significantly reduced after ARNI treatment ( $20 \pm 23$  vs  $7 \pm 7$  events/h,  $P = 0.003$ ). After optimizing of HF-treatment with ARNI, we saw a significant increase in left ventricular ejection fraction (LVEF) increased ( $p < 0.001$ ), and a decrease in cycle length, apnea duration, and circulatory delay, levels of N-terminal fragment of the pro brain natriuretic peptide (NT-pro BNP) and time of oxygen saturation under 90% (T90) ( $p < 0.05$ ).

**Conclusion:** Appropriate use of ARNI can affect the phenotypic characteristics of CSA-CSR, and can improve central chemical sensitivity and hemodynamic parameters. Nevertheless, it cannot be proved that can completely reverse the periodic breathing during sleep.

**Acknowledgements:** Thomas Penzel was partially supported by a Russian Federation Government grant № 075-15-2019-1885. Novartis Pharma GmbH Germany supported the additional diagnostic effort with an unrestricted grant to Charité University Hospital. Youmeng Wang was financially supported by the China Scholarship Council (CSC) for her MD study in Sleep Medicine Center, Charité Universitätsmedizin. The CSC had no role in the design or conduct of this research.

### EFFECTS OF TRANSORAL ROBOTIC SURGERY FOR PATIENTS WITH OBSTRUCTIVE SLEEP APNEA ON SEXUAL FUNCTIONS

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**Introduction:** The impairments in sexual functioning associated with obstructive sleep apnea (OSA), including the impact on relationships and negative effect on desire, arousal, and orgasm, have been noticed in literature. In this study, we further investigated the changes of intimate and sexual relationships in patients with OSA before and after TORS (Transoral Robotic Surgery)-assisted OSA surgery.

**Materials and Methods:** All OSA patients who failed or refused CPAP

treatment and then underwent TORS-OSA surgery were prospectively enrolled. The intimate and sexual relationships questionnaire (via the Sexual Functioning Questionnaire (CSFQ-14)) and International Index of Erectile Function (IIEF-5) Questionnaire were collected pre- and post-operatively. Postoperative morbidity and complications were also recorded.

**Results:** One hundred OSA male patients with TORS-OSA surgery were enrolled (mean age, 43.1 years; mean AHI, 41.2/hr.). The CSFQ-14 increased from  $44.60 \pm 7.40$  to  $45.63 \pm 8.68$  ( $P = 0.0035$ ), the IIEF-5 changed from  $19.16 \pm 5.95$  to  $19.68 \pm 6.09$  ( $P = 0.0417$ ) after surgery. The mean AHI changed from  $41.2 \pm 22.6$  to  $24.8 \pm 20.84$ , post-operatively. The post-operative desaturation index (/hr.) and lowest oxygen saturation (%) of the polysomnography showed statistically significant improvement. No peri-operative serious complication, immediate postoperative airway obstruction or massive bleeding occurred in this cohort.

**Conclusions:** The study demonstrated that TORS-OSA surgery was effective on intimate and sexual relationships in selected OSA patients who are unresponsive to conservative OSA therapy.

**Acknowledgements:** N/A.

### ERTUGLIFLOZIN AND INCIDENT OBSTRUCTIVE SLEEP APNEA: AN ANALYSIS FROM THE VERTIS CV TRIAL

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**Introduction:** Recent data from the EMPA-REG OUTCOME trial suggest that the sodium-glucose transporter 2 (SGLT2) inhibitor empagliflozin, an antihyperglycemic medication for the treatment of patients with type 2 diabetes (T2D), may reduce the incidence of obstructive sleep apnea (OSA) in patients with T2D and cardiovascular (CV) disease [1]. VERTIS CV (NCT01986881) was the CV outcome trial of the SGLT2 inhibitor ertugliflozin [2]. The current post-hoc analysis of VERTIS CV aimed to explore the effects of ertugliflozin on reported incident OSA.

**Materials and methods:** In VERTIS CV, patients aged  $\geq 40$  years with T2D and atherosclerotic CV disease (ASCVD) were randomized (1:1:1) to once-daily placebo, ertugliflozin 5 or 15 mg. The primary endpoint was the composite of major adverse CV events. In these exploratory analyses, we evaluated the impact of ertugliflozin (pooled 5 and 15 mg doses vs. placebo) on incident OSA. Patients with prevalent OSA at baseline were excluded. Incident OSA events were based on investigator-reported events during the trial using the single preferred MedDRA term 'sleep apnea syndrome' which includes the following synonyms: hypopnea syndrome, OSA syndrome, central sleep apnea syndrome, sleep apnea, OSA hypopnea syndrome, apnea syndrome, sleep apnea syndrome, sleep apnea syndromes. Kaplan-Meier estimates for the cumulative incidence rates of OSA in each treatment group were plotted over time for patients without OSA at baseline. A stratified Cox proportional hazards regression model was constructed to assess the association between ertugliflozin treatment and incident OSA with adjustment for age, sex, geographic region, baseline body mass index (BMI), glycosylated hemoglobin (HbA1c), and estimated glomerular filtration rate, and with stratification by enrollment cohort (before and after protocol amendment).

**Results:** 8246 patients were enrolled in VERTIS CV, including 7697 (93.3%) patients without baseline OSA (pooled ertugliflozin:  $n=5136$ ; placebo:  $n=2561$ ). Baseline characteristics of patients without a history of OSA at baseline included: mean age 64.3 years; BMI  $31.7 \text{ kg/m}^2$ ; HbA1c 8.2%; 69.2% male; 88.3% White. The mean duration of follow-up was 3.5 years. The OSA incidence rate was 1.44 per 1000 person-years vs. 2.61 per 1000 person-years among patients treated with ertugliflozin vs. placebo,

respectively, corresponding to a 48% relative adjusted hazard reduction (HR 0.52; 95% CI: 0.28–0.96,  $P=0.04$ ). The Kaplan-Meier plot showed an early differentiation in the incidence of OSA with ertugliflozin vs. placebo, with separation of the curves apparent at Month 6.

**Conclusion:** In VERTIS CV, the SGLT2 inhibitor ertugliflozin reduced the incidence of OSA in patients with T2D and ASCVD. These data contribute to the growing body of literature that SGLT2 inhibitors may have a significant beneficial impact on OSA.

**Acknowledgments:** Sponsored by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA in collaboration with Pfizer Inc., New York, NY, USA.

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### EVALUATION OF SLEEP-DISORDERED BREATHING IN CHILDREN AND ADOLESCENTS REFERRED TO THE SLEEP WARD OF QAZVIN CHILDREN'S HOSPITAL DURING 2014-2019

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**Introduction:** Polysomnography is a method for examining information obtained from physiological changes in the body related to sleep and wakefulness, as well as a gold standard for diagnosing respiratory diseases. The aim of this study was to diagnose respiratory disorders in children and adolescents with sleep disorders using polysomnography.

**Materials and Methods:** In this cross-sectional retrospective study, the complete data of 112 children and adolescents aged 0-18 years who were referred to the sleep ward of Qazvin Children's Hospital due to sleep disorders and polysomnography were examined for respiratory disorders. The results of polysomnography, prevalence and severity of obstructive sleep apnea (OSA) in these children were determined.

**Results:** The most common sleep disorder was restless sleep which was seen among 68 (60.71%) patients. 104 (92.85%) patients had sleep apnea. Also 66 (58.92%) patients with Severe OSA syndrome, 19 (16.96%) patients with moderate OSA syndrome, 14 (12.5%) patients with mild OSA syndrome and 5 (4.46%) patients also had central sleep apnea. Also, 88 (78.57%) of the subjects had less than normal sleep efficiency (less than 90%) and 34 (30.35%) had normal and desirable sleep efficiency. Treatment recommendations for 46 (41.7%) patients, 27 (24.10%) patients and 20 (17.85%) patients, respectively; total adenotonsilectomy, medical therapy for OSA and non-invasive ventilation (NIV).

**Conclusions:** OSA was diagnosed in a large number of children in this study. Therefore, serious attention to informing and educating parents, and screening for good respiratory disorders and wakefulness in children seems necessary.

### FEASIBILITY OF AMBULATORY BLOOD PRESSURE MONITORING IN THE PREDICTION OF OBSTRUCTIVE SLEEP APNEA SYNDROME

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**Introduction:** In European guidelines for management of arterial hypertension (AH), obstructive sleep apnea syndrome (OSAS) is considered a common condition that alters the course of this disease. It was found that nocturnal episodes of apnea are accompanied by significant fluctuations in blood pressure (BP). There are data confirming the independent role of OSAS in the pathogenesis of daytime increase in BP. The issue of OSAS diagnostics is topical due to high costs and availability of polysomnography. Thus, designing available OSAS screening techniques is extremely important. Ambulatory blood pressure monitoring (ABPM) is widely used in clinical practice, which makes it attractive for the early

diagnosis of OSAS in asymptomatic individuals. The aim of the study was to assess the possibility of using ABPM for the selection of individuals at high risk of OSAS among AH patients.

**Materials and Methods:** The study involved 67 patients (mean age 48.4±9.2 years) with grade I-II AH who received standard antihypertensive therapy with angiotensin-converting enzyme inhibitors as monotherapy or in combination with a thiazide-like diuretic.

We examined 68 males (72.3%) and 26 females (27.7%). The diagnosis of OSAS was made using night respiratory polygraphy. The study groups were formed as follows: group 1 (n=25) – patients with AH, group 2 (n=42) – patients with AH in combination with OSAS. The groups were comparable in gender composition, duration and degree of AH, and the received antihypertensive therapy.

**Results:** The target BP values were achieved in all patients (100%) from group 1 and in 80% of patients from group 2. Patients in group 2 compared with patients in group 1 were characterized by higher mean DBP at night (Avg. 68.0; 73.0] vs 62.0 [59.0; 71.0],  $p=0.028$ ), SBP variability during the day (Var. SBP 16.0 [14.0; 22.0] vs 11.5 [10.5; 15.5],  $p=0.024$ ), daytime DBP variability (Var. DBPd 18.0 [13.0; 20.0] vs 9.5 [8.0; 13.0],  $p=0.00017$ ) and at night (Var. DBPn 12.0 [8.0; 14.0] vs 7.0 [6.0; 10.0],  $p=0.025$ ).

The relationship between the studied parameters and the severity of OSAS was established: Avg. DBPd ( $r=0.39$ ;  $p=0.030$ ), Var. DBPd ( $r=0.57$ ;  $p=0.00013$ ), Var. DBPn ( $r=0.37$ ,  $p=0.028$ ).

Increased Var. DBPd was found to be a significant predictor of OSAS in patients with AH (OR=11.88; 95% CI=2.11-66.88).

The predictive value of Var. DBPd was analyzed using ROC analysis. If Var. DBPd value  $\geq 12$  mmHg with a sensitivity of 74.07%, and specificity of 91.67%, the presence of OSAS can be predicted in AH patient. The area under the curve was 0.87 (95% CI: 0.73–0.96),  $p<0.0001$ , which indicates a good predictive power of the model. The predictive value of a positive result is 95.24%, the predictive value of a negative result is 64.71%.

**Conclusions:** Var. DBP value  $\geq 12$  mm Hg possesses a high sensitivity and specificity for predicting OSAS in AH patients who receive standard antihypertensive therapy. This warrants using the studied ABPM parameter for the selection of patients requiring polysomnography.

### FEASIBILITY OF AMBULATORY BLOOD PRESSURE MONITORING IN THE PREDICTION OF OBSTRUCTIVE SLEEP APNEA SYNDROME

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**Introduction.** In European guidelines for management of arterial hypertension (AH), obstructive sleep apnea syndrome (OSAS) is considered a common condition that alters the course of this disease. It was found that nocturnal episodes of apnea are accompanied by significant fluctuations in blood pressure (BP). There are data confirming the independent role of OSAS in the pathogenesis of daytime increase in BP. The issue of OSAS diagnostics is topical due to high costs and availability of polysomnography. Thus, designing available OSAS screening techniques is extremely important. Ambulatory blood pressure monitoring (ABPM) is widely used in clinical practice, which makes it attractive for the early diagnosis of OSAS in asymptomatic individuals.

**Purpose.** To evaluate the feasibility of ABPM for the selection of individuals at high risk of OSAS among AH patients.

**Material and methods.** The study involved 67 patients (mean age 48.4±9.2 years) with grade I-II AH who received standard antihypertensive therapy with angiotensin-converting enzyme inhibitors as monotherapy or in combination with a thiazide-like diuretic.

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**Results.** The target BP values were achieved in all patients (100%) from group 1 and in 80% of patients from group 2. Patients in group 2 compared with patients in group 1 were characterized by higher mean DBP at night (Avg. 68.0; 73.0] vs 62.0 [59.0; 71.0],  $p=0.028$ ), SBP variability during the

day (Var. SBP 16.0 [14.0; 22.0] vs 11.5 [10.5; 15.5],  $p=0.024$ ), daytime DBP variability (Var. DBPd 18.0 [13.0; 20.0] vs 9.5 [8.0; 13.0],  $p=0.00017$ ) and at night (Var. DBPn 12.0 [8.0; 14.0] vs 7.0 [6.0; 10.0],  $p=0.025$ ).

The relationship between the studied parameters and the severity of OSAS was established: Avg. DBPd ( $r=0.39$ ;  $p=0.030$ ), Var. DBPd ( $r=0.57$ ;  $p=0.00013$ ), Var. DBPn ( $r=0.37$ ,  $p=0.028$ ).

Increased Var. DBPd was found to be a significant predictor of OSAS in patients with AH (OR=11.88; 95% CI=2.11–66.88).

The predictive value of Var. DBPd was analyzed using ROC analysis. If Var. DBPd value  $\geq 12$  mmHg with a sensitivity of 74.07%, and specificity of 91.67%, the presence of OSAS can be predicted in AH patient. The area under the curve was 0.87 (95% CI: 0.73–0.96),  $p<0.0001$ , which indicates a good predictive power of the model. The predictive value of a positive result is 95.24%, the predictive value of a negative result is 64.71%.

**Conclusion.** Var. DBP value  $\geq 12$  mm Hg possesses a high sensitivity and specificity for predicting OSAS in AH patients who receive standard anti-hypertensive therapy. This warrants using the studied ABPM parameter for the selection of patients requiring polysomnography.

### FEASIBILITY OF TRANSCATHETER CAVAL VALVE IMPLANTATION TO IMPROVE SLEEP-DISORDERED BREATHING IN PATIENTS WITH SEVERE TRICUSPID REGURGITATION—A PILOT STUDY

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**Introduction:** Chronic heart failure (CHF) is a growing problem which can affect over 25 million people in the world. The prevalence of heart failure in developed countries is generally around 1–2% and more than 10% in patients above 70 years. Caval valve implantation (CAVI) has been evaluated as an inoperable treatment option for patients with severe symptomatic tricuspid regurgitation (TR). The aim of our study is to study the effect of CAVI on sleep disorder breathing (SDB) in patients with right heart failure and TR.

**Materials and Methods:** Twenty right heart failure patients with severe symptomatic TR were enrolled. These patients underwent ApneaLink, echocardiography, cardiopulmonary exercise (CPET), and laboratory testing. This study was single-center and nonblinded.

**Results:** After CAVI, there were no significant changes in sleep parameters, echocardiographic variables, laboratory tests, lung function, and CPET.

**Conclusions:** In conclusion, these data may suggest that CAVI have no effect on SDB; but additional follow-up fully powered studies with appropriate statistical analyses are required.

**Acknowledgements:** We thanked Professor Thomas Penzel and Professor Christoph Schöbel for contributing to coordinating this project. Youmeng Wang was financially supported by the China Scholarship Council (CSC) for her MD study in Sleep Medicine Center, Charité Universitätsmedizin. The CSC had no role in the design or conduct of this research.

### GENDER AND MENOPAUSAL STATUS CORRELATE WITH SLEEP SURGERY OUTCOME

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**Introduction:** With recognized anatomic and physiological differences between males and females, it is critical to describe outcomes of sleep surgery with respect to gender. The objective of this study is to compare the subjective and objective outcomes of phase I sleep surgery with respect to gender and age.

**Materials & Methods:** This was a retrospective review of adult subjects who presented to a single center for surgical evaluation of OSA from

January 2019 to June 2021. Only subjects undergoing phase I surgery (turbinate reduction, septoplasty, nasal valve surgery, DOME, tonsillectomy, preservation palatopharyngoplasty, tongue base reduction, genioglossus advancement, and upper airway stimulation), who also had complete pre and post-operative PSG data were included. Objective measures were post operative apnea hypopnea index (AHI), oxygen desaturation index (ODI), and lowest oxygen saturations (LOS). Subjective outcomes include Epworth Sleepiness Scale (ESS), and Nasal Obstruction and Septoplasty Effectiveness (NOSE) questionnaires. The groups were matched for age and pre-operative BMI.

**Results:** Twenty-six subjects met inclusion criteria, of which 12 were female and 13 were males. Of the females 5 were post-menopausal. The average male pre-operative AHI, ODI, lowest SpO<sub>2</sub>, and ESS were 34.4±28.7, 30.2±28.3, 80.7±6.6, and 10.3±5.6 respectively. Pre-operative values for females were, 31.9±19.2, 18.47±20.4, 82.8±8.4, and 12.5±4.8 respectively. The average AHI reduction in males was 25.5±29.1, and for females it was 8.3±21.0 ( $p=0.042$ ). Specific to post-menopausal females, Average AHI reduction was -8.3±14.4 and 20.2±16.6 for pre-menopausal females ( $p=0.01$ ). The average ESS reduction in males was 3.1±3.2 ( $p=0.22$ ) and for females 5.5±5.4 ( $p=0.001$ ).

**Conclusions:** In this cohort, pre-menopausal women have higher objective surgical success rate (Sher's criteria) after phase I surgery as compared to post-menopausal women. Men respond more favorably than women to phase I surgery based on AHI reduction, but not with ESS. Gender and menopause status are important factors in evaluating efficacy of sleep surgery.

**Acknowledgements:** Nil

### HEART RATE RESPONSE AND SLEEP APNEA SPECIFIC HYPOXIC BURDEN TO APNEAS AND HYPOPNEAS PREDICTS INCIDENT ATRIAL FIBRILLATION IN MODERATE TO SEVERE OBSTRUCTIVE SLEEP APNEA

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**Introduction:** Obstructive Sleep Apnea (OSA) is associated with an increased risk of atrial fibrillation (Afib). Recent studies have shown that OSA is a heterogeneous disorder and conventional indices of OSA severity are limited for risk stratification. We have recently shown that the OSA-related cardiovascular risk is associated with an elevated pulse rate response to apneas and hypopneas during sleep ( $\Delta$ HR) and high levels of the Sleep Apnea Specific Hypoxic Burden (SASHB). Here, we sought to test the association of  $\Delta$ HR and SASHB with incident Afib in individuals with moderate to severe OSA (Apnea-hypopnea index (AHI)  $\geq 15$  events/h).

**Materials and Methods:** In this study, we included individuals from the Sleep Heart Health Study (SHHS) with no history of both Afib and coronary heart disease with an AHI  $\geq 15$  events/h at baseline. As described previously, the pulse signal from baseline sleep studies was used to calculate  $\Delta$ HR and SASHB.  $\Delta$ HR was defined as the difference between a maximum pulse rate during a subject-specific search window (search window extended from the pre-event minimum to the post-event minimum of the event-related, ensemble-averaged pulse rate) and an event-related minimum pulse rate (the minimum pulse rate during apneas/hypopneas) and SASHB was defined as the "area under the SpO<sub>2</sub> curve". Incident Afib was determined using a 12-lead electrocardiogram recorded during SHHS visit 2 or by adjudication of medical records by the parent cohort at any time between SHHS visit 1 and visit 2 (~4 years). The adjusted odds ratios of incident Afib was determined using a multivariable logistic regression model adjusted by age, gender, race, body mass index, smoking, and alcohol usage at baseline.

**Results:** A total of 1,106 participants with moderate to severe OSA were included in the analysis. During the follow-up period, 131 (11.8%) participants developed incident Afib. Every 1SD increase in  $\Delta$ HR was associated with an adjusted odds ratio (OR) of 1.24 [95% CI: 1.01 - 1.51] ( $p$ -value=0.03); Every 1SD increase in SASHB, OR 1.21 [95% CI: 1.01 - 1.44] ( $p$ -value=0.03) for incident Afib. Conversely, every 1SD increase in AHI was not associated with an increased risk of incident Afib, OR 1.08 [95% CI: 0.87 - 1.32] ( $p$ -value=0.47).

**Conclusions:** In individuals with moderate to severe OSA, elevated heart rate response to apneas and hypopneas and SASHB were associated with incident Afib. Prioritizing OSA treatment for individuals with moderate to severe OSA who exhibit elevated  $\Delta$ HR and SASHB may prevent incident Afib and reduce the risk of stroke.

#### HIGH-RISK OF OBSTRUCTIVE SLEEP APNEA AMONG PATIENTS WITH ATRIAL FIBRILLATION

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**Introduction:** Obstructive sleep apnea (OSA) is a common sleep breathing disorder and is prevalent among patients with cardiovascular disease. Atrial fibrillation (AF) represents the most prevalent cardiac arrhythmia with significant morbidity and mortality. This study aims to elucidate the association between these two common disorders

**Materials and Methods:** We conducted a case-control study, including patients diagnosed with AF and subjects without past or current AF who visited cardiology clinics. The OSA symptoms were assessed using the Berlin questionnaire, a validated tool to stratify the participants into “low-risk” or “high-risk” for OSA. Also, the demographic characteristics of participants and their comorbidities were collected during the interview.

**Results:** A total of 460 participants, 160 with AF and 300 without AF, were included in this study. Their mean age (SD) was 61.4 (11.1) years, ranging from 22 to 92 years, 262 (57.0%) were men, and 162 (35.2%) were current smokers. Both groups were similar in age, gender, body mass index (BMI), and smoking ( $p>0.05$ ). The proportion of participants with high-risk for OSA was higher among patients with AF (76.3%) than the controlled group (24.7%) ( $p<0.001$ ). The binary logistic regression model shows a significant association between AF and OSA after adjustment for relevant confounders, with an adjusted odds ratio of 5.48 (95% CI 2.74 to 10.95,  $p<0.001$ ). Among the AF group, those with high-risk for OSA were older, with a mean (SD) age of 64.5 (11.7) than those with low-risk for OSA (53.9 (12.8)), ( $p<0.001$ ). Patients with AF and high-risk for OSA were likely more likely to be men, obese, and smokers compared to those with low-risk for OSA ( $p<0.05$ ). Compared to AF patients with low-risk for OSA, those with high risk for OSA had a higher prevalence of HTN, dyslipidemia, DM, HF, ( $p<0.001$ ).

**Conclusions:** The study findings shed light on a significant association between OSA and AF independent of traditional OSA risk factors. Further investigations will be required to define the pathophysiological connection between these two diseases.

#### HYPGLOSSAL NERVE STIMULATION AND OXYGEN THERAPY: AN EFFECTIVE COMBINED TREATMENT FOR EMERGENT CENTRAL SLEEP APNEA

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**Introduction:** Hypoglossal nerve stimulation (HNS) is an alternative treatment for obstructive sleep apnea (OSA) in case of failure of conventional treatment by continuous positive airway pressure (CPAP) and mandibular advancement device (MAD). Treatment-emergent central sleep apnea (TECSA) arising under CPAP or MAD is a well-known entity but few cases have been described in relation to HNS. We report the case of two TECSA arising under HNS, that resolved with a combined treatment of oxygen therapy (OT).

**Materials and Methods:** We report the cases of 2 women of respectively 74- and 63-year-old known for a severe OSA with a failure of conventional treatment with CPAP and MAD.

**Results:** The control PSG after oxygen supplementation showed a

significant decrease in both the obstructive and central events. The apnea/hypopnea index (AHI) decreased from 36.8/hour to 8.4/h and 81.6/h to 8.3/h respectively. The central apnea decreased from 10.7/h to 1/h and from 1.4/h to 0 respectively.

**Conclusions:** The development of central apnea after HNS is not well documented in the literature. With a combined treatment of HNS and OT, we observed an objective improvement of the sleep disorder and of the quality of sleep, which can be explained by stabilization of the retro control respiratory loop gain.

**Acknowledgements:** Beharry Avinash<sup>a</sup>; Salati Victoria<sup>a</sup>; Heinzer Raphael<sup>c</sup>; Chatelain Sibylle<sup>b</sup>; Lamercy Karma<sup>a</sup>

#### ICHOSA (INTRA CEREBRAL HEMORRAGE AND OBSTRUCTIVE SLEEP APNEA) PROJECT: FIRST RESULTS

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**Introduction:** OSAS can impair ischemic stroke risk especially by alteration of intracranial pressure, blood flow, glucose metabolism, atherogenesis, blood coagulation, cardiac arrhythmia and arterial hypertension, determining a worse functional outcome. In OSA patients arterial hypertension (AH) is related to drug-resistance and modification in nocturnal blood pressure profile. About OSA and ICH few data are available in literature, most anecdotal. We can speculate that OSA can affect on ICH by AH.

**Materials and Methods:** We sought to test whether suspected OSA is more prevalent in ICH group than in controls. In order to limit potential confounding variables associated with acute ICH, we tested by Berlin Questionnaire (BQ) and Epworth Sleepiness Scale (ESS) referring to the previous 3 months before ICH 111 ICH patients consecutively referred to Modena Stroke Unit and matched by sex, age, BMI and Charlson Comorbidity Index (CCI) with 111 ischemic stroke patients and 111 controls. Secondarily, we tried to assess if OSA in ICH could affect on functional outcome (mRS).

**Results:** In ICH patients we found BQ positivity in 30,6% vs 25,2% in ischemic stroke patients vs 13,5% in controls ( $p=0.01$ ). Moreover BQ positive ICH patients had more disability, mortality, length of recovery, AH, drug resistance hypertension and nocturnal blood pressure profile alteration, especially non dipper pattern, than BQ negative ICH.

**Conclusions:** The results suggest that OSA could be considered a risk factor and a negative prognostic factor in ICH patients, as described before in ischemic stroke patients. This phenomena probably is related to blood pressure alteration caused by sleep breathing disorder.

**References:** -Obstructive sleep apnea syndrome. A probably cause of therapy refractory hypertension in intracerebral hemorrhage. Wessendorf et al. Nervenarzt.1999. -Obstructive sleep apnea is frequent in patients with hypertensive ICH and is related to perihematoma edema. Pontes-Neto et al. Cerebrovasc Des. 2009.

#### IDENTIFYING THE SITE AND PATTERN OF PHARYNGEAL COLLAPSE USING POLYSOMNOGRAPHIC AIRFLOW SHAPES

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**Introduction:** The site and pattern of pharyngeal collapse have clear implications for efficacy of non-CPAP therapies for obstructive sleep apnea

(OSA), but are currently not directly recognizable using polysomnography. Notably, patients with complete concentric collapse at the palate (CCCp) or lateral wall collapse during drug-induced sleep endoscopy (DISE) respond less favorably to hypoglossal nerve stimulation or oral appliance therapy than patients with tongue-base collapse. Multiple small endoscopy studies have now demonstrated that the airflow shape profile as measured during endoscopy reflects the upper airway site and pattern of collapse, yet no large study has utilized a full polysomnography to provide predictive insight into these characteristics of collapse measured separately via DISE.

**Materials and Methods:** Retrospective cohort analysis identified 181 patients with both polysomnography and DISE results. Six simplified flow-shape characteristics were identified as candidate interpretable predictors of CCCp (primary outcome variable, N=42/181), including negative-effort dependence (scoopiness), inspiratory skewness, and peak flow in early inspiration. Mean values for each characteristic during hypopnea breaths provided representative values for each patient. Multivariable logistic regression modelling combined the six characteristics to predict the site of collapse. Odds ratios for true CCCp between predicted subgroups were quantified before and after leave-one-out cross-validation. Partial collapse categories were excluded from primary analyses (N=9 for concentric palate). Secondary analysis examined complete lateral wall-, tongue-base-, or epiglottic- collapse.

**Results:** In multivariable regression, CCCp was associated with all six characteristics, notably greater scoopiness ( $\beta=17.4\pm 3.8$  per SD (0.14),  $p<0.0001$ ), skewness ( $\beta=14.0\pm 5.3$  per SD (0.12),  $p=0.009$ ), and early inspiratory peak flow ( $\beta=11.3\pm 6.7$  per SD (0.08),  $p=0.003$ ) compared to patients without concentric palatal collapse (pseudo- $R^2=0.20$ , model- $P=0.0039$ ). Odds ratios [95%CI] for CCCp in predicted CCCp vs. predicted non-CCCp were 9.8 [4.0-23.8] before and 3.0 [1.4-6.1] after cross-validation. Analysis using separate training (N=86) and validation (N=86) yielded similar results (OR=3.1 [1.1-8.3]). Results were upheld after adjustment for baseline AHI and body mass index as existing predictors. Separate cross-validated models using the same flow-shape characteristics provided promising prediction of complete lateral wall- (N=53, cross-validated OR=4.6[2.1-10.2]), tongue-base- (N=64, OR=2.1[1.1-4.2]) and epiglottic- (N=30, OR=2.6[1.2-5.8]) collapse. Characteristics between CCCp and lateral walls were similar (scoopiness, left skewed), and diametrically opposed to tongue-base and epiglottic characteristics. An exploratory model discriminated between CCCp or complete lateral wall collapse (N=31) vs. complete tongue-base or epiglottic collapse (N=41, total N=72, OR=4.3[1.6-11.8] after cross-validation, pseudo- $R^2=0.33$ ).

**Conclusions:** Polysomnographic flow shape analysis holds promise for non-invasive recognition of the pharyngeal site and pattern of collapse without the need to perform DISE. Characteristics are similar between patients with CCCp and lateral wall obstruction, but clearly different from those with tongue-base or epiglottic obstruction. Considering the latter subgroup is best suited to therapies advancing the tongue or mandible, airflow shape characteristics may provide insight into the success/failure of site-specific OSA therapies.

#### IMPACT OF SLEEP DISORDERED BREATHING ON PSYCHOSOCIAL STRESS FACTORS OF PATIENTS COMPLAINING OF PAIN WITHIN OROFACIAL REGION: PRELIMINARY REPORT

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**Introduction:** Sleep-related breathing disorders (SRBD) is the most common group of sleep disorders and a major public health concern. Obstructive sleep apnea (OSA) is the most prevalent, ranging from 9% to 38% in the general population. OSA is associated with several physiological changes, including intermittent hypoxia, sympathetic activation, sleep fragmentation and metabolic dysregulation. Persistent snoring is also part

of this group, with a controversial impact on health and a reported prevalence ranging from 10% to 60% in the absence of OSA. A growing body of work has demonstrated that OSA and habitual snoring are associated with cognitive, behavioural and psychosocial problems, thus negatively influencing patient's quality of life. This can be extended to several clinical populations, such as patients experiencing orofacial pain or discomfort and therefore compromise therapeutic outcomes. The goal of this work was to explore associations between the respiratory distress caused by self-reported sleep breathing conditions and psychometric variables as indicators of psychosocial stress and associated wellbeing using data extracted from the WISE platform.

**Material and Methods:** In this cross-sectional study with 415 patients seeking care at the orofacial pain unit of University of Zurich, Switzerland, the sample was characterized from a demographic perspective, of the presence of self-reported sleep-disordered breathing and its relation with psychometric variables obtained through validated questionnaires for the Swiss populations, namely IPQ, DCQ, GAD-7, IEQ, PCS, PHQ-4, PHQ-9 e PHQ-Str. The effect of confounders such as gender, age, BMI, typical pain intensity and employment status on the psychometric evaluations was also analysed. For all analyses, the statistical significance was set at  $p \leq 0.05$ .

**Results:** From the patients who responded to the screening question "During the last 4 weeks, how much have you been bothered by any of the following problems: snoring/apnea during sleep?" (N=415), most were female (N=57; 62.6%) and more than half were 40-59 years old (N=49; 53.9%). Most patients reporting snoring or sleep apnea were workers (N=56; 61.5%) and retired people reported the second highest prevalence (N=15; 16.5%), reflecting the underlying factor of age. For all the assessed domains (depression, anxiety, injustice experience, illness perception, dysmorphic concern, distress and pain-related catastrophizing), the percentage of patients reaching a clinically relevant score was higher for the group with self-reported respiratory distress, except for dysmorphic concern. Concerning the multiple regression analyses performed, the key finding was that respiratory distress was positively associated with all domains except dysmorphic concern, being a statistically significant predictor of GAD-7, IEQ and PHQ-4. For all analyses, the statistical significance was set at  $p \leq 0.05$ .

**Conclusion:** Our study has important practical implications as they highlight the importance of assessing sleep variables in clinical evaluations. Even though we worked with a subjective assessment of snoring and sleep apnea, the findings herein presented support the relation described in previous epidemiologic studies, which have consistently demonstrated that sleep disordered breathing is associated with depression and anxiety symptoms. In this particular sample of patients complaining from pain within the orofacial region this could be even more important and strongly affect prognosis.

#### IMPROVING CPAP COMPLIANCE: TRANSCUTANEOUS NASAL VALVE STABILIZATION

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**Introduction:** CPAP compliance poses a tremendous challenge in the non-surgical management of obstructive sleep apnea. Nasal obstruction contributes greatly to this, and surgical intervention to improve nasal breathing can therefore be the difference in treatment efficacy. Nasal valve collapse is a common cause of obstruction and is the area of maximum resistance in the upper airway. The dynamic collapse of the upper lateral cartilage during inhalation contributes to the development of symptoms related to nasal obstruction, and is one of the anatomical regions to address when considering surgical correction of nasal obstruction. We describe a transcutaneous approach to nasal valve stabilization and present preliminary outcomes post operatively regarding effects on CPAP use, as well as evaluating functional and cosmetic outcomes using validated outcomes such as Standardized Cosmesis and Health Nasal Outcome Survey (SCHNOS), Nasal Obstruction Symptoms Evaluation (NOSE) score, and also the Lateral Wall Insufficiency (LWI) scoring system. SCHNOS is a validated outcome measure that evaluates both function/obstruction

(SCHNOS-O) and nasal cosmesis (SCHNOS-C)

**Methods:** A retrospective chart review of patient was completed from 5/1/2021 to 7/25/21 for patients with nasal obstruction associated with valve collapse with or without septal deviation and turbinate hypertrophy. Pre and post operative SCHNOS, LWI grading system scores, and NOSE scores were obtained, as well as evaluating CPAP usage before and after surgery. **Results:** 20 patients met inclusion criteria. The mean score for SCHNOS-O and SCHNOS-C decreased from 65 to 25 ( $p<.05$ ) and 15 to 10 ( $p<.05$ ) respectfully. The mean score for NOSE decreased from 55 to 15 ( $p<.03$ ) and the mean decrease in LWI was from 1.8 to 0.4 ( $P<.02$ ). All patients found CPAP to be less intrusive post operatively with higher reported usage rates. **Conclusion:** For patients with nasal valve collapse, a transcutaneous approach to stabilize the nasal valve can be utilized to stabilize the upper lateral cartilage. This minimally invasive but highly effective surgery improves nasal function and CPAP adherence without altering the cosmesis of the nose.

### IMPROVING POSITIVE AIRWAY PRESSURE THERAPY ADHERENCE WITH COGNITIVE-BEHAVIORAL INTERVENTIONS: A META-ANALYSIS

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**Introduction:** The first-line treatment of obstructive sleep apnea (OSA) is positive airway pressure therapy (PAP). However, patient adherence with PAP therapy is a critical aspect in the management of OSA. Indeed, poor adherence, ranging between 23% to 89%, hinders the effectiveness of treatment and increases risk of mortality. Non-pharmacological interventions are promising for promoting adherence to PAP therapy. The aim of our meta-analysis is to quantify the efficacy of Psychoeducation, Behavioral, and Cognitive-Behavioral interventions on PAP adherence in OSA patients through a meta-analysis.

**Materials and Methods:** A systematic search of the relevant literature was performed by three independent researchers in Pubmed, Psychinfo, Cinhal, Embase, Scopus, and Medline up to April 2021. We include Randomized Controlled Trial (RCT) with Psychoeducation, Behavioral, and Cognitive-Behavioral interventions in order to improve positive airway pressure adherence, in OSA patients. The publication bias has been evaluated qualitatively following Cochrane Collaboration guidelines, moreover, abstracts conference have been searched in special issues of the most relevant journals in the field. The classical meta-analysis model was estimated using Hedges method. PAP adherence (i.e. mean of PAP usage in hours per night) was the principal outcome, and the follow-up duration (FU, i.e. time between baseline and the final evaluation) was used as covariate in the model.

**Results:** 47 RCT were selected (N intervention=3571; N controls=3537). Psychoeducational (EDU) interventions were proposed in 32 RCT studies (N intervention=1878; N controls=1814), and the results suggest that the EDU interventions' effects on PAP adherence is medium (RE model  $d=0.56$ , CI 0.18-0.93). 10 RCT administered Behavioral (BEH) intervention to 1462 OSA patients compared with 1493 controls, and the meta-analysis showed adherence improvement with a medium intervention's effect (RE model  $d=0.44$ , CI 0.20-0.67). Cognitive-Behavioral interventions (CBT) were proposed in 5 RCT studies (N intervention=231; N controls=230), and the results displayed a medium-large CBT interventions' effect (RE model  $d=0.69$ , CI 0.16-1.22). No effect of follow-up duration was found in all three models.

**Conclusions:** This meta-analysis provides evidence of a medium to large positive effect of Psychoeducation, Behavioral, and Cognitive-Behavioral interventions compared to the control group, on PAP adherence in OSA patients. CBT therapy on PAP adherence seems to lead to most benefits in terms of treatment adherence.

**Acknowledgements:**

### INCIDENCE AND RISK FACTORS OF CHRONIC OPIOID USE AFTER SLEEP APNEA SURGERY

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**Introduction:** The opioid crisis is an ongoing health problem and financial burden in the US, with surgeons being the second highest prescriber of opioids. Amongst obstructive sleep apnea (OSA) subjects undergoing surgery, there's a paucity of data on the patterns of perioperative opioid prescription and its sequelae.

The aim of the study is to assess the prevalence and risk factors of persistent, prolonged and inappropriate use of postoperative opioids after sleep apnea surgical procedures.

**Materials and Methods:** Using the IBM MarketScan Commercial and Medicare Supplemental research database, subjects who underwent different sleep surgery procedures (UPPP, multilevel soft tissue surgery and skeletal surgery) between January 1, 2007, and December 31, 2015, were identified. Subjects under 18 years old, had no insurance coverage 1 before and after the surgical procedure, had an additional anesthesia event in the year following surgery, and filled an opioid prescription within the year prior to surgery were excluded.

**Main outcomes and measures:** Opioid prescription patterns in the immediate postoperative period. Outcomes included rates of persistent opioid use (prescriptions filled 90-180 days postoperatively), rates of prolonged opioid use (prescriptions filled 181-365 days postoperatively) and inappropriate opioid use (prescriptions exceeding 100 MME). Evaluated variables comprised of patient demographics, surgical procedure category, and pertinent comorbidities.

**Results:** A total of 10,766 surgical procedures met inclusion criteria. The most common surgical procedure was multilevel surgical procedures with UPPP accounting for 51.4%. There was a trend of increased rates of perioperative opioid prescription.

On multivariable logistic regression analysis, perioperative opioid prescription and smoking were independent risk factors for inappropriate opioid use (OR= 31.51,  $p<0.001$ ; OR= 1.41,  $p=0.016$  respectively). Opioid prescription and hypertension were independent risk factors for continuous persistent opioid use (OR=37.8,  $p<0.001$ , OR=1.38,  $p=0.008$ ). Perioperative opioid prescription, and previous opioid dependence diagnosis, smoking and male gender were associated with continuous prolonged opioid use (OR=73.1, 8.13, 1.95, 1.55, respectively;  $p<0.001$ , 0.020, 0.024, 0.032, respectively).

**Conclusions:** Perioperative opioid prescription is an independent risk factor for persistent, prolonged and inappropriate opioid prescription after OSA subjects undergoing sleep surgery.

**Acknowledgements:**

### INDEPENDENT PREDICTORS OF LONG-TERM MORTALITY OF PATIENTS WITH MODERATE TO SEVERE SLEEP WITH REDUCED LEFT VENTRICULAR EJECTION FRACTION AFTER MYOCARDIAL INFARCTION

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**Introduction:** Sleep apnea (SA) has a high prevalence in patients after myocardial infarction (MI). While SA might be a modifiable risk factor, recent data suggest that SA is severely underdiagnosed in patients after MI. There is a limited evidence about long-term prognosis of patients with moderate to severe sleep apnea with reduced left ventricular ejection fraction (REF) after MI. We therefore prospectively investigated the prognosis.

**Materials and Methods:** We prospectively studied 782 consecutive

patients admitted to the hospital with the diagnosis of acute MI. The study was conducted in two tertiary care institutions, where primary percutaneous coronary intervention (PCI) is the standard of care in the treatment of acute MI. All subjects underwent sleep evaluations using a portable diagnostic device after at least 48 hours post-admission, provided they were in stable condition. Patients were followed for median follow-up of 44 months.

**Results:** Almost all patients (98%) underwent urgent coronary angiography and 91% of patients underwent primary PCI. 175 (22.4%) patients had technically inadequate limited sleep studies (less than 4 h recording time or inability to score study due to excessive artifact). We therefore analyzed the data from 607 patients who had good quality sleep study records. SA was present in 63% of patients after MI with PEF and in 72% of patients with REF (LVEF < 45%),  $p=0.05$ . Moderate to severe SA was present in 33.1% of patients after MI. There was a higher total mortality in REF (21.7%) than in PEF (10.6%) patients after MI in the group of moderate to severe SA ( $p=0.033$ ). Independent predictors of mortality according to the multivariate analysis were type 2 diabetes mellitus (OR 5.003, 95% CI 1.968 to 12.717,  $p=0.001$ ), history of previous MI (OR 4.633, 95% CI 1.832 to 11.718,  $p=0.001$ ), age (OR 2.326, 95% CI 1.417 to 3.819,  $p=0.001$ ) and apnea index (OR 1.216, 95% CI 1.023 to 1.445,  $p=0.027$ ).

**Conclusions:** MI patients with moderate to severe SA and left ventricular systolic dysfunction had worse long-term prognosis than those with preserved systolic function and independent predictors of long-term mortality are type 2 diabetes mellitus, history of previous MI, age and apnea index.

#### INSULIN RESISTANCE, OBSTRUCTIVE SLEEP APNEA PHENOTYPES, AND RESPONSE TO CPAP TREATMENT IN ADULTS WITH CORONARY ARTERY DISEASE

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**Introduction:** We addressed the relationship between insulin resistance and obstructive sleep apnea (OSA) phenotypes in adults with coronary artery disease (CAD), and response to treatment with continuous positive airway pressure (CPAP) after 12 months.

**Materials and Methods:** This was a secondary analysis of the RICCADSA trial, conducted in Sweden between 2005 and 2013. For the current protocol, 392 nondiabetic CAD patients (297 with OSA [apnea-hypopnea index [AHI]  $\geq 15$ /h on cardiorespiratory polygraphy, and 95 with no-OSA [AHI] < 5/h) within six months after revascularization were included. OSA patients were analyzed in two groups: Nonsleepy (Epworth Sleepiness Scale [ESS] score < 10;  $n=182$ ) vs sleepy (ESS  $\geq 10$ ;  $n=115$ ). The nonsleepy OSA group was randomized to CPAP ( $n=88$ ) or no-CPAP ( $n=94$ ), and the sleepy OSA patients were offered CPAP. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated from fasting blood glucose and insulin levels, and categorized in tertiles in order to define the upper tertile as insulin resistance at baseline.

**Results:** The HOMA-IR values ranged from 0.26 to 34.44 (median 1.9), and the upper tertile was  $\geq 2.47$ . In all, 24.2% of CAD patients with no-OSA, 33.5% of nonsleepy OSA, and 40.9% of sleepy OSA ( $p=0.039$ ) had insulin resistance based on the categorization of the entire cohort. Compared to no-OSA, nonsleepy OSA phenotype was associated with the highest tertile of HOMA-IR with an odds ratio (OR) 1.83, 95% confidence interval (CI) 1.01–3.34;  $p=0.047$ , and sleepy OSA with an OR 2.05 (95% CI 1.01–3.81;  $p=0.024$ ), adjusted for age and gender. The associations were no longer significant when body-mass-index (BMI) was entered into the model. At 12-month follow-up, there was a significant decline in the HOMA-IR values in all subgroups with the highest magnitude among the sleepy OSA phenotype. There was no correlation with CPAP adherence in the adjusted multivariate models. Improvement in the HOMA-IR values were determined by age, sex and weight change at the follow-up.

**Conclusions:** There was a significant association between OSA and insulin resistance, which was more prominent among the patients with the sleepy

phenotype in this nondiabetic CAD cohort. However, these associations were dependent on BMI, and there was a significant improvement in insulin resistance over time following revascularization, which was unrelated to CPAP treatment.

**Clinical trial registration:** Registered with [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (NCT00519597).

**Funding:** Swedish Research Council, Swedish Heart-Lung Foundation, and ResMed Foundation.

#### INTERDISCIPLINARY WEIGHT LOSS AND LIFESTYLE INTERVENTION FOR OBSTRUCTIVE SLEEP APNOEA: THE INTERAPNEA RANDOMISED CONTROLLED TRIAL

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**Introduction:** Obesity is the leading attributable cause of obstructive sleep apnoea (OSA); however, the effects of weight loss and lifestyle interventions on OSA and comorbidities still remain uncertain. We sought to determine the efficacy of an interdisciplinary weight loss and lifestyle intervention on OSA and comorbidities among adults with overweight/obesity and moderate-to-severe OSA.

**Materials and Methods:** The INTERAPNEA study was a randomised, parallel-group, open-label trial conducted at the University of Granada (Granada, Spain). Men aged 18–65 years with overweight/obesity and moderate-to-severe OSA treated with continuous positive airway pressure (CPAP) were recruited from a hospital-based referral centre (Hospital Universitario Virgen de las Nieves, Granada, Spain) and randomly assigned to usual-care (i.e., CPAP), or an eight-week weight loss and lifestyle intervention combined with usual-care. The primary endpoint was the change in the apnoea-hypopnoea index (AHI). Secondary endpoints comprised changes in other OSA sleep-related outcomes; body weight and composition; cardiometabolic risk; and health-related quality of life. The trial is registered with ClinicalTrials.gov (NCT03851653).

**Results:** Out of the 89 participants who underwent randomization (mean [ $\pm$ SD] age, 54 $\pm$ 8 years; mean AHI, 41 $\pm$ 22 events/hr), 49 were randomly assigned to the control group and 40 to the intervention group, from April 2019 to October 2020. The intervention group had a greater reduction in AHI (51% reduction; change in AHI, -21.2; 95% confidence interval, -25.4 to -16.9) than the control group (2.5; -2.0 to 6.9) at intervention endpoint, with a mean between-group difference of -23.6 events/hr (-28.7 to -18.5). At 6 months after intervention, the reduction in AHI in the intervention group was of 57%, with a mean between-group difference of -23.0 events/hr (-28.4 to -17.4). In the intervention group, 45% of participants no longer required CPAP at intervention endpoint; 15% attaining complete OSA remission. At 6 months after intervention, complete remission of OSA was attained by 29% of participants; 62% no longer requiring CPAP therapy. Greater improvements in body weight and composition, cardiometabolic risk, and health-related quality of life were also found in the intervention group as compared with the control group. No serious adverse events were reported.

**Conclusions:** An interdisciplinary weight loss and lifestyle intervention involving adults with CPAP-treated moderate-to-severe OSA resulted in clinically meaningful and sustainable improvements not only in OSA severity and comorbidities but also in health-related quality of life. Given the high prevalence of OSA, its complex and reciprocal interaction with obesity, and the fact that both conditions are readily treatable through an integrated behavioural intervention, health-care providers and policy-makers should, at the very least, consider this approach as a central strategy to comprehensively address the staggering impact of OSA on the health and welfare of our society.

**Acknowledgements:** Supported by the Spanish Ministry of Education and

Vocational Training; the University of Granada-LoMonaco S.L. Sleep Research Cathedra; the University of Granada Plan Propio de Investigación 2016 –Excellence actions: Unit of Excellence on Exercise and Health (UCEES); and the Regional Ministry of Economy, Knowledge, Enterprise and Universities (CECEU) of Andalusia.

#### INVESTIGATING VALUED ATTRIBUTES OF OSA CARE PATHWAY FROM THE PERSPECTIVE OF PATIENT AND HIGH-RISK INDIVIDUALS: A DISCRETE CHOICE EXPERIMENT

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**Introduction:** The current health care system is challenged with a large and rising demand for obstructive sleep apnoea (OSA) services. A paradigm shift in OSA management is required to incorporate the preferences of the end-users into the novel design of care pathways, including those with formally diagnosed patients and individuals at high risk of OSA. Understanding the preferences of existing and potential patients can help optimise the development of innovative OSA management pathways. Previous studies have examined the preferences of patients, yet these studies only focused on OSA therapies and management. Less is known regarding different attributes that construct the comprehensive OSA care pathways. This study aimed to provide empirical evidence of the values and preferences of individuals diagnosed with OSA and high-risk populations regarding their prioritisation of the distinct OSA care pathways at the stages of diagnosis, treatment and ongoing care.

**Materials and Methods:** A discrete choice experiment (DCE) was undertaken to capture the preferences of patients with an established diagnosis of OSA (n=421) and those undiagnosed but at high risk of having OSA (n=1033). The DCE questionnaire was integrated into a cross-sectional web-based survey which gathered information on demographics, OSA diagnosis status and symptoms, patient satisfaction, treatment motivations, options and compliance, general health and quality of life measured using EQ-5D-5L and FOSQ-10. Participants were adults ≥18 years of age recruited from an online panel in October 2019. The DCE approach used mixed logit regression models to determine preferences relating to eight salient features of the OSA management pathway, i.e. initial assessment, setting and diagnosis costs, waiting times, diagnostic test results interpretation, treatment options, provider of ongoing care and frequency of follow up visits.

**Results:** The findings indicate that all eight attributes investigated were statistically significant factors for respondents. Generally, both groups preferred low diagnostic costs, fewer follow-up visits, minimum waiting time for sleep study results, and sleep specialists to recommend treatment and as ongoing care providers. Distinct variation was found in all other attributes. Results from the Swait-Louviere test indicated that the data from 'undiagnosed, high-risk OSA' and 'diagnosed with OSA' groups cannot be pooled. Management of OSA in primary care was acceptable to both groups and was the most preferred option by the high-risk group for sleep study testing and ongoing care provision.

**Conclusions:** This study provides important insights into the characteristics of the OSA care pathway that are most valued by OSA diagnosed and undiagnosed, high-risk groups. Given the substantial unmet demand for OSA services due, in part, to the scarcity of sleep specialists, sharing the burden with primary care and utilising community-based management models can broaden access to sleep study testing and expedite OSA diagnosis and therapy. The DCE results offer a promising approach for systematic incorporation of patients and high-risk groups preferences into the future design and delivery of care pathways for OSA management.

**Acknowledgements:** The authors thank the Clinical Research Excellence (CRE) group of the Adelaide Institute for Sleep Health for the support in collecting the data.

#### INVESTIGATION OF THE PREVALENCE OF OBSTRUCTIVE SLEEP APNEA SYNDROME IN PATIENTS WITH SUBCLINICAL HYPOTHYROIDISM

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**Introduction:** It is known that hypothyroidism contributes to the pathophysiology of Obstructive Sleep Apnea Syndrome (OSAS) and these two diseases are related. It is thought that the prevalence of OSAS may also increase in subclinical hypothyroidism. Although subclinical hypothyroidism in OSAS patients has been investigated in many studies, only a few studies have been performed on the prevalence of OSAS in patients with subclinical hypothyroidism. The aim of this study is to determine the prevalence of OSAS in the study group with, and the control group without the diagnosis of subclinical hypothyroidism and to compare these two groups in terms of demographic characteristics, chronic diseases, and especially polysomnographic data.

**Materials and Methods:** A total of 120 patients were included in the study, and divided into two groups according to the diagnosis of subclinical hypothyroidism. A study group consisting of 60 patients with newly diagnosed subclinical hypothyroidism and a control group of 60 patients with normal thyroid functions were formed. Demographic, anthropometric, polysomnography data, and Epworth sleepiness scale scores of the patients were recorded and compared.

**Results:** Distribution of genders, mean ages, chronic diseases, body mass indexes, neck circumferences, and Epworth sleepiness scale scores of both groups were similar. Any significant difference in the prevalence and severity of OSAS was not detected in the patient group compared to the control group. A significant difference was found in the nocturnal desaturation and oxygen desaturation indexes of the group with subclinical hypothyroidism with obstructive sleep apnea compared to the control group.

**Conclusions:** This study showed that there was no increase in OSAS prevalence in patients with subclinical hypothyroidism, but demonstrated that nocturnal desaturation was significantly increased in OSAS patients diagnosed with subclinical hypothyroidism. It is thought that the diagnosis and treatment of OSAS in these patients may be important in preventing cardiovascular complications associated with nocturnal hypoxemia.

**Acknowledgements:** AE conceived the study. The protocol was designed by MB and AE, in collaboration. Patient inclusion and data collection were performed by GA. Statistical analyses were done and analyzed by GA and AE. The first draft of the manuscript was written by GA. All authors contributed to the study with a considerable critical review of the manuscript and approval of the final version.

#### IPOSSIA INTERMITTENTE NOTTURNA E FRAMMENTAZIONE DEL SONNO: DUPLICE MECCANISMO DI NEURODEGENERAZIONE? SINDROME DELLE APNEE OSTRUTTIVE DEL SONNO E DISTURBO DA MOVIMENTI PERIODICI DEGLI ARTI A CONFRONTO

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**Introduzione:** Studi recenti hanno dimostrato che i disturbi del sonno possono essere considerati un fattore di rischio per il deterioramento cognitivo e che la riduzione della qualità e della quantità del sonno notturno potrebbe modificare sia il metabolismo cerebrale che alterare le concentrazioni di biomarcatori liquorali di neurodegenerazione. Questo studio ha l'obiettivo di valutare il sonno, i biomarcatori liquorali, e il metabolismo del glucosio cerebrale in pazienti affetti da sindrome delle apnee ostruttive del sonno (OSAS) e in pazienti affetti da disturbo da movimenti periodici degli arti (PLMD), confrontandoli con un gruppo di soggetti di controllo.

**Metodi:** I pazienti affetti da OSAS e da PLMD sono stati sottoposti a tomografia a emissione di positroni con 18F-fluoro-2-deossi-D-glucosio (PET 18F-FDG), polisonnografia e puntura lombare per quantificare i livelli liquorali di  $\beta$ -amiloide<sub>42</sub> (A $\beta$ <sub>42</sub>), tau totale e tau fosforilata. Tutti i pazienti sono stati confrontati con controlli, non affetti da disturbi del sonno o da patologie neurodegenerative.

**Risultati:** Sono stati inclusi 20 pazienti affetti da OSAS, 12 pazienti con PLMD e 15 controlli. Si documenta che la qualità del sonno e la struttura del sonno sono alterate sia nei pazienti OSAS che nei PLMD rispetto ai controlli. I pazienti OSAS e PLMD hanno mostrato livelli di A $\beta$ <sub>42</sub> più bassi rispetto ai controlli. I pazienti OSAS hanno mostrato un aumento significativo della captazione di glucosio nelle regioni temporo-frontali e del cervelletto, nonché un ridotto consumo di glucosio nelle regioni temporo-parietali rispetto ai controlli. I pazienti con PLMD hanno mostrato un aumento del consumo di glucosio a livello del giro paraippocampale sinistro e nel caudato sinistro rispetto ai controlli.

**Conclusioni:** L'alterazione del sonno notturno e l'ipossia notturna presenti nei pazienti affetti da OSAS, più che l'esclusiva frammentazione del sonno presente nei pazienti con PLMD, sono state associate all'alterazione della A $\beta$ <sub>42</sub> liquorale e del metabolismo glucidico cerebrale. In particolare, si è osservata la riduzione dei livelli liquorali di A $\beta$ <sub>42</sub> e l'alterazione della captazione cerebrale di glucosio in aree cruciali per la neurodegenerazione, come la corteccia temporale, che tendono a modificarsi patologicamente in maniera precoce, evidenziando il ruolo dei disturbi del sonno nella possibile genesi di processi neurodegenerativi tipici della Malattia di Alzheimer.

#### IS OBSTRUCTIVE SLEEP APNEA A RISK FACTOR FOR SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 INFECTION?

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**Introduction:** Coronavirus Disease 2019(COVID-19) and obstructive sleep apnea(OSA) share many demographic characteristics and comorbidities. We aimed to evaluate the prevalence of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)infection in patients diagnosed with OSA and the effect of OSA on the severity of the infection in these patients.

**Materials and Methods:** In this retrospective observational study, the records of cases who had polysomnography(PSG) confirmed OSA in the last five years were reviewed. OSA was diagnosed using overnight PSG. Whether the subjects have been tested for SARS-CoV-2 with PCR and the test results were recorded. The electronic medical records were queried for the results of the SARS CoV-2 polymerase-chain-reaction(PCR) tests in this population. For patients with positive tests, the demographic data, PSG results, clinical, laboratory, and radiological findings of COVID-19 were recorded. Comorbidities were ascertained by ICD-10-CM coding and medical record data. A case of Covid-19 was defined by a positive result on a PCR assay of a specimen collected on a nasopharyngeal swab.

**Results:** Our analysis included 1317 OSA patients diagnosed by PSG. A review of the medical records demonstrated that 51 patients have been tested for SARS-CoV-2 with PCR. The reasons for testing were suspicion of infection, contact tracing, scanning before hospital admission or interventional procedures, or screening for travel. We identified 14 patients with positive PCR results for SARS-CoV-2. The mean age of the 14 patients was 48.9 ± 12.1 years. The majority of the patients were male (n=13, 93%). The mean BMI was 29.7 ± 2.4 kg/m<sup>2</sup>. Eight(57%) cases had mild OSA, three(21%) had moderate OSA, and three(21%) had severe OSA. Three cases were asymptomatic. Main complaints were chest pain(n=6, 43%), fever(n=5, 36%), fatigue(n=3, 21%), cough(n=3, 21%), shortness of breath(n=3, 21%), loss of taste and smell(n=2, 14%), and diarrhea(n=1, 7%). Two patients(14%) had DM and two (14%) had hypertension. Two patients(14%) did not need radiological evaluation. Others underwent computed tomography(CT) scanning; normal CT findings was observed in six cases(43%); involvement was unilateral in three cases(21%) and bilateral in three (21%) cases. The mean percentage of oxygen saturation was 97.4±3.0(90-99) on initial evaluation. All the patients underwent outpatient treatment and no hospital or intensive care unit(ICU) admission, progression to respiratory failure or mortality was observed.

**Conclusions:** We have observed that the prevalence of COVID-19, the need for hospitalization, and progression to respiratory failure, namely severe infection did not seem to increase in OSA patients. In our large OSA population, no hospital admission or death occurred due to COVID-19. In conclusion, our results provide some initial data regarding COVID-19 risk in a large OSA population. We demonstrated that OSA can not be considered as one of the underlying medical conditions predisposing to increased risk or poor outcome in COVID-19. Poor COVID-19 related prognosis, if exists, may be attributed to other risk factors or comorbidities accompanying OSA

#### LATE-ONSET CONGENITAL CENTRAL HYPOVENTILATION SYNDROME :A CASE WITH RET GENE MUTATION

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**Introduction:** Congenital central hypoventilation syndrome (CCHS) usually occurs in the neonatal period, with an incidence rate of about one in 200000. It has obvious family aggregation and inheritance characteristics, and 90% are related to PHOX2B gene mutations. We summarized the clinical characteristics of a male patient diagnosed as CCHS in adulthood. The purpose of this study was to explore the relationship between the RET proto-oncogene point mutation and the onset of congenital central hypoventilation syndrome.

**Materials and Methods:** With the consent of the patient and his families, the peripheral venous blood of the patient and his parents was collected to extract the genome, and the whole-exon sequence and PHOX2B gene sequencing were performed. We summarized the clinical data and molecular genetic results, analyzed the relationship between genotype and clinical phenotype for the better diagnostic, follow-up and prognosis.

**Results:** The patient developed nocturnal sleep hypopnea, with hypoxemia and hypercapnia since childhood (10 years old), and was finally diagnosed in adults. After the patient admitted to the hospital, relevant examinations were completed. According to the clinical manifestation of hypoxemia and hypercapnia during sleep, it was considered as congenital central hypoventilation syndrome. He was given ventilator-assisted ventilation during sleep, and the symptoms improved. The auxiliary examination excluded the primary heart, lung, brain, neuromuscular and metabolic diseases. PSG results suggested hypopnea syndrome with moderate hypoxemia. At the same time, he was diagnosed as moyamoya disease by digital subtraction angiography. PHOX2B and the whole-exon gene sequencing showed that the patient and his mother both have a heterozygous mutation in exon 12 of RET gene (c.2246g > C) and a heterozygous mutation in exon 60 of RNF213 gene(c.14429g > A ); the patient's father has no mutations of the RET gene or RNF213 gene. None of the three have found any mutations in the PHOX2B gene. His mother's cranial vascular magnetic resonance also showed symptoms of moyamoya disease, but have no clinical manifestations of congenital central hypoventilation syndrome or congenital Hirschsprung disease (HSCR).

**Conclusions:** In this case, we report a case of congenital central hypoventilation syndrome with a new RET gene mutation site c.2246g > C (p.R749T) and the patient also has RNF213 gene mutation which caused moyamoya disease.

**Acknowledgements:** We would like to thank the patient and his parents who participated in this study and provided their blood samples for research.

#### MANAGEMENT OF COMORBID INSOMNIA AND SLEEP APNEA WITH MANDIBULAR ADVANCEMENT DEVICES: FIRST RESULTS FROM A MULTI-CENTRIC CASE-CONTROL STUDY ON THE THERAPEUTIC OUTCOMES

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**Introduction:** Comorbid insomnia and Sleep Apnea (COMISA) frequently interact potentiating several health problems. For instance, COMISA was showed to increase the risk of cardiometabolic disorders when compared with each isolated condition in different settings. Other outcomes as cognitive impairment and quality of life measures are also negatively impacted by this comorbid condition in face of its single components. On the other hand, therapeutic compliance was shown to be affected in patients indicated for CPAP therapy because of respiratory disturbances and this is even worse when insomnia and respiratory disturbance co-occur therefore compromising treatment response. Meanwhile there is no studies on the effect of Mandibular Advancement Devices (MADs) in COMISA patients even though this option promote compliance in other clinical scenarios (eg. obstructive sleep apnea). This study aimed to objectively assess treatment outcomes in COMISA adult patients treated with MADs and compare it.

**Materials and Methods:** Patients with isolated Obstructive Sleep Apnea (OSA) (n=35; 51,4% males) and COMISA as defined by OSA+ Sleep Latency>30min (n=31; 58,1% males) derived from 4 different centers (Portugal, Spain and Brazil) and were treated with MAD for their sleep disordered breathing being retrospectively compared regarding major clinical and polysomnographic outcomes.

**Results:** OSA and COMISA groups didn't differ neither regarding age (50,8±12,1 vs 54,8±8,1; p=0,12), Body Mass Index (25,8±3,1Kg/m<sup>2</sup>; p=0,9) or pre-treatment Apnea Hypopnea Index - AHI (26,9 ev/h±14,4 vs 25,2 ev/h±10,6; p=0,6). Post-treatment AHI remained slightly higher and above the normal threshold in COMISA group (6,4 ev/h±6,9) while achieving normal levels (<5/h) in OSA group (3,7 ev/h±3,2); p=0,04. Sleep latency significantly improved from 63,6±46 min to 22,8±20,8 min; p=0,001 in COMISA group without changes in OSA group.

**Conclusions:** To our knowledge, this is the first study showing that MAD can be an effective tool for managing COMISA patients with significant impact on both respiratory and insomnia related therapeutic outcomes. Furthermore, the different responses of COMISA versus OSA patients to MAD regarding AHI and sleep onset insomnia improvement supports the need of better phenotyping this frequent comorbid condition.

#### MANDIBULAR MOVEMENTS ARE A RELIABLE NONINVASIVE ALTERNATIVE TO ESOPHAGEAL PRESSURE FOR MEASURING RESPIRATORY EFFORT IN PATIENTS WITH SLEEP APNEA SYNDROME

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**Introduction:** Differentiation between obstructive and central apneas and hypopneas requires quantitative measurement of respiratory effort (RE) using esophageal pressure (PES), which is rarely implemented. This study investigated whether the sleep mandibular movements (MM) signal recorded with a tri-axial chin sensor (Sunrise, Namur, Belgium) is a reliable surrogate of PES in patients with suspected obstructive sleep apnea (OSA).

**Materials and methods:** In-laboratory polysomnography (PSG) with PES and concurrent MM monitoring was performed. PSGs were scored manually using AASM 2012 rules. Data blocks (n=8042) were randomly sampled during normal breathing (NB), obstructive or central apnea/hypopnea (OA/OH/CA/CH), respiratory effort-related arousal (RERA), and mixed apnea (MxA). Analyses were: evaluation of the similarity and linear correlation between PES and MM using the longest common subsequence (LCSS) algorithm and Pearson's coefficient; description of signal amplitudes; estimation of the marginal effect for crossing from NB to a respiratory disturbance for a given change in MM signal using a mixed linear regression.

**Results:** Participants (n=38) had mild to severe OSA (median AH index 28.9/h; median arousal index 23.2/h). MM showed a high level of synchronization with concurrent PES signals. Distribution of gyroscope MM signal amplitude differed significantly between event types: median (95% confidence interval) values of 0.60 (0.17–2.43) for CA, 0.83 (0.23–4.71) for CH, 1.93 (0.54–5.57) for MxA, 3.23 (0.72–18.09) for OH, and 6.42 (0.88–26.81) units for OA. Mixed regression indicated that crossing from NB to central events would decrease gyroscope MM signal amplitude by -1.23 (CH) and -2.04 (CA) units, while obstructive events would increase gyroscope MM signal amplitude by +3.27 (OH) and +6.79 (OA) units (all p<10<sup>-6</sup>).

**Conclusion:** In OSA patients, MM signals facilitated the measurement of specific levels of RE associated with obstructive, central or mixed apneas and/or hypopneas. A high degree of similarity was observed with the PES gold-standard signal.

#### MAXILLARY EXPANSION FOLLOWED BY MAXILLOMANDIBULAR ADVANCEMENT: INDICATIONS AND EARLY OUTCOMES

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**Introduction:** Skeletal surgery addresses certain anatomic deficiencies in patients with obstructive sleep apnea. Specifically, patients with narrow high arched palates, mandibular deficiencies, concentric collapse of the velum, or lateral pharyngeal wall instability are phenotypes best treated with either maxillary expansion or maxillomandibular (MMA) surgery. These interventions decrease nasal resistance, prevent posterior tongue displacement, and stabilize key airway musculature to prevent collapse during sleep. The purpose of this study is to evaluate the outcomes of patients undergoing both maxillary expansion followed by MMA.

**Methods:** A retrospective chart review of patients was completed from 7/1/2014 to 7/1/2021 for patients with OSA associated with maxillary transverse deficiency and maxillomandibular deficiencies. Pre and post-operative AHI, RDI, ODI, lowest O<sub>2</sub> saturation, ESS, and NOSE were analyzed

**Results:** 38 patients met inclusion criteria. The mean age at time of surgery was 35 ± 9.7 and the BMI 28.7 ± 5.95. The mean pre-op AHI, ODI, RDI was 35.3 ± 23.6, 29.8 ± 22.7, and 36.5 ± 24.7 respectively. The lowest oxygen saturation was 82.4 ± 9.5. The average pre-op ESS and NOSE were 9.37 ± 5.8 and 11.8 ± 7.5 respectively. Following DOME, the AHI, ODI, RDI was 14.8 ± 15.7, 9.82 ± 6.01 (p<0.065) and 19.7 ± 13.3 (p<0.065) respectively. The lowest O<sub>2</sub> post-DOME was 87.75 ± 5.44 (p<0.199). Following both DOME and MMA, the AHI, ODI, RDI was 12.33 ± 13.73 (P<0.004), 9.31 ± 8.56 (p<0.027) and 10.1 ± 3.46 (p<0.064) respectively. The lowest O<sub>2</sub> post-DOME and MMA was 88.14 ± 2.85 (p<0.002)

**Conclusions:** For OSA patients with narrow high arched palate, maxillary expansion followed by maxillomandibular advancement is a predictable sequence to achieving treatment success. Following skeletal surgery, patients can expect decrease in AHI, ODI, and RDI, as well as improvements in daytime symptoms for both sleepiness and nasal obstruction.

#### NEUROANATOMICAL CORRELATES OF RESPIRATORY EVENT DURATION IN OLDER ADULTS WITH UNTREATED SLEEP APNEA

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**Introduction:** Sleep apnea is common in older adults and associated with adverse clinical outcomes including cognitive impairment and cerebrovascular disease. Of the many physiological dimensions of sleep apnea, apnea-hypopnea event duration, an indicator of arousal threshold, has

been reported to be particularly strongly associated with both cardiovascular outcomes and mortality. However, there are few data concerning the neuroanatomical correlates of respiratory event duration in older adults. In this study, we hypothesized that the duration of respiratory events is associated with differences in regional brain volumes.

**Methods:** We studied 223 community-dwelling older adults from the Rush Memory and Aging Project (mean [SD] age 83.3 [6.7] years; 28% male) with untreated sleep apnea (AHI > 5) with hypoxia. We assessed sleep apnea physiology using the WatchPAT device (Itamar Medical) and computed the mean duration of desaturation events. We used multiple linear regression models to relate this to 68 (34 per hemisphere) regional cortical and 20 subcortical grey matter volumes as the outcomes, assessed by magnetic resonance imaging, parcellated using Freesurfer.

**Results:** Shorter mean event duration, indicative of a lower arousal threshold, was associated with lower volume of the left pars triangularis [Estimate = 10.79; SE = 3.09;  $p < 0.001$ ; FDR = 0.05] and fusiform gyrus [Estimate = 23.68; SE = 7.17;  $p = 0.001$ ; FDR = 0.05], in models adjusted for age, sex, years of education, and intracranial volume (ICV). In additional analyses, these associations remained significant when we controlled for other measures of sleep apnea severity (AHI, ODI, mean SaO<sub>2</sub>) and potential confounders (BMI, dementia, stroke, vascular risk factors and diseases)

**Conclusion:** In older adults with sleep apnea, a lower arousal threshold, as measured by a shorter desaturation duration, is associated with lower volumes in the left pars triangularis and fusiform gyrus. This data suggest that atrophy of these areas may be either a consequence of or contributor to a low arousal threshold in older adults with sleep apnea.

#### NEWLY DIAGNOSED OBSTRUCTIVE SLEEP APNEA IN COVID-19 PNEUMONIA PATIENTS: PROSPECTIVE ANALYSIS FROM A DEDICATED OUTPATIENT SETTING POST-HOSPITALIZATION - PRELIMINARY RESULTS

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**Introduction:** COVID-19 is a multisystem disease associated with a relevant symptomatic burden after acute infection. However, newly diagnosed obstructive sleep apnea (OSA) data remains largely understudied, mainly after hospital discharge in symptomatic patients. Previous reports have presented diverging prevalence of OSA in COVID-19 pneumonia patients post-hospitalization, but it is increasingly recognized that it can be an extraordinarily high rate. STOP-BANG is a validated questionnaire for screening of outpatients for OSA, with some studies showing a sensitivity as high as 90% for detecting OSA, in different global regions. We aim to evaluate if STOP-BANG questionnaire can be useful as a screening tool for OSA in COVID-19 pneumonia patients post-hospitalization, validating it with ambulatory polysomnography.

**Materials and methods:** We performed a prospective observational study of 389 consecutive patients admitted to Pulmonology Post-COVID-19 Consultation between 05/2020 and 12/2021, according to the Consultation Protocol. Clinical data, including sleep symptoms were extracted. All patients were screened with STOP-BANG questionnaire. Patients with previous OSA diagnosis were excluded (14; 3.6%). One-hundred and twenty-six (32.4%) patients with high risk of OSA were proposed to overnight polysomnography using Nox-T3, and 53 (42.1%) patients already concluded the examination. Correlations were made between clinical symptoms, STOP-BANG score and OSA severity, according to Apnea hypopnea index (AHI).

**Results:** OSA was diagnosed in 49 (92.5%) of the patients submitted to the examination. Median age was 60 years (range: 28 to 76 years) and the majority was male (36; 73.5%). Fatigue during daytime and snoring were the most common complaints. Our cohort had a high prevalence of vascular risk factors (Arterial hypertension 61.2%; Dyslipidemia 20.4%; Diabetes mellitus 12.2%). 10.2% were overweight (BMI > 25) and 71.4% were obese (BMI > 30).

Median STOP-BANG score was 5 (IQR 4–5). Eighteen patients (36.7%) had an AHI between 5 and 15, indicating mild OSA. Eighteen patients (36.7%) had an AHI of 15 to 30, indicating moderate OSA, whereas 13 patients

(26.5%) had signs of severe OSA (AHI of  $\geq 30$ ). We found that STOP-BANG score  $\geq 3$  did show a positive correlation with the presence of OSA.

**Conclusions:** Our preliminary and real-life data results support the requirement to implement a Pulmonology Post-COVID-19 Consultation that includes the use of sleep questionnaires on a regular basis. STOP-BANG questionnaire is highly predictive of the presence of OSA in COVID-19 pneumonia patients post-hospitalization. A possible high rate of undiagnosed OSA in this population may be an explanation for the frequent and persistent symptomatic burden, namely fatigue symptoms. This is one of the largest cohorts of COVID-19 pneumonia patients post-hospitalization in an outpatient setting submitted to OSA screening. Several findings diverge from previous literature which emphasizes the need for further prospective studies.

#### NEW TREATMENTS FOR CENTRAL SLEEP APNOEA IN HEART FAILURE: SAMPLE SIZE REQUIRED TO DETECT A SAFETY SIGNAL

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**Introduction:** Central sleep apnoea (CSA) and Cheyne-Stokes respiration (CSR) are common patterns of sleep-disordered breathing in patients who have heart failure with reduced ejection fraction (HFrEF). The prevalence of CSA/CSR in this population is approximately 25–40%, and this increases in parallel with heart failure severity. In addition, CSA/CSR is an independent risk marker for poor prognosis and death in patients with heart failure. This provides a sound rationale for the treatment of CSA/CSR in HFrEF patients. However, the large, randomised controlled Treatment of Sleep-Disordered Breathing with Predominant Central Sleep Apnoea by Adaptive Servo Ventilation in Patients with Heart Failure (SERVE-HF) trial was neutral for the primary combined endpoint and unexpectedly showed an increased mortality risk (all-cause and cardiovascular) in patients randomized to adaptive servo ventilation (ASV). Therefore, the safety of new treatments targeting CSA/CSR in patients with HFrEF is an important topic. To help better inform the design of future studies evaluating therapies for CSA in patients with HFrEF, this analysis determined the number of events and sample sizes required to detect a between-group difference in all-cause mortality.

**Materials and Methods:** Data from the SERVE-HF study were used in sample size calculations, which were performed using the R-package rpart in R version 4.0.2 (R Core Team 2020). The control group event rate was 0.093 events/year and the assumed true hazard ratio (HR) for all-cause death in the treatment versus control group was 1.28, with an accrual time of 5 years and a minimum follow-up time of 3 years. The calculations were based on an event-driven non-inferiority study with a survival endpoint, using a one-sided alpha (significance level) of 0.025 and beta (1–power) of 0.2.

**Results:** The number of patients and events needed to demonstrate safety of a new treatment ranged from 851 and 349, respectively, for a non-inferiority margin HR of 1.35, to 3924 and 1607, respectively, at the strictest non-inferiority margin HR value of 1.15. A point estimate (HR) above 1.3 is often used to define non-inferiority in cardiovascular trials based on FDA recommendations for assessment of the cardiovascular safety of new treatment agents. In the current analysis, a trial utilizing a non-inferiority HR of 1.3 would need 456 events and need to enrol 1114 patients over a 5 year study with a minimum follow-up time of 3 years.

**Conclusions:** Future studies of new treatments for CSA/CSR in the HFrEF patient population need to focus on safety, include a large sample size and detect a large number of events over long-term follow-up to be able to reliably detect between-group differences in objective endpoints such as all-cause mortality, and therefore any potential safety signals.

**Acknowledgements:** Study funded by ResMed

### NIGHT-TO-NIGHT VARIABILITY OF AUTOMATICALLY DERIVED PHYSIOLOGICAL ENDOTYPIC TRAITS IN PATIENTS WITH OBSTRUCTIVE SLEEP APNEA

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**Introduction:** Emerging data suggested physiological endotypic traits (e.g., loop gain) contribute to precision medicine in obstructive sleep apnea (OSA). However, the clinical utilities of endotypic classification have been limited by technical complexity. In addition, the night-to-night variability of derived endotypic traits has not been extensively studied. In the current project, we implemented an established endotyping methodology into clinical polysomnographic studies and studied the night-to-night variability of endotypic traits in moderate-to-severe OSA patients.

**Materials and Methods:** A previously published methodology ([1]) for derivation of physiological endotypic traits in OSA from standard polysomnographic sleep recordings was adapted and refined for use in polysomnography data sets recorded with the EMBLA A10 system. Detailed information from nasal flow, apnea/hypopnea detection, and arousal classification was used in the analysis. The new algorithm was validated in comparison with the previously published implementation on a set of simulated data based on the underlying model of the ventilatory control system. The evaluation of night-to-night variability was performed using data from a clinical trial with 2 consecutive in-lab overnight polysomnographic recordings. Data has been evaluated by comparing the performance in terms of recognizing the endotypic trait loop gain (LG) as a proof-of-concept.

**Results:** Using simulated data, both algorithms performed almost identically ( $p < 0.001$ , ICC=0.99), confirming the validity of the underlying modeling technique. Night-to-night variability in LG was moderate for the new implementation ( $p < 0.001$ , ICC = 0.71), with a mean difference of 0.005 (95% CI: -0.04 – 0.05).

**Conclusions:** Automatic derivation of physiological endotypic traits from polysomnographic recordings is feasible and reproducible. LG varied moderately between consecutive nights, indicating that a single night assessment of endotypes may be sufficient to support clinical decision-making. Using the new implementation of the previously described technique, we were able to adjust the processing according to the devices used in our protocols, eliminate various technical limitations, and reduce overall variability.

[1] Terrill PI, Edwards BA, Nemati S, Butler JP, Owens RL, Eckert DJ, White DP, Malhotra A, Wellman A, Sands SA. Quantifying the ventilatory control contribution to sleep apnoea using polysomnography. *Eur Respir J*. 2015 Feb;45(2):408-18. doi: 10.1183/09031936.00062914. Epub 2014 Oct 16. PMID: 25323235; PMCID: PMC4348093.

### OBSTRUCTIVE SLEEP APNEA AND LUNG CANCER: A SYSTEMATIC REVIEW AND META-ANALYSIS OF 4,885,518 PARTICIPANTS

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**Introduction:** In 2020, lung cancer was the leading cause of cancer deaths, and was the most common cancer in men. Though obstructive sleep apnea (OSA) has been postulated to be carcinogenic, epidemiological studies are inconclusive. We conducted this systematic review and meta-analysis to investigate the associations between OSA and the incidence and mortality of lung cancer.

**Materials and Methods:** Four electronic databases (PubMed, Embase, Cochrane Library, and Scopus) were searched from inception till 6 June 2021 for randomized controlled trials and observational studies examining the association between sleep apnea and incident lung cancer. Two

reviewers selected studies, extracted data, graded the risk of bias using the Newcastle-Ottawa scale and the quality of evidence using GRADE. Random-effects models were used to meta-analyze the maximally covariate-adjusted associations.

**Results:** Seven studies were included in our systematic review; among which four were suitable for meta-analysis, comprising a combined cohort of 4,885,518 patients. Risk of bias was low to moderate. OSA was associated with a higher incidence of lung cancer (HR 1.25, 95%CI 1.02 to 1.53), with substantial heterogeneity ( $I^2=97%$ ). Heterogeneity was eliminated, with a stable pooled effect size, when including the three studies with at least 5 years of median follow-up (HR 1.32, 95%CI 1.27 to 1.37,  $I^2=0%$ ).

**Conclusions:** In this meta-analysis of 4,885,518 patients from four observational studies, patients with OSA had approximately 30% higher risk of lung cancer, compared to those without OSA. We suggest more clinical studies with longer follow-up as well as biological models of lung cancer be performed to further elucidate this relationship.

**Acknowledgements:** We would like to thank Dr See and Professor Toh for their guidance and advice through this project.

### OBSTRUCTIVE SLEEP APNEA IMPACT ON PHYSIOLOGY: INSIGHTS FROM A MOUSE MODEL AND A CASE-CONTROL STUDY

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**Introduction:** Obstructive sleep apnea (OSA) is associated with a host of comorbidities, including cardiopulmonary and metabolic disorders. However, the presence of multiple confounding factors and limited access to peripheral human samples, outside of blood, limits our understanding of the complex mechanisms of OSA. Intermittent hypoxia (IH) is a major clinical feature of OSA, but the impact of IH on the development and progression of OSA associated disorders have yet to be clearly elucidated. We explored pathophysiologic changes in a mouse model of IH to better understand how these changes occur over time in patients with OSA. This work will allow us to validate our murine model of IH as a tool to study physiologic consequences for patients with OSA.

**Materials and Methods:** Ten-week-old C57BL/6J mice were exposed to six weeks of IH during their inactive phase followed by six weeks of recovery in normoxic conditions. Physiologic parameters were evaluated weekly throughout the study. In a separate series of experiments, we also recruited a cohort of humans with OSA ( $n = 8$ , age:  $56 \pm 3$  years, Apnea and hypopnea index (AHI):  $68.4 \pm 24.3$ ) both before ( $t_{0M}$ ), 4 months after ( $t_{4M}$ ), and 2 years after ( $t_{24M}$ ) treatment with continuous positive airway pressure (CPAP). We compared physiologic parameters from this group to those taken from healthy control subjects ( $n = 8$ , age:  $48 \pm 3$  years; AHI:  $4.3 \pm 0.4$ ).

**Results:** In our mouse model, IH impacts several physiologic variables, including body temperature ( $p < 0.05$ ), that rebound after recovery from exposure to normoxic conditions. Patients with OSA also experience similar changes prior to treatment with CPAP, relative to control subjects, such as increased axillary body temperature and heart rate ( $p < 0.05$ ). Some of these physiologic parameters also recover after treatment with CPAP.

**Conclusions:** Long-term exposure to IH during the inactive phase leads to physiologic changes in mice that are also seen in patients with OSA. Furthermore, recovery of these parameters after exposure to normoxic conditions is similar to what is seen in patients treated with CPAP. These findings provide insight into our understanding of the role of IH in OSA.

**Funding:** Mouse work: NIH (5K08HL148551-02), CCHMC Procter Award, and the Triological Society and American College of Surgeons Clinical Scientist Development Award (D.F.S). Human work: ERDF-CENTRO2020 (CENTRO-01-0145-FEDER-000012), ERDF-COMPETE2020-FCT (POCI-01-0145-FEDER-029002, UIDB/04539/2020, UIDP/04539/2020); FCT (PD/BD/135497/2018); FULBRIGHT; FLAD; IBRO.

### OBSTRUCTIVE SLEEP APNEA SEVERITY IS ASSOCIATED WITH ABNORMAL MYOCARDIAL <sup>82</sup>RUBIDIUM PET BLOOD FLOW RESERVE

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**Introduction:** Epidemiologic studies have established an association between markers of obstructive sleep apnea (OSA) severity and cardiovascular disease (CVD). Coronary microvascular disease (CMD) is a marker of CVD prognosis and a precursor to several CVDs including heart failure with preserved ejection fraction (HFpEF). However, no studies have examined the association between clinical and polysomnographic features of OSA and CMD. In this study we examine the association between markers of OSA severity such as the frequency of upper airway obstruction, hypoxia severity and clinical symptoms of sleepiness, with CMD.

**Materials and Methods:** This is a cross-sectional analysis of N=346 patients who underwent diagnostic overnight polysomnography and cardiac positron emission tomography (PET) perfusion imaging with rubidium (<sup>82</sup>Rb) within a large health care system from 2015–2019. Obstructive features were categorized using the apnea-hypopnea index (AHI) into three major groups mild or no OSA (AHI <15), moderate OSA (AHI 15 – 29), severe OSA (AHI 30 or more). Hypoxia severity was determined using the T90% index (percentage of sleep spent with < 90% O<sub>2</sub> saturation) while sleepiness was defined as Epworth sleepiness scale (ESS) ≤15. We defined abnormal myocardial blood flow (MBF) reserve (MFR) as the ratio of stress to rest MBF <1.5 after rate-pressure product correction. Multivariate logistic regression analyses were conducted to compute the odds ratios (OR) of abnormal MFR for each of the OSA severity categories. The model was adjusted for age, sex, body mass index (BMI), current cigarette smoking, diabetes, hypertension, hyperlipidemia, history of stroke or transient ischemic attack (TIA), history of a myocardial infarction or revascularization. The analysis for the AHI was further adjusted for ESS and T90%.

**Results:** Patients with abnormal MFR were older (62 vs 59 years). However, there was no association between gender, BMI, hypertension, hyperlipidemia, or race, and abnormal MFR. The frequency of abnormal MFR increased with worsening AHI (*P* trend 0.019). There was no statistically significant change in abnormal MFR frequency across T90% tertiles or between ESS groups. In both univariate and multivariate analyses, persons with severe OSA by AHI were more than twice as likely to have abnormal MFR compared to those with mild or no OSA (OR for fully adjusted model 2.40 [95% CI: 1.29 – 4.47]) or those with non-severe OSA (OR for fully adjusted model 2.22 [95%CI: 1.27 – 3.86]). The association between OSA severity by AHI and abnormal MFR was preserved when analysis was restricted to participants who did not have a prior CAD history. There was no interaction by age (≥60 years vs < 60 years), gender or race (Black, White, Hispanic) and AHI on the association with abnormal MFR. There was no association between T90% or sleepiness and abnormal MFR.

**Conclusions:** Severe OSA was associated with abnormal MFR. This suggests that frequency of obstruction may be a better measure of CMD likelihood than hypoxia or sleepiness symptoms alone. Future studies should focus on the role of MFR in risk stratification and prognosis of patients with OSA and the impact of OSA-specific therapy on MFR.

### OBSTRUCTIVE SLEEP APNEA SYMPTOM SUBTYPE TRANSITIONS OVER FIVE YEARS ARE ASSOCIATED WITH INCREASED CARDIOVASCULAR DISEASE INCIDENCE RISK

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**Introduction:** Efforts to characterize clinical heterogeneity of obstructive sleep apnea (OSA) resulted in the identification and replication of symptom-based subtypes. Individuals with moderate-severe OSA that are excessively sleepy are at increased risk of cardiovascular disease (CVD). There is limited evidence about whether OSA patients that worsen their symptom presentation over time are at increased cardiovascular burden. This study aimed to assess the association between five-year transitions among OSA symptom subtypes and incidence of CVD in a community-based cohort.

**Materials and Methods:** Participants of the Sleep Heart Health Study with complete baseline and 5-year follow-up data on symptom presentation, polysomnographic data and CVD outcomes were included (N=2,643). We used latent transition analysis on 14 symptom items to determine symptom subtype transitions in participants diagnosed with OSA (apnea-hypopnea index [AHI] ≥5) across both visits. The primary outcome was incidence of CVD, defined as first occurrence of a composite of coronary heart disease, heart failure or stroke after the follow-up visit (median CV follow-up: 6.7 years). Cox proportional hazards models were used to assess the association between symptom subtype transitions and CVD incidence, adjusted by relevant demographic and cardiovascular risk factors.

**Results:** Four OSA symptom subtypes were identified at baseline and follow-up visits: minimally symptomatic, disturbed sleep, moderately sleepy and excessively sleepy. When compared to participants without OSA at baseline and follow-up visits, those with OSA that transitioned from moderately sleepy to excessively sleepy had increased CVD incidence risk (HR=2.09; 95%CI=1.27–3.45; p=0.004), independent of other CV risk factors. Increased CVD incidence risk was also observed in participants who transitioned from moderately sleepy to excessively sleepy when compared to those that remained moderately sleepy (HR=2.02; 95%CI=1.20–3.40; p=0.008) and in participants who transitioned from disturbed sleep to excessively sleepy when compared to those that remained with disturbed sleep (HR=3.25; 95%CI=1.03–10.23; p=0.044).

**Conclusions:** Five-year transitions across OSA symptom subtypes are associated with increased CVD incidence risk when adjusted by other relevant cardiovascular risk factors. Participants that transitioned from moderately sleepy or from disturbed sleep to excessively sleepy were at higher CVD risk. Results of this study might inform the role of symptom progression on CVD risk in OSA.

**Acknowledgements:** American Heart Association (20CDA35310360), National Institutes of Health (U01HL53916, U01HL53931, U01HL53934, U01HL53937, U01HL53938, U01HL53940, U01HL53941, U01HL64360 R24 HL114473, 75N92019R002).

### ONE-STAGE MULTILEVEL SURGERY FOR TREATMENT OF OBSTRUCTIVE SLEEP APNEA SYNDROME

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**Abstract: Introduction:** We report the results of one-stage multilevel upper airway surgery for patients who could not tolerate continuous positive airway pressure (CPAP). **Materials and Methods:** Patients treated

with multilevel surgery at a University Hospital in 2015–2019 were identified from a prospectively maintained database. The inclusion criteria were age 18–70 years, body mass index (BMI) <35 kg/m<sup>2</sup>, apnea–hypopnea index (AHI) >20, and lingual tonsil hypertrophy grade 3 or 4. Drug-induced sleep endoscopy (DISE) was performed before surgery in all patients. Multilevel surgery was performed in one stage and included expansion sphincter pharyngoplasty (ESP), coblation tongue base reduction (CTBR), and partial epiglottectomy (PE) as required. The outcome measures were postoperative AHI, time percentage oxygen saturation <90%, and Epworth Sleepiness Scale (ESS) score. **Results:** Twenty-four patients were included: median age 49.1 years, average BMI 27.26 kg/m<sup>2</sup>, and 90% men. Ten patients received ESP plus CTBR plus PE, eight received ESP plus CTBR, and six received ESP plus PE. The mean preoperative AHI was 33.01 at baseline, and improved to 17.7 ± 13 after surgery ( $p < 0.05$ ). The ESS score decreased from 11 ± 5.11 to 7.9 ± 4.94 ( $p < 0.05$ ). The surgical success rate according to Sher's criteria, was 82.3%. The median follow-up was 23.3 months (range 12–36). **Conclusions:** These findings suggest that multilevel surgery is a safe and successful procedure for the treatment of moderate to severe obstructive sleep apnea–hypopnea syndrome (OSAHS). Multilevel surgery seems appropriate for patients with OSAHS whose treatment is not tolerable or as first-line treatment in selected patients with well-defined airway obstruction, based on the detection of upper airway (UA) collapses using DISE. Multilevel surgery in one step seems to help reduce the risk of UA collapse in younger, non-obese patients with moderate to severe OSAHS.

**Acknowledgments:** The authors are grateful for the technical support of the Sleep Unit and the library service at a University Hospital.

#### ORAL CAVITY, LINGUAL FRENULUM AND HEAD FORWARD POSTURE IN CHILDREN AT RISK OF OSAS

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**Introduction:** Obstructive sleep apnea syndrome (OSAS) is a disorder that occurs during sleep and is characterized by partial or complete obstruction of the upper airways leading to impaired ventilation. Pediatric OSAS may lead to serious health consequences in child's development for example: arterial hypertension, insulin resistance, hyperactivity, daytime sleepiness and learning difficulties. Many risk factors for pediatric OSAS have been described including obesity, increased waist circumference, allergic rhinitis, narrowing of the pharynx and hypertrophy of the palatine tonsils and adenoids. Moreover recent studies have described short frenulum, leading to abnormal orofacial development, as a potential risk factor for OSAS in children. In addition by reduction of tongue mobility, ankyloglossia impairs sucking, chewing and swallowing and requires the use of additional cervical muscles. This hyperactivity of the cervical muscles may cause their shortening and induces a forward head posture. The aim of this study was to evaluate lingual frenulum, oral cavities and head posture in children at risk of OSAS.

**Materials and Methods:** The study included children aged 3–17 without craniofacial abnormalities. In the first part of the study children's guardians were asked to fill in the Pediatric Sleep Questionnaire (PSQ), afterwards children at risk of OSAS (8 or more points) were enrolled to the study group. A control group was established randomly from patients with negative PSQ results. Physical examination performed in both groups included assessment of the following: length of the lingual frenulum; oropharynx in Mallampati classification; palatine tonsils size in Pirquet scale; presence of the high arched palate, malocclusion and head forward posture (HFP). Moreover, children's guardians were asked to assess their child's time spent with electronic mobile devices, such as smartphones or tablets.

**Results:** 1,500 PSQ questionnaires were distributed, with less than half (713) of them being returned correctly filled in. In the second part of the study 131 children were evaluated, 65 in the study and 66 in the control group. The mean ages were 9.5±3.0 and 9.4±3.1 years, respectively. Among children from the study group the presence of the higher grades (III and IV)

in the Mallampati classification, Pirquet scale (III – IV), crossbite and high arched palate were significantly more frequent compared to the control group ( $p < 0.001$ ). Moreover, children at risk of OSAS had significantly shorter lingual frenulum ( $p = 0.01$ ), higher HFP measure ( $p = 0.03$ ) and spent longer time using mobile devices ( $p < 0.001$ ). Additionally, a statistically significant correlation between mobile device use and HFP was found regardless of OSAS risk.

**Conclusions:** Conducted study found an association between certain features in oral cavity and the risk of OSAS. Evaluation of these elements is an easy procedure, and may be useful in screening for OSAS in children. Furthermore, the forward head posture and use of mobile devices was also associated with a higher risk of sleep apnea.

**Acknowledgments:** None

#### OROPHARYNGEAL STIMULATION WITH THE TONGUE-RIGHT-POSITIONER (TRP) DEVICE ON OSA PATIENTS

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**Introduction:** The Tongue-Right-Positioner (TRP) is a sensorimotor tongue stimulation device. It acts on tongue position and functions and consequently on the neural control of the tongue and other pharyngeal dilators muscles and soft palate. Effects of TRP may act both on obstructive events and the oxygen saturation during sleep.

**Materials and Method:** Observational multi-centric retrospective study was carried out in 20 patients with diagnosed OSA. They underwent sleep studies before (T0) and during treatment (T1) with the TRP appliance. At T0, there were seven severe, ten moderate, and three mild OSA patients. There were nine females and 11 males. The average age was 53±12.8 years; the average body mass index (BMI) 24.6±3.6; average treatment duration until T1: 11.3±8.2 months use. All 20 patients were compliant and used TRP the whole night every day during the treatment period.

**Results:** Average AHI was reduced from 27.7±13.4 at T0 to 14.3±10 at T1. TRP treatment was successful in 13 patients (65%). Complete response (AHI≤10/h) was achieved in 8 of 20 patients (40%), including one patient with AHI≥30 at T0. Five of 20 patients (25%), including four patients at T0 with AHI≥30, achieved a partial response (50% decrease in AHI but AHI>10). Seven patients (35%) were poor responders (less than 50% reduction in AHI). Average AHI in supine position dropped from 32.3±21 at T0 to 23.3±15.5). Average REM sleep AHI dropped from 29±13.2 at T0 to 18.2±6.9. Average arousals dropped from 21.7±12.1 at T0 to 13.2±7.5 events/hour.

Average mean SpO<sub>2</sub> (mSpO<sub>2</sub>) increased from 93.3±2.4% at T0 to 94.9±1.3%. At T0, mSpO<sub>2</sub> <90% in 3, 90%–95% in 11, and ≥95% in 6 patients. At T1, all patients had mSpO<sub>2</sub> >90%; 11 had mSpO<sub>2</sub> ≥95% and the remaining 9 had mSpO<sub>2</sub> 90%–95%. Anti-correlation between mSpO<sub>2</sub> variation during treatment with its baseline level ( $r = -0.775$ ;  $p$ -value < 0.001) suggests that the effect of TRP is inversely proportional to patients' initial mSpO<sub>2</sub> level.

**Discussion:** The nightly use of the TRP device increases phasic and tonic activity of the tongue and related oropharyngeal muscles, promotes nasal breathing, and thereby decreases respiratory efforts. Moreover, nasal breathing promotes the admixture of nasal nitric oxide (NO) in the inhaled breath. Therefore, it can increase the volume of inhaled air and, through the vasodilating effect of inhaled NO, the amount of oxygen in the blood (ventilation perfusion match), thus the mSpO<sub>2</sub>.

**Conclusion:** The TRP appliance as a mono-maxillary device with good comfort and high compliance in patients can significantly reduce obstructive events (AHI), improve oxygen saturation during sleep. We recommend TRP alone in mild to moderate OSA to achieve a complete response. In addition, the AHI reductions noted in supine position suggest its use alone or in combination with a CPAP.

## OUTCOME OF OSA SUBJECTS UNDERGOING BOTH MAXILLOMANDIBULAR ADVANCEMENT AND HYPOGLOSSAL NERVE STIMULATION

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**Introduction:** Upper airway stimulation (UAS) for the management of obstructive sleep apnea (OSA) has shown consistent and effective results with the STAR trial. However, there are three important exclusion criteria that includes 1) Complete concentric collapse at the velum 2) body mass index (BMI)>32 kg/m<sup>2</sup>, and 3) Apnea-hypopnea index (AHI) > 65/h. Maxillomandibular advancement (MMA) is an effective treatment for OSA by using skeletal movements to expand the pharyngeal airway. While there are no absolute contraindications, subjects with very high AHI and/or BMI may need further treatment.

**Materials and Methods:** This is a retrospective/prospective chart review of subjects who underwent UAS between 2016 to 2020, with prior MMA. Inclusion criteria were: 1) adults older than 18 years, 2) polysomnography confirmed OSA, and 3) previous MMA now presenting with relapse of symptoms; or 4) pre-planned MMA followed by UAS.

**Results:** In the MMA-relapse group, the mean time to UAS was 16.25 years. Mean AHI prior to UAS was 21/h, and is decreased to 4.93/h. All subjects had severe sleep apnea (AHI>30), yet the exact AHI values were missing in some. In the planned multi-stage subjects, mean AHI decreased from 81.37/h to 15/h with MMA. One subject achieved surgical cure (4.6/h). The other two proceeded to UAS within a year, with mean AHI reduction from 15/h to 2.55/h.

**Conclusions:** Upper airway stimulation can serve as both a therapy for post-MMA long term relapse or for patients with high AHI. The combination of these two extrapharyngeal surgical treatments has been effective in our small cohort. The two therapies may be highly complementary and offer a continuum of surgical care that was previously unavailable.

**Acknowledgements:**

## PAP TITRATION IN PATIENTS WITH OSA AND DEPRESSION: MORE DIFFICULT, MORE DIVERSE, MORE VARIED

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**Introduction:** Nearly 20 years ago it has been shown that 21.1% of all adults with depression may suffer also from obstructive sleep apnea (OSA) due to a structured phone interview. Recent research underlines psychiatric disorders as a high risk factor for OSA. Acker et al. (2017) showed in 322 patients with a polysomnographically measured AHI > 9/h that 21.5% suffered from a clinically significant depression. Additionally, OSA was found by polygraphy in 23.7% of patients in German Psychiatric Hospitals (Behr et al. 2018).

**Materials and Methods:** We compared parameters of OSA and PAP-treatment in 203 OSA patients with clinically significant depression and 125 OSA controls without a psychiatric comorbidity. All patients with initial PAP titration underwent a polysomnographic setting of one night with manually PAP titration followed by one control night. Control patients were matched by sex and gender and by being treated at the same day as the patient. Depression was rated as significantly if the patients took at least one antidepressant, sleep inducing medication (19.7%) was not counted as an antidepressant.

**Results:** Patients with and without clinically significant depression didn't differ in age (56.2 ± 11.9 vs 57.3 ± 11.2 years), gender, BMI (33.8 ± 7.8 vs 32.8 ± 5.9), ESS (8.4 ± 4.3 vs 7.6 ± 4.1), nor in AHI (30.2 ± 19.9 vs 32.2 ± 22.1), index of desaturation or other OSA parameters before initial PAP therapy. Patients with depression reported more often difficulties in initialing sleep (45.8 vs 23.2%) despite a higher intake of sleep medication (19.7 vs 3.2%), difficulties in maintaining sleep didn't differ. Initial PAP therapy was done in 90 (44.5%) patients with depression and in 69 (54.4%) of the control group thereby showing more bilevel-S titrations in depressed patients than in controls (n = 41 vs 27). Significantly more depressed patients refused PAP maintenance within the

polysomnographic setting (8.5 vs 4.8%). Within patients being recorded to control former PAP pressure (n = 67 vs 42), e.g. in cases of professional drivers, therapy on bilevel-S devices were more often found in patients with OSA and depression (16.4 vs 7.1%). Additionally, in cases of insufficient PAP therapy patients without depression (n = 5) were mostly switched to bilevel-ST/ASV/NIV (80%). In contrast, patients with OSA and depression (n = 24) switched to bilevel-S (37.5%), bilevel-ST/ASV/NIV (33.3%) or back from bilevel to CPAP/APAP (25%).

**Conclusions:** PAP-treatment was much more difficult and diverse in patients with OSA and depression than in patients without a psychiatric comorbidity. Depressed patients need much more time and patience from both, the physicians and the complete medical staff.

## PATHOPHYSIOLOGICAL MECHANISMS OF EXACERBATED OSA WITH LIGHTER SLEEP

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**Introduction:** Lighter non-REM sleep is associated with exacerbated obstructive sleep apnea (OSA) severity, but the underlying pathophysiological mechanisms are not fully understood. Here we use direct physiological measurement to explore whether lighter sleep promotes pharyngeal obstruction via 1) reduced neural drive (lower arousal threshold) or 2) deficits in pharyngeal pathophysiology per se (greater collapsibility, reduced muscle effectiveness).

**Materials and methods:** 59 patients with mild-to-severe OSA (apnea-hypopnea index, AHI=5 to 91 events/h) underwent overnight polysomnography with additional measurements of ventilatory drive (intraesophageal diaphragm EMG) and oronasal ventilation (mask and pneumotach). Within each non-REM sleep stage (N1, N2, N3), we determined gold-standard OSA pathophysiologic traits: *airway collapsibility* (ventilation at eupneic drive, also known as 'vpassive'), *muscle effectiveness* (change in ventilation per change in drive), *arousal threshold* (ventilatory drive at arousal), and *loop gain* (ventilatory instability). Mixed model analysis examined the effects of N1 (light sleep) and N3 (deeper sleep) versus N2 on the pathophysiological traits.

**Results:** Data for analysis was available in N=50 (N1), N=50 (N2) and N=18 (N3) patients respectively. Lighter sleep substantially raised the apnea-hypopnea index (+18[13,24] events/h N1 vs. N2, estimate[95%CI]; 78% increase) whereas deeper sleep lowered the apnea-hypopnea index (-18[-22,-11] events/h N3 vs. N2; all P<0.0001). In light sleep, the arousal threshold was substantially reduced (-26[-36,-15] %<sub>eupnea</sub> N1 vs. N2; +36 [9,67] %<sub>eupnea</sub> N3 vs. N2) and was accompanied by lower average levels of drive (-38[-43,-34] %<sub>eupnea</sub> N1 vs. N2; +31[23,38] %<sub>eupnea</sub> N3 vs. N2). *Collapsibility* was increased in light sleep (-7[-10,-5] %<sub>eupnea</sub> N1 vs. N2, ventilation at matched eupneic drive), but was unchanged with deep sleep. Deficits in *muscle effectiveness* or *loop gain* were not detected in lighter sleep.

**Conclusions:** The greater OSA severity in lighter non-REM sleep is accompanied by a substantially lower arousal threshold and lower average drive, supporting the notion that lower drive contributes to the exacerbation of OSA in lighter sleep. Independent of drive, greater collapsibility in light sleep may indicate a neurophysiological mechanism of pharyngeal dysfunction that is specific to sleep onset. Improved OSA in deep sleep was accompanied exclusively by a higher arousal threshold and elevated drive, without evidence of improved pharyngeal pathophysiology per se.

## PATIENT EXPERIENCES OF UPPER AIRWAY STIMULATION FOR TREATMENT OF OBSTRUCTIVE SLEEP APNEA: A QUALITATIVE ANALYSIS

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**Introduction:** Upper airway stimulation (UAS) is an effective alternative treatment for patients with moderate to severe obstructive sleep apnea (OSA) who are unwilling or unable to adhere to continuous positive airway pressure (CPAP) therapy. UAS requires patients to activate the therapy nightly, and although adherence is generally higher than with CPAP, some patients still do not use UAS consistently. The purpose of this study was to qualitatively explore patients' experiences with UAS and identify potential unique factors associated with its use.

**Materials and Methods:** A sample of 24 OSA patients who received UAS treatment were identified from a university hospital via electronic medical record review and from the ADHERE registry, an international, multicenter registry of patients who received an UAS implant. To obtain diverse experiences of UAS recipients, 12 patients categorized as high users with mean usage of  $\geq 4$  hours/night and 12 categorized as low users with  $< 4$  hours/night or self-report of nonuse participated in structured interviews. Interviews explored patients' experiences with UAS, barriers and facilitators to UAS use, and advice for new UAS recipients. Demographic and clinical data including the Insomnia Severity Index (ISI) and Generalized Anxiety Disorder Scale (GAD-7) was collected.

**Results:** Participants were, on average, 69 years old, male (71%), White (92%), had at least some college education (79%), and were married (54%). Low users were younger, less educated, more likely to be female, Black, and have comorbidities as compared to high users. Compared to high users, insomnia severity and anxiety symptoms were higher among the low users, with moderate insomnia (ISI: 3.6 vs. 15.2) and mild anxiety (GAD-7: 3.4 vs. 6.9). The amplitude and frequency of UAS stimulation settings at activation were similar between the groups. Four key concepts emerged in the qualitative analysis that highlighted the experiences of OSA patients treated with UAS: 1) reason for getting UAS treatment, 2) effects of UAS treatment, 3) barriers and facilitators of UAS treatment, and 4) advice for new UAS recipients. Both high and low users identified dislike of CPAP as a primary reason for getting UAS treatment and low users also frequently identified getting a better night's sleep as a reason. High users reported more positive experiences with UAS treatment, such as improvements in mental and physical health and convenience of treatment as facilitators of use. Low users tended to focus on the negative aspects of treatment, especially interference of sleep due to stimulation which was a barrier to use. Advice for new UAS recipients were reflective of the experiences that users had with treatment.

**Conclusions:** The differing experiences of UAS treatment between the high and low users may have been partly due to prevalent insomnia symptoms among the low users. Sleep clinicians need to evaluate patients for insomnia and initiate treatment prior to UAS implantation as doing so may increase the likelihood of adherence. Further research should explore the impact of health literacy and differential effects of race related to UAS use.

**Acknowledgements:** This work was supported by research funding from Inspire Medical Systems, Inc.

#### PERCEPTION OF NASAL FUNCTION AND COSMESIS AFTER MAXILLOMANDIBULAR ADVANCEMENT FOR OBSTRUCTIVE SLEEP APNEA

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**Introduction:** Maxillomandibular advancement (MMA) is one of the most effective procedures for managing severe obstructive sleep apnea (OSA). MMA is known to have potentially deleterious effects on the nose. The contemporary MMA seeks to optimize both form and function with a reduction in rates of corrective nasal surgery (down to less than 7%). For procedures that require skeletal movement of the midface, nasal form and function are important considerations for both surgeons and patients with obstructive sleep apnea (OSA). The SCHNOS is a heavily validated tool that quantifies both nasal function and cosmesis. We used this tool to evaluate the effect of the contemporary MMA.

**Materials and Methods:** This is a prospective study evaluating subjects undergoing skeletal sleep surgery namely MMA for OSA from September 2020 to 2021 at the Stanford Sleep Surgery Division. The outcome measure used to assess nasal function and cosmesis was the validated Standardized

Cosmesis and Health Nasal Outcomes Survey (SCHNOS) and the Epworth sleepiness Scale (ESS). Inclusion criteria were subjects with available scores and who underwent either an MMA or a lefort 1 osteotomy.

**Results:** Twenty-six patients met the inclusion criteria. The SCHNOS-O (obstruction) and SCHNOS-C went from 48.07 (25.96) to 21.92 (26.04) ( $p < 0.001$ ) and from 14.11 (19.39) to 5.76 (9.55) ( $p = 0.068$ , respectively) after an average of 64 days. The SCHNOS-C did not change significantly though there was a trend towards improvement with SCHNOS-5 (self-esteem due to nasal appearance) showing the significant improvement ( $p = 0.0103$ ). ESS showed significant improvement ( $p < 0.001$ ) from 9.32 (6.14) to 3.28 (3.08).

**Conclusions:** We have previously published methods to optimize nasal function and cosmesis for patients undergoing MMA. Our study shows the contemporary MMA does not result in undesirable nasal cosmetic outcomes. The nasal function significantly improved and showed a correlation with sleepiness.

**Acknowledgements:**

#### PHARYNGEAL SITE OF COLLAPSE AND COLLAPSIBILITY ESTIMATED FROM AIRFLOW PREDICT ORAL APPLIANCE TREATMENT EFFICACY

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**Introduction:** Efficacy of oral appliance therapy is variable, limiting its potential as first-line therapy. Site and severity of pharyngeal collapse are known determinants of success/failure with oral appliance therapy. Specifically, risk factors for an incomplete response to oral appliances include a more collapsible upper-airway, complete concentric collapse of the palate (CCCp), and collapse at oropharyngeal lateral walls. Collapsibility can be estimated from clinical polysomnography, but site of collapse detection remains limited. We recently developed a method for differentiating patients with CCCp and lateral wall collapse from those with tongue-base or epiglottic collapse using airflow from polysomnography (Op de Beek *et al* World Sleep 2022). In the current study, we applied this method to investigate the utility of including polysomnographic site of collapse with collapsibility for predicting oral appliance treatment responses.

**Methods:** Eighty-one patients with OSA (median[IQR] apnea-hypopnea index, AHI: 34[22,54]events/h, age: 50[45,56]years, 20 women, BMI: 30 [27,34]kg/m<sup>2</sup>) were assessed via polysomnography at baseline and on oral appliance treatment. From the baseline study, collapsibility was estimated using the average reduction in ventilation per respiratory event ("event depth"). For site of collapse, a continuous variable describing the probability of CCCp and lateral walls versus tongue base and epiglottis was estimated; briefly, six recognizable flow-shape characteristics (including greater inspiratory scoopiness, skewness, earlier peak flow) calculated from breaths within scored hypopneas were combined using linear regression (trained to predict results of drug-induced sleep endoscopy: cross-validated OR=4.3[1.6-11.8], pseudo-R<sup>2</sup>=0.33). We tested the hypothesis that a complete response to oral appliance therapy (>50% reduction in AHI and treatment AHI<10 events/h) is associated with absence of predicted CCCp or lateral wall collapse, adjusting for collapsibility (logistic regression).

**Results:** Oral appliance therapy reduced the AHI by 55[35,58]% and produced 31/81 complete responders. In the regression model, site-of-collapse explained unique heterogeneity in the response to oral appliances (likelihood ratio test,  $p = 0.047$  vs collapsibility alone). Regression modelling revealed that the association between oral appliance response and CCCp or lateral wall collapse was contingent on collapsibility (interaction OR[95%CI]=13[1.2,150],  $p = 0.03$ ). Specifically, in those with greater collapsibility (event depth=52%, +1SD), the likelihood of a complete

response to oral appliance therapy was low in those with CCCp or lateral walls collapse (OR=48[1.2,1.9x10<sup>3</sup>], p=0.04), but site-of-collapse was not a risk factor in those with average collapsibility (event depth=41%, mean). Likewise, greater collapsibility was a clear risk factor for incomplete responses to therapy in patients with CCCp or lateral wall collapse (OR=18 [2.3,148] per ΔSD collapsibility, p=0.006), but not in tongue base or epiglottic collapse.

**Conclusions:** Here we demonstrate potential utility of including site-of-collapse information obtained from routine sleep studies for predicting whether OSA can be efficaciously managed with oral appliances. Our study demonstrated that concentric collapse at the palate or lateral wall collapse, when combined with severe collapsibility, greatly reduces the likelihood of a favorable response to oral appliances. Identification of patients with signs of tongue base collapse or milder obstruction on polysomnography may be useful for augmenting treatment efficacy.

### PHENOTYPES IN OBSTRUCTIVE SLEEP APNEA: NEW PROMISES WITH A HOME-BASED DIGITAL MEDICINE SOLUTION

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**Introduction:** In this study, we evaluated a new digital medicine solution (DMS) to identify relevant clinical phenotypes of obstructive sleep apnea syndrome (OSA) combining self-reported clinical data and indices provided by mandibular movements (MM) analysis supported by artificial intelligence (AI).

**Method:** 1117 consecutive adults (18 to 89 years old) referred for OSA suspicion were included. Input data for phenotyping included self-reported symptoms, anthropometric/demographic data, co-morbidities with related treatment from an on-line questionnaire and metrics from a connected home sleep test device (Sunrise, Namur, Belgium) using an AI-based analysis of MM signal to describe sleep state, arousals and the level of respiratory effort.

**Results:** Using k-prototype clustering method, we identified from DMS 4 distinct clinical phenotypes: C1 to C4. The frequencies of C1, C2, C3 and C4 were 31.8%, 33.4%, 25.8%, 9.0%, respectively. C1 to C4 matched for age (years) and body mass index (kg/m<sup>2</sup>): 37.9 (23.0 to 57.2), 50.1 (30.4 to 70.8), 52.8 (31.6 to 72.0), 55.1 (34.7 to 74.7), and 25.3 (19.7 to 40.2), 32.0 (23.3 to 45.9), 32.7 (23.5 to 45.4), 34.5(25.2 to 52.7), all mean (95% CI) respectively. Males were overrepresented in C3 and C4. C1 presented with a higher prevalence of insomnia and a lower risk of OSA while the other subjects reported from C2 to C4 with increasing frequencies of witnessed apnea, gasping and choking, waking up due to excessive respiratory effort, nycturia and comorbidities. These clusters were then compared to OSA severity evaluated by polysomnography (PSG). Severity revealed by DMS was consistent to PSG OSA severity: from C1 to C4, mean apnea-hypopnea index = 6.3, 15.6, 37.5 and 72.1; mean O2 desaturation index = 3.9, 13.8, 37.3 and 69.8, respectively. The clusters C2, C3 and C4 were associated with higher risks of cardiovascular comorbidities (OR = 4.5 to 7.8 for hypertension, 4.5 to 6.9 for diabetes, 6.8 to 18.4 for heart failure and 3.1 to 5.4 for cerebrovascular stroke; all p values < 10<sup>-6</sup>).

**Conclusion:** AI-based home sleep testing of MM combined to on-line questionnaire provides easy assignment of a given patient to relevant clinical phenotype and therefore dedicated OSA care.

### PITOLISANT EFFICACY IN EXCESSIVE DAYTIME SLEEPINESS FOR PATIENTS WITH OBSTRUCTIVE SLEEP APNEA

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**Introduction:** Pitolisant a Histamin H3-receptor inverse agonist waking agent for Excessive Daytime Sleepiness (EDS) treatment in narcolepsy showed efficacy on EDS in Obstructive Sleep Apnea (OSA) patients with EDS treated respectively with and without Continuous Positive Airway Pressure (CPAP). Its efficacy and safety at 20mg/day was evaluated through an Individual patient data meta-analysis vs placebo.

**Materials and Methods:** Epworth Sleep Scale (ESS) and Oxford Sleep Resistance (Osler) tests were co-primary endpoints tested at 0.025 significance and Fatigue (Pichot Scale) was secondary.

**Results:** A significant mean ESS reduction of -3.06[95%CI -4.1,-2.02], P< 0.001 was found with Pitolisant versus placebo and 81% more patients decreased final ESS to less than 10 (RR= 1.81 [95%CI 1.36, 2.39], p< 0.001). The Osler Final/Baseline was also 18% better (ratio=1.18[95%CI 1.02,1.35], P=0.022). A clinically meaningful EDS effect of Pitolisant measured by the aggregate Z-score on ESS and Osler was 0.71([0.46, 0.97], P< 0.001). Finally, a significant mean Pichot Fatigue reduction of -1.23[[-2.29,0.18], P=0.022) was found. These effects were shown invarian across various subgroups of the population (age,gender,work conditions). Finally these effects were not impacted as to whether or not CPAP was used. Side effect incidence was similar in both groups.

**Conclusions:** These results confirm pitolisant efficacy on EDS and Fatigue symptoms in sleepy OSA patients versus placebo, evaluated by the ESS, Osler, EDS Z-score and Pichot Fatigue, irrespective of CPAP use.

**Acknowledgements:**

### PITOLISANT LONG TERM EFFECT IN SLEEPY OBSTRUCTIVE SLEEP APNEA PATIENTS WITH CPAP

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**Introduction:** Pitolisant is a histamine H3-receptor antagonist/inverse agonist waking agent reducing sleepiness in narcolepsy. HAROSA1 1 year study evaluated Pitolisant 20mg/d (P) efficacy and safety on residual excessive daytime sleepiness (rEDS) in obstructive sleep apnea patients (OSA) treated with CPAP with a good compliance.

**Materials and Methods:** 2 periods were defined in HAROSA1: a 12 weeks double blind period (DB) comparing P vs placebo (pl) (n=244) and then was proposed a 40 weeks open label period (OL) with P (n=206). The primary criteria was the Epworth sleep scale (ESS) change and the main secondary criteria were sleep latency OSler test (OSL), Pichot fatigue score (PF) and safety.

**Results:** After 1 year, in patients with P during DB, we observed an additional ESS reduction -1.21 ± 3.12, an increase of OSL and an improvement of PF -1.6 ±

5.8 during OL. In patients with pl during DB and P during PO, we observed an ESS reduction  $-4.07 \pm 5.29$ , an increase of sleep latency and improvement of PF  $-1.2 \pm 5.8$ . Most frequent side effects were headaches, insomnia, nausea, vertigo without cardiovascular impact observed.

**Conclusions:** After 1 year, OSA patients with CPAP and presenting rEDS treated with Pitolisant during DB were improved during OL on ESS, OSL and PF: Pitolisant efficacy was maintained during 1 year. OSA Patients with CPAP presenting rEDS with placebo during DB, then treated with Pitolisant (OL) were improved with a similar ESS reduction. Pitolisant showed a favourable benefit risk balance to manage rEDS in OSA patients with CPAP. **Acknowledgements:** to HAROSA 1 study investigators

#### PITOLISANT LONG TERM EFFECT IN SLEEPY OBSTRUCTIVE SLEEP APNEA PATIENTS WITHOUT CPAP

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**Introduction:** Pitolisant is a histamine H3-receptor antagonist/inverse agonist waking agent reducing sleepiness in narcolepsy. HAROSA2 1 year study evaluated Pitolisant 20mg/d (P) efficacy and safety on excessive daytime sleepiness (EDS) in moderate to severe obstructive sleep apnea patients (OSA) refusing CPAP.

**Materials and Methods:** 2 periods were defined in HAROSA2: a 12 weeks double blind period (DB) comparing P vs placebo (pl) (n=268) and then was proposed a 40 weeks open label period (OL) with P (n=236). The primary criteria was the Epworth sleep scale (ESS) change and the main secondary criteria were sleep latency OSler test (OSL), Pichot fatigue score (PF) and safety.

**Results:** After 1 year, in patients with P during DB, we observed an additional ESS reduction  $-1.6 \pm 3.4$ , an increase of OSL and an improvement of PF  $-1.4 \pm 5.9$  during OL. In patients with pl during DB and P during PO, we observed an ESS reduction  $-5.2 \pm 5.4$ , an increase of sleep latency and improvement of PF  $-2.9 \pm 6.2$ . Most frequent side effects were headaches, insomnia, nausea, vertigo without cardiovascular impact observed.

**Conclusions:** After 1 year, OSA patients without CPAP presenting EDS treated with Pitolisant during DB were improved during OL on ESS, OSL and PF: Pitolisant efficacy was maintained during 1 year. OSA Patients without CPAP presenting EDS with placebo during DB, then treated with Pitolisant (OL) were improved with a similar ESS reduction. Pitolisant showed a favourable benefit risk balance to manage EDSr in OSA patients refusing of not tolerating CPAP.

**Acknowledgements:** to all HAROSA 2 study investigators

#### POLYPHENISM AS A PUTATIVE PHENOTYPIC DETERMINANT FOR THE EMERGENCE OF TREATMENT-RELATED CENTRAL SLEEP APNEAS

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**Introduction:** Treatment Emergent Central Sleep Apneas (TECSA) are common in patients with Obstructive Sleep Apnea (OSA) following treatment with Positive Airway Pressure (PAP) systems, Oral Devices (OD), either for mandibular advancement or tongue repositioning, and Surgical Maxilomandibular Advancement (SMA). Yet, not only therapeutic responses are different among patients using the same treatment but also the emergence of central events differ between them. This is possibly related with phenotypic characteristics which should therefore be assessed and evaluated. From the available literature, this work aimed to identify phenotypic features linked to different responses regarding the emergence of central events after OSA treatment.

**Materials and Methods:** A qualitative analysis of the available literature was done and whenever possible, patients were divided according to their treatment response as: 1. emergence of central sleep apneas (CSAs) with reduction or resolution of associated obstructive events (OE), 2. emergence of CSAs without resolution or aggravation of OE, 3. resolution of the CSAs independent from OE (e.g those not included in a mixed sleep apnea event); and also according to the type of associated events: 1. mixed events or 2. independent CSAs. A critical discussion followed such observations.

**Results:** In the literature, TECSA and its particular direction throughout exacerbation or resolution differ between patients according to some characteristics and according to the type of event.

**Conclusions:** Taken together these findings seems to suggest that TECSA could represent a polyphenetic trait which can be linked to endotypic factors therefore manifesting a phenotypic expression. Whether is also possible a therapeutic-tool dependent response, this hypothesis remain elusive. However, as those findings may account for a clinical significant impact on OSA patients and may clarify some important aspects of Central Sleep Apnea pathophysiology, future research should adequately assess and confirm this hypothesis.

#### POSITIONAL THERAPY IN A PATIENT WITH REFRACTORY TREATMENT-EMERGENT CENTRAL SLEEP APNEA

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**Introduction:** Treatment-emergent central sleep apnea (TE-CSA) is a condition characterized by central respiratory events that can arise with the use of positive airway pressure (PAP) therapy during treatment of obstructive sleep apnea (OSA). It is usually transient in nature and resolves after continuous PAP therapy most of the time. In cases of persistent TE-CSA, adaptive servo-ventilation (ASV) is a common treatment as it affords a backup respiratory rate to support central apneas, and studies have shown ASV's ability to improve the apnea-hypopnea index (AHI) in patients with TE-CSA. While worsening sleep apnea in the supine position is a known phenomenon in OSA and central sleep apnea (CSA), worsening positional TE-CSA is rarely reported and to date poorly understood. Positional therapy is a strategy that has been shown to be effective in treating both OSA and central sleep apnea (CSA) but has not been established as a treatment option for TE-CSA. We are presenting a rare case of persistent positional TE-CSA that was refractory to standard treatments and only improved after adding positional therapy.

**Case report:** This is the case of a 60-year-old woman with symptomatic moderate obstructive sleep apnea who experienced progression to treatment-emergent central sleep apnea (TE-CSA) after initial treatment with positive airway pressure (PAP) therapy. A prolonged trial with continuous PAP (CPAP) or bilevel PAP (BPAP) was not possible because the patient experienced periods of pressure intolerance and adaptive servo-ventilation (ASV) was pursued. However, ASV titration revealed a persistent and positional preference for central respiratory events. She was fitted for a mandibular advancement device and had serial home sleep studies with device adjustment that continued to reveal inadequate control of her apneic events. After having used CPAP for 72 days, BPAP for 26 days, ASV for 78 days, and a mandibular advancement device, the patient was evaluated for HGNS therapy. Her HGNS titration re-demonstrated persistent central events with a supine AHI of 43.4 and a lateral AHI of 2.9, indicating a strong positional component of her refractory TE-CSA. Positional therapy was initiated with good control of the patient's apnea with HGNS use during lateral sleep and resolution of the patients reported sleep

related symptoms.

**Conclusions:** The final improvement in our case of TE-CSA resulted from positional therapy in concert with HGNS. The patient's successful lateral sleep therapy for positionally exacerbated TE-CSA demonstrates the benefit of a well-known sleep apnea treatment for this rarely described condition. Positional therapy continues to be invaluable in treating various forms of sleep apnea and may be effective for patients with positional TE-CSA who are refractory to other common therapies.

#### POSITIVE AIRWAY PRESSURE UTILIZATION, MAJOR ADVERSE CARDIOVASCULAR EVENTS INCIDENCE RISK AND MORTALITY IN MEDICARE BENEFICIARIES WITH OBSTRUCTIVE SLEEP APNEA

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**Introduction:** Positive airway pressure (PAP) is the first line treatment for moderate-severe or symptomatic obstructive sleep apnea (OSA). Randomized controlled trials have established that PAP therapy has beneficial impact on cardiovascular and metabolic functions. However, evidence on the benefits of PAP for preventing major adverse cardiovascular events (MACE) is limited. We aimed to determine the association between PAP utilization and incidence of MACE and all-cause mortality in a large sample of Medicare beneficiaries.

**Materials and Methods:** Medicare beneficiaries (>65 years) with at least 5 years of consecutive enrollment to part A and B and  $\geq 2$  distinct OSA claims were collected from multi-state (Kansas, Missouri, Iowa, Wisconsin, Nebraska, Minnesota, Texas, Utah, North Dakota, South Dakota and Indiana), multi-year (2011-2017) Medicare fee-for-service claims data. We further required at least 1-year enrollment before the first OSA claim. Evidence of PAP utilization and index date was defined based on the first Healthcare Common Procedure Coding System PAP initiation codes (E0601, E0470, E0471) after first OSA diagnosis. MACE was defined as the first occurrence of myocardial infarction, coronary revascularization, stroke, or heart failure (identified by diagnostic and procedure code claims) after PAP initiation. Analyses were adjusted by age at initial OSA diagnosis, sex, race and presence of hypertension, type 2 diabetes, obesity, and evidence of MACE prior to the index date.

**Results:** Our sample included 212,445 eligible Medicare beneficiaries with evidence of OSA diagnosis (mean [SD] age 75 [5.7] years; 45.2% women; median [Q1, Q3] follow-up 4 [2.0, 4.9] years at censoring). Five-year MACE cumulative incidence rate was 59.3% and the mortality rate was 17.8%. In adjusted analyses, OSA patients with evidence of PAP utilization (50.8%) had significantly lower MACE incidence risk (HR=0.812; 95%CI=0.803-0.822;  $p<0.0001$ ) when compared to those without evidence of using PAP. OSA patients with evidence of PAP utilization also had significantly lower mortality risk (HR=0.575; 95%CI=0.560-0.591;  $p<0.0001$ ). Pre-existing hypertension, type II diabetes and obesity were also significantly associated with increased mortality and MACE risk.

**Conclusions:** PAP utilization based on device initiation derived from claims data is associated with lower MACE incidence and mortality in older adults that are Medicare beneficiaries.

**Acknowledgements:** American Heart Association (20CDA35310360), Patient-Centered Outcomes Research Institute (RI-CRN-2020-003-IC); NIH CTSA NCATS Frontiers: University of Kansas Clinical and Translational Science Institute (UL1TR002366); Tier 2 grant, University of Missouri.

#### POSTOPERATIVE ATRIAL FIBRILLATION AND RISK FOR REOCCURRENCE AT LONG-TERM IN ADULTS WITH OBSTRUCTIVE SLEEP APNEA UNDERGOING CORONARY ARTERY BYPASS GRAFTING IN THE RICCADSA COHORT

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**Introduction:** Postoperative Atrial Fibrillation (POAF) occurs up to 33% after coronary artery bypass grafting (CABG) in patients with coronary artery disease (CAD). Obesity is one of the risk factors for POAF following CABG. Obstructive sleep apnea (OSA) is also common in patients with CAD, and may contribute to POAF, since obesity and OSA co-exist. Less is known regarding the reoccurrence of AF in patients with POAF and concomitant OSA following CABG.

**Materials and Methods:** In the current secondary analysis of the Randomized Intervention with Continuous Positive Airway Pressure (CPAP) in Coronary Artery Disease and Obstructive Sleep Apnea (RICCADSA) trial, we included 157 patients with CABG, who underwent a home sleep apnea testing, in average 73±30 days after the surgical intervention. POAF was defined as a new-onset AF occurring during or within the 30 days following the CABG. After excluding 10 patients with chronic AF, 147 remained as the final study population.

**Results:** POAF was observed in 50 (34.0%). The occurrence of POAF across the apnea-hypopnea-index (AHI) categories <5.0 events/h (no-OSA); 5.0-14.9 events/h (mild OSA); 15.0-29.9 events/h (moderate OSA); and  $\geq 30$  events/h (severe OSA) were 11.1%, 29.2%, 32.1%, and 46.9%, respectively ( $p=0.042$ ). In a multivariate logistic regression model, there was a significant risk increase across the AHI categories with the highest odds ratio for severe OSA (odds ratio 7.03, 95% confidence Interval 1.42-34.73;  $p=0.017$ ) independent of age, sex and body-mass-index. During a median follow-up period of 67 months, only 2 patients (none with POAF) were hospitalized due to AF.

**Conclusions:** Severe OSA is associated with POAF in patients with CAD undergoing CABG. Notwithstanding, those patients do not seem to have an increased risk for reoccurrence of AF at long-term regardless of the treatment of OSA with CPAP.

**ClinicalTrialRegistration:** clinicaltrials.gov NCT00519597.

**Acknowledgements:** The study was funded by the Swedish Research Council, Swedish Heart and Lung Foundation, and ResMed Foundation.

#### POST REIMBURSEMENT ANALYSIS OF THE IMPACT OF SOLRIAMFETOL PRESCRIPTION ON CPAP ADHERENCE (SOPRANO): DESIGN OF A NATIONWIDE RETROSPECTIVE ANALYSIS IN REAL-WORLD CPAP-TREATED FRENCH PATIENTS WITH OSA

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**Introduction:** The first-line primary treatment for obstructive sleep apnoea (OSA) is continuous positive airway pressure (CPAP); however, CPAP adherence remains problematic for many patients. Excessive daytime sleepiness (EDS), the chief complaint by OSA patients, may persist in 9–22% of OSA patients despite adequate CPAP adherence. Solriamfetol is a dopamine and norepinephrine reuptake inhibitor approved in the EU and US for the treatment of residual sleepiness in this clinical context. An improvement in residual EDS might impact adherence to CPAP. In published large, pivotal, randomised, controlled trials, solriamfetol did not affect CPAP adherence; however, this finding has not been confirmed in real-world treatment scenarios. The SOPRANO post reimbursement study will evaluate the impact of solriamfetol prescription on CPAP adherence in a nationwide real-world population of French patients with OSA.

**Methods:** Data pertaining to CPAP reimbursement and solriamfetol use will be extracted from the French National Health Data System repository (Système National des Données de Santé [SNDS]) for patients receiving a first administration of solriamfetol between 01 September 2021 and 30 June 2023. In France, reimbursement for CPAP devices is conditional upon treatment adherence; thus, reimbursement data are representative of different levels of adherence (adherent [ $\geq 112$  h over 4 weeks], intermediary adherence [ $\geq 56$  to  $<112$  h over 4 weeks], and low adherence [ $<56$  h over 4 weeks]). Monthly adherence scores (3, adherent; 2, intermediary adherence; 1, low adherence; 0, no CPAP equipment) will be analysed for comparison between the 6 months prior to and after solriamfetol initiation. The study population will consist of CPAP users with OSA who had  $\geq 1$  CPAP reimbursement within the 12 months prior to initiation of solriamfetol. Additional inclusion criteria are available data for monthly CPAP

reimbursement within each month of the 6 months prior to solriamfetol initiation and  $\geq 3$  dispensations of solriamfetol within the 6 months following solriamfetol initiation.

**Results:** The primary objective of this study is to assess CPAP adherence (via reimbursement rates) prior to and following initiation of solriamfetol treatment using real-world data from the SNDS (estimated CPAP population, >1 million individuals). The primary endpoint is the proportion of participants with CPAP reimbursement rates that are decreased, increased, or unchanged between the two 6-month periods (prior to and following solriamfetol initiation). The study aims to report data for approximately 3,000 participants initiating solriamfetol, with final follow-up data expected in September 2024.

**Conclusion:** The results of the SOPRANO study will help determine whether solriamfetol treatment affects CPAP adherence in a real-world OSA population.

**Acknowledgements:** This study was supported by Jazz Pharmaceuticals.

### PRECISION IN PERFORMING DISTRACTION OSTEOGENESIS MAXILLARY EXPANSION FOR OSA

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**Introduction:** Establishing nasal breathing is critical for airway stabilization in the surgical treatment of OSA. Patients with narrow maxilla and high arch palate present with limited response to standard septal, turbinate and valve procedures for nasal obstruction. The objective is to achieve distraction osteogenesis maxillary expansion (DOME) osteotomies safely and reduce morbidity including prolonged V2 paresthesia and nasolabial deformity.

**Methods:** Prospective cohort (observational) study performed in a tertiary referral center where subjects with high arched palate and narrow maxilla underwent minimally invasive nasal endoscopic (MINE) for DOME (MINE DOME) and/or guided with patient specific 3D printed guides from August 2019 to July 2021. Nasal Obstruction Symptom Evaluation (NOSE) score, mean time to opioid cessation and mean duration of cranial nerve V2 hypoesthesia were collected.

**Results:** Twenty subjects underwent MINE-DOME. Mean Nasal Obstruction Symptom Evaluation (NOSE) score decreased from 58.9 to 15.8 ( $p=0.004$ ). Mean time to cessation of opioid use was 1 day. The mean duration to full V2 recovery was 5.6 weeks.

**Conclusion:** DOME is an effective for treatment of nasal obstruction in OSA patients with narrow, high-arched maxilla. We report our outcomes of subjects undergoing DOME with a minimally invasive and patient specific approach. Techniques described can be easily adopted by sleep surgeons.

### PRECISION ORAL APPLIANCE THERAPY: THE PRIME TIME TREATMENT FOR OSA

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**Introduction:** A growing body of research has established that Oral Appliance Therapy delivers non-inferior outcomes in comparison to CPAP. CPAP was previously considered the "gold standard" due to its high efficacy in eliminating obstructive events. However, despite improvements in technology, the "effectiveness" of CPAP has been compromised by poor real-world compliance. Technological improvements have improved the "effectiveness" of Oral Appliance Therapy. This study reports the efficacy of a novel, precision engineered Oral Appliance Therapy device for the primary treatment of all severities of OSA.

**Materials and Methods:** For this retrospective, private practice investigation, OAT outcomes data was analyzed for consecutively treated patients ( $n=115$ ) with complete pre/post sleep studies.

The sample was comprised of 48.6% females and 51.4% males. Mean pre-treatment AHI was 24.1 +/- 19.2, RDI 30.7 +/- 17.2 and O2 Nadir 84% +/- 5.7%. OSA severity was distributed as 41.7% mild, 33.0% Moderate and 25.2% Severe.

All patients were diagnosed by a board certified sleep physician via a PSG or HST and treated by a AADSM certified dentist. Digital Scans (TRIOS, 3 Shape) and digital bite registrations were recorded with a George Gauge utilizing a 3mm bite fork and were obtained on all patients. The patients were consecutively ordered with complete follow up data, many did not return for follow ups.

**Bite and Titration Protocol:** With comfort in mind the initial protrusion was set at approximately 40-60% and varied according to the degree of overbite and overjet, the severity of the OSA and the presence or absence of TMJ symptoms. All patients were fitted with a ProSomnus (IA) Sleep Device (ProSomnus Sleep Technologies, Pleasanton, CA) and titrated according to their subjective symptoms (snoring, hypersomnolence, jaw discomfort). An efficacy study was obtained with a HST after titration and compared to the initial HST or PSG.

**Results:** Outcome data on 115 patients were retrospectively reviewed. The pre-treatment AHI was 24.1 +/- 19.2. Post treatment residual AHI was 6.1 +/- 6.4 with an AHI reduction of 69.2% +/- 21.2%. 74.8% of the patients were treated successfully per >50% & < 10 AHI success metric. 56% of the patients were treated to an AHI of < 5. O2 Nadir improved by 4.6 percentage points overall. Additionally, patients had a reduction in UAR airflow as evidenced by a 55% reduction of RERAs.

**Conclusions:** The data shows that a precision oral appliance is capable of successfully treating patients with all levels of severity, with the majority of patients treated to an AHI < 5, 29 severe patients with an average AHI of 5.15 were treated to a final average of 9.9. Additionally, patients successfully saw a reduction in upper airway resistance airflow as evidenced by the reduction of RERA's of 55% for 37 of the patients, showing that a precision oral appliance can have a significant impact on the upper airway. The results of this study suggest that precision oral appliance therapy be considered as the primary form of therapy for all levels of the severity of OSA depending on the preference of the patient.

**Acknowledgements:** None

### PREDICTING DISTRACTION OSTEOGENESIS MAXILLARY EXPANSION (DOME) SUCCESS IN MANAGING NASAL OBSTRUCTION IN OSA

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**Introduction:** This study attempted to identify correlated factors of distraction osteogenesis maxillary expansion (DOME) success in treating adult obstructive sleep apnea (OSA) with narrow hard palatal roof and nasal obstruction.

**Materials and Methods:** This retrospective study reviewed adult OSA subjects who underwent DOME treatment and had postoperative sleep studies from September 2014 to February 2020. Peri-operative data reviewed included Epworth Sleepiness Scale (ESS), Nasal Obstruction Symptom Evaluation (NOSE) and upper airway assessment.

**Results:** Forty-four adult subjects were included. There were significant improvements in NOSE scores ( $11.4\pm 5.4$  to  $3.9\pm 3.5$ ,  $p<0.0001$ ), ESS scores ( $11.6\pm 5.1$  to  $7.0\pm 5.4$ ,  $p<0.0001$ ), AHI ( $18.8\pm 16.9$  to  $9.3\pm 16.9$ ,  $p<0.001$ ), hypopnea index ( $15.7\pm 13.1$  to  $8.8\pm 8.7$ ,  $p<0.001$ ) and the percentage of REM sleep ( $14.1\pm 7.6\%$  to  $21.0\pm 7.8\%$ ,  $p=0.007$ ) after DOME. The cure rate of inferior turbinate hypertrophy (64.0% vs. 25.0%,  $p=0.038$ ) and nasal septum deviation (59.1% vs. 20.0%,  $p=0.060$ ) was higher in the success group. Lesser REM sleep (OR, 0.85; 95%CI, 0.73 to 1.00,  $p=0.045$ ) and the reduction of NOSE (OR, 1.03; 95%CI, 1.00 to 1.06,  $p=0.059$ ) were associated with surgical success.

**Conclusions:** DOME treatment can reduce OSA severity (especially hypopneas), improve nasal obstruction and sleep quality in adult OSA patients with nasal obstruction and narrow, high-arched maxilla. Patients with less REM sleep and peri-operative change in nasal obstruction were more likely to benefit from DOME.

**Acknowledgements:** The authors thank Dr. Yifei Ma from Stanford University for his statistical help in this study. This study was supported by Capital's Funds for Health Improvement and Research (CFH-2020-4-1055).

## PREDICTORS OF VOLTAGE AMPLITUDE IN PATIENTS WHO RESPOND TO HYPOGLOSSAL NERVE STIMULATION FOR OBSTRUCTIVE SLEEP APNEA

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**Introduction:** Hypoglossal nerve stimulation (HNS) is an established and widely-available treatment alternative for patients with obstructive sleep apnea (OSA) who do not tolerate continuous positive airway pressure. There is a need to improve post-implantation management, specifically effective and efficient titration of device settings. This study aimed to determine patient characteristics that correlate with effective voltage amplitudes.

**Materials and Methods:** This retrospective review evaluated Patients who underwent HNS implantation at two academic sleep surgery centers between November 2014 and October 2019. Patients who received diagnostic preoperative sleep studies and postoperative efficacy studies, and who demonstrated response to therapy as defined by Sher's criteria ( $\geq 50\%$  reduction in apnea-hypopnea index [AHI] to  $\leq 20$  events/hour) were included. Linear multivariate regression analysis was used to correlate patient demographics, physical exam findings, drug-induced sleep endoscopy (DISE) findings, and sleep study data with patients' final, effective voltage amplitude.

**Results:** One hundred sixty-eight Patients met study criteria. The mean (SD) age was 61.3 (10.7) years, 120 participants were men (71.4%), and mean body mass index (BMI) was 28.7 (6.6) kg/m<sup>2</sup>. When controlling for age, gender, and BMI, preoperative complete oropharyngeal lateral wall collapse on DISE ( $p = 0.005$ ) and low nocturnal mean oxygen saturation ( $p = 0.02$ ) significantly correlated with higher effective voltage amplitude.

**Conclusions:** This is the first study to evaluate patient characteristics that correlate with voltage amplitude needed to achieve therapeutic response in OSA Patients with HNS. Patients with more severe oropharyngeal lateral wall collapse and lower mean nocturnal oxygen saturation require higher voltages to achieve success.

**Acknowledgements:** Yifei Ma for his assistance with statistical analysis.

## PREVALENCE OF SLEEP-DISORDERED BREATHING IN AN AFRICAN GENERAL POPULATION: THE BENIN SOCIETY AND SLEEP (BESAS) STUDY

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**Introduction.** There are currently no data on the prevalence of sleep-disordered breathing (SDB) in the African general population. This study aimed to objectively determine the prevalence of, and factors associated with, SDB in a large population-based sample in Benin, West Africa.

**Methods.** The Benin Society and Sleep (BeSAS) population-based study was conducted from April 2018 to January 2021. Participants were recruited from both urban and rural areas. Subjects underwent polygraphy at home using a type III device. Clinical and morphometric data were also collected. SDB severity categories were defined according to apnoea-hypopnoea index (AHI): mild-to-severe (AHI  $\geq 5/h$ , moderate-to-severe (AHI  $\geq 15/h$ ) or severe (AHI  $\geq 30/h$ ).

**Findings.** For the 1810 participants with complete polygraphic data (age 46 $\pm$ 15 years, 64.2% women), the prevalence (95% confidence interval [CI])

of mild-to-severe SDB (AHI  $\geq 5/h$ ) was 43.2% (40.9–45.5), of moderate-to-severe SDB (AHI  $\geq 15/h$ ) was 11.6% (10.2–13.1), and of severe SDB (AHI  $\geq 30/h$ ) was 2.7% (2.0–3.5). The prevalence of mild-to-severe ( $p < 0.001$ ) and moderate-to-severe ( $p = 0.006$ ) SDB was significantly higher in men than in women. Individuals aged  $\geq 60$  years had a higher prevalence of SDB than younger participants in each severity category ( $p \leq 0.001$ ). In addition, SDB was more prevalent in participants living in urban versus rural areas ( $p < 0.001$ ), and there was a gradual increase in SDB prevalence with increasing BMI ( $p < 0.001$ ). Factors independently associated with SDB were advanced age, large neck circumference, and snoring in both sexes. After multivariable adjustment, severe SDB was independently associated with hypertension (odds ratio 3.99 [95% CI 1.04–15.33];  $p_{\text{trend}} = 0.044$ ) in women but not in men.

**Conclusion.** The BeSAS study provides the first objective evaluation of SDB prevalence and associated factors in Africa. The high prevalence of SDB identified should stimulate the development of public health policies to prevent and treat this condition in African countries.

**Acknowledgement.** Ligue Pulmonaire Vaudoise, Switzerland for funding.

## PULSE WAVE AMPLITUDE DROPS (PWAD) : A NEW BIOMARKER OF CARDIOVASCULAR RISK IN PATIENTS WITH OBSTRUCTIVE SLEEP APNEA IN HYPNOLAUS AND ISAACC COHORTS

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**Introduction:** This study aimed to investigate the value of pulse wave amplitude drops (PWAD) index during sleep as a biomarker of cardiovascular risk in patients with obstructive sleep apnea (OSA).

**Materials and Methods:** This is a prospective analysis of two cohorts: 1) the HypnoLaus population-based cohort, in which 1941 participants underwent home polysomnography, and 2) a subset from the ISAACC multicentre, prospective, randomised, controlled trial (CPAP vs usual care vs OSA-) assessed using respiratory polygraphy including 692 patients with acute coronary syndrome. PWAD were derived from photoplethysmography obtained by using a pulse oximeter and detected using a validated algorithm. PWAD with amplitude  $>30\%$  and duration  $>4$  heartbeats were identified. The total number of PWAD during sleep was averaged per hour of sleep as the PWAD index (number of  $>30\%$  drops in PWA per hour). Participants were divided into subgroups according to the presence of OSA (apnea/hypopnea +/-15/h) and the median PWAD index among OSA+ (high PWAD index or low PWAD index) of each cohort. Primary endpoint was the incidence or recurrence of a composite of cardiovascular events. Multivariable-adjusted Cox regressions adjusted for age, sex, body mass index, alcohol, smoking, diabetes, hypertension, lipid-lowering drugs, and beta-blockers were performed in both cohorts.

**Results:** After 49.2 $\pm$ 12.1 months and 24.3 $\pm$ 5.8 months of follow up, 3.9% and 16.9% developed a cardiovascular event in the HypnoLaus and ISAACC cohorts respectively. In HypnoLaus, OSA+/Low PWAD index group had a higher incidence of cardiovascular events compared to OSA+/high PWAD index group (HR 2.16, 95%CI 1.07–4.34;  $p = 0.031$ ) and compared to OSA-group (HR 1.96, 95%CI 1.11–3.46;  $p = 0.020$ ). In ISAACC, OSA+/low PWAD index untreated group had a higher incidence of cardiovascular events compared to OSA- group (HR 2.06, 95% CI 1.08–3.94;  $p = 0.028$ ). This difference disappeared when this group was treated with CPAP. Untreated OSA+/high PWAD index participants were not at increased risk compared to the OSA- group (HR 1.60, 95%CI 0.79–3.26;  $p = 0.192$ ).

**Conclusions:** In OSA+ patients, low PWAD index was independently associated with a higher incidence or recurrence of cardiovascular events

in both cohorts, and ISAACC data showed that CPAP treatment was associated with decreased cardiovascular risk in OSA+/low PWAD index patients. Prospective interventional studies should select patients not only based on the AHI but also on additional cardiovascular risk biomarkers such as PWAD index to better define a population for whom treatment of OSA might have a positive impact on cardiovascular risk.

#### QUALITY OF LIFE AFTER LARGE MAXILLOMANDIBULAR ADVANCEMENT SURGERY FOR OBSTRUCTIVE SLEEP APNEA USING A SINGLE-ITEM GLOBAL INSTRUMENT

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**Introduction:** From a public health standpoint, quality of life (QOL) improvement in chronic disease has gained traction as a key focus in recent years, with obstructive sleep apnea (OSA) as one of the targeted chronic diseases. The association between untreated OSA and poor QOL has been investigated and repeatedly reported in the literature, as many of the most common presenting symptoms of OSA include excessive daytime sleepiness, fatigue, social and emotional difficulties, which are all closely tied to subjective quality of life. The gold standard treatment for OSA is continuous positive airway pressure (CPAP) therapy, which has been shown to improve QOL in OSA patients. However, the impact of CPAP therapy is limited by low adherence rates. Patients who do not tolerate CPAP are candidates for surgical intervention to ameliorate airway obstruction. Among surgical interventions, maxillomandibular advancement (MMA) surgery is one of the most successful surgical interventions with consistently high rates of surgical success (86% success rate in largest meta-analysis). MMA surgery works by expanding the skeletal framework, increasing both the retro-labial and retrolingual airway by pulling the soft palate, tongue and associated muscles forward. Using drug induced sedated endoscopy (DISE), MMA has also shown to reduce pharyngeal collapsibility at the lateral pharyngeal wall during inspiration. The efficacy of MMA has been proven even when accounting for patient factors including age, weight, history of soft tissue surgery, and disease severity. While it has been well documented that MMA is effective at drastically reducing AHI and respiratory disturbance index (RDI) in OSA, there is scant literature regarding the QOL pre- and post-operatively for patients who have undergone sleep surgeries, including MMA. Prior studies have demonstrated mixed results regarding associations between AHI or RDI and QOL. Our objective was to evaluate the change in quality of life (QOL) after maxillomandibular advancement (MMA) surgery in a large cohort and determine possible predictors.

**Materials and Methods:** Following IRB approval, we performed a retrospective review, of patients undergoing MMA surgery for OSA with pre and 1-year post MMA completed QOL questionnaire at Stanford Hospital from May 2014 to December 2018. The primary outcome was the overall change in QOL using a single-item global Likert scale instrument. Secondary outcomes were change in Apnea Hypopnea Index (AHI), Body Mass Index (BMI), Epworth Sleepiness Scores (ESS), lowest saturation of oxygen (SpO<sub>2</sub> nadir), oxygen desaturation index (ODI) and the Nasal Obstruction Symptom Evaluation (NOSE) scores.

**Results:** In this cohort, 44 subjects were identified with QOL questionnaires completed. This simple QOL questionnaire showed significant improvement in patients after their MMA surgery ( $p < 0.001$ ). Additionally, all clinical measures after MMA surgery significantly improved ( $p < 0.05$ ). Robust regression model shows only preoperative SpO<sub>2</sub> to correlate significantly with QOL, in both unadjusted and demographic-adjusted models.

**Conclusions:** We present the largest cohort evaluating the impact of MMA surgery on QOL. Herein, we utilized a single-item global Likert scale instrument, and reported a correlation between preoperative SpO<sub>2</sub> nadir and patient's QOL.

**Acknowledgements:** None.

#### RANDOMISED CONTROLLED TRIAL ON THE EFFICACY OF AUDIO-VISUAL HEALTH EDUCATIONAL MATERIALS ON CPAP ADHERENCE: THE AHEAD TRIAL

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**Introduction:** Obstructive sleep apnoea (OSA) is a prevalent chronic disease with significant health implications, for which achieving >4 hours per night on continuous positive airway pressure (CPAP) is essential for effective treatment. Educational videos to improve CPAP adherence are of interest as a low cost intervention, however previous trials have shown mixed results. This study aimed to compare CPAP usage following standard of care education (SOCE), with the usage following the addition of educational videos, customised to incorporate low health literacy communication, motivational and self-efficacy techniques.

**Materials and Methods:** Adults with OSA recommended treatment with CPAP, were recruited and randomised in a single blinded method, to watch short educational videos following their in laboratory CPAP study or SOCE. The primary outcome was CPAP usage at 2mths and secondary outcomes were usage at 12mth and proportion of patients with adequate usage >4hrs/night.

**Results:** 195 patients met the eligibility criteria and were randomised to video education (n = 96) or to SOCE (n = 99). There was no significant difference in compliance at 2mths (median usage 1.7hrs IQR 0-6.2 SOCE, 4.4hrs IQR 0-6.7 video education  $p = 0.1$ ), however at 12mths there was increased usage in the video education arm (median 0hrs IQR 0-5.4 standard of care, 3.8hrs IQR 0-6.87  $p = 0.05$ ). The proportion with adequate CPAP usage >4hrs/night at 12mths was higher in the video education group (33, 33% versus 48, 50%  $p = 0.01$ ).

**Conclusions:** Long-term adherence to CPAP is enhanced by the addition of educational videos that incorporate low health literacy communication and motivational techniques, compared to SOCE.

**Acknowledgements:** Staff of the PA hospital sleep disorders laboratory. ACTRN12619000523101.

#### REGULATION OF CB1R/AMPK/PGC-1 $\alpha$ SIGNAL PATHWAY ON THE CHANGES OF MITOCHONDRIA IN HEART AND CARDIOMYOCYTES OF MICE WITH CHRONIC INTERMITTENT HYPOXIA OF DIFFERENT SEVERITY

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**Introduction:** This study aimed to evaluate the effects of chronic intermittent hypoxia (CIH) on the mitochondria of mouse heart (in vivo) and H9C2 cardiomyocytes (in vitro), the role of CB1R/adenosine 5'-monophosphate-activated protein kinase (AMPK)/peroxisome proliferator-activated receptor- $\gamma$  coactivator-1 $\alpha$  (PGC-1 $\alpha$ ) signaling pathway in the above process.

**Materials and Methods:** Thirty-two C57BL/6 mice were randomly divided into a normal group (NC); 4 weeks of CIH group (4W CIH); 6 weeks of CIH group (6W CIH); and 6 weeks of CIH treated with targeted blocking of CB1R group (6W CIH+AM251). H9C2 cardiomyocytes were divided into a normal group (NC); 6h CIH group (6h CIH); 18h CIH group (18h CIH); and 18h of CIH treated by targeted blocking of CB1R group (18h CIH+AM251). The CIH animal and cell models were created in an intermittent hypoxia chamber. The cardiac function of mice was determined;

heart tissue and ultrastructural changes were observed. Apoptosis, reactive oxygen species (ROS) and mitochondrial membrane potential were detected; and MitoTracker staining was used to observe cardiomyocyte mitochondria. Western blot, immunohistochemistry and cellular immunofluorescence were used.

**Results:** The 4W CIH group had a significantly higher ejection fraction (EF), heart rate (HR), mitochondria synthesis, and expression of CB1R, AMPK and PGC-1 $\alpha$  compared to the NC group; however, there was no significant difference in heart morphology between the two groups. Compared with the NC group, the 6W CIH group had significantly increased EF, HR, cardiac tissue injury, mitochondrial injury, and CB1R expression as well as significantly decreased mitochondrial synthesis and expression of AMPK and PGC-1 $\alpha$ . Targeted blocking of CB1R was able to increase the expression of AMPK and PGC-1 $\alpha$  and improve the heart injury induced by severe CIH. Compared with NC group, there was no significant difference in apoptosis between H9C2 cells in the 6h CIH group and NC group. However, reactive oxygen species, mitochondria membrane potential, and the expression of CB1R, AMPK and PGC-1 $\alpha$  were significantly higher in the 6h CIH group. Compared with NC group, the 18h CIH group presented higher apoptosis, reactive oxygen species, mitochondrial fragmentation, and CB1R expression as well as lower membrane potential and expression of AMPK and PGC-1 $\alpha$ . Targeted blocking of CB1R was able to improve H9C2 cardiomyocyte injury induced by severe CIH and increase the expression of AMPK and PGC-1 $\alpha$ .

**Conclusion:** The mild CIH can directly activate the AMPK/PGC-1 $\alpha$  pathway, promote mitochondrial synthesis in cardiomyocytes, and protect cardiac structure and function. Severe CIH can increase the expression of CB1R and inhibit the AMPK/PGC-1 $\alpha$  pathway, resulting in structural damage and disturbance of myocardial mitochondria synthesis, and further changes in cardiac structure. After targeted blocking of CB1R, AMPK and PGC-1 $\alpha$  increased, which alleviated the injury of heart and cardiomyocytes mitochondria caused by severe CIH.

**Keywords:** obstructive sleep apnea, chronic intermittent hypoxia, cardiovascular, mitochondria, CB1R, AMPK, PGC-1 $\alpha$

**Acknowledgements:** Thanks to the Sleep Center of the second Hospital of Shanxi Medical University and Shanxi Key Laboratory of Birth Defect and Cell Regeneration for their support to this study.

## REM-RELATED OBSTRUCTIVE SLEEP APNEA: PREVALENCE AND DEFINITIONS USING DECISION TREES MODELS

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## REM-Related Obstructive Sleep Apnea: Prevalence and Definitions Using Decision Trees Models

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## ABSTRACT

**Study Objectives:** This study aimed to estimate the prevalence of rapid-eye-movement-related obstructive sleep apnea (REMROSA) and to determine the most accurate diagnostic criteria.

**Method:** This was a retrospective cohort study that used three sets of criteria to define patients with REMROSA. These criteria were defined as strict, intermediate and lenient depending on the apnea-hypopnea index (AHI), (AHI during rapid eye movement sleep) REM-AHI/(AHI during nonrapid eye movement sleep) NREM-AHI, NREM-AHI, and REM duration. Decision tree (DT) models were used to estimate the accuracy of each set of criteria and corroborate the decision to select a specific definition.

**Results:** The study included 902 patients, with male predominance. The prevalence of REMROSA was 19.5%, 24.9%, and 39.3% for the strict, intermediate, and lenient criteria, respectively. No significant differences were observed in the patients' characteristics between the three definitions. Compared to the NREMROSA patients, the REMROSA patients were more likely to be younger females. The DT models revealed that all 3 definitions were highly accurate; however, the lenient criteria were the most accurate in classifying the patients.

**Conclusion:** REMROSA is a common condition. The clinical and polysomnographic features were similar among REMROSA groups regardless of the definition. Based on the DT models, the definition using the most lenient criteria was the most accurate for identifying REMROSA patients.

**Keywords:** sleep-disordered breathing; rapid eye movement; obstructive sleep apnea; definition; sleep apnea syndromes

## REPRESENTATION LEARNING FOR ANOMALY DETECTION IN SLEEP IDENTIFYING PEDIATRIC MOUTH BREATHING THROUGH CONVOLUTIONAL AUTOENCODERS

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**Introduction:** Identifying mouth breathing during sleep in a reliable, non-invasive way is a challenge for sleep researchers. While mouth breathing is difficult to capture, it is a condition with high relevance in pediatric sleep research, as chronic mouth breathing can have negative health implications for children. So far, sleep recordings must be manually reviewed by a sleep technologist, which is both time consuming and expensive. This research aims to automatically distinguish between mouth and nose breathing with representation learning through convolutional autoencoders based on data from RIP belts and oronasal cannula.

**Materials and Methods:** Unsupervised reconstruction-based anomaly detection aims to identify mouth breathing without labelled sleep recordings, by using the recording from an oronasal cannula and RIP belts. The sleep recording is split into subsequences of 10 seconds which are labelled as "mouth breathing" if it contains at least 3 seconds of mouth breathing. A convolutional autoencoder is trained on the data and learns the properties of the majority class "nose breathing". It encodes the data through multiple non-linear transformations into a low dimensional latent space and decodes it back in the same way. The resulting reconstruction will deviate from the original sequence, but this deviation is encouraged, as it is not a random error but the result of thousands of learned weights and bias terms within the neural network. The reconstruction error is used as an anomaly score to distinguish between the normal and anomalous class, since reconstructing an unknown pattern is more difficult for the autoencoder.

**Results:** Training the autoencoder on labelled nose breathing sequences results in a reconstruction error that is on average twice as high for mouth breathing as it is for nose breathing. This implies that the autoencoder learns representations of the nose breathing, but not of the mouth breathing. This allows us to classify all sequences above a set threshold as mouth breathing, which achieves a precision of 63.3%, capturing 71.9% of all mouth breathing sequences in the test set.

**Conclusions:** The proposed machine learning model is able to automatically distinguish between mouth breathing and nose breathing in children using the signals from an oronasal cannula and RIP belts without using any labelled mouth breathing sequences in the training. These results can be used to design less invasive methods for conducting sleep studies for children.

**Acknowledgements:** The authors thank Sigurveig Sigurðardóttir and Michael Clausen, the supervisors of the iFAAM study for allowing me to use the data for my project. They also thank sleep technologists Marta Serwatko, Kristín Anna Ólafsdóttir and Sigríður Sigurðardóttir who set up the sleep study devices for the children to sleep at home with. Additionally, Sigríður and Kristín manually scored the sleep studies. The project was supported financially by the Icelandic Research Fund 2016–2019, no. 174067, Nordforsk 2018–2021, (NordSleep, no. 90458) and the Landspítali University Hospital Science Fund 2019–2020 (no. 893831). Nox Medical (Reykjavik, Iceland) additionally supported the study by supplying the researchers with the A1 sleep recorders and consumables needed for the sleep studies.

#### RESPIRATORY EVENT TYPE AND THE PRESENCE OF DESATURATION AFFECT THE CARDIOVASCULAR RESPONSE TO RESPIRATORY AROUSALS

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**Introduction:** Obstructive sleep apnea (OSA) is characterized by complete and partial breathing obstructions, respectively called apneas and hypopneas. The obstructions often cause arousals from sleep, which can elicit cardiovascular responses including vasoconstriction and heart rate increase. However, factors affecting the magnitude and timing of these responses have not been extensively studied. Thus, we aimed to characterize arousal response in photoplethysmography (PPG) signal, hypothesizing that apneas lead to stronger but slower changes than hypopneas and so do events with blood oxygen desaturation compared to those without.

**Materials and methods:** Retrospective analysis was performed on polysomnographic data from 867 suspected OSA patients. Arousal periods together with the preceding and following 10-second segments were extracted from PPG signals. For these segments, mean instantaneous frequency and instantaneous amplitude signals were derived. Changes in the derived signals were detected by fitting three consecutive logistic functions to each signal. The changes were further categorized to detect frequency increases and amplitude decreases. The frequency and amplitude levels before and after arousal-induced changes and delays between arousal starts and the changes in PPG signal were compared between arousals caused by apneas and hypopneas with and without  $\geq 3\%$  desaturation. For comparison, samples of stable sleep were extracted and mean instantaneous frequencies and instantaneous amplitudes were computed.

**Results:** Frequency increases in PPG signal were observed in 79.3% and amplitude decreases in 82.4% of the arousals. The median frequency increased to 112.5% of stable sleep median after arousals following hypopneas. After arousals from apneas, the increase was to 117.9%. The median amplitude decreased to 73.9% of stable sleep median after arousals from respiratory events without desaturations. During respiratory events with desaturations, the median amplitude increased to 117.2% before arousals, decreasing to 88.9% after arousals. After hypopnea-related arousals without desaturation, the median delays of both frequency and amplitude changes were 3.8 s. For hypopnea-related arousals with desaturations, the median delays were 4.5 s for frequency and 4.2 s for amplitude. For all apnea-related arousals, the median delays were 5.3 and 4.5 s, respectively, with no significant difference between apneas with and without

desaturation.

**Conclusions:** It was found that apneas lead to larger frequency increases than hypopneas, and that desaturation causes larger amplitude decreases. The delays of these changes were found to be longest after apnea-induced arousals, and after hypopnea-induced arousals lengthened by desaturations. Thus, many of the hypothesized effects were observed. Additionally, the presence of desaturation was found to modulate upwards the pre-arousal baselines from which the amplitude changes start.

**Acknowledgments:** This study was supported by the European Union's Horizon 2020 research and innovation program under grant agreement no. 965417, NordForsk (NordSleep project 90458) via Business Finland (5133/31/2018), Academy of Finland (323536), the Research Committee of the Kuopio University Hospital Catchment Area for the State Research Funding (5041767, 5041794, 5041803, and 5041804), The Finnish Cultural Foundation (Central Fund), Foundation of the Finnish Anti-Tuberculosis Association, Maud Kuistila Memorial Foundation, Päivikki and Sakari Sohlberg Foundation, The Research Foundation of the Pulmonary Diseases, and Tampere Tuberculosis Foundation.

#### SAS-CARE I: SLEEP DISORDERED BREATHING IS ASSOCIATED WITH WHITE MATTER HYPERINTENSITIES IN STROKE PATIENTS

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**Introduction:** White matter hyperintensities (WMH) are frequent in the aging population, are associated with such cardiovascular risk factors as hypertension, diabetes mellitus, and are linked with an increased risk of stroke. Sleep disordered breathing (SDB) is highly prevalent in stroke patients and is associated with an increased risk of WMH. The association between SDB and WMH in stroke patients remains poorly known. This study aims to investigate the association between SDB and both the prevalence and localization of WMH in stroke patients.

**Patients and Methods:** This is a secondary analysis of the SAS-CARE I study (NCT01097967). Of the 207 patients with an acute cerebrovascular event, we analyzed a subset of 101 patients who underwent both an MRI and a polysomnography (PSG) at the acute phase of stroke. WMH severity and localization were assessed by two independent raters, using the Fazekas and the Wahlund score. We further compared the impact of SDB ( $AHI \geq 20 \cdot h^{-1}$ ) on WMH severity adjusting for age, sex, and hypertension with a multinomial logistic regression model.

**Results:** Study participants were predominantly male (74.3%), had a mean age of  $60.75 \pm 10.00$  years, and mostly with mild-to-moderate stroke/TIA (mean admission NIHSS  $3.5 \pm 4.6$ ). 35.7% of the patients had an SDB with an  $AHI \geq 20 \cdot h^{-1}$ . 31.7% of patients showed no WMH (Fazekas 0), 52.5% mild WMH (Fazekas 1), and 15.8% showed moderate to severe WMH (Fazekas 2–3). According to Wahlund score, WMH are more frequent in frontal (58.4%), followed by parieto-occipital (36.6%), basal ganglia (28.7%), infratentorial (25.7%), and temporal (12.9%) lobes. The proportions of patients with an  $AHI \geq 20 \cdot h^{-1}$  were significantly different between “no WMH” (16.1%) and “mild WMH” groups (50.9%) (Chi-square on group level:  $p = 0.004$ , pairwise comparison on “no WMH” vs “mild WMH”:  $p = 0.007$ ). Multinomial logistic regression showed that this significant difference persisted after adjustment for age, sex, and hypertension. (Relative Risk of  $AHI \geq 20 \cdot h^{-1}$  in “mild WMH” vs “no WMH”: 3.83,  $p = 0.03$ ).

**Conclusions:** Based on this preliminary analysis, SDB appears to be significantly associated with mild WMH but not moderate to severe WMH. We are currently investigating the determinants of these associations, as well as the impact of SDB subtypes and the associations with WMH localization.

**Acknowledgments:** We would like to thank all contributors to the SAS-Care Study group.

**Support statement:** This study was supported by the Swiss National Science Foundation (SNF-320030\_149752).

### SEQUENTIAL AND CONCOMITANT THERAPY OF MANDIBULAR ADVANCEMENT DEVICE AND HYPOGLOSSAL NERVE STIMULATION IN SEVERE OBSTRUCTIVE SLEEP APNEA: A CASE REPORT

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**Introduction:** Obstructive sleep apnea (OSA) is a multifactorial disorder with more than 50% of patients reported comorbid temporomandibular (TMD) condition. Hypoglossal neurostimulation therapy (HGNS) has been approved for patients with moderate to severe OSA who cannot tolerate continuous positive airway pressure (CPAP). The HGNS stimulates key airway muscles, and the maintained muscle tone prevents airway occlusion and apneic events during sleep. With tongue activation, the pharyngeal walls become less compliant and dilate laterally, enlarging the retrolingual and retropalatal levels of the airway.

**Materials and Methods:** In this case report, we describe a case of severe OSA (AHI=72.55 and 91% O<sub>2</sub>) with severe sleep-related bruxism. A 41-year-old male presented with his chief complaint of memory impairment, lack of concentration, excessive daytime sleepiness, unrefreshed sleep, and headaches. The Epworth Sleepiness Scale (ESS) revealed above the average daytime sleepiness score of 12/24. Relevant measurements were considered, such as BMI of 25.1, the neck circumference of 15.5, and cephalometric analysis depicted a low mandibular angle and reduced hyoid bone-to-mandible distance. CPAP therapy was implemented for a few months without any resolution to his symptoms. Treatment protocol for the OSA and sleep-related bruxism was initiated with further referral to the sleep physician to assess the efficacy of the sleep appliance therapy. Impressions and bite registration were completed, and MAD was fabricated with an initial 70% mandibular advancement as a starting point, along with a morning repositioning device instructed to be used with jaw-muscle exercises.

**Results:** In collaboration with the sleep physician, it was determined that the patient is a good candidate for hypoglossal nerve stimulation (HGNS) therapy. After implantation, the device was activated, and amplitude was adjusted within a certain range predefined by the physician. 3 months later, the sensor's information was processed based on an additional sleep study which revealed the most beneficial voltage of 2.8V within a range of 2.5V–3.5V to be delivered with each inhalation, along with measurement of sensation threshold and functional threshold of 2.2V and 2.3V. The MAD was selected and modified to allow more freedom for lateral excursions in severe bruxism. An anterior gap of about 7 mm was created by placing an acrylic material bilaterally in the molar region for the involuntary tongue protrusion as well as management of severe clenching and grinding. The concomitant therapy of HGNS and MAD appliance improved the overall day and night symptoms, and the sleep quality has remained substantial since then.

**Discussion:** An implanted medical device that reduces OSA occurrence by electrically stimulating the hypoglossal nerve is reserved for candidates who have failed or cannot tolerate CPAP. This case report demonstrated successful management of severe OSA in collaboration with other specialists applying a combination therapy of MAD and HGNS therapy.

**Acknowledgements:** Authors declared no conflict of interest and no financial support provided for this case report.

### SEQUENTIAL AND CONCOMITANT THERAPY OF MANDIBULAR ADVANCEMENT DEVICE AND HYPOGLOSSAL NERVE STIMULATION THERAPY IN A PATIENT WITH SEVERE OSA AND CHRONIC BRUXISM: A CASE REPORT

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**Introduction:** Obstructive sleep apnea (OSA) is a multifactorial disorder with more than 50% of patients reported comorbid temporomandibular

(TMD) condition.<sup>1</sup> Hypoglossal neurostimulation therapy (HGNS) has been approved for patients with moderate to severe OSA who cannot tolerate continuous positive airway pressure (CPAP). The HGNS stimulates key airway muscles, and the maintained muscle tone prevents airway occlusion and apneic events during sleep. With tongue activation, the pharyngeal walls become less compliant and dilate laterally, enlarging the retrolingual and retropalatal levels of the airway.

**Report of Case:** In this case report, we describe a case of severe OSA (AHI=72.55 and 91% O<sub>2</sub>) with severe sleep-related bruxism. A 41-year-old male presented with his chief complaint of memory impairment, lack of concentration, excessive daytime sleepiness, unrefreshed sleep, and headaches. The Epworth Sleepiness Scale (ESS) revealed above the average daytime sleepiness score of 12/24. Relevant measurements were considered, such as BMI of 25.1, the neck circumference of 15.5, and cephalometric analysis depicted a low mandibular angle and reduced hyoid bone-to-mandible distance. CPAP therapy was implemented for a few months without any resolution to his symptoms. Treatment protocol for the OSA and sleep-related bruxism was initiated with further referral to the sleep physician to assess the efficacy of the sleep appliance therapy. Impressions and bite registration were completed, and MAD was fabricated with an initial 70% mandibular advancement as a starting point, along with a morning repositioning device instructed to be used with jaw-muscle exercises. In collaboration with the sleep physician, it was determined that the patient is a good candidate for hypoglossal nerve stimulation (HGNS) therapy. After implantation, the device was activated, and amplitude was adjusted within a certain range predefined by the physician. 3 months later, the sensor's information was processed based on an additional sleep study which revealed the most beneficial voltage of 2.8V within a range of 2.5V–3.5V. The MAD was modified with an anterior gap of about 7 mm was created by placing an acrylic material bilaterally in the molar region for the involuntary tongue protrusion as well as management of severe clenching and grinding. The concomitant therapy of HGNS and MAD appliance improved the overall day and night symptoms, and the sleep quality has remained substantial since then.

**Discussion:** An implanted medical device that reduces OSA occurrence by electrically stimulating the hypoglossal nerve is reserved for candidates who have failed or cannot tolerate CPAP. This case report demonstrated successful management of severe OSA in collaboration with other specialists applying a combination therapy of MAD and HGNS therapy.

**Support:** Authors declared no conflict of interest and no financial support provided for this case report.

### SHARED DECISION MAKING IN OBSTRUCTIVE SLEEP APNEA

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**Introduction:** **i)** To describe shared decision making (SDM) in obstructive sleep apnea (OSA) discharge consultations with communication trained ear, nose and throat (ENT) surgeons, **ii)** to describe correlation between patient and observer based evaluations of SDM in those consultations and **iii)** to describe positive airway pressure (PAP) treatment adherence and significant weight reduction six years after discharge.

**Materials and Methods:** Consecutive patients referred to the otorhinolaryngology department at Akershus University Hospital with suspected OSA between 2015 and 2016 participated. Discharge consultations with newly diagnosed patients with OSA and body mass index >30 were video filmed. Four physicians had received communication training and consented to be video filmed. Patients could by protocol choose no treatment, primary pharyngeal surgery, primary weight reduction with a follow-up consultation or positive airway pressure (PAP) treatment. SDM was evaluated qualitatively by modified content analysis and quantitatively by the

CollaboRATE self-report questionnaire and the “Observer OPTION<sup>5</sup>” rating scale. Treatment adherence and weight reduction was assessed by telephone interview and journal inspection at six year follow-up. PAP full users were defined as using PAP for  $\geq 5$  days per week and  $\geq 4$  hours per night. Significant weight loss was defined as 10% reduction of baseline weight.

**Results:** Eighteen consultations were video filmed. The content analysis revealed that the patient perspectives only briefly were explored at discharge. The treatment decision was PAP in 17 of 18 patients. One patient was scheduled for nasal septoplasty combined with lifestyle advice. Median CollaboRATE questionnaire score in OSA patients was 29 (26, 30). Mean “Observer OPTION<sup>5</sup>” score in video filmed patients was 65.6 (SD 1.6, range 55–80). The correlation between SDM assessed by CollaboRATE self-report and by the “Observer OPTION<sup>5</sup>” rating scale was low (Pearson’s  $r=0.09$ ). After six years, three patients had stopped using PAP and nine patients were full users. No participant had achieved a 10% weight loss.

**Conclusions:** Despite little focus on the patient perspective, scores on the CollaboRATE and “Observer OPTION<sup>5</sup>” instruments were high, meaning that SDM to a large degree did happen. The relation between SDM assessed by self-report and by the rating scale was weak and may indicate assessment of different constructs. PAP adherence was high.

**Acknowledgements:** We would like to thank dr. Thorarinn Arnar Olafsson, all participants and the staff of the ASAP clinical cohort for their important contributions. Analysis and follow-up interviews were funded by Nord-Forsk.

#### SKELETAL SURGERY IN TREATING OBSTRUCTIVE SLEEP APNEA: GENDER SPECIFIC OUTCOMES

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**Introduction:** The prevalence of obstructive sleep apnea differs greatly between genders, with reported male predominance. Studies have shown differences in airway anatomy, collapsibility, hormones, arousal response, and fat distribution. Diagnostic criteria and hence treatment of sleep apnea is not gender specific, and few studies have evaluated the surgical efficacy between genders. In this study, we analyze the differences in response between males and females with both subjective and objective measures.

**Materials and Methods:** A retrospective chart review of patients was completed from 7/1/2013 to 7/1/2021 for patients with OSA. Pre and post-operative apnea hypopnea index (AHI), oxygen desaturation index (ODI), lowest oxygen saturation, Epworth sleepiness scale (ESS), Fatigue severity scale (FSS), and Nasal obstruction symptom evaluation (NOSE) were analyzed. Pediatric patients were excluded from review. Both groups were match for age ( $\pm 5$  years) and for preoperative BMI.

**Results:** 88 patients met inclusion criteria. Of those, 74 were males and 14 were females. The average pre-operative male AHI, ODI, lowest SpO<sub>2</sub>, and ESS were  $46.6 \pm 23.8$ ,  $40.1 \pm 32.3$ ,  $83.4 \pm 6.9$ , and  $8.6 \pm 5.1$  respectively. Post operative results were  $10.6 \pm 7.7$ ,  $7.3 \pm 6.9$ ,  $88.8 \pm 4.5$ ,  $5.1 \pm 4.3$ , respectively. Pre operative values for females were  $28.7 \pm 16.4$ ,  $12.6 \pm 11.4$ ,  $87.0 \pm 7.9$ , and  $13.0 \pm 7.2$  respectively. Post operative values for females were  $8.4 \pm 8.2$ ,  $5.3 \pm 6.2$ ,  $88.2 \pm 4.9$ ,  $6.7 \pm 5.3$  respectively. The average preoperative AHI was higher in males compare to females, while the average preoperative ESS was higher in females. The average AHI reduction for males was  $36.0 \pm 21.1$  (77.2% reduction) and for females  $20.3 \pm 19.7$  (70.7% reduction) with  $p < 0.04$ . The average ODI reduction for males was  $31.7 \pm 24.6$  (81.7% reduction) and for females  $2.4 \pm 7.7$  (58% reduction) with  $p < 0.004$ . The average reduction of ESS for males was  $4.1 \pm 5.04$  and for females  $7.2 \pm 8.6$  ( $p < 0.09$ ).

**Conclusions:** Maxillomandibular advancement is an effective treatment for patients with obstructive sleep apnea. Males have a higher percentage decrease in AHI and ODI and have greater improvements in lowest SpO<sub>2</sub> than females. Females however, have a greater reduction in reported symptoms than males, even with less reduction in overall AHI. The difference in response is likely secondary to non-anatomic factors that ought to be considered when evaluating the sleep apneic patient.

#### Acknowledgements: SLEEP APNEA, CPAP AND ME

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As evident through published literature, poor CPAP treatment adherence can result in significant ramifications for the improvement of a number of psychiatric disorders such as depression and anxiety (Zheng et al., 2019). A decade ago, one of us co-authored a review on CPAP adherence. The range of CPAP adherence in published studies was between 28%, using the widely accepted criterion of CPAP use of four hours four days a week, and 84% when using the criterion of six hours six days a week (Shapiro and Shapiro, 2010). In a subsequent study, it was shown in two clinics with very high adherence rates that the adherence increased by a further 7%, in both, to 84% and 91% respectively following the provision of a 40-page highly illustrated booklet “Sleep Apnea, CPAP and Me” to each patient. The presumption was that in clinics with lower adherence rates, a greater increase in adherence may be found due to the implementation of the booklet.

The above-mentioned booklet was designed to serve the broad purpose of educating patients about diagnosis, CPAP treatment and adverse consequences of Sleep Apnea. In this report, we describe the results of a survey comprising 21 questions to evaluate the usefulness and efficacy of this booklet in a patient’s journey from being diagnosed with Sleep Apnea to their current therapy compliance. Questions related to the patient’s feedback on the booklet’s content and whether any improvements were required. To date, 80 surveys have been administered to random clinic patients diagnosed with Sleep Apnea. We found that 81% of the total number of patients responded that when starting their CPAP therapy, the content included in the booklet would have answered most pre-treatment questions they initially had. Notably, in a section included in the survey allowing for open-ended responses, one patient stated that this booklet “gave me more information than the “unsure” internet...this booklet should be in every family physician’s waiting room.”

As a result, based on patient feedback from administered surveys, following is an example of a topic that we will expand on when reprinting this booklet.

- Of all the pages in the booklet, a higher proportion of responses indicated that page #7, ‘Medical problems associated with OSA’, was the most helpful and impactful. Therefore, in the newer edition of the booklet, we will be expanding on this topic.

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#### SLEEP ARCHITECTURE IN REM-OSA AND NREM-OSA: ANALOGIES AND DIFFERENCES

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**Introduction:** The prevalence, the clinical significance and treatment recommendations of obstructive sleep apnea (OSA) occurring exclusively or predominantly during REM sleep (REM-OSA) remain still unclear, while there is agreement in considering REM-OSA as a distinct OSA phenotype (Varga 2019). Based on the lack of studies investigating the effect of REM-related apnea on sleep architecture, the aim of our study was to evaluate

polysomnographic (PSG) parameters in REM-OSA patients in comparison to NREM-OSA. In addition, subjective daytime somnolence and possible correlations among PSG parameters were investigated.

**Materials and Methods:** We retrospectively compared PSG parameters of consecutive REM-OSA patients referred to our sleep centre with NREM-OSA patients, age- and AHI-matched. REM-OSA patients fulfilled three criteria combined (overall AHI > 5/h, REM-AHI/NREM-AHI  $\geq$  2 and total REM sleep time > 30 min), while NREM-OSA patients showed overall AHI > 5 and NREM-AHI > REM-AHI. Daytime somnolence was evaluated by means of Epworth Sleepiness Scale (ESS). Mann-Whitney test and Spearman correlation test were used. Statistical analysis was set at  $p < 0.05$ .

**Results:** Twenty REM-OSA patients (mean age  $47.95 \pm 15$  yo, 9M, 11F) and 20 NREM-OSA patients (mean age  $55.35 \pm 18.48$  yo; 11M, 9F) were included. The two groups did not differ for BMI and ESS. As to sleep macrostructure, in REM-OSA patients we found significant higher Sleep Efficiency ( $p = .016$ ), Sustained Sleep Efficiency ( $p = .019$ ) and stage N3 percentage and duration ( $p = .028$ ,  $p = .05$ ) than NREM-OSA patients. Total Sleep Time, REM sleep, stage N1 and stage N2 sleep percentages and duration were comparable in the two groups. In addition, mean duration of apneas and hypopneas during REM sleep was significantly longer in REM-OSA compared to NREM-OSA group ( $p = 0.029$  and  $p = .024$ , respectively). On the other hand, data about oxygen saturation (SaO<sub>2</sub>) (Oxygen Desaturation Index, mean SaO<sub>2</sub>, minimal SaO<sub>2</sub>, the percentage of *time spent* at SaO<sub>2</sub> below 90% and mean SaO<sub>2</sub> desaturation) were comparable between two groups. Lastly, periodic limb movements index was significantly lower in REM-OSA than NREM-OSA group ( $p = 0.025$ ). No correlation between ESS and PSG parameters was found. AHI in REM do not show correlation with age and BMI, whereas AHI in NREM showed a strong positive correlation with age ( $R = .618$ ,  $p < .001$ ) and a weak positive correlation with BMI ( $R = .345$ ,  $p = .029$ ).

**Conclusions:** Our findings show that sleep disruption is more prominent in NREM-OSA patient than REM-OSA. Although apneas and hypopneas occurring during REM-sleep are more prolonged in REM-OSA patients, they seem to have a better quality of sleep than NREM-OSA as demonstrated by higher sleep efficiency and slow-waves sleep and lower PLMI. REM and NREM-OSA patients, when sharing the same degree of disease severity, reported similar subjective daytime somnolence. Finally, AHI during REM, unlike AHI during NREM, does not correlate with age and BMI, probably because it depends on a different underlying mechanism.

**Acknowledgements:** Varga AW, Mokhlesi B. REM obstructive sleep apnea: risk for adverse health outcomes and novel treatments Sleep Breath. 2019 Jun;23(2):413–423

#### SLEEP BREATHING DISORDERS AND ORTHOPEDIC SPINAL SURGERY: THE IMPORTANCE OF A MULTIDISCIPLINARY APPROACH

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**Introduction:** Arthrogyposis in children refers to a group of heterogeneous disorders in which multiple joint contractures in two or more different body areas are present at birth. Limbs, spine, neck or jaw can be affected. Spinal and jaw deformities, concomitant with a low body mass index (BMI) may have an impact on the respiratory function. Although impaired sleep is a frequent problem in subjects with genetic syndromes, sleep breathing disorders (SBD) are commonly underestimated.

**Materials and Methods:** We report a case of a 12 years and 4 months boy with arthrogyposis multiplex congenita and concomitant severe thoracic lordosis with consecutive thoracic insufficiency syndrome who presented in our pediatric sleep clinic. The patient was referred by the orthopedic surgeon for complete respiratory function evaluation before surgical correction of spinal deformity. We retrospectively analyzed parameters from investigations recorded by our medical team from September 2018 to April 2021 before and after surgical treatment: BMI, pulmonary function

tests, sleep studies, manual titrations of non-invasive ventilation (NIV) parameters and imaging studies.

**Results:** The first evaluation of the patient in our clinic revealed a severely underweight child with BMI under the 5<sup>th</sup> percentile, restrictive ventilatory pattern on spirometry FVC=31%. The sleep study showed obstructive sleep apnea, with SpO<sub>2</sub> nadir=75%, with elevated transcutaneous CO<sub>2</sub>. NIV during sleep was initiated according to the manual titration and cough assist therapy was recommended during day time for bronchial secretions clearance and alveolar recruitment. After 6 months the child presented with dyspnea and decrease in FVC on spirometry. A decision was made for surgical correction of thoracic lordoscoliosis and subsequent reduction of thoracic and right lower lobar bronchus compression.

Postoperative reassessment showed a significant improvement in the respiratory function followed by adjusting the NIV settings with the polysomnographic titration. The compliance for NIV therapy during sleep was 94.4%. The BMI improved.

**Conclusions:** A collective effort of key-specialists involved in the complex management of patients with arthrogyposis is essential, requiring a multidisciplinary approach with medical, surgical, rehabilitation, social and psychological care, including genetic counseling. Polysomnography (PSG) included in clinical practice help in earlier recognition of SBD and monitoring medical and surgical treatment. A proactive respiratory assessment during wake and sleep is important to prevent progressive decline of lung and diaphragm functions in patients with congenital disorders.

#### SLEEP DISORDERED BREATHING IN PAEDIATRIC PATIENTS WITH DOWN SYNDROME: DIAGNOSTIC AND THERAPEUTIC APPROACH AND LINGUISTIC VALIDATION OF A SCREENING QUESTIONNAIRE

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**Introduction:** Obstructive sleep apnea syndrome (OSAS) is a syndrome characterized by repeated episodes of partial or complete obstruction of the upper airways. Sleep fragmentation due to apneas results in various day and night symptoms that worsen the quality of life of patients. In addition to the adult population, the pediatric population is also subject to this syndrome, with an estimated prevalence between 1.2% and 5.8%.

Down Syndrome (DS) is the most common chromosomal alteration associated with intellectual disability, with an estimated prevalence of 1/800 births worldwide. Among the morphological characteristics typical of the syndrome are included some craniofacial malformations, which increase the predisposition of these subjects to the development of OSAS; among these, we find the hypoplasia of the maxilla and mandible, the relative macroglossia, and, in addition to the structural characteristics, also the decreased muscle tone.

The prevalence of OSAS in DS patients has significantly increased, with an estimate of between 45% and 76%.

The purpose of this study is to create a diagnostic-therapeutic approach of OSAS in a pediatric population with DS, affirming the fundamental role of the dentist within the multidisciplinary team.

**Materials and Methods:** to implement this process, was first validated a questionnaire for screening OSAS in children with DS, as there is no valid questionnaire in the literature, and administered to 139 parents of patients with DS. As a second step, it was performed level III polygraphs on 8 pediatric patients with DS, to be able to formulate a diagnosis and prevalence data. Subsequently, 2 patients were evaluated from an orthodontic point of view, collaborating, and having positive results in polygraphy, in order to direct them to a therapeutic path that was subsequently concluded by the multidisciplinary team with the choice of the most suitable treatment for the type of patient.

**Results:** The questionnaire was successfully validated in Italian, given the excellent results obtained in the validation process. The administration to 139 parents of patients with DS reported that 47% of them experienced positive OSAS symptoms in their children. As regards the results obtained from the polygraphs, 6 patients were positive, out of 8 polygraphs performed. From the orthodontic evaluations were found some common characteristics, such as the transverse contraction of the upper jaw, and the patients, after multidisciplinary evaluation, were referred to different

treatments.

**Conclusions:** At the end of this study, it can therefore be affirmed that the role of the dentist is fundamental in intercepting sleep breathing disorders, and is a fundamental part of the multidisciplinary team that deals with treating patients who have been diagnosed with OSAS.

#### SPINDLE CHARACTERISTICS AS POLYSOMNOGRAPHIC BIOMARKERS FOR SLEEP BREATHING DISORDERS IN CHRONIC OPIOID USERS

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**Introduction:** EEG spindles are important for memory and cognition.<sup>1</sup> Subjects with severe obstructive sleep apnea (OSA with AHI >30) have lower spindle densities compared to individuals without OSA.<sup>2</sup> Sleep breathing disorders are common in chronic pain patients on long term opioids but the breathing disorders in such patients is distinguished from the usual OSA by high prevalence of central apneas<sup>3</sup>. These patients often complain of increased daytime sleepiness and impaired daytime functioning. In this study we wished to determine whether the distinct breathing disorders of chronic opioid users are associated with impaired spindle activity as is the case in the usual OSA.

**Materials and Methods:** 167 chronic pain patients on opioids for three months or more, who were referred from pain clinics, and had undergone in-lab polysomnography (PSG), were retrospectively evaluated. This was a planned post-hoc analysis of a prospective cohort study conducted at five pain clinics.<sup>4</sup>

Spindle characteristics (density, power, frequency) in stage 2 sleep (N2) were measured. Statistical analyses were performed to assess whether the Apnea Hypopnea Index (AHI), lowest sleep SpO<sub>2</sub>, Oxygen Desaturation Index (ODI), percentage of time with oxygen saturation below 80% and 90% (CT80 and CT90) are correlated with spindle characteristics.

**Results:** AHI, had a negative correlation with all spindle characteristics (power: correlation factor = -0.25, P-value= 0.002), (frequency: correlation factor = -0.186, P-value= 0.021), (density: correlation factor = -0.309, P-value = 0.000) in stage 2 of NREM sleep.

There was a positive correlation between "Lowest SpO<sub>2</sub>" and "Average C3 and C4 spindle frequency and Density in N2". (For lowest SpO<sub>2</sub> and spindle frequency Pearson Correlation = 0.166, P-Value = 0.039 and for spindle density Pearson Correlation = 0.208, P-Value = 0.009).

In addition, there was a negative correlation between ODI and "Average C3 and C4 spindle frequency and density in N2". (For ODI and spindle frequency, Correlation Coefficient= -0.172 and P-value=0.034. For ODI and spindle, Correlation Coefficient= -0.258 P-value= 0.001).

There was also a strong statistical correlation between CT90 and average spindle frequency in stage 2 sleep (Correlation Coefficient= -0.269, p= 0.001).

**Conclusions:** In chronic opioid users, spindle frequency, density, and power in stage 2 sleep are reduced as a function of sleep apnea severity. These findings may have further clinical implications for neurocognitive outcomes in this population.

#### STRESS ON PERIODONTAL LIGAMENTS CAUSED BY FOUR MANDIBULAR ADVANCEMENT DEVICES FOR OSAS TREATMENT: A FINITE ELEMENT METHOD STUDY

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**Introduction:** Obstructive Sleep Apnea Syndrome (OSAS) is a respiratory disorder that occurs with recurrent episodes of partial (hypopneas) or total (apneas) airway obstruction during sleep. The disease has great epidemiological value and several comorbidities. OSAS therapy is based on the use

of a Continuous Positive Airway Pressure mask (CPAP) which is considered the gold standard solution. Mandibular Advancement Devices (MAD) represent an efficient therapy in the treatment of mild and moderate OSAS. The oral device has the function of ensuring mandibular protrusion to reduce the collapse of oropharyngeal tissues during sleep. Despite having a better compliance than CPAP, MADs constitute a long-term therapy that is accompanied by side effects such as occlusal changes (reduction of overjet and overbite and loss of posterior contacts) and their use is not recommended in cases of active periodontal disease (grade II or III dental mobility or the absence of a sufficient number of teeth to give retention to the device). The present study aims to compare the stresses generated at the level of the periodontal ligaments of healthy teeth induced by four different types of MAD. The simulations were carried out with the Finite Element Method (FEM).

**Materials and Methods:** Starting from the CBCT of the skull of a young adult patient, three-dimensional models of the jaws were created. The mandibular advancement devices (Orthoapnea, Herbst, Somnodent Flex and Somnodent Avant) were scanned using a laser probe and then superimposed on the patient's digital model. Using a FEM analysis, the stresses and deformations induced by the four MADs on the periodontal ligaments of the teeth of both arches were evaluated following an advancement of the devices of 9.5 mm which is considered therapeutic.

**Results:** Orthoapnea has high and concentrated stress values, especially in the anterior maxillary and mandibular area with 4.26 kPa as maximum value. Herbst and Somnodent Flex, instead, present very similar stress values, mainly concentrated on lateral teeth. The forces are very mild and distributed. The maximum values are 3.27 kPa for Somnodent Flex and 3.56 kPa for Herbst. For Somnodent Avant the maximum stress is 4.53 kPa on periodontal ligaments.

**Conclusions:** The study found that bilateral propulsion devices exert lower and more distributed stresses on the periodontal ligaments of the teeth of the two arches compared to anterior mechanism devices that strongly concentrate stress on the teeth and ligaments of the anterior sextant. Therefore, they may be advisable to patients with compromised periodontal health in the anterior area.

**Acknowledgements:**

#### OROFACIAL MYOFUNCTIONAL THERAPY IN OBSTRUCTIVE SLEEP APNEA - PATIENTS' EXPERIENCES, ADHERENCE TO TREATMENT AND THE IMPORTANCE OF TRUST IN THE PATIENT - THERAPIST RELATIONSHIP

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**Introduction:** Obstructive sleep apnea (OSA) is a common health problem in the population. Treatment with positive airway pressure (PAP) is effective, but adherence is poor. Accordingly, new treatment options are warranted. Orofacial myofunctional therapy (OMT) is a promising, new treatment for OSA based on focused exercises<sup>1</sup>. Further, trust in the patient - therapist relationship is an important factor for adherence and satisfaction<sup>2</sup>. **We aim to study experiences and adherence to OMT and the trust relationship between a therapist and motivated patients with OSA.**

**Material and method:** A convenience sample of 12 patients with mild or moderate OSA will be interviewed post OMT treatment with exploratory semi-structured interviews. The patients will be recruited by the project leader (HHS) based on their interest in OMT treatment after having read about it in the media. They will be assessed for eligibility based on inclusion and exclusion criteria and provided informed consent prior to participation. OMT comprises of a revised version of the exercises described by Guimarães<sup>3</sup>. The OMT exercises will focus on the tongue, soft palate and facial muscles. Participants will be evaluated at baseline with

the expanded orofacial myofunctional evaluation with scores (OMES-E) protocol, the Friedman classification and tongue range of motion ratio (TRMR). The participants will have weekly telemedicine consultations for 10 weeks. They will also complete a digital sleep diary.

In this study we will explore OMT experiences and adherence mechanisms by exploratory, qualitative, semi-structured interviews after three months of OMT. This will be important as adherence to treatment is a challenge in OSA treatment and better treatment and self-management tools are needed. The interview guide will focus on:

- General information about the patient
- Perception of sleep quality
- Experiences with OMT treatment
- Facilitators and barriers to OMT treatment
- Experiences with digital sleep- and exercise diary
- Social relationship and treatment adherence
- Interactions with healthcare professionals and trust

The study has been approved by Regional Committee for Medical and Health Research Ethics South East Norway

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### STUDIO ELETTROFISIOLOGICO DEL TRONCO-ENCEFALICO NELLA SINDROME DELLE APNEE OSTRUTTIVE DEL SONNO E VALUTAZIONE DELL'EFFETTO DELLA TERAPIA CON CPAP

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**Introduzione:** Il riflesso trigemino-facciale può essere studiato e misurato attraverso la tecnica elettrofisiologica del Blink Reflex Test. Le risposte registrate, in particolare R2, sono integrate a livello del bulbo da neuroni che hanno una relazione anatomica e funzionale con la formazione reticolare e le strutture tronco-encefaliche. La sindrome delle apnee ostruttive del sonno (OSAS) è un disturbo del sonno frequente che può essere trattato con la ventilazione continua a pressione positiva (CPAP). L'obiettivo primario del presente studio è stato quello di valutare e confrontare il Blink Reflex dei pazienti OSAS con un gruppo di controllo per la valutazione della funzionalità delle risposte riflesse tronco-encefaliche. L'obiettivo secondario è stato identificare gli effetti del trattamento con CPAP su tali risposte elettrofisiologiche.

**Metodi:** Studio osservazionale e longitudinale che ha arruolato pazienti affetti da OSAS e un gruppo di controllo di soggetti sani. Tutti i partecipanti sono stati sottoposti a visita neurologica, polisonnografia e al Blink Reflex Test. Inoltre, in un sottogruppo di pazienti complianti al trattamento con CPAP è stato rivalutato al follow-up con il Blink Reflex Test.

**Risultati:** Sono stati inclusi 22 pazienti affetti da OSAS (86.4% maschi; 57.82±10.64 anni), e 10 controlli (70% femmine; 56.30±5.48 anni). Al baseline, i pazienti OSAS avevano una media dell'indice di apnea-ipopnea (AHI) di 38.26±17.27 e un indice medio di desaturazione di ossigeno (ODI) pari a 36.31±22.06. I pazienti affetti da OSAS presentavano una maggiore latenza nel R2 destro ipsilaterale (33.23±3.68) e controlaterale (34.67±4.18) in confronto a quelli dei controlli (30.53±2.63 ; 31.78±2.74). Nel sottogruppo di pazienti OSAS complianti alla CPAP (n=16; 87.5% maschi; 58.75±9.67 anni), si è osservato una diminuzione significativa dell'AHI dopo l'utilizzo della CPAP (T0 36.80±16.66; T1 3.23±2.91). Inoltre, si è osservato che la latenza del R2 destro ipsilaterale e controlaterale diminuiva dal baseline (R2i 33.88±2.61; R2c 35.65±3.92) al follow-up per effetto del trattamento con CPAP (R2i 31.92± 3.34; R2c 33.27±4.40).

**Conclusioni:** I pazienti affetti da OSAS presentano una alterazione della

funzionalità troncoencefalica probabilmente dovuta al danno mielinico ed assonale causato dall'ipossia notturna e dalla scarsa efficienza di sonno. Il trattamento con CPAP, ripristinando la corretta saturazione notturna e la struttura del sonno, sembra ristabilire tale alterazione. Tale studio mette in luce le numerose complicanze dell'OSAS anche a livello funzionale ed elettrofisiologico delle strutture troncoencefaliche.

### STUDY OF THE EFFECT OF OBSTRUCTIVE SLEEP APNEA ON TELOMERE LENGTH AND ITS ASSOCIATED MECHANISMS

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**Introduction:** Growing cross-sectional evidence suggests the contribution of obstructive sleep apnea (OSA) in the molecular pathways of aging related to the maintenance of telomere length, through the accumulation of damage by greater levels of inflammation and reactive oxygen species. However, to date, only a couple of studies investigated the role of OSA or its treatment on telomere in a longitudinal approach. In this sense, the present study aimed to investigate the effect of OSA and its treatment with continuous positive airway pressure (CPAP) on the variation of telomere length and its associated mechanisms.

**Materials and Methods:** A 6-month randomized, double-blind and sham-controlled clinical trial was conducted. Participants were randomized to use CPAP or sham-CPAP and attended 7 visits, in which they underwent clinical assessment and had their blood collected to determine mean leukocyte telomere length (LTL) and the dosage of metabolic and inflammatory markers.

**Results:** Among 127 individuals that we contacted, 46 met the inclusion criteria. At baseline, individuals in both groups were homogeneous. After 3 months of treatment, we observed an effect of the treatment on LTL, in which the SHAM group (1.0117±0.1552 vs 0.9457 ± 0.0747) showed a more expressive reduction than the CPAP group (1.0960±0.1122 vs 1.0521±0.1094). After 6 months of treatment, we observed a reduction of depressive and anxiety symptoms and sleepiness, as well as an improvement in sleep quality. We found a time-related stability on LTL in individuals undergoing CPAP treatment (1.0960±0.1122, 1.0521±0.1094, 1.0675±0.1225). We also analyzed the correlation between deltas LTL with TNF-α and IL-6. We observed a significant correlation between LTL and TNF-α (rho=-0.354, p<0.001). Interestingly, when we stratified by intervention, we no longer observed the correlation in CPAP group (rho=-0.150, p=0.195), but a stronger negative correlation between SHAM and TNF-α (rho=-0.475, p=0.08).

**Conclusions:** We could conclude that CPAP, when compared with the sham-CPAP, was effective in normalizing the polysomnographic parameters and the subjective complaints normally reported by individuals with OSA. Regarding the main outcome of the study, we observed an effect of the treatment on the stability of the LTL.

**Acknowledgements:** This work was supported by grants from Associação Fundo de Incentivo à Pesquisa (AFIP) and Fundação de Amparo à Pesquisa de São Paulo (FAPESP).

### SUDOMOTOR DYSFUNCTION IN MODERATE TO SEVERE OBSTRUCTIVE SLEEP APNEA SYNDROME AND THE EFFECTS OF CPAP TREATMENT

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**Introduction:** cardiovascular autonomic dysfunction is commonly observed in patients affected by obstructive sleep apnea syndrome (OSAS). Since sudomotor function has not been fully investigated, the aim of our study was to evaluate the skin conductance in a cohort of patients with moderate to severe OSAS, both in basal condition and after CPAP treatment.

**Materials and Methods:** we consecutively enrolled moderate to severe

OSAS de novo patients diagnosed by polysomnography (apnoea-hypopnea index, AHI > 15/h). Exclusion criteria were diabetes mellitus and polyneuropathy. The sudomotor function assessed through *Sudoscan*, which records the electrochemical skin conductance (ESC), was performed in basal conditions and after 7 days of CPAP treatment. Statistical analysis was performed by means of Wilcoxon test, Mann-Whitney U test and Spearman's correlation coefficient. Statistical significance was set at  $p < .05$ .

**Results:** twenty-four patients (19 men, 5 women), mean age of  $58.3 \pm 9.5$  y.o., body mass index (BMI) of  $30 \pm 4.3$  kg/m<sup>2</sup>, affected by moderate to severe OSAS were recruited. Average AHI was  $45.7 \pm 15.4$  events/h and mean nocturnal oxygen saturation (SpO<sub>2</sub>) was  $92.8 \pm 2.6$  %. Eleven of 24 OSAS patients had pathological baseline hands ESC (ESC < 60 us), while baseline feet ESC was pathological only in one subject (ESC < 70 us). Patients with hands sudomotor dysfunction (mean hands ESC  $46.8 \pm 9.7$  uS) did not differ from the subjects with normal sudomotor function (mean hands ESC  $75.4 \pm 8.4$  us) for age, BMI, AHI, SpO<sub>2</sub>, glucose levels, cardiovascular and pneumological comorbidities. In patients with hands sudomotor dysfunction we observed a significant correlation of hands ESC with age ( $R = -0.67$ ,  $p = .02$ ) and mean nocturnal SpO<sub>2</sub> ( $R = 0.75$ ,  $p = .007$ ). Furthermore, in patients with basal sudomotor dysfunction, CPAP treatment induced an increase of hands ESC ( $46.8 \pm 9.7$  uS vs  $54.9 \pm 12.8$  uS,  $p = .014$ ), although in 8/11 subjects hands ESC values were persistently pathological.

**Conclusions:** sudomotor dysregulation is not infrequent in moderate to severe OSAS patients since in our study sudomotor function was impaired in upper extremities in 45% of untreated OSAS patients. In these patients basal hands ESC positively correlated with nocturnal mean oxygen saturation, suggesting a possible association between sudomotor dysfunction and nocturnal chronic intermittent hypoxia. Short-term CPAP treatment may partially restore such dysfunction. The persistence of abnormalities in sudomotor function in most patients may be due to the short-term treatment and to the central remodelling of autonomic control, requiring a long-term ventilotherapy.

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## SULTHIAME REDUCES LOOP GAIN AND INCREASES THE AROUSAL THRESHOLD - INSIGHTS FROM A RCT IN PATIENTS WITH MODERATE TO SEVERE OSA

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**Introduction:** Mechanical methods constitute the mainstay of therapy in obstructive sleep apnea (OSA). An effective and well-tolerated pharmacological alternative has actively been sought after. Sulthiame (STM), a drug with carbonic anhydrase (CA) inhibitory properties and used in Rolandic epilepsy, has been applied in a drug repurposing program addressing sleep disordered breathing. Recent research has identified major endotypic traits such as the loop-gain (LG) and the arousal threshold (ArTh), which dominate certain forms of OSA.

**Materials and Methods:** This was a double-blind, randomized, placebo-controlled dose guiding, safety and tolerability study of STM in 68 patients with moderate/severe OSA. Patients were 18-75 years old, had a BMI between 20 and 35 kg/m<sup>2</sup>, an Apnea Hypopnea Index (AHI)  $\geq 15$  and had terminated previous CPAP due to non-acceptance or non-tolerability. Major exclusion criteria were central sleep apnea syndrome and dominant Cheyne-Stokes respiration. Patients were normotensive or had well controlled hypertension at study start. Polysomnography was assessed twice during two consecutive nights at baseline and follow-up. A target

STM dose of 200 and 400 mg o.d. ( $n = 12$  and  $25$ , respectively) or corresponding placebo ( $n = 22$ ) was established during four weeks by a titration procedure yielding a stable dose during the last two weeks of follow-up. LG and the ArTh during NREM sleep were determined at baseline and follow-up using an established mathematical modelling of ventilatory drive during naturally occurring breathing disruptions (Ref 1). The study was approved by the regional research ethics committee (Dnr: 045-18, 2018-02-07) and posted in the EU Clinical Trials Register (EudraCT N°: 2017-004767-13).

**Results:** The mean (SD) AHI at baseline was 53.9 (21.1), 61.1 (24.1) and 55.2 (22.3) in the placebo, STM 200 mg and 400 mg groups, respectively. The reduction of the AHI during therapy in the three groups were 3.0 (10.5), 20.5 (14.2) and 22.2 (12.5). Corresponding LG values at baseline were 0.66 (0.15), 0.69 (0.14) and 0.59 (0.11) and the changes following STM therapy were -0.02 (0.08), -0.18 (0.08) and -0.19 (0.10) after placebo, STM 200 mg ( $p < 0.001$ ) and 400 mg ( $p < 0.001$ ), respectively. The baseline ArTh was 1.17 (0.22), 1.20 (0.19) and 1.15 (0.18) and the changes during STM therapy were -0.02 (0.10), +0.07 (0.21) and +0.14 (0.20) ( $p < 0.1$  and  $p < 0.003$ , placebo vs respective drug therapies). The reduction in NREM-LG was linearly correlated with the reduction in NREM-AHI after STM ( $R = -0.44$ ,  $p < 0.03$ ).

**Conclusions:** A post-hoc analysis of data from a safety and tolerability study of STM in patients with OSA demonstrated a dose-dependent reduction of the LG. Moreover, the ArTh was increased after SMT. The observed reduction of sleep-disordered breathing after STM appears to include most patients with OSA but may be particularly pronounced in those with high LG and/or a low ArTh.

Ref. 1: Terill et al, <https://pubmed.ncbi.nlm.nih.gov/25323235/>

## <sup>18</sup>F-FDG PET, COGNITIVE, AND CSF BIOMARKERS IN PATIENTS WITH OBSTRUCTIVE SLEEP APNOEA BEFORE AND AFTER CONTINUOUS POSITIVE AIRWAY PRESSURE TREATMENT

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**Introduction:** Dysregulation of cerebral glucose consumption, alterations in cerebrospinal fluid (CSF) biomarker levels, and cognitive impairment have been reported in patients with obstructive sleep apnoea (OSA). Based on these recent observations, OSA is considered a risk factor for Alzheimer's disease (AD) because it can trigger neurodegenerative processes. This study aimed to measure cognitive performance, CSF biomarkers, and cerebral glucose consumption in adult patients with moderate to severe OSA compared to controls and to evaluate the effects of beneficial continuous positive airway pressure (CPAP) treatment on these biomarkers over a period of 12 months.

**Materials and Methods:** Thirty-four patients with OSA and 34 controls were included in the study. Participants underwent <sup>18</sup>F-fluoro-2-deoxy-D-glucose positron emission tomography (<sup>18</sup>F-FDG PET), cognitive evaluation, and CSF AD biomarker analysis. A subgroup of 12 OSA patients treated with beneficial CPAP and performing the 12-month follow-up were included in the longitudinal analysis, and cognitive evaluation and <sup>18</sup>F-FDG PET were repeated.

**Results:** Significantly reduced glucose consumption was observed in the bilateral praecuneus, posterior cingulate cortex, and frontal areas in patients with OSA than in controls. At baseline, OSA patients also showed lower  $\beta$ -amyloid<sub>42</sub> and higher total-tau and phosphorylated-tau CSF levels than controls. Increased tau protein levels correlated with a reduction in brain glucose consumption in different brain areas. In the longitudinal analysis, OSA patients showed an improvement in cognition and an increase in <sup>18</sup>F-FDG uptake in several brain areas.

**Conclusions:** Cognitive impairment, reduced cerebral glucose consumption, and alterations in CSF biomarkers were observed in patients with moderate to severe OSA. The alteration of these cognitive, nuclear

medicine, and CSF biomarkers can reinforce the hypothesis of AD neurodegenerative processes triggered by OSA. Notably, cognition and brain glucose consumption improved after beneficial CPAP treatment in the longitudinal analysis. Further studies are needed to evaluate the long-term effects of CPAP treatment to clarify whether restoration of OSA condition can prevent cognitive impairment and AD dementia.

#### SYSTEM VALIDATION STUDY FOR NOVEL WEARABLE SLEEP APNEA SCREENING DEVICE

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**Introduction:** The gold standard for sleep apnea diagnosis is full polysomnography (PSG) performed in a sleep laboratory. The method is expensive, limited access and can be uncomfortable for the patient. Previously developed home sleep apnea testing (HSAT) devices usually require technical skills not every patient has, and this increases the risks of inadequate recordings and unnecessary re-testing.

An inexpensive and easy-to-use wearable collar system (Nukute) was used in sleep apnea screening. The system includes a piezo-electric microphone for recording tracheal sounds, an accelerometer and a pulse oximeter. The screening results were compared to PSG.

**Material and methods:** 40 concurrent overnight recordings with the Nox A1 PSG and the new system were made in two Finnish University Hospitals. The average age of the subjects was 45.56 ( $\pm$ SD 15.85) years and BMI 27.12 ( $\pm$ SD 4.50) kg/m<sup>2</sup>. 50 % of the participants were male.

In the new device, tracheal sounds were used to derive airflow-related signals and activity and position information were derived from accelerometer data. Oxygen saturation and heart beat information was obtained from the pulse oximeter. Sleep specialists scored both measurements independently. We compared both the individually scored apnea and hypopnea events and the AHI and REI values between the two systems (Apnea Hypopnea Index from the NOX A1 and Respiratory Event Index from the new system).

**Results:** The number of scored events for NOX A1 / Nukute system was 1505/1738 apneas and 1841/1963 hypopneas. Mean AHI was 12.77  $\pm$  17.36 events/h and mean REI was 11.89  $\pm$  18.47 events/h. The correlation coefficient between AHI and REI was 0.96. With Bland-Altman analysis the mean difference between AHI and REI was 0.87 (95% CI: -0.80, 2.55) events/hour with median difference 0.60 events/h.

AHI/REI cut-off values > 5, > 15 and > 30 events/h were used to determine how well different sleep apnea severities were detected. Measurements were classified positive when AHI/REI was above the cut-off. Accuracies using cut-offs > 5, > 15 and > 30 events/h were 93 %, 93 % and 98 %, respectively.

**Conclusions:** The results with the new validated system are in very good agreement with the PSG, showing no systematic bias with respect to the reference method.

Sleep apnea severity scoring is detected by the new system with nearly perfect agreement compared to the PSG.

In addition to its reliability, the simplicity of its use and its lower cost comparing to other systems in the market, the collar device is a promising screening tool for sleep apnea and other related sleep disorders.

**Acknowledgements:** The authors would like to thank all patients included in this study.

#### TARGETED COMBINATION THERAPY BASED ON ENDOTYPES RESOLVES OBSTRUCTIVE SLEEP APNOEA

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**Introduction:** Obstructive sleep apnoea (OSA) is a multi-factorial disorder with varying degrees of anatomical and non-anatomical endotypes that contribute to OSA pathogenesis. Current treatment models for OSA generally follow a “one size fits all” trial and error approach where continuous positive airway pressure (CPAP) is offered as first line therapy in >90% of cases. This is despite the complex nature of the disorder and knowledge that ~50% of patients prescribed fail to use CPAP at all or use it sub optimally. Mandibular advancement splints (MAS) is an effective therapy option for many patients but does not resolve OSA in ~50% of cases. To explore the potential for physiology-informed targeted therapy for OSA, this study aimed to resolve OSA in these individuals by combining MAS with other targeted therapies based on OSA endotype characterisation.

**Methods:** Nineteen people with OSA (apnoea-hypopnoea index (AHI): 40 $\pm$ 20 events/h), not fully resolved with MAS alone (AHI>10 events/h) were recruited. OSA endotypes were assessed via a detailed physiology night. Targeted combination therapy was delivered in three phases. Phase one involved combining existing anatomical interventions to MAS such as an oral expiratory positive airway pressure valve (EPAP) and a supine-avoidance device. Participants with residual OSA (AHI>10 events/h) following phase one went onto phase two, where one or more targeted non-anatomical therapies was added according to each individual's endotype characterisation. Non-anatomical therapies included oxygen therapy (4L/min) to reduce unstable respiratory control (high loop gain), 10mg zolpidem to increase arousal threshold, or 80/5mg atomoxetine-oxybutynin (ato-oxy) for poor upper-airway muscle responsiveness. Any remaining with unresolved OSA underwent phase three: MAS plus EPAP was combined with CPAP.

**Results:** OSA was successfully treated (AHI<10 events/h) in all but one participant with combination therapy. Addition of existing anatomical therapies- EPAP and supine-avoidance therapy to MAS, resolved OSA in 53% of participants (MAS alone vs. phase one therapy: 26 $\pm$ 16 vs. 15 $\pm$ 14 events/h, n=10). Six participants were then treated effectively with the addition of phase two therapies: four with oxygen, one with 80/5mg ato-oxy and one required both oxygen and 80/5mg ato-oxy. Of the remaining participants, two were resolved with phase three (CPAP) combination therapy and one remained unresolved after oxygen followed by CPAP (unable to tolerate CPAP and ineligible for pharmacotherapy due to concomitant medications).

**Discussion:** In people with OSA who have an incomplete monotherapy response, targeted combination therapy informed by individual pathophysiology may be a viable treatment alternative.

#### TELEMONITORING OF NIV THERAPY MAY REDUCE NEED FOR CONTROL VISITS

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**Introduction:** Noninvasive ventilation (NIV) therapy with bilevel devices has become a clinical routine treatment not only in acute but also in long-

term chronic hypercapnic respiratory failure. Home NIV therapy is usually started and controlled in a clinical setting and requires several days of hospitalization according to our clinical routine. Telemonitoring (TM) of home NIV therapy three months after initiation phase may reduce the need of hospital control visits.

**Materials and Methods:** All patients with acute or elective initiation of home NIV therapy during 2018–2019 in Turku University Hospital were under cloud-based TM for three months after discharge from the hospital. The following data were gathered retrospectively: gender, age, BMI, the main causative disease for NIV therapy (COPD, OSA or OHS), Charlson comorbidity index (CCI), pack years as well as the TM data regarding the need for inward or outward control visits, adherence to NIV therapy with usage hours and patient survival.

**Results:** Altogether 376 patients (59% men) were included. Mean age was 69.3 (SD 12.7) years, BMI 31.9 (SD 9.6) kg/m<sup>2</sup> and pack years 27.7 (SD 24.2). After three months on TM, 222 (55%) patients continued NIV therapy. The total discontinuation rate was 154 (45%), of which 51 (33%) patients were deceased. There were no differences in gender, age, BMI, pack years or the causative diseases for NIV therapy between those who continued or discontinued NIV therapy. In logistic regression analysis CCI was lower in patients continuing than discontinuing NIV therapy 1.8 (SD 1.5) vs. 2.5 (SD 1.9), respectively ( $p < 0.001$ ). As expected, those who discontinued NIV therapy had lower using hours 2.1 (SD 3.1) vs. 6.3 (SD 2.6), respectively ( $p < 0.001$ ). Only 42 (27%) of all quitters came to control visit after TM period compared to 216 (97%) of those continuing NIV ( $p < 0.001$ ). From patients continuing NIV, 111 (50%) needed inward hospital controls because of problems of mask fitting or other difficulties in NIV use but rest of them were scheduled for outward hospital control visit with the aid of TM data. The majority (59%) of survived NIV quitters did not need any control visit.

**Conclusions:** Depending on your clinical practise, with TM the home NIV therapy you may reduce the need for hospital control visits because of early dropouts from the NIV therapy (deceased, patient's own will or multimorbidity). Secondly, a large proportion of those continuing NIV and adhering to the therapy can be controlled at outward hospital visits.

**Acknowledgements:** Supported by foundation of Foundation of the Finnish Tuberculosis Resistance Association and Respiratory Disease Research Foundation.

#### THE ADHERENCE INDEX: THE COMBINATION OF TRADITIONAL PSG INDICES AND ODDS RATIO PRODUCT PREDICT LONG-TERM ADHERENCE WITH POSITIVE AIRWAY PRESSURE THERAPY IN OBSTRUCTIVE SLEEP APNEA

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**Introduction:** It is well-established that adherence to the gold-standard treatment of obstructive sleep apnea (OSA) with positive airway pressure (PAP) therapy is poor and can range between 30–60% adherence across studies. This, along with the shortage of PAP therapy devices due to the recent Philips-Respironics recall makes it increasingly important to identify who will adhere to PAP therapy and who will not. Early identification of an individual patient's probability of long-term PAP adherence could help focus resources and improve treatment outcomes. We determined if conventional polysomnographic (PSG) markers and measures of sleep depth based on the Odds Ratio Product (ORP) would predict adherence with PAP therapy twelve months after it was started.

**Materials and Methods:** Patients with severe OSA (N=236; AHI =72.2 ± 34.1; 102 females) underwent a split-night PSG, preceded by measurement of arterial blood gases (ABG) and completion of a questionnaire focused on sleep patterns and symptomatology. All patients were prescribed PAP therapy (84% received CPAP, 16% received BiPAP). Patient adherence with PAP therapy twelve months later was categorized as “Never used” (n=20), “Quit using” (n=34), “Poor adherence” (n=61), and “Good adherence” (n=121). Multiple linear regression analysis with backward elimination of conventional PSG variables and the ORP during diagnostic PSG was performed to create an Adherence Index that predicted PAP adherence. Variables were removed from the model until only those with p values <0.10 remained.

**Results:** Diagnostic PSG markers that were strong predictors of long-term PAP in the model were AHI, ORP during non-rapid eye movement sleep (ORP NREM), and mean nocturnal SpO<sub>2</sub> (overall model:  $r^2 = 0.12$ ,  $F(2,232) = 10.8$ ,  $p < 0.001$ ). The Adherence Index derived from these measures was strongly predictive of PAP adherence twelve months later in individual patients. A higher Adherence Index in a patient was associated with a greater probability of falling into the good adherence category ( $r^2 = 0.98$ ). With an Adherence Index of 4.0, the probability of good adherence was as high as 90%.

**Conclusions:** This study highlights the utility of diagnostic PSG markers (AHI, NREM ORP, and SpO<sub>2</sub>) as predictors of treatment adherence. Inclusion of the Adherence Index can assist in the development of a precision-based approach to PAP management, and the identification of patients who may require additional resources to promote adherence. Prediction of patients who might be more likely to have good adherence to PAP therapy becomes particularly important during times of PAP device shortages.

#### THE ASSOCIATION BETWEEN SLEEP QUALITY, HEALTH STATUS, AND DISABILITY DUE TO BREATHLESSNESS IN COPD PATIENTS

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**Introduction:** Chronic obstructive pulmonary disease (COPD) increases susceptibility to sleep disturbances. This study aimed to evaluate the association between COPD severity criteria with sleep quality.

**Materials and Methods:** 158 patients in Rasul Akram Hospital of Iran university of medical sciences, Tehran, Iran, from April 2019 to March 2021 diagnosed with COPD were examined using the Pittsburgh Sleep Quality Index (PSQI), COPD assessment test (CAT), modified Medical Research Council (mMRC) dyspnea scale, spirometry, and pulse oximetry.

**Results:** Of 158 subjects, 125 patients were male (79%), and 33 were female (21%). The mean subject's age and FEV1/FVC ratio were 62.6 ± 11.5 and 65.6 ± 14.9 %, respectively. The mean CAT scoring and SpO<sub>2</sub> saturation reported 16.2 ± 7 and 91.5 ± 10.8 %, respectively. The mean PSQI score was 8.2 ± 3.8. The association between PSQI score with FEV1 and FEV1/FVC ratio was not statistically significant ( $p = 0.64$  and  $0.58$ , respectively), whereas the association between PSQI scores with CAT score ( $p < 0.0001$ ,  $r^2 = 0.51$ ) and dyspnea severity ( $p < 0.0001$ ,  $r^2 = 0.29$ ) were statistically significant. The patients with higher CAT score demonstrated poor sleep quality, particularly in longer sleep latency ( $p = 0.001$ ,  $r^2 = 0.056$ ), bad subjective sleep quality ( $p < 0.0001$ ,  $r^2 = 0.286$ ), lower sleep efficiency ( $p = 0.002$ ,  $r^2 = 0.077$ ), higher sleep disturbance ( $p < 0.0001$ ,  $r^2 = 0.225$ ), daytime dysfunction ( $p < 0.0001$ ,  $r^2 = 0.259$ ), and sleep medication intake times a week ( $p = 0.01$ ,  $r^2 = 0.069$ ). Dyspnea severity was attributed to bad subjective sleep quality ( $p < 0.0001$ ,  $r^2 = 0.069$ ), higher sleep disturbances ( $p = 0.005$ ,  $r^2 = 0.08$ ), and daytime dysfunction ( $p < 0.0001$ ,  $r^2 = 0.108$ ).

**Conclusions:** The PSQI has a significant association with the CAT and mMRC for COPD patients and is linked to the disease's severity.

**Acknowledgements:** We thank all Rasul Akram Hospital staff and patients who collaborated with us in this study.

#### THE ASSOCIATION OF POLYMORPHISM IN MTNR1B WITH MELATONIN LEVEL AND THE RISK OF OBSTRUCTIVE SLEEP APNEA SYNDROME DEVELOPMENT IN PATIENTS WITH ARTERIAL HYPERTENSION

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**Introduction.** The cardioprotective effect of melatonin has been established, which is manifested through the activation of type 2 melatonin receptors. It is worth studying the association of variants of the MTNR1B

gene, which encodes the type 2 melatonin receptor, with the peculiarities of melatonin production and the risk of obstructive sleep apnea syndrome (OSAS) in patients with arterial hypertension (AH).

**Purpose.** To study the prevalence of the MTNR1B gene variants in patients with AH and to analyze their association with the level of melatonin and the risk of OSAS development.

**Materials and methods.** The study included 67 patients with I-II degree AH. The mean age of the surveyed patients was  $48.4 \pm 9.2$  years, of which 53 were males (79.1%), and 14 females (20.9%).

In order to detect OSAS, respiratory monitoring was carried out using the SOMNOchek micro system (Weinmann, Germany).

Polymorphisms of the MTNR1B gene were determined by real-time polymerase chain reaction.

Daily melatonin production was assessed by concentration of 6-sulfatoxymelatonin (6-SMT) in 24-hour urine.

Based on the results of respiratory monitoring, the study cohort was divided into 2 groups: the main group ( $n=42$ ) – patients with AH in combination with OSAS, the comparison group ( $n=25$ ) – patients with AH. Statistical analysis of the study material was carried out using the Statistica 10.0 software package (StatSoft, Inc.).

**Results.** Patients in the main group compared to the patients in the comparison group showed higher level of 6-SMT in daily urine ( $82.29 [46.62; 140.62]$  vs  $35.28 [19.02; 91.89]$  ng/ml, respectively;  $p=0.031$ ) and in its daytime portion ( $91.57 [60.77; 160.99]$  vs  $33.0 [15.88; 103.60]$  ng/ml, respectively;  $p=0.037$ ). Correlation analysis established the presence of positive associations of moderate strength between the apnea / hypopnea index and the level of 6-SOM in daily urine ( $r=0.43$ ;  $p=0.00065$ ) and its daytime portion ( $r=0.40$ ;  $p=0.00079$ ).

The prevalence of CC, CG and GG genotypes of the MTNR1B gene in patients of the main group was 28(66.7%), 11(26.2%) and 3(7.1%), respectively, in patients of the comparison group – 8(32.0%), 13(52.0%) and 4(16.0%). In patients of the main group, the CC genotype was more common than in patients in the comparison group ( $p=0.019$ ). The calculation of the odds ratio established that the CC genotype of the MTNR1B gene is a risk factor for OSAS (OR=4.25, 95% CI: 1.48-12.23). Carriers of the CC genotype, in comparison with carriers of the CG and GG genotypes of this gene, showed higher level of aMT6s in daily urine ( $83.33 [45.27; 129.34]$  and  $50.68 [19.02; 85.92]$  ng/ml, respectively;  $p=0.037$ ).

**Conclusion.** In AH associated with OSAS, there is an increase in the level of 6-SMT in daily urine due to its daytime production, which correlates with the severity of OSAS and is associated with the CC genotype of the MTNR1B gene. Carriers of the CC genotype of the MTNR1B gene show higher daily level of melatonin. The presence of the CC genotype of this gene acts as a factor of predisposition to OSAS in patients with AH (OR= 4.25; 95% CI: 1.48-12.23).

**Благодарности:**

#### THE COGNITIVE IMPAIRMENT FEATURE IN OBSTRUCTIVE SLEEP APNEA

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**Introduction:** Obstructive sleep apnea (OSA) is characterized by repetitive episodes of complete (apnea) or partial (hypopnea) obstruction of the upper airway during sleep. Untreated OSA could result in cognitive dysfunction though the mechanism is still unclear. To better understand the cognitive impairment features in OSA, we tried to estimate the cognition impaired profile of patients with OSA based on a systematic review and meta-analysis of the literature.

**Materials and Methods:** Databases of Web of Science, PubMed, Cochrane Library, and Embase were searched with the keywords of (sleep apnea) and (cognitive or cognition or dementia) until March 2021. Two reviewers independently screened retrieved records according to our listed inclusive and exclusive criteria and extracted the scores for responsive scales from eligible studies. Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of literature and Stata 15.0 worked for all statistical analyses. Standardized mean difference (SMD) and 95% confidence interval (CI) were calculated for the summary effect for each cognition test between OSA

patients group and non-OSA patients group, which were used to standard for the impaired characteristics for responsive cognition domains.

**Results:** A total of 57 articles were included, with 3962 OSA (AHI $\geq$ 5) patients and 3020 non-OSA (AHI $<$ 5) subjects, to research the impairment profile for global cognition and 5 specific domains (psychomotor speed, executive function, verbal memory, language, and visuospatial/constructional function). Our results revealed, compared with non-OSA group, there was a significant decline in global cognition for OSA group estimated by MoCA (SMD [95%CI] = -1.178 [-1.542, -0.814],  $p<0.001$ ). Besides, we also found that the impaired cognition domains covering psychomotor speed (SMD [95%CI] = 0.568 [0.169, 0.966],  $p=0.005$ ), executive function (SMD [95%CI]= 0.883 [0.545, 1.222],  $p<0.001$ ), verbal memory (SMD [95%CI]= -0.673[-0.977,-0.368],  $p<0.001$ ), language (SMD [95%CI]= -0.298[-0.568,-0.027],  $p=0.010$ ), and visuospatial/constructional function (SMD [95%CI]= -0.478 [-0.835,-0.121],  $p=0.009$ ).

**Conclusions:** In addition to global cognitive decline, our results supported that psychomotor speed, executive function, verbal memory, language, and visuospatial/constructional function domains are specifically impaired for OSA patients.

**Acknowledgements:** We acknowledge the contributions from the authors in our included publications.

#### THE EFFECT OF AGE AND GENDER ON THE CLINICAL PHENOTYPE OF SLEEP APNEA

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**Introduction:** Sleep apnea is increasingly prevalent public health problem. The majority of sleep apnea studies have been performed in working-age people. Little is known about sleep apnea in people over 70 years of age, and in people over 80 years of age, it has hardly been studied at all. There is also much to be learned about the impact of gender on the specific features of sleep apnea. The aim of our study was to provide insight into differences in anthropometric determinants, respiratory variables, and perceived symptoms of sleep apnea across all age groups and genders.

**Materials and Methods:** We conducted a comprehensive registry study of all patients over 18 years of age diagnosed with sleep apnea at Turku University Hospital in 2012-2019. Total of 13651 patients were included (63% male; mean age 56.6, SD 13.5) and of those, 2010 patients ranged in age from 70 to 80 years and 457 were over 80 years of age at the time of diagnosis. Data from cardiorespiratory polygraphy, Body Mass Index (BMI), and scores of Epworth Sleepiness Scale (ESS), depression scale (DEPS) and the 12-item General Health Questionnaire (GHQ-12) were collected from electronic medical records using a search algorithm.

Patients were stratified into groups based on gender and age (below 70, 70-80 and over 80 years of age) to assess the clinical characteristics. Factors contributing to subjective daytime sleepiness were examined using linear regression analysis.

**Results:** BMI was highest in the youngest age group (mean BMI  $33.2 \pm 17.0$ ) compared to the very elderly (mean BMI  $30.0 \pm 15.6$ ;  $p<0.001$ ). However, still 70% of over 80-year-olds were overweight or obese. Women below 70 years of age had the highest ESS scores ( $p<0.05$ ) even though severity of sleep apnea according to AHI was lowest in this group (mean AHI  $26.7 \pm 20.3$ ). GHQ-12 and DEPS scores were highest in the oldest age group ( $p<0.001$ ). The association between AHI and the ESS score had a statistically significant correlation only in men over 80 years of age (Spearman rho 0.2,  $p<0.05$ ). In the linear multivariate model higher age and higher AHI seemed to be the most important determinants of subjective daytime sleepiness measured with ESS ( $p<0.001$ ) while gender did not reach significance.

**Conclusions:** As shown in previous studies the link between obesity and sleep apnea in the elderly is somewhat weakened and our results confirm this. Our findings also suggest that there are unforeseen relationships between daytime sleepiness and age in both genders. Future studies are needed to investigate the presence of sleep complaints in the very elderly and specify how they adapt to the CPAP treatment.

**Acknowledgements:** Supported by foundation of Väinö and Laina Kivi.  
**THE EFFECT OF APAP AND CPAP TREATMENT ON THE NOCTURNAL BLOOD PRESSURE FLUCTUATION IN OSA WITH HYPERTENSION PATIENTS**

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**Introduction:** Obstructive sleep apnoea (OSA) is a prevalent disease associated with cardiovascular events. Hypertension is one of the major intermediary mechanisms leading to long-term cardiovascular adverse events. (CPAP) is the primary treatment for OSA and induces a small but significant reduction in BP. (CPAP) is the primary treatment for OSA and significant reduction in BP. this study will estimate the nocturnal blood pressure by pulse conduction time (PTT) using German SOMNOscreen™ plus PSG monitoring system, which may be to explore the clinical characteristics and mechanism of OSA patients complicated with hypertension.

**Abstract:** To investigate the effects of automatic titration positive airway pressure ventilation (APAP) and continuous positive airway pressure (CPAP) on nocturnal blood pressure fluctuation in obstructive sleep apnea (OSA) complicated with hypertension patients. **Methods:** From March to September 2021, we monitored 28 patients with OSA complicated with hypertension all night, and estimated their nocturnal blood pressure by pulse conduction time (PTT) using German SOMNOscreen™ plus PSG monitoring system. Record indicators including respiratory disturbance index (AHI), hypopnea index (HI), oxygen reduction index (ODI<sub>4</sub>), mean oxygen saturation (MSaO<sub>2</sub>), minimum oxygen saturation (LSaO<sub>2</sub>), percentage of time when oxygen saturation is lower than 90% in total recording time (SIT90), nocturnal blood pressure fluctuation (NPBF), PTT decline index, heart rate acceleration index, etc. To compare the NPBF in OSA complicated with hypertension patients before and after APAP and CPAP treatment.

**Results:** A total of 28 patients with moderate and severe OSA complicated with hypertension, aged 26–79 years, including 18 males and 10 females, 19 Han and 9 Uyghur patients. NPBF was calculated by measuring PTT under the normal sleep state, APAP and CPAP treatment. The NPBF index of 28 patients with OSA complicated with hypertension was [(22.1 ± 18.2) times / hour vs. (13.0 ± 12.5) times / hour] before and after APAP treatment. The NPBF index in 28 patients with OSA complicated with hypertension was [(24.5 ± 21.8) times / hour vs. (10.3 ± 8.9) times / hour] before and after CPAP treatment, and the NPBF index was [(14.2 ± 13.1) times / hour vs. (10.3 ± 9.0) times / hour] with APAP and CPAP treatment, the maximum systolic blood pressure [(171.4 ± 21.0) mmHg vs. (160.8 ± 23.6) mmHg] and [(172.4 ± 22.0) mmHg vs. (161.2 ± 20.2) mmHg], the mean systolic blood pressure were [(130.2 ± 15.5) mmHg vs. (124.5 ± 12.6) mmHg] and [(132.6 ± 15.1) mmHg vs. (124.4 ± 11.5) mmHg] Before and after APAP, CPAP treatment respectively, which all the differences were statistically significant ( $P < 0.05$ ). **Conclusion:** APAP and CPAP treatment can reduce the amplitude of maximum, mean systolic blood pressure and NPBF in patients with OSA complicated with hypertension in the first night, The Degree of decline on NPBF in CPAP treatment was lower than that in APAP treatment.

**Acknowledgements:** Foundation: National Natural Science Foundation (82160023); Xinjiang Natural Science Foundation youth Fund project (2020D01B06)

**THE EFFECT OF INTERMITTENT HYPOXIA ON HUMAN EMBRYONIC STEM CELLS DERIVED CARDIOMYOCYTES. IN-VITRO CELLULAR MODEL FOR OBSTRUCTIVE SLEEP APNEA**

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**Introduction:** Cardiovascular (CV) morbidity is the leading cause of death in obstructive sleep apnea (OSA) patients. Considering the fact that nocturnal positive pressure does not alter CV sequela, it is imperative to understand the consequences of Intermittent Hypoxia (IH) at the

myocardial cellular level in order to look for new therapeutic options.

**Materials and Methods:** In order to study the effect of IH on human cardiomyocytes (hES-CM) we differentiated human embryonic stem cells to beating cardiomyocytes. Using the OxyCycler system we induced IH cycles, alternating between 2% for 8 minutes and 21% for 4 minutes, (60 cycles total) to the CM. We immunostained for the hypoxia marker Hif-1 $\alpha$  to validate our IH protocol. In addition, we also quantified the NF- $\kappa$ B subunits p65 and p50 as markers of inflammation and ERK 1/2 and Erbin as markers for myocardial hypertrophy and assessed them with a high-throughput phenotypic assay (Operetta-Perkin Elmer). Evaluation of the IH effect on cell physiology was quantified by cells beating rate.

**Results:** IH induced an increase of Hif-1 $\alpha$  expression, validating our in vitro system and the protocol used to induce IH. We observed a significant increase in NF- $\kappa$ B sub-units p65 and p50 expression ( $p < 0.001$ ). ERK 1/2 and Erbin expression was increased in cells exposed to IH ( $p < 0.001$ ). Finally, IH decreases the number of beats per minute as compared to cells under normoxia ( $p < 0.001$ ).

**Conclusions:** We demonstrated co-activation of inflammatory and myocardial hypertrophy signaling in human CM following IH exposure. This study supports the search for new pharmacological agents to improve CV outcome in OSA.

**Acknowledgements:** Israel Science Foundation (ISF 1344/15)

**THE EFFECT OF PIMAVENSERIN ON AROUSAL THRESHOLD AND OTHER ENDOTYPIC TRAITS IN OBSTRUCTIVE SLEEP APNEA**

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**Rationale:** Recent research has shown that pharmacotherapy may be a viable way to treat obstructive sleep apnea (OSA). The combination of atomoxetine, a noradrenergic agent, and the antimuscarinic oxybutynin had promising effects on OSA severity, presumably due to its action at the hypoglossal motor nuclei. However, more recently, oxybutynin was hypothesized to mainly have a hypnotic effect that counteracts atomoxetine's wake promoting properties. Here we sought to test whether a new pathway to reduce arousability, through the anti-serotonergic pimavenserin, could pave the way for a better drug fit to associate with atomoxetine. Specifically, we aimed to test the effect of pimavenserin on arousal threshold and the other endotypes that contribute to OSA pathogenesis (i.e., loop gain, upper airway muscle responsiveness, pharyngeal physiology; primary outcome). Pimavenserin's supposed mechanism of action is through antagonism of 5-HT<sub>2A</sub> receptors in the dorsal raphe, which should selectively suppress CO<sub>2</sub>-mediated arousals without affecting the CO<sub>2</sub>-induced ventilatory response. An increase in arousal threshold can also have a beneficial effect on OSA severity (secondary outcome).

**Methods:** OSA participants were studied in a randomized, crossover, double-blinded design. Patients received either placebo or pimavenserin 34 mg 4 h prior to in-lab polysomnography. Patients were instrumented with an oronasal mask attached to a pneumotachograph for the measurement of airflow, and an esophageal catheter to record diaphragm EMG (EMG<sub>di</sub>). Questionnaires of sleepiness (i.e. Epworth Sleepiness Scale, Visual Analog Scale) and blood pressure plus heart rate were recorded before and after the overnights. Validated algorithms were used to extract the endotypes from the polysomnography (the relation between flow and EMG<sub>di</sub> was plotted in the form of *endograms*, where V<sub>passive</sub> and V<sub>active</sub> represented ventilation at eupneic and maximal sleep drive, respectively: arousal threshold was EMG<sub>di</sub> at V<sub>active</sub> and loop gain was derived from flow).

**Results:** Data are still blinded and the estimated recruitment completion time is February 2022. With that in mind, 9/21 OSA patients have been enrolled so far, of which 5 have finished both overnights (age 48 ± 19, BMI 32 ± 7, mean ± SD). In 4, arousal threshold was substantially higher on one night compared to the other (137.5[62.4] vs. 107.4[41.6] %V<sub>eupnea</sub>, median [IQR] of nights with higher vs. lower arousal threshold). According to grouping based on higher vs. lower arousal threshold, there was no noticeable difference in V<sub>passive</sub> (83.6[20.2] vs. 85.2[10.4] %V<sub>eupnea</sub>) or V<sub>active</sub> (90.0[17.9] vs. 92.1[8.0] %V<sub>eupnea</sub>), but loop gain was decreased (0.53[0.10] vs. 0.60[0.03]) in the nights with higher arousal threshold. Pimavenserin

did not cause safety concern in the treated population.

**Conclusions:** Pimavanserin may increase the arousal threshold in OSA patients, without major side effects and without affecting pharyngeal muscle responsiveness and ventilatory responses to apneas/hypopneas; however, data are being still collected. If these findings will be confirmed at unblinding, we could have a safer hypnotic than oxybutynin (burdened by several anticholinergic effects) to associate with atomoxetine for the treatment of OSA. Further study will need to assess the durability of pimavanserin on the arousal suppression effect, and the potential combination with atomoxetine on OSA severity over time.

#### THE EFFECT OF SLEEPING POSITION ON THE EFFICACY OF HYPOGLOSSAL NERVE STIMULATION FOR OBSTRUCTIVE SLEEP APNEA

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**Introduction:** Hypoglossal nerve stimulation (HNS) therapy is a safe and effective second-line treatment for patients with obstructive sleep apnea (OSA). However, not all patients who meet current selection criteria respond to therapy. Previously published outcomes data suggest that sleeping position may play a role in therapy response. This study assessed the effect of supine and non-supine sleeping positions on the efficacy of HNS therapy.

**Materials and Methods:** This retrospective cohort study evaluated Patients implanted with HNS at an academic sleep surgery center from June 2015 to June 2020. Patients with pre- and postoperative positional sleep study data were included. The change in supine and non-supine apnea-hypopnea index (AHI) from pre- to postoperative timepoints were compared.

**Results:** Of ninety-eight Patients evaluated, twenty patients met inclusion criteria. The mean (SD) age was 67.2 (7.7) years, 14 participants were men (70.0%), and mean body mass index (BMI) was 27.1 (3.4) kg/m<sup>2</sup>. There was a greater reduction in mean non-supine AHI (32.7%) than supine AHI (17.7%). The percentage of patients who demonstrated treatment response defined by Sher's criteria when using non-supine AHI was greater than when using supine AHI (60.0% vs. 36.8%). Linear univariate regression analysis showed a high correlation between non-supine postoperative AHI and overall postoperative AHI ( $r = 0.89$ ).

**Conclusion:** HNS may be more effective in the non-supine position. Superior efficacy in the non-supine position may drive overall HNS efficacy. It is important to evaluate sleeping position preference during patient selection and to counsel Patients on positional therapy as an adjunct to HNS therapy.

#### THE EFFECTS OF CPAP THERAPY ON METABOLIC PROFILE AND SUBJECTIVE SLEEP PARAMETERS IN PATIENTS WITH OSA: A PROSPECTIVE TRIAL STUDY

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**Introduction:** Obstructive sleep apnea (OSA) is a clinical sleep disorder characterized by complete or partial repetitive episodes of airway collapse during sleep. Several studies confirm a positive association between OSA and metabolic syndrome. Continuous positive airway pressure (CPAP) is the main treatment for patients with moderate and severe OSA. CPAP therapy in adults with OSA results in reduction in sleepiness, blood pressure and improvement of metabolic profile. In this study we aimed to evaluate the effects of CPAP therapy on various components of metabolic syndrome and subjective sleep parameters in patients with OSA.

**Materials and Methods:** In this prospective trial study, 28 patients with moderate and severe OSA (Baharloo sleep clinic, Tehran, Iran) enrolled. Patients were asked to fill out the validated Persian version of questionnaires including ESS, ISI, STOP-BANG and BDI-II, before and after treatment

with CPAP. Weight and blood pressure were recorded before and after treatment. Only 14 patients agreed to blood sampling before and after CPAP therapy. Fasting blood samples were analyzed for measuring the levels of FBS (fasting blood sugar), TG (triglyceride), Total cholesterol, HDL, LDL, AST, and ALT.

**Results:** Diastolic blood pressure, ISI and STOP-BANG score significantly decreased after treatment (P value: 0.008, 0.022 and 0.004, respectively). FBS and TG levels decreased after treatment, but only TG levels had significant difference (P value: 0.46 and 0.016, respectively).

**Conclusions:** CPAP therapy had positive effects on diastolic blood pressure, TG levels and ISI score in our study.

**Acknowledgements:** The authors are thankful to all the staff of Occupational Sleep Research Center (Baharloo hospital, Tehran, Iran)

#### THE EFFICACY AND DOSAGE OF ACETAZOLAMIDE IN PATIENTS WITH OBSTRUCTIVE SLEEP APNEA: PRELIMINARY RESULTS OF A DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED TRIAL

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**Introduction:** Acetazolamide, a carbonic anhydrase inhibitor, has received some attention as a potential treatment for obstructive sleep apnea (OSA). By producing metabolic acidosis, the drug reduces ventilatory instability (i.e. high loop gain), which is a key contributor to the pathogenesis of OSA. However, there are limited data about the clinical efficacy and optimal dosage of acetazolamide in patients with OSA. Therefore, this study aims to assess the effect of acetazolamide, administered in two different dosages, on OSA severity.

**Materials and Methods:** In this double-blind, parallel-group study, participants with moderate to severe OSA were randomized to receive either placebo, acetazolamide 250 mg, or acetazolamide 500 mg for 6 weeks. Changes in apnea-hypopnea index (AHI) and oxygen desaturation index (ODI) were assessed by in-laboratory polysomnography. Arterial blood gas analysis was performed before and during treatment to evaluate acid-base status and gas exchange. Side effects were registered and quantified by a visual analogue scale. All reported values are medians (Q1–Q3) unless otherwise specified.

**Results:** Twenty-seven individuals were included for this interim analysis (22 males [81.5%], age 54.0 [47.0–58.0] years, AHI 24.9 [17.7–34.1] events/h, body mass index 28.7 [26.6–31.6] kg/m<sup>2</sup>), of which 24 completed the study (n=8 with placebo, n=9 with acetazolamide 250 mg, and n=7 with acetazolamide 500 mg). Three patients dropped out due to insufficient symptom control (n=1 with placebo and n=1 with acetazolamide 250 mg) or side effects (n=1 with acetazolamide 500 mg). Treatment with acetazolamide significantly improved the AHI (250 mg, 49.2% [39.9–61.1],  $P < 0.001$ ; 500 mg, 46.6% [21.7–47.7],  $P = 0.003$ ) and ODI (250 mg, 36.1% [11.5–60.5],  $P = 0.01$ ; 500 mg, 41.2 [35.2–61.3],  $P = 0.006$ ). The placebo group showed a reduction in AHI of 40.6% (16.4–61.2,  $P = 0.02$ ) and in ODI of 14.3% (-19.9 to 29.4,  $P = 0.39$ ). Compared to placebo, acetazolamide caused a significantly higher reduction in ODI ( $P = 0.02$ ), but not in AHI ( $P = 0.41$ ). Although bicarbonate (20.4% [6.5–26.7],  $P < 0.001$ ) and arterial pH (0.5% [0.1–0.7],  $P < 0.001$ ) were both reduced by acetazolamide, these changes were not associated with therapeutic outcome. Paresthesia was most pronounced in patients treated with acetazolamide 500 mg. However, the overall severity of side effects was comparable in all groups ( $P = 0.52$ ).

**Conclusions:** Acetazolamide can improve nocturnal breathing in patients with OSA. Based on our preliminary findings, a low dosage may be as effective as a higher one, minimizing potential side effects such as paresthesia. Further research is needed to predict which patients might benefit from this pharmacological therapy.

**Acknowledgements:** The authors would like to thank Adelheidis Hoogewijs for coordinating the study.

## THE PREVALENCE OF TREATMENT-EMERGENT CENTRAL SLEEP APNEA IN MANDIBULAR ADVANCEMENT DEVICE THERAPY

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**Introduction:** Treatment-emergent central sleep apnea (TECSA), formerly known as complex sleep apnea, describes the appearance or worsening of central sleep apnea while undergoing treatment for obstructive sleep apnea (OSA). TECSA often appears to be a self-limiting problem that can resolve spontaneously with ongoing treatment. TECSA is well studied in CPAP therapy with an estimated prevalence of 8%. However, there is little published data on the occurrence of TECSA in other treatment modalities. Based on a few case reports, mandibular advancement devices (MAD), the leading alternative to CPAP, may provoke TECSA. The aim of this study is to gain insight in a large study population into the prevalence of TECSA with the use of MAD.

**Materials and methods:** This retrospective study includes a total of 124 patients (age 52 ± 12 years; male 81.5%; BMI 27.6 ± 3.4 kg/m<sup>2</sup>; baseline AHI 28.3 ± 13.4 events/hour) with moderate to severe OSA on baseline polysomnography (PSG) who received a custom-made titratable MAD from January 2019 to December 2020 at the Antwerp University Hospital (Belgium). Control polygraphy (PG) or PSG was performed once the target protrusive position, guided by subjective relief of cardinal symptoms, was attained. Since different diagnostic criteria to define TECSA are used in literature, in this study, prevalence was calculated according to three definitions, which are based on previous studies. For the first and most broad definition, the number of central events had to increase with MAD, totaling a central apnea/hypopnea index (CAHI) ≥ 5 events/hour. For purposes of clarification, these patients are labeled as TECSA-1. TECSA-2 are patients who had a significant decrease (>50%) in obstructive events and had a CAHI ≥ 5 central events/hour at follow-up. Finally, for the third and most strict definition (TECSA-3), patients not only had to meet the latter criteria, but also had to show predominant central sleep apnea (i.e., central events are >50% of total events) with MAD.

**Results:** The median time interval between start with MAD therapy and follow-up sleep study was 100 days (94 – 134) (median (Q1 – Q3)). Following MAD treatment, the mean AHI decreased from 28.3 (±13.4) to 10.3 (±12.2) events/hour (p<0.001), the mean obstructive AHI (OAHI) decreased from 26.8 (±12.9) to 8.0 (±6.9) events/hour (p<0.001) and the mean CAHI decreased from 1.7 (±3.3) to 1.5 (±3.5) events/hour (p=0.930). Nine patients (7.3%) met diagnostic criteria for TECSA-1, seven (5.6%) for TECSA-2, and four (3.2%) for TECSA-3. Among patients identified with TECSA-3, three had a CAHI of <5 events/hour at baseline and could be labeled as “new-emergent”.

**Conclusions:** In this retrospective exploratory pilot study, the prevalence of TECSA in patients who are treated with MAD was examined in a large study population. Depending on the definition used, TECSA was found in 3% to 7% of patients treated with MAD.

**Acknowledgements:** The authors are grateful for the administrative and organizational support of the secretarial staff of the Special Dentistry Care department and the Otorhinolaryngology department.

## THE ROLE OF SLEEP-DISORDERED BREATHING ON COGNITIVE FUNCTION AFTER STROKE

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**Background and aim:** Sleep-disordered-breathing (SDB) is associated in the general population with cognitive changes. Cognitive changes and SDB are very frequent in stroke patients. However, little is known about the impact of SDB on cognitive changes after stroke. The aim of this study was to investigate this association.

**Patients and Methods:** This project is a part of the prospective multicenter eSATIS study (Duss et al, *Trials* 2021). Demographics, anthropometrics, stroke characteristics and sleep-disordered breathing (SDB) by respirometry were assessed at admission. Longitudinal assessments of cognitive tests were performed within 5 days post-stroke and at 3 months post-stroke. The assessments included tests of language (Bern word finding test), attention (Alertness task), vigilance (Psychomotor vigilance task [PVT]), executive function (Go-noGo task, Victoria Stroop test, Trail making test) as well as verbal (Digit span test, Hopkins verbal learning test [HVL]) and visual memory (Corsi block tapping test, Brief visuospatial memory test [BVMT]). Treatment of SDB was attempted in all patients during the acute phase.

**Results:** A total of 118 patients with the complete data (age: 64.84±14.04 years; female sex: 44 (38%) patients; National Institute of Health Stroke Scale (NIHSS) score at admission: 6.94±5.75 points) were included in the current analysis. SDB (defined by an apnea-hypopnea index (AHI) ≥20/h) was found in 66 (56%) patients. Treatment of SDB was started in 33 (50%) SDB patients. Multiple linear regression analysis with adjustment for age and sex and NIHSS score at the time of the assessment of cognitive functioning showed that the presence of SDB as an independent variable was associated with worse attention (Alertness task, median reaction time: +11.53 seconds for SDB vs no-SDB (defined by an AHI <5/h), p=0.031), vigilance (PVT, number of false starts: +2.58 false starts, p=0.024) and visual memory (total recall score of BVMT: -3.52 points, p=0.032; delayed recall score of BVMT: -1.62 points, p=0.031). In the 72 patients re-assessed in the subacute phase, the presence of untreated SDB (n=26) was associated with less improvement in attention (total number of omissions in Bells test: +1.47 omissions for untreated SDB vs no-SDB, p=0.008; Alertness task, median reaction time: +0.40 seconds, p=0.026) and verbal memory (recognition discrimination index of HVL: +0.93 points, p=0.004) after adjustment for age, sex and baseline cognitive parameters.

**Conclusions:** These results suggest the existence of an association of SDB with cognitive deficits in both the acute and to a lesser extent subacute phase of stroke. Further research is needed to investigate the impact of cardiovascular comorbidities and stroke characteristics on this association and potential treatment implications.

## THE SEVERITY AND MORPHOLOGY OF INTERMITTENT HYPOXEMIAS ARE RELATED TO IMPAIRED DAYTIME ALERTNESS

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**Introduction:** Obstructive sleep apnea (OSA) -related impaired alertness has been associated with increased morbidity in OSA patients. However, as conventional OSA severity metrics are poorly linked to impaired vigilance, it has been suggested, that oxygen saturation (SpO<sub>2</sub>)-based metrics could better describe the impaired vigilance. Thus, we aimed to study whether the characteristics of blood oxygen desaturations differ between psychomotor vigilance task (PVT) groups (i.e., non-impaired vigilance vs. impaired vigilance) formed based on the number of lapses.

**Materials and methods:** 863 suspected OSA patients underwent a PVT prior to the full in-lab polysomnogram (PSG). The conventional OSA parameters consisting of the apnea-hypopnea index, oxygen desaturation index, and arousal index were calculated. Additionally, multiple SpO<sub>2</sub>-based parameters, i.e., average SpO<sub>2</sub>, time spent with SpO<sub>2</sub> under 90%,

desaturation area, fall area, recovery area, and desaturation depth were computed. The desaturation area (DesaturationArea100), fall area (FallArea100), recovery area (RecoveryArea100), and desaturation depth (Depth100) were also computed using 100% SpO<sub>2</sub> value as a baseline. Furthermore, patients were grouped into quartiles based on PVT lapses (Q1–Q4), and the empirical cumulative distribution functions (CDF) of the parameters were compared between the first (Q1, PVT lapses < 5; n = 225) and the last (Q4, PVT lapses > 36; n = 223) quartiles, i.e., patients with non-impaired vigilance and impaired vigilance, respectively. Finally, the association between the parameters and vigilance was investigated using binomial logistic regression models, adjusted with age, sex, body mass index, smoking status, depression, anxiety, and hypertension.

**Results:** Of the analyzed patients, 55.4% were males and the median age of the patients was 57 years. The CDFs revealed that the patients in Q4 had greater desaturation areas and recovery areas, and deeper desaturations compared to patients in Q1 when 100% baseline was considered. Logistic regression corroborated that these desaturation parameters were significantly linked to impaired vigilance. The odds ratios of DesaturationArea100 (OR = 1.55), RecoveryArea100 (OR = 1.65), and Depth100 (OR = 1.73) were elevated in Q4 compared to Q1. Age (OR = 0.73) and gender (OR = 1.01) were also significantly linked to impaired vigilance while other adjusted comorbidities were not. Additionally, the odds ratios of desaturation area (OR = 1.56), recovery area (OR = 1.71), and depth (OR = 1.64) were increased notably for impaired vigilance patients even without baseline reference at 100%, when adjusting parameters were taken into consideration. In contrast, conventional OSA parameters were not significantly associated with impaired vigilance in any model.

**Conclusions:** The results show that the desaturation event characteristics are more strongly associated with impaired vigilance compared to the conventional OSA severity parameters. Hence, desaturation parameters, such as – recovery area and desaturation depth especially with 100% baseline reference should be considered in more detail while evaluating the OSA severity in patients with impaired vigilance.

**Acknowledgements:** This work was financially supported by the European Union's Horizon 2020 Research and Innovation Programme (965417), the Academy of Finland (323536), Nordforsk (90458) via Business Finland (5133/31/2018), the Research Committee of the Kuopio University Hospital Catchment Area for the State Research Funding (5041767, 5041794, 5041805, 5041787, and 5041803), The Research Foundation of the Pulmonary Diseases, Finnish Anti-Tuberculosis Association, Tampere Tuberculosis Foundation, Instrumentarium Science Foundation, and Orion Research Foundation.

#### THE SNORING INDEX AS AN INDICATOR FOR NON-ALCOHOLIC FATTY LIVER DISEASE IN PATIENTS WITH SLEEP APNOEA SYNDROME

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**Introduction:** Obstructive sleep apnoea syndrome (OSA) is suspected to be associated with the development or progression of non-alcoholic fatty liver disease (NAFL). The aim of this prospective and descriptive study was to determine potential predictive factors for NAFL in patients with mild, moderate and severe obstructive sleep apnoea.

**Materials and Methods:** OSA patients (n = 66) were assessed for the presence of NAFL and liver fibrosis predictive factors. OSA-associated measures were assessed by polysomnography or home sleep apnea testing (HSAT). NAFL-associated measures were collected by blood laboratory analysis and upper abdominal sonography with transient elastography to determine the degree of hepatic steatosis and fibrosis. A correlation analysis was performed between sleep-specific, demographic and liver-specific parameters.

**Results:** A total of 66 patients (25 women, 41 men age 25–83 years) with moderate to severe OSA (mean AHI = 34.3/h) were studied. In particular, CAP score on elastography, predictive of hepatic steatosis, showed a highly significant positive correlation with the presence of snoring (p = 0.0003). Other clinically significant associations were percentage of oxygen saturation below 90% (t90), which correlated with abdominal circumference

(p = 0.005), body mass index (BMI) (p = 0.035) and CAP score (p = 0.02). Interestingly, the AHI as a measure of OSA severity did not correlate significantly with liver-specific parameters in elastography or other laboratory parameters.

**Conclusions:** The most valuable predictor in OSA patients for the presence of NAFL was the snoring index. This could lead to the assumption that patients who snore should be screened for steatosis. This correlation was independent of the AHI. In addition, oxygen saturation, especially desaturations below 90%, seems to be associated with steatosis as well as metabolic syndrome-associated traits (BMI, abdominal girth). Further studies are needed to validate these results.

**Acknowledgements:**

#### TRAJECTORIES OF RESIDUAL APNEA-HYPOPNEA INDEX ASSOCIATED WITH MASK CHANGES IN CONTINUOUS POSITIVE AIRWAY PRESSURE-TREATED OBSTRUCTIVE SLEEP APNEA PATIENTS

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**Introduction:** There is growing evidence of a significant impact of the type of mask on the residual apnea-hypopnea index (rAHI). However, automated tools incorporated in continuous positive airway pressure (CPAP) remote monitoring platforms for identification of the influence of mask changes on rAHI are lacking. Our goal was to develop a robust automated data analysis method for assessing the impact of mask changes on rAHI according to the type of mask switch (nasal to full-face mask or vice-versa).

**Materials and Methods:** From a CPAP telemonitoring database of 3,581 patients, we analyzed the impact of mask changes on rAHI trajectories. An interrupted time series design was applied to rAHI time series at an individual patient level to compare the observed rAHI after a mask-change to what would have occurred without such a mask-change. From the overall database, rAHI time series before masks changes were modelled using Bayesian structural models with synthetic controls. Mask changes were classified into three groups (no effect, harmful, beneficial). The best data analysis approach was chosen using blinded classification performed by an experienced respiratory physician.

**Results:** Bayesian structural time series was the best analysis method in terms of agreement with the physician's classification, with an accuracy of 0.79 for the complete data set. Changes from a nasal to facial mask were more often harmful than beneficial: 13.4% vs 7.6% (p-value < 0.05), with a clinically relevant increase in average rAHI greater than 8 events/hour in 4.6% of the changes. Changes from facial to nasal mask were less often harmful than beneficial: 6.0% vs 11.4% (p-value < 0.05).

**Conclusions:** We have established an end-to-end data analysis method to automatically classify the impact of mask changes over fourteen days after the switch. Such an automated analysis included in routine CPAP remote monitoring platforms would be particularly appropriate for raising alerts after harmful mask changes. This would reduce the workflow of home care providers and facilitate early remedial actions.

**Acknowledgements:** We thank the French National Research Agency.

#### TRIAL DESIGN: SOLRIAMFETOL'S EFFECT ON COGNITIVE HEALTH IN APNEA PARTICIPANTS DURING A RANDOMIZED PLACEBO-CONTROLLED STUDY (SHARP)

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**Introduction:** Patients with excessive daytime sleepiness (EDS) associated with obstructive sleep apnoea (OSA) may experience cognitive

impairment; EDS and cognitive impairment affect occupational and social functioning, reduce quality of life, and increase occupational and motor vehicle accident risk. Solriamfetol (Sunosi™) is a dopamine/norepinephrine reuptake inhibitor approved in the EU and US to treat EDS associated with OSA. The objective of this global study is to assess whether solriamfetol reduces cognitive impairment in patients with EDS associated with OSA.

**Methods:** This phase 4, randomised, double-blind, placebo-controlled, crossover trial (NCT04789174) is enrolling adults with OSA and associated EDS (Epworth Sleepiness Scale score >10) and impaired cognitive function defined by an age-adjusted scaled score  $\leq 8$  on the Wechsler Adult Intelligence Scale, Fourth Edition Coding subtest and a score  $\geq 9$  on the British Columbia–Cognitive Complaints Inventory (BC-CCI). Coding tests like the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) Coding subtest and other symbol-digit and digit-symbol substitution tests objectively measure cognitive function and are sensitive to pharmacologic alleviation of cognitive dysfunction; the BC-CCI is a subjective measure of cognitive complaints. Participants are randomised (1:1) to 2 weeks of placebo or solriamfetol (75 mg/day for 3 days, then 150 mg/day) during treatment period 1. After a 1-week washout, participants receive 2 weeks of the opposite treatment during treatment period 2. Assessments at baseline and after each treatment period include RBANS Coding administered 2, 4, 6, and 8 hours post-dose (using rotating versions to minimise learning effects) and the BC-CCI. The primary endpoint is change from baseline after each treatment period in the average of 2- and 4-hour post-dose RBANS Coding scores. A secondary endpoint is change from baseline after each treatment period in BC-CCI score.

**Results:** With a target enrolment of 116 participants, this study is powered to detect a placebo-subtracted RBANS Coding treatment effect of 3 points (Cohen's  $d=0.33$ , one-sided  $\alpha=0.025$ ). The sample size is adaptive by design and may increase to 164 pending interim analysis. Enrolment began in April 2021, and the study is currently ongoing in the US, the UK, Italy, Spain, Canada, and the Netherlands. As of the 10th of January 2022, 45 participants have been randomised across 20 study sites in North America (United States and Canada) and 9 sites in Europe (Italy, Spain, the Netherlands, and the United Kingdom).

**Conclusion:** This ongoing study is the first to examine solriamfetol's impact in participants with EDS associated with OSA on cognitive impairment, an important symptom that increases patients' accident risk and reduces daily functioning.

**Acknowledgements:** This study was supported by Jazz Pharmaceuticals.

#### ULTRASOUND BACKSCATTER IMAGING FOR UPPER AIRWAY TISSUE COMPOSITION CORRELATES WITH OBSTRUCTIVE SLEEP APNEA SEVERITY

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**Introduction:** The pathophysiology of obstructive sleep apnea (OSA) is complex with anatomic and non-anatomic factors. Addressing upper airway collapsibility during sleep is a common and primary goal for both medical and surgical therapy. A non-invasive way to characterize tissue composition and muscle tone can be helpful with OSA diagnosis and assessment of treatment. Tissue composition, such as liver steatosis, has been characterized by ultrasound backscatter signals for non-invasive severity grading. In this pioneering study using ultrasound backscatter imaging, we investigated upper airway tissue composition and its correlation with OSA severity.

**Materials and Methods:** 51 subjects (14 female) with mean age of  $39.1 \pm 11.7$ , mean BMI of  $25.8 \pm 4.2$ , and mean AHI of  $17.9 \pm 16.1$  were consented from the Stanford Sleep Surgery Clinic between July 2020 and May 2021. OSA was confirmed via attended or home sleep studies. Ultrasound radio-frequency (RF) data of the upper airway was acquired through 3D submental ultrasound imaging standardized with a 30-degree scan (15 degrees above and below the Hyoid to external acoustic meatus plane). Laser aligned ultrasound probe scans the palatal, oropharyngeal, and hypopharyngeal airway. Echogenicity and backscatter signals were

analyzed by an FDA-cleared ultrasound backscatter analysis software (AmCAD-US). Statistical comparisons against the OSA severity were performed using two-tailed t-tests and nonparametric Mann-Whitney tests.

**Results:** At the upper palatal region, significant differences in ultrasound backscatter signal is observed between subjects with mild (AHI < 15) and moderate to severe (AHI  $\geq 15$ ) OSA (p-value = 0.0003). Backscatter signals from the upper palatal region and BMI correlate with moderate to severe OSA using logistic regression analysis (p-values of 0.0039 and 0.0454, respectively), and are independently associated with AHI in multiple regression analysis (p-values of 0.0146 and 0.0184, respectively). Significant differences are also found in the lower palatal and upper oropharyngeal region with p-values of 0.0049 and 0.0424, respectively. Multivariate analysis show that backscatter signals are significantly associated with AHI independent of BMI.

**Conclusions:** Ultrasonic backscatter signals have been used effective to characterize tissue composition in conditions such as liver steatosis to grade disease severity. Modifying the technology for the upper airway muscles in OSA patients, we found significant positive correlations between ultrasound backscatter signals and AHI.

#### UPPER AIRWAY RESISTANCE SYNDROME IS ASSOCIATED WITH HIGH CYCLIC ALTERNATING PATTERN

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**Introduction:** Upper Airway Resistance Syndrome (UARS) is suspected in individuals with excessive daytime sleepiness, fatigue, and sleep fragmentation associated with increased respiratory effort. UARS can negatively impact daytime function. Conventional polysomnography parameters do not demonstrate significant abnormalities in UARS patients but increase in RERAs. Sleep abnormalities may not be indicated by AASM current manual in UARS patient. Cyclic alternating pattern (CAP) is a periodic electroencephalogram activity of non-REM sleep that expresses a condition of sleep instability. The objective of the study was to compare CAP components between UARS patients and health individuals.

**Material and Methods:** Fifteen subjects with UARS and 15 age- and sex-matched controls had their sleep study blinded analyzed. UARS criteria were the presence of sleepiness (Epworth Sleepiness Scale – ESS  $\geq 10$ ) and/or fatigue (Modified Fatigue Impact Scale  $\geq 38$ ) associated with an apnea/hypopnea index (AHI)  $\leq 5$  and a respiratory disturbance index (RDI)  $> 5$  events/hour of sleep, and/or flow limitation in more than 30% of total sleep time. Control group criteria were AHI  $< 5$  events/hour, RDI  $\leq 5$  events/hour and  $< 30\%$  of TST with flow limitation and ESS  $< 10$ , without sleep, clinical, neurological, or psychiatric disorder. CAP electroencephalogram of both groups was analyzed.

**Results:** The number of CAP cycles in NREM 1 stage was significantly higher in UARS patients compared to controls ( $3.0 \pm 1.1$  vs  $0.5 \pm 0.2$ , respectively,  $p < 0.001$ ). Mean phase B duration in NREM 1 stage was significantly higher in UARS patients compared to control group ( $31.3 \pm 8.1$  vs  $3.1 \pm 1.4$ ,  $p < 0.001$ ). Mean phase B duration in both NREM 2 and 3 were also significantly higher in UARS patients ( $28.3 \pm 1.0$  vs  $25 \pm 0.9$ ,  $p = 0.02$  and  $25.3 \pm 1.1$  vs  $21.7 \pm 1.0$ ,  $p = 0.02$ , respectively). There was a significant positive correlation between ESS and number of CAP cycles in NREM 1 ( $r = 0.5$ ,  $p < 0.01$ ) and mean phase B duration in NREM 1 ( $r = 0.6$ ,  $p < 0.001$ ). There was also a significant positive correlation between Beck Depression Inventory score (BDI) and number of CAP cycles in NREM 1 ( $r = 0.4$ ,  $p < 0.05$ ), mean phase B duration in NREM 3 ( $r = 0.4$ ,  $p < 0.05$ ) and mean phase B duration in NREM 1 ( $r = 0.4$ ,  $p < 0.05$ ).

**Conclusion:** A higher number of CAP cycles NREM 1 and an increased length of CAP sequences in NREM 1, 2 and 3 in UARS suggest altered sleep regulation leading to sleep instability. An increased number of CAP cycles correlated to subjective excessive daytime sleepiness and depression symptoms suggests CAPs clinical importance.

## UPREGULATED HEME BIOSYNTHESIS INCREASES OBSTRUCTIVE SLEEP APNEA SEVERITY: A PATHWAY-BASED MENDELIAN RANDOMIZATION STUDY

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**Introduction:** Obstructive sleep apnea (OSA) is a common disorder associated with increased risk of cardiovascular disease and mortality. The underlying molecular pathways for OSA are unknown. Iron and heme metabolism, implicated in carotid body ventilatory control and in OSA comorbidities, was associated with OSA phenotypes in recent admixture mapping and gene enrichment analyses. However, its causal contribution was unclear. In this study, we performed pathway level transcriptional Mendelian randomization (MR) analysis to examine the causal relationships between iron and heme related pathways and OSA.

**Materials and Methods:** Primary analysis was conducted considering the expression level of four iron/heme Reactome pathways as exposures and four OSA traits as outcomes. Discovery two-sample MR analysis was performed using cross-tissue local expression quantitative trait loci from the Genotype-Tissue Expression portal and published genome-wide association summary statistics. Significant pathways ( $p < 6.25 \times 10^{-3}$ ) were then followed-up by one-sample MR analysis using high coverage DNA and RNA sequencing data from the Multi-Ethnic Study of Atherosclerosis (MESA) generated by the Trans-Omics for Precision Medicine project. Secondary analysis was performed for 37 additional iron/heme Gene Ontology pathways.

**Results:** Primary analysis identified a significant putative causal association between up-regulated heme biosynthesis pathway with higher sleep time percentage of hypoxemia ( $p = 6.14 \times 10^{-3}$ ). This association was supported by consistency of point estimates in MESA ( $p = 0.187$ ). Suggestive evidence was also observed between this pathway with increased apnea hypopnea index, and other overnight hypoxemia traits.

**Conclusions:** This study suggests a causal association between increased heme biosynthesis and OSA severity. Future work is needed to further identify the mechanisms for this association, evaluate heme biosynthesis gene expression as a biomarker of OSA severity, and to address reverse causality.

**Acknowledgements:** This work was supported by NHLBI R01HL153814, NHLBI R35HL135818, and SRSF 018-JP-18.

## USE OF A DIGITALLY MILLED ORAL APPLIANCE FOR THE TREATMENT OF SEVERE OBSTRUCTIVE SLEEP APNEA

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**Introduction:** Mandibular advancing oral appliances (OAs) are commonly used for the treatment of mild to moderate obstructive sleep apnea (OSA) but are less accepted as a therapy for severe OSA, likely due to their supposed lower rate of therapeutic success in that population. However, the preference for OAT over CPAP and relative lack of other non-surgical treatment options highlights the need for acceptance of OAT for all severities of OSA.

**Materials and Methods:** Data from two prospective studies conducted for the purpose of validating an in-home auto-titration test that predicted response to OAT (MATRx plus; Zephyr Sleep Technologies, Calgary, Alberta, Canada) were evaluated. Study participants ( $n = 109$ ) received an OA that was CAD/CAM generated from digital intraoral scans (ProSomnus® Sleep Technologies, Pleasanton, CA). The OAs consisted of sets of upper and lower trays that, when interfaced together, allowed for advancement of the mandible. Oral appliances were set to the target protrusion provided by the auto-titration test. Participants predicted to not respond to OAT were assigned a sham protrusion.

Oral appliance therapy was initiated at the target position, sham position, or highest tolerated protrusion (for participants who were unable to have their OA inserted at target). Once participants were habituated to OAT, a 2-

night home sleep apnea test was conducted to assess treatment effectiveness. The mandible was advanced as necessary to lower the respiratory event index (REI).

**Results:** Eighty male and 29 female participants with a mean age of  $50.2 \pm 9.4$  years, mean BMI of  $31.9 \pm 5.0$  kg/m<sup>2</sup>, mean baseline REI of  $29.4 \pm 19.4$  h<sup>-1</sup>, and median Epworth Sleepiness Scale (ESS) score of 9.1 participated in the studies.

Overall, a high rate of therapeutic success was achieved, with 62.1%, 79.5%, and 73.2% of participants with mild, moderate, and severe OSA, respectively, achieving a decrease in REI from baseline  $\geq 50\%$ . Similarly, 87.2% of the moderate and 68.3% of the severe cohort achieved an REI  $< 15$  h<sup>-1</sup>. Of those who achieved an REI  $< 15$  h<sup>-1</sup>, the mean protrusive position of the OA was  $81.2 \pm 17.4\%$  and  $86.4 \pm 16.2\%$  for the moderate and severe cohorts, respectively.

Of note, the time spent at  $< 90\%$  saturation (T90) and the lowest SpO2 value (LSpO2) did not differ significantly among OSA severities at outcome ( $p = 0.184$  for T90;  $p = 0.311$  for LSpO2).

**Conclusions:** The OAs used in the studies provided efficacious treatment for most individuals with severe OSA. The lack of difference in T90 and LSpO2 among severities could indicate that disease burden might be alleviated even when event-based indices (e.g., REI) suggest only moderate improvement. Though more study into the effect of OAT on disease burden is warranted, the results indicate that OAT could be a suitable alternative to CPAP for severe OSA and that oxygen-based parameters might provide valuable insight into therapeutic success.

**Acknowledgements:** Study data were collected by and used with the permission of Zephyr Sleep Technologies. ProSomnus Sleep Technologies provided the OAs used in the studies.

## USING ACTIGRAPHY AS A MEASURE OF CORTICAL AROUSALS IN CARDIOPULMONARY SLEEP STUDIES

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**Introduction:** Obstructive sleep apnoea (OSA) now recognized as one of most common respiratory disorders of childhood. OSA can result in lasting effects on children such as daytime sleepiness, behavioural issues, poor concentration/academic performance and in the longer term pulmonary hypertension. Due to cost-effectiveness and convenience for families, there has been an increase in the use of ambulatory cardiovascular (level 3) studies to diagnose OSA in children. One of the diagnostic criteria for OSA in children set by the American Association of Sleep Medicine (AASM) is the presence of a cortical arousal. The lack of electroencephalography (EEG) monitoring in ambulatory studies means there is a risk that obstructive hypopnoeas are underdiagnosed.

Previous studies have investigated the use of autonomic markers as a surrogate for cortical arousals. One small scale study has suggested that spikes in movement actigraphy correlates with cortical arousals. This study aims to assess whether movement actigraphy is a reliable substitute for EEG-measured post-hypopnoeic cortical arousals.

**Materials and Methods:** Eligibility for patients will be as follows:

Patients at an established clinic at a district general hospital

Newly referred

Age 2-12 years

Clinical findings of OSA

All patients will receive the same Polysomnography study, however three physiologists will score the studies using three differing techniques to identify obstructive hypopnoeas:

Drop in SpO2  $> 3\%$  or cortical arousal

Drop in SpO2  $> 3\%$  or spike in movement actigraphy (blinded to cortical arousals)

Drop in SpO2  $> 3\%$  (blinded to cortical arousals and movement actigraphy)

**Results:** A repeated measures ANOVA will be used in order to determine the differences between AHI for participants between conditions and a correlation between cortical arousals (EEG) and movement (actigraphy) after obstructive hypopnoeic episodes will be calculated.

**Conclusions:** This study assesses the risk of underdiagnosing OSA in ambulatory cardiovascular studies that are already used within practice.

## VALIDATION OF INSOMNIA QUESTIONNAIRE AND ESTIMATION OF COMISA IN A LARGE, POPULATION BASED COHORT

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**Introduction:** The prevalence of Co-morbid insomnia and sleep apnea (COMISA) has been reported to be 30%-50% in obstructive sleep apnea (OSA). Patients with COMISA typically have more difficulties with treatment adherence than patients with either insomnia or OSA alone. This study aims to validate questionnaire-based insomnia diagnoses and to estimate prevalence of COMISA among participants of a large, population based cohort.

**Materials and Methods:** Five hundred and thirty-nine subjects in Akershus Sleep Apnoea Project I examined with in-hospital polysomnography during 2006-2008 were included (44 % females, aged 30-65 years). OSA was defined by apnea-hypopnea index (AHI)  $\geq 5$ . Five hundred and thirty subjects completed Bergen insomnia scale (BIS), a self-report questionnaire that generates both a diagnosis of insomnia according to clinical diagnostic criteria (insomnia present or absent) as well as a sum score. Among of them, 209 subjects were re-examined by BIS and had a face-to-face modified Duke interview during 2020-2021. To validate BIS diagnoses against Duke interview, the sensitivity, specificity and the Cohen's Kappa coefficient of agreement were calculated. In addition, BIS sum score of 9, 12, 15, 18 and 21 was used for defining an optimal cut-off level. SPSS 20.0 (IBM, Chicago, IL) was applied for data analyses,  $p$  value  $< 0.05$  was considered statistically significant.

**Results:** Two hundred and ninety-four (55.5%) subjects had OSA, three hundred and five (57.5%) subjects fulfilled the BIS diagnostic criteria for insomnia, furthermore, one hundred and eighty-two (34.3%) and one hundred and eighty-nine (35.7%) subjects had COMISA at baseline based on BIS diagnostic criteria and BIS cut-off value of 12. Eighty-nine (42.6%), Eighty-nine (42.6%) and One hundred (47.8%) subjects met the insomnia criteria applying Duke interview, BIS diagnostic criteria and BIS cut-off value of 12, respectively at follow-up.

**Conclusions:** BIS diagnostic criteria and BIS sum score of 12 showed good validity against the diagnostic interview for assessing insomnia. A high prevalence of COMISA was found in the cohort.

**Acknowledgements:** This work was supported by EU H2020 grant 965417 and NordForsk (NordSleep project 90458).

## VALUE OF SURGICAL AND NON-SURGICAL TREATMENT FOR SLEEP APNEA: A CLOSER LOOK AT HEALTHCARE UTILIZATION

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**Introduction:** Obstructive sleep apnea (OSA) affects millions of people globally and has tremendous implications from both societal and economical standpoints. The estimated direct and indirect economic burden is \$150 billion. The purpose of this study is to evaluate healthcare utilization of patients with OSA treated with CPAP "gold standard" treatment and surgery to understand the impact of each on the healthcare system over time. To date, limited studies have analyzed this from a population standpoint using real-world data.

**Methods:** Using IBM MarketScan research database, adults ( $> 18$ ) who had an OSA diagnosis identified based on the 9th International Classification of Diseases code (ICD-9) between 2007 and 2015, were identified. This cohort was further subdivided into 3 groups based on the intervention received: group 1 no treatment, group 2 had CPAP and 3 had surgery. Cohorts were compared after propensity score matching (PSM) to control for all potential confounders and create homogeneous groups by risk factors. The primary outcome was the cumulative health care expenditure in each group. We also evaluated the difference between the 3 groups without enrollment of month 0 as a proxy of the overall health of subjects after

treatment. Secondary outcomes were the overall average expenditure and its 3 main categories: inpatient, outpatient, and pharmaceutical payments.

**Results:** A total of 4,978,649 subjects had a diagnosis of OSA in the designated period. In the adjusted models after PSM, the ratio of enrolled matched subjects in group 1 and 2 to group 3 was set to be 2:2:1, therefore, we enrolled 36,100 in each of groups 1 and 2. Average monthly expenditure was higher in the surgical group \$1,076.82 versus 915.52 and 867.14. Group 3 showed higher cumulative expenditure (\$26,920.39) with a trend towards converging with groups 1 and 2 by the end of year 2 (\$24,874.86 and \$22,790.98). However, on eliminating the intervention cost, group 3 showed significantly the least expenditure (\$17,351.87) compared to group 1 and 2 (\$22,440.96 and \$20,913.17, respectively). Group 3 showed the least average monthly expenditure (\$142.16) in pharmaceutical payments compared to groups 1 (\$169.97, the highest) and 2 (\$164.53). Group 3 showed the highest average monthly expenditure \$718.84 in outpatient payments compared to group 1 (\$539.48) and 2 (\$513.31, least). For inpatient payments, group 1 showed the highest monthly expenditure (\$285.54) followed by group 1 (\$233.79) and group 3 (\$215.81, least). The monthly average payment was not significantly higher in group 3 compared to group 2 ( $p=0.561$ ). When month 0 was excluded, CPAP group spent significantly less than the non-treated group in average overall, inpatient and outpatient payments (\$871.38 vs \$935.04,  $p<0.001$ ; \$233.79 vs \$285.54,  $p<0.001$ ; and \$513.31 vs \$539.48,  $p=0.032$  respectively).

**Conclusion:** The CPAP group spent significantly less than the non-treated group in all payments. When the cost of the interventions was eliminated, the monthly payments of surgery group was significantly less than CPAP and the non-treated groups in all payments. Cumulative expenditure after surgery is less than those with CPAP by the 5<sup>th</sup> year of use when evaluated using prediction models.

**Acknowledgement:** (none)

## VARIANTS OF CANDIDATE GENES ASSOCIATED WITH THE RISK OF OBSTRUCTIVE SLEEP APNEA

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**Introduction:** The researches of the associations between a series of variants from different candidate genes and obstructive sleep apnea (OSA) are inconsistent among different publications. Here, we performed a comprehensive analysis to estimate the contribution of variants from candidate genes to the risk of OSA in total population and subgroups by ethnicity.

**Materials and Methods:** Qualitative analysis was conducted to find the relationships for all included genes by Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG). Then, quantitative analysis of both allele model and genotype models were applied to evaluate the risk variants for OSA. Furthermore, a similar analysis was performed in different ethnic groups.

**Results:** We included 149 publications containing 72 genes for qualitative analysis. Among them, we included 89 articles containing 26 variants from 15 genes for quantitative analysis. Through allele model, we found 10 risk variants for OSA with the ORs of 1.21-2.07 in total population, including rs1801133 of *MTHFR*,  $\epsilon 4$  of *ApoE*, -1438G/A of *5-HT2A*, -308G/A of *TNF- $\alpha$* , Pro1019Pro of *LEPR*, rs1130864 and rs2794521 of *CRP*, D/I of *ACE*, LPR and VNTR of *5-HTT*. We found that the variant of  $\epsilon 2$  of *ApoE* could uniquely decrease the risk of OSA in East Asian subgroup, while other 6 variants, including  $\epsilon 4$  in *ApoE*, -308G/A in *TNF- $\alpha$* , Pro1019Pro in *LEPR*, D/I in *ACE*, LPR and VNTR in *5-HTT*, could increase the risk of OSA. As for European subpopulation, we only found that -308G/A in *TNF- $\alpha$*  could increase the risk for OSA. In terms of genotype models, we found the dominant model and recessive model contributed differently for different variants.

**Conclusions:** 11 variants from the candidate genes are associated with the risk of OSA, which also showed ethnicity differences in East Asian and European subgroups.

**Acknowledgements:** We appreciate the contributions from all authors.  
**WHY OSA DURING PREGNANCY SHOULD AND CAN BE TREAT WITH MAD: A CASE REPORT**

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**Introduction:** Obstructive Sleep Apnoea in pregnant women are under-diagnosed and can be extremely challenging due to the changes to the upper airway, such as mucosal hyperemia, narrowing of the oropharyngeal diameter, and increased Mallampati score, as well as decreased functional residual capacity and increased oxygen consumption that can produce or exacerbate this pathology. OSA is correlated with other comorbidities in pregnancy such as chronic hypertension, gestational hypertension, pre-eclampsia; gestational diabetes; and cardiomyopathy and large, retrospective database studies have shown evidence of increased morbidity and mortality for pregnant women with OSA.

OSA can also be a risk factor for complications during delivery, but also to the future mother and baby born. Need a team of experts capable of **recognizing** symptoms associated with poor sleep and available for a multidisciplinary intervention, including ENT specialist, internal medicine physician and a sleep dentist.

MAD has been shown effectiveness and high level of adherence by patients with OSA but there are scarce evidence in OSA pregnant woman.

**Materials and Methods:**

**Results:**

**Report of Case:** The authors present a clinical case of a 37-year-old pregnant woman with a clinical history of a previous pregnancy complicated of pre-eclampsia and two previous spontaneous abortions with no hypertension and no diabetes.

The examination revealed:

**Intra-Oral Exam** of a class I molar and canine a mild overbite, Mallampati Class III, tongue muscle hypertonus, slight signs of edentulous tongue, dental signs of bruxism, mandibular tori.

In a more detailed **Facial Profile and Postural Evaluation** we can easily identify an anterior head and cervical posture, a concave facial profile, short mandible, double chin, anterior rotation of the scapula's and a compensatory vertebral column curves.

The **Cephalometric Facial Aesthetic Analysis**, instead the classic cephalometric analyses based on a teleradiograph and to avoid rx exposure, the authors decided for the facial analyses of Arnet. Patients revealed a skeletal class II, a mild retrognathic mandible, a brachycephaly crano-facial growth, no lips seal, showing signs of mouth breathing. Under the hypotheses of OSA, the patient performed a type II sleep study during the first trimester of pregnancy that confirmed a mild IAH and significant upper airway resistance.

**Conclusions:** Recommended for Treatment Plan: the therapy with a MAD totally costume made, allowing titration, personalized and individualized respecting physiologic mandibular movements were initiated, as well as correction of vitamins and minerals, reduction of carbohydrates, improved sleep habits and support of educational psychologists with sleep experience.

The patient had a close follow up with mensal appointments across the sleep team and were performed two more type II sleep studies under MAD at 24<sup>th</sup> and 38<sup>th</sup> weeks of pregnancy respectively with perfect control of her OSA. No complications during pregnancy or delivery were reported. Offspring perfectly well.

**Acknowledgements:** The authors stress the importance that an early intervention during pregnancy reveals to be an excellent treatment option with excellent results eliminating AHI, improving ODI, decrease risk factor for pregnancy complications, increase recovery after delivery

**A DEEP NEURAL NETWORK SIGNIFICANTLY IMPROVES SLEEP STAGE CLASSIFICATION IN WRIST-WORN ACCELEROMETER DATASETS**

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**Technology/Technical**

**Introduction:** Large-scale Biobank datasets with accelerometer measurements allow us to better understand how sleep is associated with major disease outcomes. Unfortunately, existing methods still struggle with accelerometry-based sleep stage classification. Further, these methods have been validated only on small polysomnography (PSG) datasets (n <= 100). We thus developed a deep neural network for sleep staging on a large-scale PSG dataset (n ~ 1000). The eventual goal is to derive new sleep phenotypes that can be potentially used for epidemiological analysis.

**Materials and Methods:** We developed a deep neural network composed of three components: a convolutional network to extract the features, a bi-directional Long-Short-Term-Memory (LSTM) to model the temporal dependency and a fully-connected network to generate the sleep stage classifications. The Raine study was used for training the model. Every single participant has undergone one night of concurrent PSG and accelerometer (ActiLife GT3X) recording in a sleep clinic. We trained and tested the model using five-fold cross-validation with a train/validation/test split of 64/16/20. The model performance was evaluated on its overall sleep stage classification and summary sleep parameters agreement against PSG. We also assessed the possibility of differential bias by looking at: i) Pearson correlation coefficient between the model performance with age and apnea-hypopnea index (AHI) ii) independent T-test that compares the model performance in males and females.

**Results:** In total, 1006 participants from the Raine study were included, with 573 females and 433 males aged between 40 and 81 years (mean age = 56.08, SD=5.91). The overall Kappa score and balanced accuracy for five-stage classification (W, N1, N2, N3, REM) were .40 and .56. After combining all the NREM stages into one class, the Kappa score and balanced accuracy were .46 and .66. In terms of summary statistics, the model overestimated total sleep time [M=16.52 min (CI 95%: 10.37, 22.68 min)], total REM time [M=38.9 min (CI 95%: 33.88, 43.91 min)], and sleep efficiency [M=0.04% (CI 95%: .02, .05%)]. The model underestimated sleep onset latency [M=-.31 min (CI 95%: -1.58, 0.95 min)] and total NREM time [M=22.37 min (CI 95%: -28.36, -16.38 min)]. The associations between the model performance and age (r=.09, p=.24), AHI (r=-.04, p=.62), and gender (p=.68) were not statistically significant.

**Conclusions:** We have presented a novel sleep staging model that outperforms the current state of the art (accuracy, .56 vs .39) and has a fair agreement with PSG. Thus, this model opens up potential applications in epidemiological analyses that might yield important insights into how sleep is associated with various clinical outcomes.

**Acknowledgements:** We would like to thank the funding agencies for their support, which includes Li Ka Shing Foundation and Novo Nordisk, Health Data Research, UK, National Institute for Health Research (NIHR) Oxford Biomedical Research Centre (BRC), the British Heart Foundation Centre of Research Excellence, and the Alan Turing Institute.

**AN AUTOMATED HEART RATE-BASED ALGORITHM FOR SLEEP STAGE CLASSIFICATION: VALIDATION USING CONVENTIONAL PSG AND WEARABLE ECG DATA**

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**Introduction:** Poor sleep health has been associated with several negative health outcomes. Easily deployable and inexpensive solutions to assess sleep are critical for clinicians and researchers to understand sleep's role in

health and disease and develop interventions. Increasing research indicates that heart rate (HR) is an accessible physiological signal to characterize sleep. In this work, we validated a newly developed deep-learning based sleep staging algorithm named Neurobit-HRV (Neurobit Inc., New York, USA) which solely utilizes HR derived from a single-channel ECG (Movesense: <https://www.movesense.com/>).

**Materials and Methods:** The algorithm was trained and tested on 12,404 PSGs collected globally. The processed HR is fed to the deep-learning architecture to perform classification with different granularity: 2-levels (Wake; Sleep), 3-levels (Wake; NREM; REM) or 4-levels (Wake; Light; Deep; REM) in 30-second epochs, compliant with the AASM standard. The algorithm was validated using an open-source dataset (You Snooze You Win, Physionet CinC dataset, n=994 participants) and a proprietary dataset (Z3Pulse, n=52 participants). For the former, the ECG was isolated from conventional PSG recordings; for the latter, the Z3Pulse device was used. This wearable is a chest worn, wireless sensor recording HR, body position, activity and temperature. A simultaneous PSG was collected using SOMNOtouch. We evaluated the performance of the 2-, 3-, and 4-levels models in both datasets using Accuracy (A), Cohen's kappa (K), Sensitivity (SE), Specificity (SP). Additionally, the performance of the algorithm was evaluated in relation to age, AHI score, and biological sex.

**Results:** **CinC** - The highest value of accuracy was achieved by the 2-levels model (0.8797 [0.8740 0.8846]). The predictions obtained in the 3-levels model obtained the best value of K (0.6025 [0.5914 0.6136]). The classification of REM segments was equivalent comparing the 3-levels and 4-levels models. Similarly, the performance was stable comparing NREM segments for the 3-levels model against Light segments for the 4-levels model. In the latter model, the lowest value of SE (0.3831 [0.3628 0.4034]) and the highest value of SP (0.9612 [0.9563 0.9661]) were obtained for the classification of Deep sleep segments. AHI and biological sex did not impact any of the outcome metrics. A significant decrease of performance by age was reported across the models.

**Z3Pulse** - The highest value of accuracy was achieved by the binary classification of the 2-levels model (0.8812 [0.8668 0.8955]), whereas the prediction obtained in the 3-levels model obtained the best value of K (0.611 [0.5818 0.6401] and 0.6117). For classification of the sleep states, the lowest value of SE (0.6163 [0.5710 0.6617] and 0.6115) and the highest value of SP (0.9606 [0.9536 0.9676] and 0.9605) were obtained for the classification of Deep sleep segment.

**Conclusions:** Results demonstrate the feasibility of accurate sleep staging based on HR, derived from ECG acquired via PSG or wearable devices. The combination of the illustrated sleep staging algorithm with an inexpensive device, provides a cost-effective and non-invasive solution easily deployable in the home, with the potential of providing a convenient and affordable alternative to PSG for large-scale sleep characterization in the field.

**Acknowledgements:** N/A

## A NON-CONTACT VERIFICATION PROCEDURE FOR PROMPT CHARACTERIZATION OF SUNDRY BREATHING TYPES IN SLEEP

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**Introduction:** The ordinary character of specific biometric modulation in continuous-wave adaptive bio-radar signal with frequency adjustment at breathing process in sleep mostly caused by reciprocal movements of skin of abdominal and thoracic areas due to periodic contractions of muscles was verified with standard respiratory plethysmography functional characteristics on the base of cross correlation and spectral analysis.

**Materials and Methods:** Verification of contactless continuous-wave adaptive bio-radar with respiratory plethysmography belt perimeteric sensor data during simultaneous experimental registration of sundry breathing types was carried out defining functional relationships between the two signals in both time and frequency domains based on pairwise correlation and spectral functions calculation and estimation of their main generalized characteristics.

**Results:** Estimated values of cross-correlation coefficient from 0.84 to 0.94 denoted close linear relationship between the signals in time domain. Calculated estimations of effective width of cross-spectrum revealed

concentrations of the main interaction power of these signals in narrow frequency band corresponding to the character range of breathing activity. Obtained values of average levels of coherence from 0.67 to 0.69 for quiet breathing and from 0.73 to 0.93 for rapid breathing in effective band of cross-spectrum indicated statistical significance of pairwise spectral estimates and presence of stable linear relationship between the two signals in frequency domain.

**Conclusions:** Thus, results of performed pairwise correlation and spectral analysis of frequency adjusted continuous-wave adaptive bio-radar and perimeteric belts respiratory plethysmography data recorded simultaneously for different types of breathing revealed tight linear relationship between the corresponding signals both in time and frequency domains making it suitable for contactless sleep monitoring applications.

**Acknowledgements:** A current project is supported by the grant of the President of the Russian Federation (NS-2553.2020.8) for leading scientific schools and Russian Foundation for Basic Research (RFBR) welcome leap perspective framework.

## A NOVEL GENERIC ALGORITHM FOR ANALYSIS OF THE PULSE WAVE SIGNAL DURING SLEEP

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**Introduction:** The finger pulse waveform, detected by photoplethysmography (PPG), shows changes in blood volume in the microvascular bed of the fingertip. PPG is simple, non-invasive, and commonly used in sleep diagnostic devices to reflect oxygen saturation (SpO<sub>2</sub>). Current research has addressed other PPG features that may provide information on autonomic, cardiac, and vascular function.

**Materials and Methods:** This study describes the development of a web solution using HTML/Flask as a GUI (graphical user interface) and a Python backend for practical extraction of PPG-derived parameters. The Python backend computes several parameters including pulse wave amplitude (PWA), peak-to-peak interval (PPI), pulse propagation time (PPT), and the augmentation index (AIX) from a raw PPG signal in European data format (EDF). The raw PPG signals can be exported from most available recording devices. The web interface enables the user to run the algorithm on an entire cohort of recordings or to perform an in-depth analysis of the PPG waveform in specific time frames of one recording.

**Results:** A prototype of the algorithm allowed extraction of relevant pulse wave features, displaying summary reports, as well as exporting these features. A first proof-of-concept trial used the prototype to analyze PPG waveform signals from 10 ambulatory polysomnography recordings (A1 system, Nox Medical, Iceland) from subjects with suspected sleep apnea. On average, 30018 artifact-free pulse waves were extracted from 6-10 hours of sleep recordings. Feature extraction for PWA, PPI, PPT, AIX was successful in all recordings (4 hours and more for each subject).

**Conclusions:** This work describes the first prototype of a web-based, cross-platform PPG analysis tool. In the current version, it computes several features of the PPG-derived finger pulse wave on top of the information provided by oxygen saturation and pulse rate. The new technology allows easily accessible visualization and relevant summary statistics. Future developments include extraction of additional PPG features and calibration of a cardiovascular risk algorithm based on the newly proposed SCORE risk matrix.

## APPROXIMATION OF INFLUENZA-LIKE ILLNESS RATES USING SLEEP AND CARDIORESPIRATORY DATA FROM A SMART BED

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**Introduction:** Pathophysiologic responses to viral infections affect sleep duration, quality, and concomitant cardiorespiratory function. Real-world, longitudinal monitoring of sleep metrics using a Smart Bed could prove to

be invaluable for infectious disease detection. Previously we leveraged sleep metrics from a smart bed to build a COVID-19 symptom detection model. Analysis of pre-pandemic data with this model indicated that our results may generalize to detecting symptoms of other influenza-like illnesses (ILI). Here we investigated whether seasonal ILI trends reported by US Center for Disease Control and Prevention (CDC) can be approximated from aggregation of individual ILI symptom predictions.

**Materials and Methods:** An IRB approved survey with COVID-19-specific questions was presented to opting-in Sleep Number customers from August to November 2020 in the USA. COVID-19 test results were reported by 3546/9370 respondents (249 positive; 3297 negative). Sleep duration, sleep quality, duration of restful sleep, time to fall asleep, respiration rate, heart rate, and motion level were obtained using ballistocardiography signals from the smart bed.

Longitudinal sleep data from January 2020 to December 2020 from 122 of the positive and 1603 of the negative respondents were used to develop an individual-level COVID-19 symptom detection model. The model produces a probability of experiencing COVID-19 symptoms for each sleep session. Pre-pandemic sleep data from January 2017 to December 2019 from 4187 responders (1820 sleep sessions per night on average) were used to assess the ability of the developed model to generalize to ILI symptom detection. Weekly rates of high-scoring sleep sessions between January 2017 and June 2018 were fitted to the weekly ILI rates as reported by CDC using a negative binomial model. Subsequently, Pearson correlation coefficients were calculated for the predicted and reported rates between July 2018 and December 2019.

**Results:** Correlation between the predicted and CDC reference was 0.91 (+0.04 compared to the baseline model). Correlation restricted to the influenza season (week 40 of 2018 to week 20 of 2019) was 0.87 (+0.13 compared to the baseline model).

**Conclusions:** The sleep metrics measured with a smart bed platform are a unique source of longitudinal data, collected in a real-world, unobtrusive manner. This system may serve as a valuable asset in predicting and tracking the development of symptoms associated with a wide variety of respiratory illnesses, including influenza and COVID-19.

**Acknowledgements:** This study was funded by Sleep Number Corporation.

#### A RELIABLE RECOGNITION ALGORITHM FOR NON-CONTACT DETECTION OF ABNORMAL RESPIRATION PATTERNS IN SLEEP

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**Introduction:** A recognition algorithm for automated contactless monitoring of abnormal respiration patterns during sleep for frequency adjusted continuous-wave bio-radar quadrature signal components realizations was implemented using wavelet transform and neural network classifier with optimization of their structural and parametric properties.

**Materials and Methods:** Our proposed recognition algorithm was evaluated on clinically verified database of 1250 respiration patterns recorded remotely in contactless manner using continuous-wave adaptive bio-radar signal fragments spread into three classes: obstructive apnea; central apnea; eupnea. Feature space was formed using sequences of absolute values of detailing coefficients of the third level wavelet decomposition of quadrature signal components with Symlet-13 basis chosen following the principle of minimum for modified entropy criterion. A multilayer perceptron was used as a reliable classifier.

**Results:** After ten simulations of training routine the optimal number of neurons in the hidden layer was equal to 9 also corresponding to the upper boundary estimate by a theorem of Arnold-Kolmogorov with Levenberg-Marquardt learning algorithm based on average values of quality indicators: classification accuracy on the test sample; number of cycles run; total time spent. For the most successful algorithm realization the maximum recognition accuracy of the abnormal respiratory patterns of continuous-wave bio-radar on the test sample was 86.7% with average accuracy 84.2% in ten simulations of neural network classifier.

**Conclusions:** Thus, the implemented algorithm for automated recognition of abnormal respiration patterns based on application of wavelet

transform and neural network classifier turned out to be reliable in modern sleep monitoring tasks for contactless sleep apnea detection by means of adaptive bio-radar technology with frequency adjustment.

**Acknowledgements:** A current project is supported by the grant of the President of the Russian Federation (NS-2553.2020.8) for leading scientific schools and Russian Foundation for Basic Research (RFBR) welcome leap perspective framework.

#### AUTOMATIC CLEANING OF WHOLE-NIGHT SLEEP EEG DATA USING ARTIFACT SUBSPACE RECONSTRUCTION (ASR)

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**Introduction:** Whole-night EEG data are plagued by several types of large-amplitude artifacts. Many common approaches to remove these artifacts (such as channel interpolation, rejection of noisy time intervals, independent component analysis) are time-consuming and rely on user decisions. Therefore, their results are idiosyncratic and result in arbitrary signal loss. In addition, independent component analysis (ICA) cannot isolate the inconsistent artefactual scalp topographies caused by unique movements occurring during sleep. Artifact Subspace Reconstruction (ASR; Mullen et al 2015) is an increasingly-popular approach to automatically clean wake EEG data without requiring continuous user decisions as with ICA. Indeed, ASR adaptively removes large-amplitude artifacts regardless of their scalp topography or consistency throughout the recording.

**Materials and Methods:** Here we provide the first thorough validation of ASR with sleep EEG data. Specifically, we test how well the algorithm (1) removes typical sleep-related artifacts, such as those caused by eye movements, sweating and body movements, and (2) preserves biologically-meaningful large amplitude signal, in particular the slow-waves prevalent in non-REM sleep.

**Results:** First, we provide evidence that applying ASR with the parameters recommended for wake EEG (e.g. Chang et al 2020) substantially removes biologically-relevant slow waves and KCs in sleep EEG. Second, we provide a set of ASR parameters that can be used to obtain optimal ASR cleaning of EEG in different sleep stages. Third, we provide an EEGlab plug-in to implement ASR for whole-night sleep data (Dusk2Dawn). Finally, we show how using our pipeline (1) reduces the reliance on procedures that entail data loss (e.g. channel interpolation and rejection of noisy time intervals), and (2) makes ICA decomposition less dependent on complex and arbitrary user decisions.

**Conclusions:** ASR represents a powerful tool for automatic and rapid cleaning of whole-night sleep EEG data, which reduces the likelihood of losing biologically-relevant information compared with standard EEG cleaning procedures.

**Acknowledgements:** This research is supported by the European Research Council and the Swiss National Science Foundation.

#### AUTOMATIZED ONLINE PREDICTION OF SLOW WAVE PEAKS IN THE EEG OF YOUNG AND OLD INDIVIDUALS: WHY WE SHOULD NOT RELY ON AMPLITUDE THRESHOLDS

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**Introduction:** High quality of slow wave sleep (SWS) has been connected to healthy cognitive aging. Brain state dependent stimulation (BSDS) during SWS is a promising method to boost SWS and requires the detection of slow wave (SW) peaks in the ongoing signal. The detection of qualitatively good SW peaks might be more difficult in aging as well as in

psychiatric conditions due to decreased SW amplitudes.

**Materials and Methods:** We compared two algorithms for SW peak detection and validated these against the gold standard of offline SW detection. The algorithms were applied to data sets of 21 young and 21 older adults. The amplitude-based algorithm which bases its detections on a specific negative amplitude threshold in the ongoing signal is compared to a template-based algorithm which detects peaks based on the correlation of the ongoing signal's topography with a template of an ideal slow wave peak topography. This approach is amplitude independent, which is especially important when dealing with populations exhibiting decreased amplitudes.

**Results:** Results suggest that template-based prediction is more sensitive, precise, reliable, and valid when compared to amplitude-based detection. Especially in the older group amplitude-based prediction detects peaks that differ from the gold standard both morphologically and topographically.

**Conclusions:** Especially in older adults, amplitude-based slow wave peak prediction might be non-ideal. A template-based approach - which is multidimensional- and largely amplitude-independent - is better able to cope with the complexity of older adults' sleep physiology.

#### CIRCUL, A RING WEARABLE IN THE DETECTION OF SLEEP BREATHING ABNORMALITIES. PRELIMINARY DATA

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**Introduction:** Wearable devices have been developed that have the ability to continuously monitor physiologic variables. One device, Circul® (Bodimetrics Corp, Los Angeles CA) with a form factor of a ring, measures several variables (SpO<sub>2</sub>, movement, heart rate). We evaluated the potential utility of this device in the detection of sleep breathing disorders.

**Materials and Methods:** Data was obtained from 164 patients (age=44.8 years+12.3 (SD)) suspected of having sleep disordered breathing. While wearing the Circul device patients were studied by PSG using an established polysomnography system (Alice 5, Respirationics). The Circul data was autoscored by the software of the device; the PSG data was scored by a technician. We compared the variables for some physiological data using linear regression analysis.

**Results:** The data from the Circul device compared favorably to the data from PSG (ODI 3%:  $y=0.854x-2.1624$ ,  $R^2=0.9012$ ; Mean Sleep SpO<sub>2</sub>:  $y=1.0311x-2.9908$ ,  $R^2=0.7778$ ; Nadir Sleep SpO<sub>2</sub>:  $y=1.0582x-75221$ ,  $R^2=0.8049$ ; Minutes SpO<sub>2</sub><90%:  $y=0.9583x+6.4992$ ,  $R^2=0.8536$ )

**Conclusions:** The first results comparing Circul against PSG are very promising. It is expected that such wearable devices, in the future and if validated, may play a role in the detection of sleep breathing abnormalities and perhaps in the monitoring of therapeutic outcomes.

#### CLOSED-LOOP ACOUSTIC STIMULATION ENHANCEMENT OF SLOW WAVE SLEEP USING SLEEP-MONITORING HEADBAND

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**Introduction:** An expedited decline or abnormal disturbance of slow wave sleep (SWS) has been linked to various physical and psychological pathologies. Closed-loop acoustic stimulation (CLAS) of slow oscillations (SO; ~1 Hz) during SWS has been shown to enhance slow wave activity (SWA; ~0.5 – 4 Hz). In recent years, electroencephalography (EEG) based sleep monitoring devices (SMD) have become commercially available. Much remains unknown about the utility of real-time SMH data for CLAS and how this and the accompanying effects compare to gold standard polysomnography (PSG). Therefore the current study evaluated the utility,

accuracy, and effects of SMH data when used for CLAS during SWS compared to simultaneously recorded PSG.

**Materials and Methods:** Twenty-six healthy participants (14 males; mean ± SD age: 21.23 ± 2.76) slept a full night at our laboratory. SMH and PSG data were acquired using a ZMax headband (Hydnode) and 64-channel WaveGuard caps (ANT) connected to a Refa8 72-channel DC amplifier (TMSi). A modeling-based CLAS algorithm and procedure, developed at our laboratory, was used to target the negative-going zero crossing (180°) of SWS SOs (0.5 – 1.5 Hz) recorded in SMH EEG (AF7/F7-Fpz) during a three hour interval after SWS onset. Non-arousing acoustic stimuli (100-ms pink noise; 42.5 dB) were presented during 30-second blocks (STIM) randomly alternating with 30-second inaudible stimulus blocks (SHAM), and with 30-second waiting blocks in between. Stimulus markers were recorded in both devices. Recordings were 0.1 – 49 band-pass filtered, re-sampled to 256 Hz, and similar derivations were selected based on their physical location (15 AF7-Fpz and 11 F7-Fpz). Global signal quality was assessed through spectrograms and sleep was scored following AASM guidelines. The SWS period following stimulation interval (post-CLAS) was extracted from SMH and PSG. Similarly STIM and SHAM condition blocks were extracted. Phase accuracy of STIM and SHAM markers were computed. Welch's power estimate for 0.25 Hz bins ranging from 0.5 to 48 Hz was applied per 30-second epoch for STIM, SHAM and post-CLAS data, outliers were removed and means were log transformed. Pearson correlation coefficients (PCC) between SMH and PSG post-CLAS bins were computed. Paired samples permutation and t-tests compared STIM and SHAM bin powers, and STIM/SHAM bin power ratios between SMH and PSG. Multiple comparisons were corrected for using Holm-Bonferroni.

**Results:** Ten participants were excluded due to various sleep and technical issues. Phase accuracy did not differ between STIM and SHAM, both within and between SMH and PSG. PCC based power bin exclusion, based on the overall average PCC, resulted in further analysis of 1 – 2.25, 2.75, 3, 3.5 – 18.75, 19.5 – 20, 20.5 and 22 Hz. SMH STIM compared to SHAM showed power increases for 1 – 2.25, 3, and 3.5 Hz ( $p<.001$ ). SMH and PSG STIM/SHAM power ratios did not differ.

**Conclusions:** The present study shows that SMD EEG can be utilized for CLAS targeting of the 180° SO phase and the enhancement of SWA during SWS when compared to PSG. These findings, together with the further development of unsupervised CLAS methods are promising for ambulatory CLAS studies and interventions.

#### CLOSED LOOP LEARNING THROUGH AI AND SMART DEVICES TO OBJECTIVELY MEASURE THE DRIVERS OF ADULT SLEEP AND TO MAKE AND MEASURE INTERVENTIONS

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**Introduction:** More than half of UK adults suffer from poor sleep but are not chronic insomniacs. Poor sleep has a negative impact on health and wellbeing – e.g. mental health, disease risk for stroke and dementia. Their ability to focus goes down, as does their sense of wellbeing. Treatment often targets 'sleep hygiene' – composed of 15 discrete factors. Individual sensitivity varies greatly on each of these dimensions – e.g. 100x differential in melatonin response to evening light (Philips et al, 2019). Currently there is no adaptive, targeted mechanism for providing sleep hygiene advice. I will use AI and smart devices to capture objective measures of biological variables such as movement, light exposure and behaviour and replace guesswork with personalised plans. This will help individuals to both understand and adapt their behaviour in a personalised, targeted manner. This will be the first study of its kind in sleep. Using AI to do this will create new challenges, like dealing with bias and how to explain it to all who use it, so I am also developing new tools to safeguard against these issues.

**Materials and Methods:** Our pilot uses AI to objectively assess sleep quantity and quality drivers in a closed loop, and to make personalised recommendations. Supervised machine learning and neural networks are

used to analyse data collected from 4 smart devices in 28-day cycles from healthy adults (no insomnia or diagnosed mental health disorders). Our target variables are TST, SWS and SE. Our devices provide feature data on light, temperature, sound, stress, exercise, consumption as well as sleep behaviours like wake time consistency and napping. AI is used on baseline sleep to prioritise the influence of these drivers and to identify thresholds and sleep phenotypes. AI is used to identify target interventions based on an individual's baseline and likely responsiveness. The intervention is delivered and monitored through an app which incorporates 12 behaviour change techniques: 5 of 6 highest impact digital behaviour change techniques (BCTs) (Webb et al, 2010) & all the best sleep hygiene for healthy adults (Murawski et al, 2018). AI will learn which interventions and BCTs get the best response, generating phenotypes based on reaction to intervention. Using AI to do this creates new challenges. For example, such novel research risks bias because differences are unknown. We recruit a diverse sample and use AI to augment data to deal with differences (stratified oversampling).

**Results:** We will show case our data collection and intervention delivery app as well as report initial results on driver priority, thresholds, sleep phenotypes, and plan for intervention targeting.

**Conclusions:** Individuals differ greatly in what drives their sleep quantity and quality, and their response thresholds. Objective results are very different to a priori subjective prioritisation. Clear sleeping behaviour phenotypes exist and can simplify intervention identification.

**Acknowledgements:** None

#### COST-EFFECTIVENESS OF A WEB-BASED PROVIDER TRAINING FOR COGNITIVE-BEHAVIORAL THERAPY FOR INSOMNIA

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**Introduction:** Insomnia is a chronic and often debilitating condition impacting approximately 6–30% of adults in the general population. Insomnia is associated with numerous physical and mental health consequences including increased workplace and car accidents, increased risk and symptom severity of comorbid mental and physical health problems, and cognitive deficits. Further, insomnia is associated with a substantial economic cost to both society and the individual due to absenteeism, lost productivity, increased medical costs, and increased health care use. Despite the established prevalence, consequences and costs of insomnia, it remains under-reported and under-treated. One factor contributing to the undertreatment of insomnia is the limited number of providers trained in the front-line evidence-based treatment, cognitive behavioral therapy for insomnia (CBT-I). To address this critical training gap, the study team created a web-based CBT-I provider training platform (cbtiweb.org) which has demonstrated equivalent provider knowledge acquisition compared to an in-person workshop (i.e., the prior standard of training).

**Materials and Methods:** Economic analyses (using a microcosting framework) were used to determine whether this web-based training is cost-effective compared to in-person training. Actual costs were recorded from an institutional perspective, and costs were estimated from an independent provider perspective.

**Results:** Economic evaluation with a time horizon of 12 months indicated this web-based CBT-I training was more cost-effective than an equivalent one day in-person workshop. In-person training of 20 CBT-I providers delivered by 5 insomnia experts over 7.5 hours costs approximately 553 USD per provider trained. Although initial overhead cost of developing the web-based training was high (approximately 236,591 USD), maintenance costs were relatively low at approximately 336 USD per month. Following launch, cbtiweb.org trained an average of 104 providers per month. Cost-effective analyses revealed after 12 months the per-provider cost of cbtiweb.org training was approximately 193 USD (i.e., 360 USD less than in-person per-provider cost). Further, the per-provider costs of in-person training are expected to maintain or increase across time, whereas the per-provider costs of cbtiweb.org are expected to decrease over time. Thus,

with a time horizon of 5 years and a conservative estimate of 52 providers trained/month (i.e., half of first year rate) in years 2–5, the per-provider cost of cbtiweb.org is anticipated at 69 USD (i.e., 484 USD less than in-person per-provider cost). Additionally, the costs to each individual provider to engage in the training are substantially lower for cbtiweb.org (65 USD if CEs are required, free for no CEs) compared to in-person training (estimated at 1200 USD or more).

**Conclusions:** These results demonstrate web-based CBT-I training is a cost-effective alternative to in-person workshops in addition to other benefits including a higher potential volume of providers trained and greater accessibility. These results establish the importance of developing web-based provider trainings for empirically supported treatments to address the implementation gap and disseminate these valuable treatments.

**Acknowledgements:** This work was supported by the Department of Defense [W81XWH-16]

#### DEEP LEARNING APPLICATION TO CLINICAL DECISION SUPPORT SYSTEM IN SLEEP STAGE CLASSIFICATION

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**Introduction:** Recently, deep learning for automated sleep stage classification has been introduced with promising results. However, many challenges impede their routine application, and automatic sleep scoring algorithms are not widely used. We aimed to develop a deep learning model for use in clinical decision support systems (CDSSs) and combined convolutional neural networks and a transformer for the supervised learning of 3-class sleep stages.

**Materials and Methods:** We retrieved PSG data from our sleep center involving patients with and without sleep-disordered breathing. The data for training, validation, and test were derived from 1590, 341, and 343 polysomnography recordings, respectively. Model performance was evaluated on the test sets with recall, precision, F1 score, and weighted/unweighted accuracy to assess the effect of sleep stage class imbalances in this dataset.

**Results:** We developed the deep learning model based on CNN with a transformer algorithm for the automatic detection of sleep stage events using a single-channel EEG signal. Our developed model yielded an overall accuracy of 91.4%, comparable to that of human experts. Based on obstructive sleep apnea severity, the model's accuracy was 94.3%, 91.9%, 91.9%, and 90.6% in normal, mild, moderate, and severe cases, respectively. When considering all epochs, the model scored Wake, NREM, and REM stages as 89%, 93%, and 88% for precision and 85%, 95%, and 85% for recall, respectively. Additionally, the inference was achieved within 30 s at a 104 MHz core clock frequency and approached 1.48 s when the core clock frequency was increased to 1.5 GHz.

**Conclusions:** Our deep learning model enables accurate and rapid delineation of 3-class sleep staging within a speed of 30 s per sleep recording and could be useful as a CDSS for application in real-world clinical practice. Acknowledgments: This research was supported by a grant of the Medical data-driven hospital support project through the Korea Health Information Service (KHIS), funded by the Ministry of Health & Welfare, Republic of Korea.

#### DEEP LEARNING ENABLES ACCURATE AUTOMATIC SLEEP STAGING BASED ON AMBULATORY FOREHEAD EEG

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**Introduction:** We have previously developed an ambulatory electrode set (AES) for the measurement of forehead electroencephalogram (EEG), electrooculogram (EOG), and electromyogram (EMG). The AES has been previously proven to be suitable for manual sleep staging and patient self-application in home polysomnography (PSG)[1]. This study aimed to utilize an automatic deep learning-based sleep staging approach for signals acquired with the AES to further facilitate the diagnostics of various sleep disorders. The utilized deep learning architecture consists of a combination of convolutional and recurrent neural networks. The architecture has been previously shown to achieve excellent epoch-by-epoch sleep staging accuracy of 82.9% with a single standard EEG channel (F4-M1)[2].

**Methods:** We trained and tested the deep learning model with 135 EEG signals recorded with the AES. The PSGs were conducted for subjects suspected of sleep apnea or sleep bruxism in Finland and Australia. The accuracy of the deep learning model was evaluated with 10-fold cross-validation using manually scored AES signals as a reference. Different channel combinations were tested to determine the channel combinations leading to the best scoring accuracies. In addition to conventionally derived bipolar channels, we constructed combination channels to reject artefacts caused by poor electrode contact. Combination channels were created by calculating variance of the epochs from opposite channels (e.g., Fp1 and Fp2), and using only the epoch with lower variance.

**Results:** The best results were obtained with Fp1/Fp2 combination channel. The deep learning model achieved 5-stage sleep scoring accuracy of 79.7% ( $\kappa=0.729$ ) based on the Fp1/Fp2 combination channel when compared to manual scoring using all AES signals. The accuracy increased to 84.1% ( $\kappa=0.773$ ) for four sleep stages (W, light sleep, deep sleep, R), and to 89.1% ( $\kappa=0.801$ ) for three sleep stages (W, NREM, R). For individual sleep stages, the accuracies were 88.5%, 30.7%, 84.4%, 81.3%, and 83.4% for W, N1, N2, N3, and REM, respectively.

**Conclusion:** The utilized deep learning model accurately determined sleep stages based on two frontal EEG channels recorded with the AES. The accuracy is comparable to the inter-scorer agreement of standard EEG scorings between international sleep centers[3]. The automatic AES-based sleep staging could potentially improve the availability of PSG studies by facilitating the arrangement of self-administrated in-home PSGs. Furthermore, automatic AES-based sleep staging could be used in circumstances cumbersome for standard PSG, such as patients in stroke units.

**Acknowledgements:** We thank Sigríður Sigurðardóttir and Erna Sif Arnardóttir for their valuable contribution in the data analysis. This work was supported in part by the EU Commission Horizon 2020 Framework Programme (965417), NordForsk via Business Finland (5133/31/2018), Research Committee of the Kuopio University Hospital Catchment Area for the State Research Funding, Academy of Finland (323536), The Research Foundation of the Pulmonary Diseases, Finnish Cultural Foundation North Savo Regional Fund, Finnish Cultural Foundation, Päivikki and Sakari Sohlberg Foundation, Finnish Anti-Tuberculosis Association, Tampere Tuberculosis Foundation, and Kuopio Area Respiratory Foundation.

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## DEEP LEARNING ENABLES AUTOMATIC SLEEP STAGING FROM TEXTILE ELECTRODE-BASED HOME SLEEP RECORDINGS

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**Introduction:** Various research settings demand more accurate quantification of sleep in a home environment than what is currently achieved with questionnaires, actigraphy, or photoplethysmography-based devices [1]. One solution to maintain a simple measurement setup and increase

reliability could be implementing electroencephalography (EEG) with wearable and self-applicable textile electrodes. Therefore, we aimed to develop an automatic sleep staging method that generalizes from clinical polysomnographic data to portable home recordings of textile electrode-based forehead EEG signals.

**Materials and methods:** A standard electrooculogram (EOG, E1-M2) and manually annotated sleep stages of diagnostic polysomnographic recordings ( $n=876$ ) were used to train, validate, and test a fully convolutional neural network. Home-based ambulatory sleep recordings including standard EOG, EEG, and chin-electromyography as well as additional forehead EEG (Fp1-Fp2) recorded using a textile electrode-headband were conducted for 10 healthy volunteers. The home-based recordings were used to evaluate how the model generalized to forehead EEG signals recorded using the textile electrodes. The automatic sleep staging was compared against manual sleep staging conducted by expert sleep technicians.

**Results:** In the test set ( $n=88$ ) of the clinical dataset, the model's accuracy over 5-stage classification was 80% ( $\kappa=0.73$ , F1-score=0.74) using only the single-channel EOG. The trained model generalized well for home sleep recordings and reached 82% ( $\kappa=0.75$ , F1-score=0.72) and 87% ( $\kappa=0.82$ , F1-score=0.78) overall accuracies against manual 5-stage classification using the textile electrode-recorded forehead EEG signal and standard EOG signal, respectively. When Stage N1 and N2 were combined, the model reached 83% ( $\kappa=0.76$ , F1-score=0.83) and 89% ( $\kappa=0.84$ , F1-score=0.89) overall accuracies using the textile electrode-recorded forehead EEG signal and standard EOG signal, respectively.

**Conclusions:** The developed sleep staging model, trained on an extensive clinical dataset, generalized well to textile electrode-recorded forehead EEG signals. This could enable quantifying sleep structure in home-based research settings with reliability comparable to manual sleep staging ( $\kappa=0.76$  [2]).

**Acknowledgments:** The financial support of this study was provided by the NordForsk (NordSleep Project 90458) through the Business Finland (Grant 5133/31/2018) and through the Icelandic Center for Research; by the Academy of Finland (323536); by the Research Committee of the Kuopio University Hospital Catchment Area for the State Research Funding (Grants 5041767, 5041768, 5041789, 5041794, 5041803, 5041804 and 5041797); by the Finnish Cultural Foundation – North Savo Regional Fund and Kainuu Regional Fund; by the Respiratory Foundation of Kuopio Region; by the Research Foundation of the Pulmonary Diseases; by the Finnish Anti-Tuberculosis Foundation; by the Tampere Tuberculosis Foundation; by the Maud Kuistila Memorial foundation and by the European Union's Horizon 2020 Research and Innovation Programme (Grant 965417). FocusBand Technologies has supported this work by providing measuring equipment free of charge and through a consultation agreement with The University of Queensland. Authors would like to thank Kristín Anna Ólafsdóttir (Reykjavik University) for data annotation.

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## DETERMINATION OF THE SLEEP–WAKE PATTERN AND FEASIBILITY OF NREM/REM DISCRIMINATION USING THE NON-INVASIVE PIEZOELECTRIC SYSTEM IN RATS

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**Introduction:** The gold-standard method for sleep analysis in mammals is polysomnography (electroencephalogram [EEG] and electromyogram [EMG] recording), allowing characterization of sleep quantity and architecture by manual scoring or by software programs. Limitations of this method are specific and lengthy surgery that require recovery time and

can induce postoperative side-effects (e.g. infection or oedema), and may lead to bias in studies investigating peripheral and cerebral responses after. For example manipulation of sleep time or environmental constraints. Non-invasive techniques to record sleep characteristics have been developed particularly in mice, and one of the most promising is the piezoelectric (piezo) system. The piezoelectric cage-floor sensors have been used to successfully dissect sleep patterns in mice based on signal features related to respiration and body movements. Whereas there is a lack of non-invasive techniques to study sleep in rats, we used piezoelectric system to determine the sleep-wake pattern and the feasibility of NREM/REM discrimination.

**Materials and Methods:** We performed simultaneous recordings with the piezoelectric system and EEG/EMG telemetry recording during 7 days ( $N=14$ ). Animals were distributed in two groups, corresponding to two different photoperiod (light/dark : LD12:12 and LD16:8) leading to change in the 24-hr sleep characteristics ( $N = 7$  per group).

**Results:** The total sleep time (%/24 hr) over the 7 days recording and hourly sleep time over the last 24-hr recording were not statistically different between methods under the two photoperiods. Both methods detected higher total sleep time with the LD16:8 photoperiod compared with LD12:12 ( $p < .05$ ), and correlated significantly ( $p < .001$ ) at light and dark periods during each photoperiod. The accuracies for discrimination of sleep-wake patterns between methods were 81.9% and 84.9% for LD12:12 and LD16:8, respectively. In addition, spectral analysis of the respiratory signal given by piezo during all 10-s periods of the corresponding non-rapid eye movement and rapid eye movement sleep periods recorded by electroencephalogram/electromyogram resulted in selection of 36 features (features selection with Gram-Schmidt orthogonalization) that could be inserted in an automated non-rapid eye movement sleep and rapid eye movement sleep classification (Gradient-Boosting algorithm), with 90% accuracy with the electroencephalogram/electromyogram visual scoring.

**Conclusions:** The piezoelectric system allows a non-exhaustive analysis of sleep parameters. We showed that it can accurately record total sleep time in rat, even after a modification of sleep dynamics. Non-rapid eye movement and rapid eye movement sleep stages can be discriminate by piezoelectric system, using respiratory signals recordings. Piezoelectric system use will be interesting in pharmacological or bio-behavioural studies evaluating sleep patterns or the restorative functions of sleep in the body and the brain.

**Acknowledgements:** We thank the contribution of the IRBA animal facility team

#### DEVELOPMENT OF A CLASSIFICATION MODEL FOR SLEEP STAGING BASED ON A WEARABLE CONSUMER-BASED ELECTROEN- CEPHALOGRAM BAND - A PILOT STUDY

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**Introduction:** Sleep disorders and associated complaints have increased in the population and it is one of the main consequences of the current lifestyle. With technology advancements, the search for wearable devices and mobile apps that monitor sleep has grown about 18.5% and is moving about US\$2 billion a year. There is a lack of scientific evidence about its validation, comparison with gold standard methods (e.g. polysomnography), or certification by regulatory entities, so its safety and efficacy are not well established. Therefore, our goal was to develop a sleep monitoring methodology from the combined use of a wearable consumer-based electroencephalogram and an actigraph, using a novel classification model capable of providing technical accuracy, and therefore, techno-scientific validation in comparison with polysomnography.

**Materials and Methods:** Nine subjects (4 women - mean age  $31.0 \pm 7.3$  years - and 5 men - mean age  $30.6 \pm 2.6$  years) underwent a full-night type I polysomnography (performed and scored following the American Academy of Sleep Medicine recommendations). Simultaneously the participants used an actigraph on their non-dominant wrist and a flexible, single-channel wearable electroencephalogram band (acquisition frequency of 512 Hz) located in the left frontal region. Data from the wearable band was segmented into 30-second epochs for comparison with the

polysomnography. For each 30-second epoch, the mean and median powers of the alpha, beta, theta, and delta bands; and the mean value of actigraph activity (PIM) were extracted. A Decision Tree type classifier was trained, with stratified cross-validation ( $k = 10$ ), and then, the resulting sleep staging algorithm model was tested with the assigned groups.

**Results:** The algorithm was able to distinguish and classify the five sleep stages (W, N1, N2, N3 and REM) with a total accuracy of 90% (F1-score - macro average) and F-scores (denoting sensitivity) of 97% for REM sleep, 61% for N1, 97% for N2, 97% for N3, and 97% for wakefulness. The N1 stage presented the highest error rate, which was most often confounded with wakefulness (23%) followed by N2 (15%), and REM (8%).

**Conclusions:** This is a preliminary study that demonstrated the viability of using a consumer-based wearable-electroencephalogram band as a tool to replicate sleep staging in comparison to polysomnographic results. Among the limitations, we pointed out the battery life (mean duration of 4-6 hours), which impaired complete sleep monitoring. Future works can include improving the algorithm for classifying sleep stages (especially improving the distinction between W and N1) and applying it in a clinical sample to verify the performance of the proposed model in individuals with sleep disorders, especially insomnia and sleep apnea.

**Acknowledgements:** We would like to thank the financial support of the São Paulo Research Foundation (FAPESP).

#### DEVELOPMENT OF A FREQUENCY-DOMAIN BASED AUTOMATIC EVENT DETECTION ALGORITHM FOR EDA SLEEP SIGNALS AND COMPARISON WITH MANUAL SCORINGS

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**Introduction:** Most sleep measurements, such as electrodermal activity (EDA) sleep recordings, are manually scored, which is a time-consuming operation. In this study, we present an algorithm that automates the scoring of the EDA signal. Importantly, we also elaborate on meaningful procedures to perform the comparison between algorithm-based and manual scoring.

**Materials and Methods:** The algorithm was developed using scored signals collected within the Sleep Revolution project. During the study, it was observed that EDA events possess characteristic frequencies, i.e., EDA events were characterised by higher frequencies than other parts of the signals. Because of this, it was decided to perform the analysis in the frequency domain. The Fast Fourier transform (FFT) was used to move to the frequency domain. The application of FFT can possibly lead to ringing artefacts due to the significant scattered-ness of the signal. To minimise these artefacts, the signal was pre-processed by means of stationary wavelets transforms (SWT), thresholding, and then inverse SWT to obtain a smoother signal. The frequency range under consideration was determined by searching the literature for frequencies characteristic of the different skin potential responses, i.e., monophasic positive, monophasic negative, biphasic and triphasic.

Another kind of artefacts are generated by physical movements of the sleeping person. These anomalies are dealt with by setting thresholds, taking advantage of their high magnitudes. A feature of particular interest is the presence of EDA storms, i.e., the consequent occurrences within 5 minutes of sequences of at least 3 events in 30 seconds, and whose occurrence probability is linked to sleep stages. A main issue in the comparison between manually obtained scorings and algorithm-based scorings is how signals are manually scored, due to the lack of uniformity in the scoring sleep signals. E.g., there exist uncertainties regarding the definition of start and end of an EDA event.

**Results:** First analyses have been performed. The algorithm is able to match, on average, 42.05% of the manually scored events, with the highest percentage being 55.58% and the lowest 15.54%. These matching results require further investigations. For instance, we observe that, on average, the ratio between correctly scored events and erroneously scored events is 1.82. This value significantly rises if we consider storms detection, for which the ratio is \$11.91\$. Finally, it must be pointed out that manually scoring is not perfect, as, e.g., there might be events that were not scored and others that were erroneously scored.

**Conclusions:** Although signal filtering can be improved, the use of the

scoring algorithm already proves to be promising, especially for the detection of EDA storms, and generally for packets of events, for which this algorithm appears already to be rather accurate.

**Acknowledgements:** The study was carried out within the Sleep Revolution project. This project has received funding from European Union's Horizon 2020 research and innovation program under grant agreement no. 965417.

#### DEVELOPMENT OF A RULE-BASED TEXT MINING ALGORITHM TO IDENTIFY SLEEP COMPLAINTS IN PRIMARY CARE PROGRESS NOTES

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**Introduction:** Sleep complaints are among the most common reasons to seek medical attention, yet sleep disorders are largely underdiagnosed in primary care settings. The ability to process large collections of unstructured clinical notes might offer an opportunity to promote screening of patients suffering from significant sleep disorders. The goal of this study was to develop a simple rule-based algorithm to identify sleep complaints in progress notes from primary care encounters and validate the performance of the algorithm against manual chart review.

**Materials and Methods:** De-identified progress notes of a random sample of patients with primary care encounters at the University of Kansas Health System in 2019 were extracted from the institution's clinical research data warehouse (Healthcare Enterprise Repository for Ontological Narration). Review of 163 notes from patients enriched for presence (N=95) or absence (N=68) of sleep disorders based on the International Classification of Disease (ICD)-10 code hierarchy G47 guided the development of a vocabulary of sleep complaints and symptoms, including corresponding negation terms. The vocabulary was used to design a rule-based, regular expression matching algorithm, which was evaluated against manual chart review of the same patient cohort (training dataset). An independent set of notes from another sample of patients with primary care encounters (N=77; testing dataset) was also manually reviewed and used to assess the validation performance of the algorithm.

**Results:** In the training dataset, the algorithm had a sensitivity=75%; specificity=91%, positive predictive value (PPV)=90%, and a negative predictive value (NPV)=87%. The area under the receiver operating characteristics (AUC) curve in the training set was 0.84. When the algorithm was evaluated in the testing dataset, we found a sensitivity=53%, specificity=91%, PPV=78%, and NPV=77%. The AUC in the testing dataset was 0.78.

**Conclusions:** A simple pattern matching algorithm designed to identify sleep complaints in primary care progress notes showed good performance in the training set and acceptable performance in the testing set. Further refinement of this algorithm with potential incorporation of natural language processing might offer a feasible approach to screen patients for underdiagnosed sleep disorders using primary care clinical notes.

**Acknowledgements:** NIH CTSA UL1TR002366.

#### DROWSY CLASSIFIER USING MULTIVARIATE STATISTICAL PROCESS CONTROL BASED ON PRINCIPAL COMPONENT ANALYSIS

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**Introduction:** Drowsy at the wheel has been studied over the years since it is considered a public health problem. When an individual does not get enough sleep, it has very serious effects on safety, health, and quality of life. Consequently, this can lead to a decrease in the individual's productivity, as well as an increase in accidents at work, such as in driving. That is why it is important to understand

**Materials and Methods:** To distinguish the individual awake and drowsy

state a virtual simulation was performed. American Truck Simulator was the game-used since there are highways with long kilometers and it is possible to define a single route for all the participants. Thus, the simulation duration was about one hour or, in some cases, one and half hours. Where the maximum speeds were 30 and 55 miles per hour within a city and highway, respectively. Thereafter, the wearable device Microsoft Band 2 was used to collect biometric data, and the participant's face was recorded using a webcam to detect the blink eyes, to identify its duration and signs of drowsy. The time, frequency, geometric, nonlinear heart rate variability features, and the mean blink duration were performed in two minutes. When the blink duration was greater than 500ms, it was considered a drowsy state. However, Multivariate Statistical Process Control, based on Principal Component Analysis (MSPC-PCA) was performed to verify if detects sleepiness signs. Further to this information, each participant had to fill out four questionnaires about daytime sleepiness, the risk of obstructive sleep apnea, sleep quality, and circadian rhythm. This information was collected to identify possible sleep disorders.

**Results:** Twelve participants performed the simulation, where 83.33% are male. According to the questionnaire results, one participant is definitely morning type, four moderately morning type, five neither type and two moderately evening type. Only one participant has bad sleep quality, three have a high risk for moderate to severe obstructive sleep apnea and hypersomnia. In terms of simulation results, only three participants were analyzed individually to evaluate if our approach can be used to detect sleepiness. Moreover, the blink eyes detection helped identify the drowsy state. However, using only this approach it was not possible to identify all the sleepiness peaks. Thus, MSPC-PCA helped detect more signs of sleepiness, that were validated using the recorded video.

**Conclusions:** Using this approach it was possible to confirm that blinking eyes duration can detect peaks of sleepiness but is not sufficient. Besides that, biometric data collected from a wearable device, with low cost, also showed promising results when MSPC-PCA is applied. As future work, it is important to evaluate the remaining participants and what happens in the biometric data moments before it shows signs of drowsiness.

**Acknowledgements:** This study was supported by the NORTE-01-0247-FEDER-039720 program.

#### EVALUATING THE IMPACT OF SOCIAL MEDIA USAGE AND BLUE LIGHT ON PRE-SLEEP AROUSAL AND SLEEP AMONG YOUNG WOMEN

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**Introduction:** The use of social media in bed is linked with increased arousal and poor sleep. Blue light that is emitted in this process also might disturb sleep. To examine the impact of blue light and social media usage before sleep on the development of pre-sleep arousal and experiencing poor sleep, the present study investigated three conditions: social media use in bed with blue light exposure, social media use with a blue light filter, and no use of a smartphone in bed.

**Materials and Methods:** In a randomized within design, each individual underwent all three one-week conditions. 79 young women ranging 16 to 24 years ( $M_{\text{age}} = 21.19$ ,  $SD = 1.42$ ) filled out a sleep diary and the Pre-Sleep-Arousal Scale.

**Results:** ANOVAs revealed a higher pre-sleep arousal when using social media with blue light than in the control condition without smartphone use in bed. Cognitive pre-sleep arousal was higher throughout all the conditions than somatic pre-sleep arousal. Regarding sleep, sleep quality was found to be lower when using social media with blue light than in the control condition, while no difference was found between social media use with and without blue light filter. No significant differences could be observed for total sleep time and sleep latency.

**Conclusions:** The results support initial assumptions that content, but not melatonin suppression by blue light causes arousal and thereby sleep problems. Future research should gain inside of which media content is harmful to derive precise recommendations for smartphone usage before sleep.

**Acknowledgements:** Non.

## EXPERIENCE WITH OVER 10,000 SLEEP TELEMEDICINE VISITS FOR DIAGNOSIS AND TREATMENT OF OSAS

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**Introduction:** Since March 2020 BlueSleep has completed over 10,000 telemedicine consultations for diagnosis and treatment of sleep apnea exclusively by real-time telemedicine consultations using HIPAA-compliant video conferencing.

**Materials and Methods:** This is a retrospective chart review of all virtual consultations performed between March 13, 2020 and December 31, 2021 at the BlueSleep center. This period coincided with the lockdown in New York City because of the COVID19 Pandemic. 10,171 telemedicine consultations were performed both for new and existing patients. No patients under the age of 18 were evaluated. The median patient age was 40 years old; 2,412 males, 1,098 females. Diagnosis of sleep apnea was performed with disposable single-night or multi-night Home Sleep Tests (HST) with WatchOne (Itamar Medical) or Nightowl (Ectosense). Patients were given instructions for HSTs via asynchronous videos. HST data was transmitted to a portal for scoring and interpretation. Follow-up visit was by telemedicine, and treatment options including oral appliance therapy and CPAP were discussed. Surgical options were not available during the lockdown. If oral appliance therapy was chosen by the patient, a virtual visit with a dental professional was scheduled before sending a home impression kit. Home impressions were guided in real time with a dental professional. Dental impressions were submitted to the dental labs for fabrication of Mandibular Advancement Devices (MAD), and sent to the patient for a virtual home delivery by the dental professionals. A follow-up virtual visit was scheduled after the 4-week titration period, and depending on subjective results of decreased snoring and decreased daytime sleepiness, the patient was then instructed to repeat a HST for efficacy evaluation. If the patient chose CPAP, CPAP was shipped to the home, and a follow-up visit was scheduled for a virtual set-up visit, followed by compliance visits. All patients were scheduled for continuous telemedicine follow-up visits.

**Results:** 10,171 visits were completed including first and follow-up visits. A total of 289 single-night and 2,275 multi-night HSTs were performed. 2,348 patients were diagnosed with OSA. 36% with mild OSA, 41% of patients with moderate OSA, and 23% with severe OSA. 1,163 had no OSA. 53% of patients were treated with OAT, 20% with CPAP. 271 patients were treated for primary snoring. 256 patients were treated for insomnia. 31 patients were diagnosed with Narcolepsy, and 636 patients were diagnosed with "other".

**Conclusions:** A fully virtual model for diagnosis and treatment for obstructive sleep apnea and other sleep disorders is feasible and desirable. Telemedicine allows greater convenience (less time lost from work), and availability (greater geographic availability), and is a lower cost option.

**Acknowledgements:** We wish to thank the entire BlueSleep staff that has helped make our service to patients available during the Covid 19 Pandemic.

## FACTORS THAT IMPACT POSITIONAL THERAPY UTILIZATION AND COMPLIANCE

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**Introduction:** In a recent report, a majority of Italian patients reported at least one complaint while using Night Shift positional therapy (PT) (e.g., difficulty initiating sleep, awakened by the vibration, neck or back pain, etc.)<sup>1</sup>. This study investigated the frequency of similar complaints in U.S. patients.

**Materials and Methods:** A quality survey was conducted in all 475 patients who purchased PT directly from the manufacturer (Advanced Brain Monitoring, Inc., Carlsbad, CA) between April 2018 and August 2021. An online questionnaire was developed and the survey, conducted over a three-month period, began with email notifications. A total of 468 emails

were delivered, and 449 patients received at least one telephone follow-up attempt. Patients were offered a free PT neck-strap for completing the survey.

**Results:** Direct contact was made with 158 patients, of which 25 refused or were unable to respond, and four claimed to have never used PT. In the 129 cases with feedback, 50% claimed to use PT regularly, 25% found PT to be ineffective, and 9% discontinued use due to design features (i.e., neck strap was uncomfortable (5%), PT woke them up (2%), and battery-related issue (2%). Of the remaining patients who discontinued use, 4% reported it trained them to stay off their back, 3% changed to a different therapy, 2% used it only when traveling, and 2% lost weight and claimed to no longer need therapy.

Of the 129 Patients who provided feedback, 83 completed the web-based survey (age 65+11 years, range 36-80 years, 31% female). Prior to initiating PT, 22% previously trialed CPAP, 15% tried oral appliance therapy (OAT), 33% trialed both CPAP and OAT, and 30% tried another OSA therapy. Of the patients who used CPAP prior to PT, 49% had used it for  $\geq 12$ -months and 30% for <3-months.

Seventy-seven percent of the surveyed patients (64/83) claimed to use PT at least four-hours per night. Reasons for compliant utilization included: kept me off my back (95%), slept better (53%), felt better during the day (48%), more comfortable than other therapies (48%), my physician told me to use it regularly (48%), I no longer snored (34%), and my bed partner asked me to use it (23%). In patients who discontinued use, none were encouraged by their physician to use PT, and none reported to their physician that they discontinued therapy.

When objective PT utilization was compared to self-reports, patients accurately reported utilization in 62% of the cases (28/45) and under-reported utilization in 30% of the cases (14/45). In three cases of over-reported utilization, 6-7 hours of nightly use was actually 4-5 hours in two cases and 5-6 hours in one case.

**Conclusions:** Patients would benefit from a PT trial in order to determine if the therapy might work for them. None of the patients who discontinued use were encouraged by their physician to use it.

**Reference:** 1. Efficacy and long-term follow-up of positional therapy by vibrotactile neck-based device in the management of positional OSA. De Corso E, et al. *J Clin Sleep Med* 2020;16(10):1711-1719.

## HEALTH CARE-RELATED UTILIZATION 24 MONTHS AFTER TREATMENT WITH A PRESCRIPTION DIGITAL THERAPEUTIC FOR CHRONIC INSOMNIA

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**Introduction:** Chronic insomnia is a significant public health problem, due not only to the disease itself, but its tendency to co-occur with other serious medical and psychiatric disorders. Insomnia also poses a significant economic burden on patients and healthcare organizations, with direct and indirect costs in the United States estimated to exceed US\$100 billion each year. Prescription digital therapeutics (PDTs) are a new class of software-based disease treatments that deliver evidence-based therapeutic interventions on smartphones or tablets. PDTs are clinically validated and authorized for use by the U.S. Food and Drug Administration based on rigorous clinical trial data. PDTs can be used alone or in combination with drugs and are being developed for a wide range of medical conditions including chronic insomnia.

These analyses evaluated health care-related utilization after initiation of treatment with a PDT delivering cognitive behavioral therapy for insomnia (CBT-I) to adults with chronic insomnia (Somryst<sup>0</sup>, previously called SHUTi). The PDT provides a digital version of CBT-I to patients who are clinician-supervised in outpatient settings. Content is delivered via six interactive treatment modules designed to parallel the traditional, face-to-face delivery and structure of CBT-I sessions during the 9-week prescription period.

**Materials and Methods:** We conducted a pre/post analysis of claims data that compared two-year pre- and post-index healthcare resource utilization (HCRU) in U.S. patients with self-identified sleep problems who

activated the PDT between February 1, 2012 and December 31, 2018. The index date was the date of PDT initiation, pre-index date was 24 months before the index date and the post-index date was 24 months after the index date. HCRU categories assessed were: hospitalizations, treat-and-release emergency department (ED) visits, ambulatory surgical center (ASC) visits, hospital outpatient department (HOPD) visits, office visits, and use of sleep medications.

**Results:** Analyzed were 252 patients (mean age 54.2 years, 57.5% female). Mean Charlson Co-morbidity Index score was 0.8 (interquartile range 1.48), with the top co-morbidities being lipid dysregulation (40%), back pain (37%), anxiety (32.5%) and hypertension (32%). Post-index events were reduced compared to the pre-index period for ED visits (-56.2%;  $P=0.001$ ), hospitalizations (-20.9%;  $P=0.4$ ), sleep medication use (-8.9%;  $P=0.377$ ), HOPD (-8.3%;  $P=0.522$ ), and ASC (-6.7%;  $P=0.695$ ). Office visits in the post-index period were slightly higher compared to pre-index period (+0.7%;  $P=0.891$ ).

**Conclusions:** Treatment with a PDT delivering digital CBT-I in a real-world population of patients with chronic insomnia was associated with clinically meaningful reductions in health-related services.

**Acknowledgements:** Stephen Braun, medical editor at Pear Therapeutics, Inc., provided editorial assistance in the preparation of this abstract.

### IMPROVING SLEEP OF OVERWEIGHT AND OBESE PATIENTS FROM USING A THERMOREGULATED PILLOW: REAL-LIFE DATA FROM MOONA DEVICE

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**Introduction:** There is a well-established relationship between sleep disorders and obesity. While sleep loss is associated with weight gain, obesity is associated with insomnia and sleep issues. Both overweight and sleep disturbed patients are associated with an elevated core body temperature.

The aim of this study is to characterize the effect of an active thermoregulated pillow on the overweight/obese and their sleep.

**Materials and Methods:** The Moona device controls the temperature of a pillow pad from 64°F to 95°F and has sensors to monitor temperature changes and sleep states throughout the night. A total of 321 overweight/obese (BMI > 25) users with more than 7 uses of the device and who completed the initial questionnaire (18 profile questions) participated in this study from October 2019 to July 2021. Sleep quality was measured on a scale of 1 to 5 before the first use of Moona and after each night of use. The proprietary algorithm that detects sleep/wake states per 30-sec epochs has been used to calculate the time spent asleep across the 12 first uses for each user. A total of 548 overweight/obese patients have been included in this analysis.

A survey has been proposed to Moona users in June and July 2021. A total of 45 answers of overweight/obese patients have been collected, and 10 of them reported having been diagnosed with sleep apnea. Improvement since first use of Moona has been assessed on a 5-point scale (from 'much better' to 'much worse').

Statistical analyses have been performed on Python 3.7. Mean comparisons have been accessed by student t-test with a significance level at  $p<0.05$ .

**Results:** The average age of respondents is 46 years [Q1 - Q3: 38 - 54], with an average BMI of 34 kg/m<sup>2</sup> and 79% are male. A total of 90% have reported feeling hot during the night daily or several times a week.

The sleep quality reported by overweight/obese users significantly increased with the use of the Moona device (without use: 2.6/5, average over the last seven uses: 3.7/5, t-test,  $p < 0.001$ ).

The sleep quality increased linearly over the first ten uses of the device, from 3.4/5 to 3.7/5 ( $R^2 = 0.94$ ).

Overweight/obese users have had a significant gain of 26 minutes of sleep, from 389 minutes on the first night to 415 minutes on the twelfth (t-test,  $p < 0.001$ ).

The use of the active cooling pillow pad has been shown to improve sleep apnea: 6 out of 10 overweight/obese patients with sleep apnea reported an improvement since using Moona.

**Conclusions:** The present study findings showed that an active thermoregulated pillow like Moona enhanced sleep quality, increased total sleep time in overweight/obese patients and improved reported sleep apnea

symptoms. Moona acts as a non-pharmacological and safe solution that can decrease health problems arising from poor sleep and can improve quality of life in that demographic.

**Acknowledgements:** We acknowledge all users that have contributed to this study.

### INVESTIGATING THE USE OF A WRIST-SENSOR OXIMETER FOR SCREENING OF OBSTRUCTIVE SLEEP APNEA

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**Introduction:** Oximetry has been used as a screening tool for Obstructive Sleep Apnoea (OSA) since at least 1991 and although polysomnography (PSG) remains the gold standard for diagnosing OSA, because of its time and costs, pre-screening is a valuable tool in large populations to determine which patients could benefit from further study. Overnight oximetry has been found to provide satisfactory diagnostic performance in screening for moderate and severe OSA, and when compared to questionnaire alone. However, patient reports of discomfort from finger-based oximetry are common, and loss of signal from sensor during the night also occur, and so an alternative way to measure desaturation was sought. This study tested the hypothesis that wrist-based oximetry was able to perform as well as finger-based oximetry in detecting desaturation events. We suggest a screening protocol based on suspected OSA symptoms from UK NICE guidance on Obstructive Sleep Apnoea Syndrome, Nov 2021 and a 3% ODI of five or more.

**Materials and Methods:** Diagnostic tests were performed on a consecutive series of 10 patients who presented at the London Sleep Centre for investigation into potential OSA. Participants wore the Oxitone device on their wrist, at the same time as undergoing a standard Home Sleep Apnoea Test (Philips Alice Night One) scored by a skilled physiologist as part of their routine care. Desaturation indices of both 3% and 4% were compared between both the wrist-based oximeter and fingertip-based oximetry. Patients provided feedback on comfort sleeping with the wrist sensor device as expressed on a Likert scale.

**Results:** We found a strong Spearman correlation of 0.75 ( $p<0.001$ ); the limits of agreement with the Bland-Altman test were <10 and the two-tailed Mann-Whitney U test showed no significant difference between the indices from the two devices ( $p>0.05$ ). There were no reports of patient discomfort with the screening process.

**Conclusions:** These results indicate that wrist-sensor oximetry may be used instead of finger-based oximetry in screening for OSA. A screening protocol for OSA is suggested in populations without significant cardio-respiratory or neurological disease, no severe insomnia and no significant side-effects medication. A suitable application in occupational health is to screen for OSA in vocational drivers or safety critical worker populations. The protocol is based on a symptom questionnaire of suspected OSA (UK NICE guidance on Obstructive Sleep Apnoea Syndrome, Nov 2021) and a 3% ODI of 5 or more. Cases with negative oximetry and negative symptom questionnaire responses would not require referral to a sleep center for an OSA diagnostic assessment. Cases still require referral to a sleep center for an OSA diagnostic assessment if only oximetry, or only the OSA symptom questionnaire are positive. Cases with positive OSA questionnaire responses, a 3% ODI of five or more and oximetry with a sawtooth appearance (manual affirmation), is highly specific for an OSA diagnosis. Individual sleep centres may initiate a trial of OSA therapy in such moderate to severe cases. The wrist sensor oximeter is likely to improve ease and patient compliance of future OSA screening programmes.

### LASER LINGUAL TONSILLECTOMY FOR OBSTRUCTIVE SLEEP APNEA: A FEASIBILITY STUDY

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**Introduction:** Obstructive sleep apnea (OSA) is characterized by frequent episodes of partial or complete upper airway collapse during sleep. The lingual tonsil, when hypertrophic can greatly contribute to airway obstruction during sleep. The lingual tonsil has been reduced in many ways previously including cold steel, cautery and coblation. Each of these methods is plagued by the risks of postoperative hemorrhage, severe postoperative pain, postoperative dysphagia and dysguesia. For this reason, historically the lingual tonsil has been a difficult area to address surgically in treating sleep apnea. The purpose of this study is to establish the utility and safety of the CO<sub>2</sub> laser for reduction of the lingual tonsil in the obstructive sleep apnea patient.

**Materials and Methods:** This is a retrospective cohort study including all patients who underwent CO<sub>2</sub> laser lingual tonsil reduction for obstructive sleep apnea during a two-year period at a tertiary care sleep center. The degree of preoperative and postoperative dysphagia was assessed subjectively using two surveys of dysphagia related complaints the Eating Assessment Tool (EAT-10) and the Reflux Symptom Index (RSI). Diet at the time of discharge and postoperative bleeding requiring return to the operating room were also assessed.

**Results:** 15 patients underwent CO<sub>2</sub> laser lingual tonsil reduction from April 2019 through April 2021. The cohort was 53% male, with an average age of 39.8 years. The patients were overweight with an average BMI of 28.3. The average preoperative ESS was 10.1, with an average preoperative AHI 28.3 and average preoperative SpO<sub>2</sub> nadir was 85.2%. On preoperative mueller maneuver the average degree of lingual tonsil hypertrophy was 2.6/4, and average degree of base of tongue collapse 3.1/4. The average preoperative EAT-10 was 3.6 and postoperative average EAT-10 was 3.75. The EAT-10 improved an average of 2.4 points postoperatively. The average RSI preoperatively was 10.8, and postoperatively 11. All patients went home on a regular diet. There were no incidents of postoperative bleeding.

**Conclusions:** The results of this feasibility study indicate that the use of CO<sub>2</sub> laser is a safe and effective method of lingual tonsil reduction in the patient with mild to moderate sleep apnea. Historically there has been major hesitation to address the lingual tonsil for the perceived risk of postoperative dysphagia development. The data presented here, indicating no significant change in EAT-10 or RSI scores demonstrates that CO<sub>2</sub> laser reduction of lingual tonsil does not have a negative impact on subjective swallow function. Moreover, the CO<sub>2</sub> laser reduction of lingual tonsil can safely be done in conjunction with other procedures for OSA including septoplasty, inferior turbinate reduction, tonsillectomy, adenoidectomy and uvulopalatopharyngoplasty. While safety as been established, the true efficacy of this procedure and comparison to other methods of lingual tonsil reduction remains to be determined in future studies.

#### MANUAL VERSUS COMPUTER-AIDED SCORING OF SLEEP STUDIES: PRELIMINARY RESULTS ON INTER-RATER AGREEMENT AND ANALYSIS OF SCORING TIME DIFFERENCES IN ONE SLEEP CENTER

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**Introduction:** The analysis of polysomnographic sleep recordings (PSGs) constitutes one of the most time-consuming tasks in the daily work of a sleep center. Moreover, manual PSG scoring is prone to errors and subjective interpretations. The use of (semi)automatic PSG scoring algorithms has the potential benefit of helping reducing the scoring time needed, as well as the inter-scorer variability levels, hence bringing down the associated testing costs and contributing to standardization and quality improvement in the diagnosis. However, comprehensive validations of these methods are lacking. The objective of this study is to objectively assess the differences in scoring time and inter-scorer repeatability in one sleep lab by comparing manual and computer-assisted scoring approaches

**Materials and Methods:** A total of 12 sleep technicians from the Haaglanden Medisch Centrum (HMC, The Hague, The Netherlands) were prompted to independently review the same 20 PSG recordings following the classical manual scoring approach. Blind analysis comprised separated scoring of the following subtasks: (i) sleep staging, (ii) identification of leg movements, (iii) analysis of the respiratory activity, and (iv) detection of

EEG arousals, each one amounting to 5 different recordings. Scoring was repeated with a minimum separation of 4 months, using a semi-automatic approach. In the semi-automatic setting the human expert would edit the pre-scored markings resulting from different automatic scoring algorithms. These algorithms were developed by engineers at HMC and integrated in the Polyman scoring software during the past years. For each task an automatic scoring timer was set in the background hidden to the scorer. The timer was sensitive scorer's actions automatically correcting for inactivity periods.

Analysis of inter-scorer agreement was carried out by discretizing the Time in Bed (TIB) periods into non-overlapping mini-epochs of 30s, for the sleep staging task, and of 0.5s for the remaining ones. Time discretization in the above terms resulted in the construction of *k*-dimensional contingency tables (*k*=5 for sleep staging, *k*=2 otherwise) from which standard metrics of agreement were derived. Cohen's kappa was used as reference metric for quantification of inter-scorer agreement. Hypothesis testing was carried out to check for significant differences in the scoring time between the manual and semi-automatic approaches.

**Results:** Overall inter-scorer kappa agreement between manual and semi-automatic approaches resulted respectively in 0.74(0.09) vs 0.79(0.06) for sleep staging, 0.71(0.10) vs 0.90(0.05) for limb movements, 0.58(0.21) vs 0.68(0.20) for respiratory events, and 0.57(0.12) vs 0.64(0.09) for EEG arousals. Respective differences in scoring time (in minutes) resulted in 40.77(28.50) vs 33.85(31.08) for sleep staging, 49.74(24.50) vs 22.62(16.25) for limb movements, 33.69(23.98) vs 18.92(14.08) for respiratory events, and 32.41(16.46) vs 27.61(20.47) for EEG arousals. All differences were statistically significant (Wilcoxon signed rank-test, *p* < 0.001).

**Conclusions:** Higher inter-scorer agreement and decreased scoring time was achieved using semi-automatic scoring. The trend was consistent but effect sizes varied per scoring subtask. Gain factors in scoring time ranged from 1.17 (EEG arousals) up to 2.20 (Limb movements).

**Acknowledgements:** Study initiated at HMC (2019-073). Dissemination of results funded under project ED431H 2020/10 of Xunta de Galicia.

#### NON-INVASIVE SLEEP-MEASURING DEVICES FOR THE PREVENTION OF ALZHEIMER'S DISEASE: A SYSTEMATIC REVIEW OF VALIDITY STUDIES

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**Introduction:** Changes in sleep during mid-to-late life are associated with increased risk for Alzheimer's disease (AD). To better understand this association, measurement tools are needed that can accurately measure these changes longitudinally.

**Materials and Methods:** We conducted a systematic review, with meta-analysis, of validity studies of non-invasive sleep-measuring devices published since 2015 that record sleep metrics associated with AD in cognitively healthy adults over 40 (mean 54.8, range 42-68 years). These metrics included the apnoea hypopnoea index (AHI), slow wave sleep (SWS) duration and slow wave activity, total sleep time (TST), sleep efficiency (SE), and rapid eye movement (REM) duration. We reviewed 51 studies, including 28 wearable and 11 non-wearable devices that operated open- and closed-access algorithms. All devices were validated against polysomnography (minimum one night).

**Results:** Measurement of AHI score was generally excellent across a range of devices. 83% of devices overestimated TST and SE. Those that performed better relied on custom algorithms and parameters, individualising classification using time series models to bring in insight from surrounding epochs. Devices generally showed moderate and poor measurement

accuracy for REM and SWS, respectively. A frontopolar electroencephalograph headband device measured REM and SWS more accurately than other devices when all three frontal channels were used, but excluded 10–13% of participant data due to poor signal quality. Other than the headband, there was no clear pattern for one device type being more accurate than others at sleep staging – e.g. location, number of sensors, or algorithm used. Only one study assessed device accuracy for slow wave or spindle activity.

Studies did not consistently report the same metrics using the same definitions. For example, mean difference was reported on 78% of macro-architectural sleep comparisons but standard deviation was often missing, and direction of difference was inconsistently reported (e.g. a positive number could mean the device had over- or under-estimated). Key accuracy metrics like sensitivity and specificity were reported in less than 10% of comparisons.

Risk of bias across studies was high, driven by use of closed-access algorithms and classification thresholds.

**Conclusions:** We identify a range of devices that could be utilised in future studies of sleep and AD risk. We discuss some of the limitations of available research and make recommendations on improvements, like metric reporting and open data access.

**Acknowledgements:** None

### PLATFORM-BASED STREAMLINING OF RESEARCH ON DIVERSIFIED SLEEP DATA

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**Introduction:** An interpretable, structured overview for visualizing vast amounts of data is beneficial for a comprehensive overview of the gathered data. In the Sleep Revolution project, we are working towards accumulating numerous data sources from sleep studies from over 40,000 participants, aiming to incorporate all available data sources into a single research platform. The main challenges to represent the data are: i) Unifying multiple data sources; ii) Making the representation a personalized and valuable tool for researchers, and; iii) To make the platform adaptable to the different researchers' needs. Research on platforms and architecture for adequate representation and visualization of large amounts of diverse data is needed, leading to the following research questions: i) How can we design and develop a system to visualize sleep-related data? ii) How can we create an adaptable, extendable, and multipurpose architecture within a platform context, using layered architecture?

**Materials and Methods:** The research method was Action Design Research, realized through iterations of the platform design and, the following tests were conducted: i) Scalability tests for reading and filtering the data; ii) Usability tests; iii) user experience tests and; iv) semi-structured interviews.

**Results:** Although platforms like these are frequently used in industry, there is a gap in the literature regarding the design and development of platforms for extracting and filtering data in research contexts. Here, attempts and prior work either lack the variety, veracity, or volume of data, and the ethical boundaries of the research context are missing from the architectural choices. We designed and developed a research platform using layered architecture design and developed an extraction system for the data. Choosing this architecture design resulted in a more reusable system that is adaptable to changes, alternative data sources, and extensions. The main preliminary findings are three-fold: i) the designed layered architecture; ii) the extraction and display system, and; iii) a set of design principles to guide others working on a project with similar traits.

**Conclusions:** Our preliminary findings are a promising start for streamlining research on diversified sleep data through the design and development of layered architecture for displaying and filtering the extracted data. However, the research platform needs further work and extensive testing to fully utilize the value and usability of the platform in more depth.

**Acknowledgements:** This research was carried out as a part of the Sleep Revolution project, which has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement no. 965417.

### POLYSOMNOGRAPHIC VALIDATION OF AN UNDER-MATRESS MONITORING DEVICE IN ESTIMATING SLEEP ARCHITECTURE AND OBSTRUCTIVE SLEEP APNEA IN ADULTS

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**Introduction:** Rapid advances in technology have led to unprecedented changes in every aspect of our lives. Various user-friendly devices and apps have been developed for self-tracking and assessment of individuals' fitness, sleep, and health. Consumer home devices have gained rising popularity among the general population for sleep monitoring. These devices are accessible, easy-to-use, non-obtrusive, and available for longitudinal monitoring. Yet, most currently available home sleep monitoring devices lack validation. The objective of this study was to evaluate the validity of an under-mattress monitoring device (Fullpower Technologies) in estimating sleep continuity and architecture, as well as estimating obstructive sleep apnea in an adult population.

**Materials and Methods:** Adult volunteers (n=102, 55% male and 45% female, aged 40.6 ± 13.7 years with a mean body mass index of 26.8 ± 5.8 kg/m<sup>2</sup>) each participated in a one-night unattended in-lab study conducted by Fullpower Technologies. Each participant slept on a queen-sized bed with Sleeptracker Monitor sensors placed underneath the mattress. Standard polysomnography (PSG) was simultaneously recorded on the same night. Researchers (FD and CK) were provided deidentified sleep studies and datasets by Fullpower for analysis. Sleep continuity measures, 30-second epoch-by-epoch sleep stages, and apnea and hypopnea events estimated by an automated algorithm from the Sleeptracker Monitor were compared with the PSG recordings, with the PSG recordings serving as the reference.

**Results:** Overall, the Sleeptracker Monitor estimated similar sleep continuity measures compared with PSG. The Sleeptracker Monitor overestimated total sleep time (TST) by an average of 6.3 minutes, and underestimated wake after sleep onset (WASO) by 10.2 minutes. Sleep efficiency (SE) was similar between the Sleeptracker Monitor and PSG (87.6% and 86.3%, respectively). The epoch-by-epoch accuracy of Sleeptracker Monitor to distinguish 4-stage sleep (wake, light, deep, and REM sleep) was 79.0% (95% CI: 77.8%, 80.2%) with a Cohen's kappa of 0.676 (95% CI: 0.656, 0.697). Thirty-five participants (34.3%) were diagnosed with obstructive sleep apnea (OSA) with an apnea-hypopnea index (AHI) ≥ 5 based on PSG. Accuracy, sensitivity, and specificity for the Sleeptracker Monitor to estimate OSA (an AHI ≥ 5) were 87.3% (95% CI: 80.8%, 93.7%), 85.7% (95% CI: 74.1%, 97.3%), and 88.1% (95% CI: 80.3%, 95.8%) respectively. The positive likelihood ratio (LR+) for AHI ≥ 5 was 7.18 (95% CI: 3.69, 14.0) and the negative likelihood ratio (LR-) for AHI ≥ 5 was 0.162 (95% CI: 0.072, 0.368).

**Conclusions:** The Sleeptracker Monitor had high accuracy, sensitivity, and specificity in estimating sleep continuity measures and sleep architecture, as well as estimating apnea and hypopnea events. These findings indicate that Sleeptracker Monitor is a valid device to monitor sleep quantity and quality among adults. Sleeptracker Monitor may also be a reliable complementary tool to PSG for OSA screening in clinical practice.

**Notes:** Andrew Cotton-Clay is co-first author.

### PUTATIVE METABOLIC MARKERS IN SLEEP DEPRIVED ADULTS: RESULTS FROM A SYSTEMATIC REVIEW

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**Introduction:** The circadian timing system (CTS) is responsible for regulating biological and physiological processes within the human body in a temporal fashion. As a challenging homeostatic and circadian behavior,

sleep takes part in about 1/3 of human life in healthy humans, and inadequate sleep negatively impact health and well-being. Metabolomics is configured as the study of metabolites and has the potential to characterize phenotypes associated with alterations in human homeostasis. Given the relationship between sleep deprivation and metabolites, finding metabolic markers of sleep deprivation would be rather important for research proposals or clinical practice.

**Material and methods:** A systematic review was conducted using MEDLINE/PubMed, Virtual Health Library (VHL), and Cochrane Library electronic databases. Studies with a population aged 18 years or older, diagnosed with sleep deprivation, submitted to metabolomics studies, and underwent polysomnography, sleep diary, Munich Questionnaire or actigraphy were included. Studies involving associated comorbidities, animals, and those with undefined methodology were excluded. The authors read titles, abstracts, and full texts independently using the pre-defined eligibility criteria, and discrepancies were discussed. For methodological quality assessment, the STROBE Initiative was used. The project protocol was submitted to the International Prospective Register of Systematic Reviews (PROSPERO) under the registration CRD42021221560.

**Results:** A total of 556 studies were found, of which 5 were selected for the review after applying the eligibility criteria. The research was conducted between 2014 and 2020, totaling 148 patients. The participants presented a diagnosis of sleep deprivation based on the response of validated questionnaires. As for the analysis of metabolites, in three of the five studies, blood samples were used; in one study, the analysis consisted of urine samples, and in the other study, the samples analyzed were both blood and urine. None of the studies analyzed saliva samples. The metabolites evaluated in the studies were acylcarnitines, amino acids, biogenic amine, glycerophospholipids, sphingolipids, lysophospholipids, organic acids, phosphatidylcholine, lysophosphatidylcholine, tryptophans, citrulline, glutamate, phosphatidylcholine, creatinine, hexoses, serotonin, and taurine.

**Conclusion:** This systematic review allowed us to define metabolic markers potentially associated with sleep deprivation, of which the main ones are acylcarnitines, amino acids, and sphingolipids. Future studies should focus on the interaction of these metabolites with phenotypic aspects associated with anthropometric parameters, as well as with micro and macrostructural aspects of sleep, which may have an eventual impact on the discriminatory sensitivity of metabolomics in these patients.

## REAL-TIME IMPLEMENTATION OF SLEEP STAGING USING INTERBEAT INTERVALS

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**Introduction:** Cardiac activity changes rapidly during sleep, enabling real-time sleep staging. Algorithms developed for sleep staging utilizing cardiac metrics have a range in performance as assessed by Cohen's Kappa and accuracy. These algorithms typically include numerous parameters or utilize entire sleep sessions for classification and are not suitable for real-time interventions. In this study, we developed a small deep neural network (DNN) algorithm to detect sleep stages using interbeat intervals (IBIs) extracted from electrocardiogram signals collected during polysomnography. This DNN algorithm is up to three orders of magnitude smaller compared with other DNN algorithms, utilizes signals which can be extracted from multiple types of cardiac measurements (including non-contact ones), and may be able to perform real-time sleep staging.

**Materials and Methods:** Electrocardiogram data from healthy sleepers and participants with sleep apnea were used for algorithm training and validation. Two additional datasets including healthy participants and participants with sleep disorders were used for algorithm testing (>1000 sleep sessions total). R-peak detection was applied to determine IBIs before resampling at 2 Hz and high-pass filtering. The resulting IBI signal was segmented into 150-second windows with 120-second overlap for input into a DNN composed of convolutional and recurrent layers. DNN output approximated the probabilities of a window belonging to light, deep, REM, or wake stages. Performance metrics included Cohen's Kappa coefficient, accuracy, and sensitivity/specificity per stage. Kappa was optimized using thresholds determined by probability ratios for each stage versus light sleep.

**Results:** Mean (SD) Kappa and accuracy for four stages in healthy participants were 0.44 (0.09) and 0.65 (0.07), respectively, with moderate sensitivity (0.46 [0.33], 0.67 [0.26]) and high specificity (0.94 [0.06], 0.90 [0.06]) for deep sleep and REM, respectively. For three stages (non-REM, REM, and wake), mean (SD) Kappa and accuracy were 0.52 (0.12) and 0.76 (0.07), respectively. Mean (SD) sensitivity for non-REM and REM was 0.86 (0.10) and 0.67 (0.26) respectively; mean (SD) specificity was 0.69 (0.15) and 0.90 (0.06) for non-REM and REM, respectively. The IBI signal spectrum revealed differences between healthy participants and those with sleep disorders, which may explain the lower DNN performance on participants with sleep disorders. Additionally, analysis of spectral DNN response showed convolutional layers were sensitive to spectral information. However, our probability ratio optimization method improved the performance deficit of the DNN by 22–57% by adjusting thresholds depending on the sleep disorder.

**Conclusions:** High specificity and moderate sensitivity for deep and REM sleep, small algorithm footprint and causal processing suggest that this algorithm could be generalized across different platforms and sources of cardiac signals to perform real-time sleep staging, and potentially direct intervention strategies during REM or deep sleep.

**Acknowledgements:** The authors thank the Computational Clinical Neurophysiology Laboratory and the Clinical Data Animation Laboratory, Massachusetts General Hospital, Boston, MA, USA, and the Sleep Disorders Center, Ospedale Maggiore, Parma, Italy, for making their datasets publicly available through PhysioNet. Medical writing support provided by Rachel C Brown, PhD, Oxford PharmaGenesis Inc, Newtown, PA, USA, and funded by Sleep Number Corporation.

## ROUND TRIP WITHOUT SLEEP – AN INFORMATION SYSTEM FOR PREDICTING SLEEP WHILE DRIVING AND DETECTING DISORDER OR CHRONIC SLEEP DEPRIVATION

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**Introduction:** Drowsiness at the wheel is one of the main factors for road accidents, due to the lack of alertness and the unconscious transition from wakefulness to sleep. Contrary to current detection systems, which are based mainly on evaluation of the driver's behaviour and only able to detect a sleep event when it already occurs, predicting drowsiness and preventing drivers before they exhibit any symptoms is key to anticipate this and provide a timed alert. Conversely, recent advances in mobile and wearable technology focused on health, with proven quality and accuracy, provides great potential for its application to the problem at hand. Hence, the aim of this project is to investigate and develop a non-intrusive and low-cost integrated preventive system that monitors, diagnosis and evaluates, in continuous and real time, drowsiness at the wheel and sleep disturbances, alerting the driver before they even exhibit any signs of sleepiness.

**Materials and Methods:** On a first stage, the goal is to create individual patterns - baseline and driving - that will be the basis for the low vigilance level alert system. A wrist worn device will be used to measure Heart Rate and Heart Rate Variability (HRV), fundamental to determine individual biometric features and driving patterns through classification algorithms. For baseline pattern definition, participants will answer four questionnaires to assess different sleep parameters: Pittsburgh Sleep Quality Index (PSQI), to determine sleep quality; Epworth Sleepiness Scale (ESS), to measure daily sleepiness; Mornigness-Eveningness, to determine circadian rhythm; STOP-Bang, to screen for obstructive sleep apnea (OSA). Furthermore, participants will also respond to a receptiveness questionnaire, to understand the level of usability of the system and its acceptability by the users, and recommended improvements. This stage will allow the classification of the driver, the definition of his basal state and the prediction of sleepiness. On a further stage, these patterns will be used for comparison with the pattern produced during the continuous driving monitoring phase, where in the case of a significant difference, an alert is issued to the driver.

**Results:** A sample data of several drivers that work in a passenger transport company will be used for assessment. Questionnaire responses were already collected and assessed, with sleep disorders and circadian rhythms results obtained for each driver. For the data collection phase, a mobile application was developed that gathers information continuously from the wearable device and makes it available to the user.

**Conclusions:** The work is in progress and for now there is a system that collects biometric data, gives feedback in real time to drivers, allows responses to questionnaires and assessment of their circadian rhythm and quality of sleep. Collaboration between the develop team and the final users was fundamental for improvements on the proposed system. Future work encompasses data collection and analysis in order to establish the patterns needed to create the alert system.

**Acknowledgements:** This study was supported by the NORTE-01-0247-FEDER-039720 program.

### SELECTIVE SLOW-WAVE SLEEP SUPPRESSION THROUGH AUDITORY CLOSED-LOOP STIMULATION

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**Introduction:** While therapeutic sleep deprivation has been shown since the 1960s to exert a strong and rapid antidepressant effect on individuals with major depressive disorder, it is also burdensome for the patients, with limited benefits due to frequent relapse after subsequent nighttime sleep. Selective suppression of slow wave sleep (SWS), potentially through modifications of synaptic plasticity, may represent an effective and more sustainable alternative, while being significantly less stressful for the patient. The purpose of this project was to develop and evaluate a fully automatized selective suppression protocol of SWS based on closed-loop auditory stimulation in a healthy population, which would allow for broader clinical implementation without the need for online supervision.

**Materials and Methods:** A new automatized SWS suppression approach was developed and evaluated in a healthy, young population (N = 15). Participants underwent a repeated measures design consisting of three sleep laboratory nights; one adaptation night and two experimental nights (auditory stimulation and sham in counterbalanced order). Stimulation was applied upon detection of SWS, until SWS was no longer detected. The SWS detection protocol relied on a topographical template of slow waves. Stimulation consisted of discrete bursts of pink noise with a randomized duration (50–500 ms) and inter-onset interval (1–4 s). A random walk (+2.5 dB, Ornstein-Uhlenbeck process) was superimposed on the linear increase of volume (40–106 dB in 60 s) to add unpredictability in volume.

**Results:** The stimulation protocol led to a significant reduction of SWS (-39.19%;  $p < 0.01$ ), with an associated increase in sleep stage N2 (+10.94%;  $p < 0.001$ ), and a decrease in REM sleep (-10.76%;  $p = 0.03$ ) as compared to sham. No other significant changes in sleep continuity or architecture were observed. Slow wave activity averaged across the night and cumulative slow wave energy at the end of the night were both significantly reduced by about 30% across channels and individuals ( $p < 0.05$ ), without changes in other frequency bands, and with changes specific to N3 sleep.

**Conclusions:** We demonstrate, to our knowledge for the first time, that a fully automatized approach can suppress SWS. Future studies are needed to investigate potential functional consequences such as changes to synaptic plasticity and depressive symptomatology in patients with major depressive disorder. Further developments bear the potential for translation to broader and even ambulatory use of automated SWS detection and modulation, and potentially for new treatment developments for major depression.

**Acknowledgements:** The project was funded through the Interfaculty Research Cooperation (IRC) 'Decoding sleep: from neurons to health and mind', University of Bern.

### SLEEP AND COVID-19. A CASE REPORT OF A MILD COVID-19 PATIENT MONITORED BY CONSUMER-TARGETED SLEEP WEARABLES

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**Introduction:** COVID-19 is a potentially severe respiratory infection caused by the SARS-CoV-2 virus, first identified in Wuhan, China in December 2019. The DNA sequence was rapidly made public and numerous research studies have followed. SARS-CoV-2 is mainly transmitted by droplets and aerosols from asymptomatic and symptomatic infected subjects. The consensus estimate for the basis reproduction number (R0) ranges between 2 and 3, and the median incubation period is 5.7 (range 2–14) days. The pandemic remains active to this day with a worldwide death toll of over 5,012,337 [1]. While most cases are mild, 5–10% of patients are hospitalized, mainly due to pneumonia with severe inflammation or acute respiratory distress syndrome. Complications are respiratory and multiorgan failure; risk factors for complicated disease are higher age, hypertension, diabetes, chronic cardiovascular, chronic pulmonary disease, and immunodeficiency. The current estimate for the infection's fatality rate is 0.5–1%, and the prediction of severe forms of the disease is still a challenge for the physician [2].

The SARS-CoV-2 pandemic has been marked by the development of the use of ambulatory medical devices and nonmedical wearables for the monitoring of patients in ambulatory settings. While the diffusion of these technologies has great potential for the production of health-related information, it is important to evaluate the way the data can be used in the medical decision-making process [3].

In this paper the evolution of SARS-CoV-2-related sleep disorders and physiological parameters are examined in a SARS-CoV-2 infected patient who was routinely wearing three consumer sleep wearables before the onset of the disease and kept them throughout disease and recovery.

**Objective Sleep Data Assessment:** The patient voluntarily recorded his sleep and wake rhythms via three consumer sleep wearables (CSW): Oura ring Gen 2 (Oura) [4], Fitbit Versa 2 (Fitbit now part of Google) [5], and iSleep Watch for AppleWatch (iSommeil) [6]. FitBit Versa 2 watch and iSleep Watch were worn alternatively on the nondominant wrist for 55 days. Oura ring was worn in real life continuously on the nondominant finger for 55 days. Those three CSW (Table 1) had heart rate sensors and 3 axis-accelerometers to estimate sleep duration (TST), WASO. Additionally, the Fitbit Versa 2 watch recorded respiratory rate, and the Oura ring recorded skin temperature and respiratory rate.

Physiological data were recorded as per the following protocol: (1) the Oura Ring was worn continuously; (2) the Apple Watch and the FitBit Versa 2 were worn in an alternating manner, 12 h each.

**Results:** The mean breathing rate, heart rate, and body temperature increased significantly during the infection (Figure 1) as previously described [7].

**Conclusions:** This case report highlights the clinical importance of sleep evaluation in COVID-19 patients and how early intervention and management of sleep disorders in the broader population may be recommended to prevent potential sleep-induced frailty in the event of an acute infectious event.

In addition, we suggest wearables could be used for early detection of infection and remote monitoring, allowing patients to report their vital signs from home.

### SLEEP REACTIVITY TO ANTICIPATORY ANXIETY: PRELIMINARY RESULTS FROM A HOME-EEG SLEEP MONITORING AND VIRTUAL REALITY STUDY

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**Introduction:** Sleep reactivity can be defined as the tendency to exhibit sleep disturbance following stress exposure. In this context, anticipatory anxiety (i.e. fear and worry before an upcoming stressful such as giving a

presentation at university) might significantly impact sleep structure. Our aim is to investigate how university stressful events impact on sleep, exposing subjects to virtual reality in order not only to induce anticipatory anxiety but also to function as desensitization.

**Materials and Methods:** 18 Master of Science students (mean age=23.67±1.54; 16 females) completed questionnaires assessing, anxiety, depression, insomnia symptoms, sleepiness, circadian rhythm and stress perceived at the baseline. In addition, they were assessed with a validated home-EEG device for sleep monitoring (Sleep Profiler) over four consecutive nights. In order to simulate a university stressor, the whole sample was instructed to perform an online presentation of a scientific article at the end of the study, the first night was used as the adaptation night, the second as baseline, and the fourth as outcome. Participants were randomly assigned to an experimental group (VR), where they have been invited to rehearse at home their presentation in a virtual environment that replicates final exposition, or to a control group (CG). Before the final presentation, subjects' anxiety was evaluated.

**Results:** No difference was found in terms of age and gender frequencies between control and experimental group. A significant increase in state-anxiety was observed in the whole sample comparing baseline to end-of-experiment ( $p<0.001$ ), with no effect of condition.

Stage 2 Non-REM sleep percentage (N2) showed a significant interaction between time and condition ( $p<0.05$ ). Subjects in the experimental condition showed a decreased N2 in the fourth night, in comparison to control group. Percentages of sub-stage labeled as Light N2 (N2 epochs with no spindles), in night 4, revealed a non-significant difference between two groups, on the other hand, showing an increased average in the control group (VR=7.8±4.3; CG=10.74±6.5). In addition, the delta of Non-REM stage 3 percentage (N3) between night 2 and 4 revealed a non-significant difference between two groups, showing an increase in VR group and a decrease in CG (VR=3.17±2.9; CG=-5.43±3.21).

**Conclusions:** Our results showed sleep reactivity differences between subjects exposed to VR and the control group. Literature suggested that behavioral exposition (desensitization) could ameliorate anticipatory anxiety to a stressor; moreover, virtual reality could support this aim. Our preliminary results suggest a sleep role in the effect of VR exposure condition on anticipatory anxiety in university stressors. The decrease of N2 in our experimental group should indicate an attempt of sleep synchronization in order to restore the organism and consolidate memories. This view might be supported by specific Light-N2 sleep, in favor of an increase of Slow Wave Sleep and possibly of sleep spindle density in our experimental sample.

**Acknowledgements:**

#### SLEEP TELEMEDICINE IN GERMANY: A DEVELOPED MODEL

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Telemedicine has advanced and grown enormously during the last 10 years. Due to the Sars-CoV2 pandemia the pace of digitalizing diagnostics and therapy in the field of sleep medicine has accelerated. In Germany the main fields of sleep telemedicine are the group of sleep disordered breathing and the group of insomnias. Although there are several initiatives which aim an inventing digital sleep technologies as telemedical recording of relevant data for the diagnostics of obstructive apnea syndrome or digital applications for the treatment of insomnia coordinated approaches are being developed.

The German Sleep Society aims on coordinating all initiatives with several approaches. Here the main focus is the standard which a needed for quality aspects. Another aspect is to transform the German health system, which is divided into the public and the private health insurance system, into a more flexible and digital friendly one accepting that sleep medicine is one of the best example to implement digital techniques for telemedicine.

The German state of the art in the field of sleep telemedicine will be reflected to open the chance for other countries to have a deeper insight in the challenges and shortcomings for implementing sleep telemedicine in a highly sophisticated health care system.

#### SOCIAL MEDIA AT NIGHT AND SLEEP QUALITY : THE RELEVANCE OF FOMO, COGNITIVE PRE-SLEEP AROUSAL AND MALADAPTIVE COGNITIVE EMOTION REGULATION

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**Introduction:** Several studies show that nighttime social media use negatively impacts sleep quality. Research has also shown that this use can be associated with the avoidance of aversive psychological states that promote cognitive pre-sleep arousal, such as Fear of Missing Out (FoMO). The use of social media to cope with other aversive cognitive states, their relationship with FoMO, and its impact on sleep are yet to be fully understood. This study aimed to explore the relationship between nighttime social media use, sleep quality, FoMO, cognitive pre-sleep arousal, and maladaptive cognitive emotion regulation (i.e. rumination, worry), while considering the impact these regulatory cognitive processes can have on the use of social media at night and sleep, at a behavioral and cognitive level (Scott & Woods, 2018), and the potential use of social media as a sleep aid.

**Methods:** Participants were 525 university students (84.2% women and 15.8% men), whose age ranged from 18 to 64 years old ( $M = 22.39$ ,  $SD = 5.62$ ). Most of them were full-time students (82.7%) from undergraduate (44.4%) and Master's degree (52,9%) courses. Measures of sleep quality, morningness/eveningness, cognitive pre-sleep arousal, worry, rumination, FoMO, nighttime screen, and social media use were obtained through student's responses to several self-report questionnaires, either online (through social media) or in pencil-paper format. Descriptive statistics (e.g., frequencies, mean, standard deviation) were used to characterize participants' demographics and patterns of nighttime social media use. Pearson correlation analyses were conducted to test the associations between variables of interest. This exploratory analysis also allowed for the selection of potentially relevant predictors for each outcome variable to conduct subsequent multiple regression analyses. Considering significantly associated variables, multiple linear regression was used to determine the most relevant predictors of cognitive pre-sleep arousal. Additionally, and to examine the unique contribution of variables of interest (e.g., FoMO, worry, rumination) in the prediction of nighttime social media use and sleep quality, after adjusting for the effect of other predictors, hierarchical multiple regression analyses were performed.

**Results:** In terms of nighttime social media use, 82.1% of students accessed social media two hours before going to sleep, 62.1% used social media while in bed and 29.7% engaged in social media, in bed, while trying to fall asleep. Lastly, 18.3% of students reported taking longer to fall asleep due to their nighttime social media use. Nighttime social media and FoMO were associated with cognitive pre-sleep arousal, rumination, and worry ( $p < .001$ ). FoMO and worry predicted higher levels of cognitive pre-sleep arousal and independently predicted higher levels of nighttime social media use. Nighttime social media use independently predicted poor sleep quality.

**Conclusions:** These results suggest that worry and FoMO can potentially impact sleep quality by promoting higher social media usage and by increasing cognitive pre-sleep arousal and that social media at night might be used as a strategy to cope with these aversive cognitive states. These conclusions can contribute to improving sleep intervention in this population.

**Keywords:** Sleep, Social media, Maladaptive cognitive emotion regulation, Worry, FoMO

#### TELEMEDICINE IN THE MANAGEMENT OF SLEEP RESPIRATORY DISORDERS

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**Introduction:** OSA(S) [Obstructive Sleep Apnoea (Syndrome)] is counted by the World Health Organization (WHO) among the chronic diseases, which affect about 80% of people over 65 years of age and it's often associated with other chronic pathologies in the same individual. It is a markedly underdiagnosed and undertreated pathology (only 40% of patients are diagnosed), a criticality that leads to an underestimation of the real prevalence of the pathology.

However, the costs of the OSA are substantial and are represented by direct healthcare costs (60% of total costs), indirect costs, related to morbidity (36%) and direct non-health costs (4%).

The ongoing evolution of the demographic dynamic, as well as the large number of patients affected by OSAS, make it necessary to make a structural and organizational change in the network of care services.

The possibility of carrying out diagnostic tests remotely and a continuous monitoring of the patient's adherence to treatment, through Telemedicine, allow on the one hand an immediate and effective corrective response to the onset of any clinical and technical problems and, on the other, a reduction in the inappropriate accesses of patients to the Sleep Centers. This paper describe a new service dedicated to patients suffering from respiratory disorders in sleep, in home ventilation therapy, with the possibility of creating a multidisciplinary Teleconsultation network, involving both specialists operating in local structures and general practitioners, and a "care network" dedicated to these patients.

**Materials and Methods:** At the base of this service there is an operations center that is based on the use of two software applications: a tele-monitoring platform (able to communicate with different types of ventilatory prosthesis at home) and a Electronic Health Record, through which it is possible to carry out televisits.

Using the telemonitoring platform, the Sleep Center can remotely acquire and analyze patient therapy and compliance data. The Electronic Health Record collects the clinical data and supports the televisits (using a Tablet operating with Wi-Fi mode or SIM card) with patients already diagnosed and in ventilatory treatment at home.

**Results:** The systems allow the sharing of data between users of the same Account or between different users and contact points (Hospital, Territorial Clinic, Medical Office), allowing the creation of a multidisciplinary network of care, involving several actors (Hospital and Territorial Specialists, General Practitioners).

The information system complies with compliance requirements and privacy regulations at European level.

**Conclusions:** Telemedicine reveals the opportunity to place the patient at the center of the care path, through a more frequent and careful monitoring of the treatment.

The possibility of creating a hospital-territory care network enhances the multidisciplinary management of the disease and teamwork.

## THE CLINICAL SUCCESS OF 213 SELF-APPLIED TYPE 2 SLEEP STUDIES

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**Introduction:** Wait times for the gold standard Type 1 polysomnograms are lengthy, and the pandemic has only increased the backlog. The need for having home sleep testing (HST) has grown, yet home sleep apnea tests can be inaccurate despite their popularity. Type 2 sleep studies incorporate more clinical data to aid in diagnosis by including measures of EEG. In this study, we assessed the reliability of self-applied Type 2 sleep recordings with the Cerebra Sleep System and the clinical significance of signal failures.

**Materials and Methods:** 213 sleep files were collected from 191 participants that had their Type 2 device shipped to their home with no prior training. Participants watched videos and read written instructions to self-apply the full Type 2 system. The lab-quality in-home PSG included a recording of EEG (Fp1, Fp2), EOG (E1, E2), EMG (chin), EMG (legs), respiratory channels (one effort or two RIP belts), nasal flow, and pulse oximetry. The study was considered successful if the head unit (EEG/EOG/EMG), Leg EMGs, nasal flow and oximetry were present for the time frame of 3 and 4 hours. Studies deemed unsuccessful were then reviewed by a

registered polysomnographic technologist to determine the interpretability of those studies.

**Results:** Based on a 4-hour success criterion, 82.6% of studies were considered successful. Of the unsuccessful 4-hour criterion studies, 56.8% (n = 21) had failures of only 1 out of 5 signals. When all failed studies were further reviewed, 18 studies (48.6% of failed studies) met sufficient criteria to score for clinical purposes. For example, some studies were missing one EEG or one leg channel, so the alternate channel was able to be used. For diagnostic purposes, the rate of success increased from 82.6% to 91% with alternate channels being used. An additional 6 recordings (3%) would still qualify as a Type 3 study bringing the success rate to nearly 94%.

**Conclusions:** We found that the Cerebra Sleep System Type 2 in-home test showed reliable performance with a high success rate. When studies did fail, in most cases, a single signal was the source of the problem. During some of those studies, scoring confidence could be achieved due to redundant signal integrity where often clinical diagnosis could still be made. For patients suspected of sleep disorders, Type 2 was a reliable and convenient mode of testing that can be scalable and reduce the backlog for in-lab polysomnography.

## THE EFFECTS OF A SLEEP ROBOT INTERVENTION ON SLEEP, DEPRESSION AND ANXIETY IN ADULTS WITH INSOMNIA – A RANDOMIZED WAITLIST-CONTROLLED TRIAL

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**Introduction:** Insomnia is one of the most common sleep disorders in adults. The hyperarousal model of insomnia emphasizes heightened arousal as an important causal and maintaining factor in insomnia. Different relaxation techniques have been found to reduce hyperarousal and improve sleep. The Somnox sleep robot is promoted as sleep enhancing through relaxation by breath guidance. The aim of the current study was to assess if a three-week intervention with daily at-home use of the sleep robot had effects on symptoms of insomnia and/or concurrent symptoms of depression and anxiety in adults, compared with a waitlist-control group. There are currently no independent scientific studies on the sleep robot, hence the study fills a gap regarding the robot's efficacy.

**Materials and Methods:** A total of 44 participants (mean age: 48.91, female: 79.55%) who met the DSM-5 diagnostic criteria of chronic insomnia were recruited to the study. The participants were randomized to a three-week intervention with the Somnox sleep robot, or to a waitlist control group. The primary outcome measure was the Insomnia Severity Index administered at baseline, mid-intervention, and post-intervention. Secondary outcome measures were the Pre-Sleep Arousal Scale and the Hospital Anxiety and Depression Scale. Additionally, sleep onset latency, wake time after sleep onset, total sleep time, and sleep efficiency, were measured both subjectively with a sleep diary, and objectively with actigraphy. Mixed-effects models were used to analyze the data. Further, adherence to the intervention was measured. Spontaneous comments about how the participants experienced the robot were logged. The prospectively published study protocol and statistical analysis plan was followed.

**Results:** The effect of the sleep robot intervention on the participants' level of insomnia symptoms was not statistically significant. The participants enclosed both positive and negative experiences with the sleep robot.

**Conclusions:** A three-week intervention with daily at-home use of the Somnox sleep robot was not found to be an effective method to relieve symptoms of insomnia in adults. Possible roads for further exploration of the sleep robot are studies on sleep disorders other than insomnia, participants of older or younger ages, and studies conducted under more controlled conditions (i.e., a sleep laboratory).

**Acknowledgements:** The research group would like to thank Niklas Jakobsson for valuable comments on the manuscript.

## THE USE AND QUALITY OF 3 NIGHTS SELF-APPLIED HOME SLEEP STUDIES

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**Introduction:** Sleep studies are moving from in-laboratory to home assessment providing an improvement in patient accessibility and lower costs. However, the current home setup of polysomnography studies is limited to professional setup and only type III sleep studies are self-applied. Also, the current standard of one night study does not account for the effects of an adaptation night nor night-to-night variability.

**Materials and Methods:** A total of 17 participants have finalized the study. Currently, another fifty participants are performing the study and the results of the complete cohort will be discussed at WorldSleep 2022. Participants were asked to self-apply polysomnography device for 3 consecutive nights with a forehead electroencephalography setup. Each participant also filled: a sleep diary and a questionnaire regarding the setup of the device for every night. Currently, the studies have been analyzed with automatic analysis (Noxturnal, Nox Medical). Only studies with  $\geq 4$  hours duration were considered successful. The sleep quality difference between nights was assessed with a one-way ANOVA.

Two standardized questionnaires: The System Usability Scale (SUS) and the AttrakDiff about personal experience using the device have been filled by participants. SUS includes 10 statements ranged from 1 (strongly disagree) to 5 (strongly agree). AttrakDiff includes 28 couples of words representing extreme opposites on a scale from 1 to 7. We used a reverse scale to calculate the points having higher points for positive statements.

**Results:** Our preliminary findings show that out of the 51 nights of studies planned, a total of 46 (90.2%) were successful. Only 1 participant did not sleep with the device for 1 night. 4 studies failed because of the amount of time slept. The quality of sleep did not improve significantly for the three nights duration as assessed by sleep efficiency, total sleep time, rapid eye movement % and sleep stage 3 %.

From the SUS, we assessed 3 out of 10 questions. Two about the personal experience (“I thought the system was easy to use” and “I think I can use the system without the support of a technical person”) both with an average point of 4.3 out of 5. The third (I would imagine that most people would learn to use the system very quickly) had an average point of 4.6 out of 5. All answers had a range between 3 and 5.

From AttrakDiff, 3 statements were used. Complicated/Simple (avg=5.3, range from 3 to 7), impractical/practical (avg=6.3 range from 4 to 7) and, confusing/clearly structured (avg=5.6 ranged from 2 to 7).

**Conclusions:** The overall quality of the self-applied sleep studies was very high. The analysis of the usability results also show that participants perceived the self-applied sleep study easy to learn and operate. No differences in sleep quality were found using automatic analysis, further data with manual scoring will be presented at the conference.

**Acknowledgments:** This research was carried out as a part of the Sleep Revolution project, which has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement no. 965417.

## TOWARDS A DIGITAL SLEEP DIARY STANDARD

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**Introduction:** A sleep diary is an important tool to gather subjective sleep data, which provides key information for the diagnosis of many sleep disorders, including insomnia. In 2012, an expert panel created a standardized sleep diary in pen-and-paper format, the Consensus Sleep Diary

(CSD).

However, the CSD has certain limitations. For one, it comes in three different versions, each with a distinct purpose. In addition, monitoring participant compliance and memory bias in a pen-and-paper design is difficult. This raises the following research question: How can a digital sleep diary be designed to impact compliance and memory bias?

**Materials and Methods:** We iteratively developed a digital sleep diary based on the extended CSD version to further the standardization process by continuously assessing multiple prototype variations, first against a pen-and-paper CSD and later on their own. Based on the evaluations, we added questions targeting the daytime performance of participants. The research period encompassed 12 months in total and 109 participants. We used Action Design Research methodology and the following approaches to validate the different versions: i) user experience tests, ii) usability tests, iii) semi-structured interviews, and iv) application analytics.

**Results:** The collected data indicates that participants, in general, prefer to use a digital rather than a pen-and-paper format because they found the digital sleep diary more engaging, accessible, and easier to comply with. To maximize the impact on participant compliance, we used a notification system to remind participants to fill out the diaries. We also personalized the diary to avoid questions that were not relevant to an individual participant. As a result, we identified five design guidelines for developing a digital sleep diary: i) utilize the environment without compromising test validity, ii) use established input methods, iii) minimize participant workload, iv) use analytics for evaluation, and v) use added value to increase compliance. We also provide a proposed mobile application design for a digital sleep diary that is in accordance with these guidelines.

**Conclusions:** The key advantages of moving the sleep diary from a pen-and-paper format to a digital format stem from the ability to interact with the participants through notifications and custom application content. The next research step is clinical validation of the final version of the digital sleep diary. This will allow us to identify inconsequential or redundant questions and thus further narrow the core of the sleep diary questionnaire.

**Acknowledgements:** We thank Bergrós Pálmadóttir Morthens, and Birta Líf Baldursdóttir for their contributions. This research was carried out as a part of the Sleep Revolution project, which has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement no. 965417.

## USING CIRCUL® FOR ASSESSING OBSTRUCTIVE SLEEP APNEA SEVERITY

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**Introduction:** There is a broad spectrum in the severity of obstructive sleep apnea. The decision to treat is usually determined by measures of severity (most often the apnea-hypopnea index) and clinical features and presence of comorbidities (e.g. hypertension, mood disorder). Therefore, the development of an easy to use, cost-effective validated instrument to accurately assess OSA severity is a worthwhile goal. We compared OSA severity measured by the oxygen desaturation Index (ODI) by the oximetric Circul® ring to the gold standard, polysomnography (PSG).

**Materials and Methods:** Circul®(Bodimetrics Corp, Los Angeles CA), a device with a form factor of a ring, continuously measures several variables (SpO<sub>2</sub>, movement, heart rate). We compared Circul® data (ODI using 3% desaturation - cODI3%) with an established polysomnographic system (Alice 5, Respiromics, Murrayville, PA). 164 patients (age=44.8 years+12.3 (SD)) suspected of having sleep disordered breathing wore the Circul device during PSG. The Circul data was autoscored by the software of the device; the PSG data was scored by a technician. OSA was defined in three ways: AHI of 5, 15 and 30 respectively. ROC curve analysis was performed. The sensitivity (S), specificity (E) for the different thresholds for cODI3% compared to the PSG AHI and PSG ODI, were calculated.

**Results:** Using the PSG-derived AHI as the reference for classification, the best cut-off points were: OSA = AHI $\geq$ 5: cODI3% $\geq$  4.3 (S 87.8%, E 93.8%); OSA = AHI $\geq$ 15: cODI3% $\geq$  13.1 (S 76%, E 100%); OSA = AHI $\geq$ 30 =: cODI3% $\geq$  16.2 (S 85.7%, E 92%); Using the ODI from the PSG as the reference for classification, the respective cut-off points were: OSA=ODI $\geq$ 5: cODI3% $\geq$  4.3 (S 93.4%, E 88.9%); OSA=ODI $\geq$ 15:cODI3% $\geq$  13.1 (S85.2%, E98.4%); OSA=ODI $\geq$ 30:cODI3% $\geq$ 18.7 (S 98.4%, E 92.2%).

**Conclusion:** Circul Oximetry demonstrated good diagnostic accuracy when compared to the gold standard in determining OSA severity.

## Women

### EXAMINATION OF PROSPECTIVE SLEEP ACROSS THE MENSTRUAL CYCLE

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**Introduction:** Women are twice as likely to develop insomnia across their lifetime compared with men. This may be explained, in part, by changes in hormones and menstrual cycle phase in reproductive-aged women. Intra- and inter-variability of menstrual cycle timing can make it difficult to accurately measure sleep quality and quantity in sleep research studies. This study aimed to examine the role of menstrual cycle phase in daily self-report and actigraphy-assessed sleep across two consecutive menstrual cycles.

**Materials and Methods:** Fifty-one women (43% Caucasian) between the ages of 18 and 35 (*m* age = 23.67, *SD* = 4.68) completed continuous sleep monitoring via actigraphy and daily sleep diaries over two menstrual cycles (*m* days = 51.29). Cycles were identified via first date of menstrual bleeding and midcycle urinary ovulation testing and were coded into four phases: perimenstrual, mid-follicular, periovulatory, and mid-luteal. The perimenstrual phase was defined as the 3 days prior to and the first 3 days of menstrual bleeding. Within- and between-person relationships between menstrual phase and sleep parameters were estimated using multistep hierarchical linear modeling. Subjective and objective measures yielded the following sleep variables: Total Wake Time (TWT<sub>sub</sub> and TWT<sub>obj</sub>), Sleep Efficiency (SE<sub>sub</sub> and SE<sub>obj</sub>), and subjective sleepiness. Pandemic-related stress and daily US and region-specific COVID-19 case counts were included as covariates in adjusted models.

**Results:** The sample had a mean a cycle length of 28.61 days (*SD* = 2.69). Regarding actigraphy data, menstrual phase predicted TWT<sub>obj</sub> and SE<sub>obj</sub>. Women spent 4-7 fewer minutes awake during the mid-follicular (*m* = 61.54, *SE* = 3.37) and mid-luteal phases (*m* = 63.11, *SE* = 3.29), compared to the perimenstrual phase (*m* = 67.54, *SE* = 3.37; *p* <.001). Sleep efficiency was higher in the mid-luteal phase (*m* = 82.50, *SE* = 0.79) compared to the perimenstrual phase (*m* = 80.71, *SE* = 0.82, *p* =.006). Subjective ratings indicated that during the perimenstrual phase women spent 8-16 minutes longer awake (*m* = 52.23, *SE* = 5.01, *p* <.001) and experienced reduced sleep efficiency of between 1-3 percentage points (*m* = 89.70, *SE* = 0.10, *p* <.001) compared to all other phases. Women also reported increased morning sleepiness in the perimenstrual (*m* = 4.71, *SE* = 0.21) compared to the periovulatory phase (*m* = 4.34, *SE* = 0.22, *p* = .02). Random coefficients models for objective and subjective sleep variables were nonsignificant, indicating that these relationships did not vary significantly between participants.

**Conclusions:** To our knowledge, this is one of the first studies to examine subjective and objective sleep prospectively across two consecutive menstrual cycles. Disturbed sleep was highest in the perimenstrual phase. Future studies should measure menstrual cycle phase when investigating sleep in reproductive age women.

### GENDER DIFFERENCES IN REM SLEEP DURATION IN PATIENTS WITH COPD AND SLEEP APNEA (OVERLAP SYNDROME)

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**Introduction:** Sleep disturbances are commonly reported by COPD (Chronic Obstructive Pulmonary Disease) patients. Patients report problems in both initiating and maintaining sleep with low sleep efficiency. In a European survey 78% of the COPD patients reported some degree of sleep disturbance along with daytime breathlessness and increased COPD exacerbations. Symptoms of dyspnea cough, wheezing, sputum, contribute to difficulty in maintenance of sleep. Women have both greater susceptibility to development of COPD with lower tobacco exposure, and likely to have more severe disease at a younger age. Further there are gender differences in both sleep efficiency and quality whereby women have better quality and efficiency of sleep, but also have more sleep related complaints. It has also been shown that the women's rhythm of sleep, subjective alertness and core body temperature all change with phase of menstrual cycle. We previously have demonstrated that men have longer duration of REM (Rapid Eye Movement) sleep as compared to women. This difference in REM duration was present in healthy subjects with no sleep apnea and persisted in patients diagnosed with mild, moderate, and severe sleep apnea. Among the different sleep stages, REM sleep has been shown to cause muscular atonia, which affects accessory muscles and influence hypoxemia. Hypothesis: We hypothesized REM sleep duration will be different between Men and Women with overlap syndrome

**Materials and Methods:** Patients with Overlap syndrome n=46 underwent overnight PSG which included, 6 channel EEG, EOG, EMG EKG along with respiratory and flow monitoring. Scoring according to AASM guidelines was done by technician and verified by physician (both blind to the study). Information on age, BMI, smoking status, medications, and use of oxygen was noted. Data analyzed and shown as mean + SD, t test- *p* <0.05 significant

**Results:** Our data showed that women with overlap syndrome (n= 23) had lower REM duration as compared to men (n= 23). REM duration averaged 17.76, ± 10 minutes in female compared to Male Patients who averaged 30.41 + 16 *p*<0.05 Both groups were similar in relation to age, BMI, current or former smoker status. 34% of the female patients were requiring oxygen, compared to 26% of male patients. Sleep architecture was maintained in both groups, N2 duration 62% in male and 61% in female patients, deep sleep duration of 9.4% in males and 15% in females.

**Conclusions:** Our data demonstrates, greater decrease in REM duration in female patients with Overlap Syndrome. Compared to our previous data in patients with OSA without COPD overlap syndrome REM duration is significantly decreased in both groups, but more significant decrease in female patients is observed. Our data suggest that REM sleep is more susceptible in female patients to arousals from hypoxemia related to sleep apnea. So, it appears the physiologic mechanism of reduced REM to improve oxygenation is better preserved in women than Men.

### IMPROVING SLEEP OF WOMEN OVER 45 THROUGH AN ACTIVE THERMOREGULATED PILLOW: REAL-LIFE DATA FROM MOONA DEVICE

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**Introduction:** Women are more likely to have poorer sleep quality and a higher risk of insomnia than men. This difference could be due to several factors, including hormones, stress levels, changes in circadian rhythms, and temperature controls. Moreover, menopausal women are even more likely to have insomnia or diagnosed sleep apnea and frequent isolated insomnia symptoms. These diagnoses are also more common in menopausal women who suffered from hot flashes.

In this context, the aim of this study is to characterize the effect of an active thermoregulated pillow on sleep of women over 45 years old.

**Materials and Methods:** The Moona device controls the temperature of a pillow pad from 64°F to 95°F and has sensors to monitor temperature changes and sleep states throughout the night. A total of 97 women over 45, with more than 7 uses of the device and who completed the initial questionnaire (18 profile questions) participated in this study from October 2019 to July 2021. Sleep quality was measured on a scale of 1 to 5 before the first use of Moona and after each night of use.

The proprietary algorithm that detects sleep/wake states per 30-sec epochs has been used to calculate the time spent asleep for each participant across the 12 first uses. A total of 98 users have been included in this analysis from October 2019 to May 2021.

Statistical analyses have been performed on Python 3.7. Mean comparisons have been accessed by student t-test with a significance level at  $p < 0.05$ .

**Results:** The average age of the studied population is 55 years [Q1 - Q3: 50 - 60], with an average BMI of  $28 \text{ kg/m}^2$  [Q1 - Q3: 21 - 30]. A total of 87 out of 97 (90%) have reported feeling hot during the night daily or several times a week. A well-established use of Moona has been noticed: an average use of 146 times and an average anteriority of 262 days.

Women over 45 have a significant gain of minutes of sleep after the use of Moona. On average, they gain 35 minutes of sleep, going from 403 minutes on the first night to 438 minutes on the twelfth use (t-test,  $p < 0.05$ ).

The sleep quality reported by the older women users significantly

increased with the use of the Moona device (without use: 2.4/5, average over the last seven uses: 3.6/5, t-test,  $p < 0.001$ ). This sleep quality increased linearly over the first ten uses of the device, from 3.4/5 to 3.7/5 ( $R^2 = 0.80$ ).

**Conclusions:** The present study findings showed that an active thermo-regulated pillow like Moona enhanced sleep quality and increased total sleep time in women over 45. Moona acts as a non-pharmacological and safe solution that can decrease health problems arising from poor sleep and can improve quality of life for women.

**Acknowledgements:** We would like to acknowledge all women who have contributed to this study.