Is there a Specific UARS Phenotype? An annotated bibliography

References for the studies presented:

1. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. *The New England journal of medicine.* 1993;328(17):1230-1235.

2. Gottlieb DJ, Whitney CW, Bonekat WH, et al. Relation of sleepiness to respiratory disturbance index: the sleep heart health study. *American journal of respiratory and critical care medicine.* 1999;159(2):502-507.

3. Gottlieb DJ, Yao Q, Redline S, Ali T, Mahowald MW. Does snoring predict sleepiness independently of apnea and hypopnea frequency? *American journal of respiratory and critical care medicine.* 2000;162(4):1512-1517.

4. Gold MS, Amdo T, Hasaneen N, Gold AR. Somatic arousal and sleepiness/fatigue among patients with sleep-disordered breathing. *Sleep & breathing = Schlaf & Atmung.* 2016;20(2):749-758.

5. Amdo T, Hasaneen N, Gold MS, Gold AR. Somatic syndromes, insomnia, anxiety, and stress among sleep disordered breathing patients. *Sleep & breathing = Schlaf & Atmung.* 2016;20(2):759-768.

Does stress manifest as sleepiness?

Individuals experiencing psychological stress experience sleep disruption and sleepiness/tiredness

6. Ekstedt, M., et al. (2006). "Disturbed sleep and fatigue in occupational burnout." Scand J Work Environ Health 32(2): 121-131.

Occupational burnout is characterized by impaired sleep which may play a role in the development of sleepiness and mental fatigue or exhaustion in burnout

7. Gronli, J., et al. (2017). "Life Threat and Sleep Disturbances in Adolescents: A Two-Year Follow-Up of Survivors From the 2011 Utoya, Norway, Terror Attack." J Trauma Stress 30(3): 219-228.

 When compared with matched controls, significantly more survivors of the 2011 mass shooting at a youth summer camp on the Norwegian island, Utoya, reported having sleep disturbances, 52.4% versus 13.6%, d = 0.93, of which onset began at the time of the shooting, chi2 = 14.9, p < .001. The prevalence of insomnia, 56.3% versus 11.0%, d = 0.73; **excessive daytime sleepiness, 34.4% versus 13.6%, d = 0.61**; symptoms of obstructive sleep apnea, 18.8% versus 0%, d = 0.70; and frequent nightmares, 37.5% versus 2.3%, d = 0.90, were all higher in the survivors than in the control.

8. Theorell-Haglow, J., et al. (2006). "What are the important risk factors for daytime sleepiness and fatigue in women?" Sleep 29(6): 751-757.

Psychological distress, insomnia, and somatic disease are the most important conditions in women reporting daytime sleepiness and fatigue. Because 1 in 5 (21%) of the women in this study reported sleepiness, fatigue, or both, interventions that improve psychiatric health and reduce insomnia are important in improving the quality of life in women with these sleep symptoms.

If one accepts that metabolic syndrome (hypertension, type 2 diabetes and hyperlipidemia) is one manifestation of chronic stress, then correlates of metabolic syndrome in OSA patients are correlates of chronic stress. Sleepiness is one important such correlate.

9. Nena, E., et al. (2012). "Sleepiness as a marker of glucose deregulation in obstructive sleep apnea." Sleep Breath 16(1): 181-186.

Daytime sleepiness in OSAS patients is associated with hyperglycemia and hyperinsulinemia. These results suggest its potential use as a surrogate marker of insulin resistance in such patients.

10. Ren, R., et al. (2016). "Obstructive sleep apnea with objective daytime sleepiness is associated with hypertension." Hypertension 68(5): 1264-1270.

A total of 1338 Chinese patients with OSA. After controlling for confounders, OSA combined with MSLT of 5 to 8 minutes increased the odds of hypertension by 95% (odds ratio, 1.95; 95% confidence interval, 1.10-3.46), whereas OSA combined with MSLT <5 minutes further increased the odds of hypertension by 111% (odds ratio, 2.11; 95% confidence interval, 1.22-3.31) compared with primary snorers with MSLT >8 minutes.

Preliminary Studies comparing the Body Sensation Questionnaire between a patient group and healthy controls:

11. Broderick, J., et al. (2012). "Self-Report Somatic Arousal Correlates with Sleep

Complaints among Females with Irritable Bowel Syndrome: A Pilot Study." J Sleep Disor:

Treat Care 1: 2.

**Objectives:** To investigate the relationship between somatic arousal and sleep complaints among females with irritable bowel syndrome (IBS), we compared self-report and objective measures of somatic arousal between females with IBS and healthy females correlating the somatic arousal measures with self-report measures of sleepiness, fatigue and sleep quality.

**Findings:** The self-report somatic arousal score distinguished females with IBS from healthy controls and for all participants, correlated significantly with the Epworth sleepiness scale, the fatigue severity scale and the Pittsburgh sleep quality index. For all participants, the self-report somatic arousal correlated negatively with the difference between sleeping and waking heart rate; an objective indicator of somatic arousal during sleep.

12. Broderick, J. E., et al. (2014). "The association of somatic arousal with the symptoms of upper airway resistance syndrome." Sleep Med **15**(4): 436-443.

**Objectives:** We tested the hypothesis that the symptoms of UARS are manifestations of chronic stress. To accomplish this, we compared self-report somatic arousal between UARS patients and healthy controls and, among all participants, correlated the level of somatic arousal with the severity of UARS symptoms.

**Findings**: Compared to healthy controls, UARS patients demonstrated increased self-report somatic arousal. For all participants, the somatic arousal scores correlated positively with the scores of the Epworth sleepiness scale, the FACIT-Fatigue scale, the Pittsburgh sleep quality index, and negatively with the SF-36 Physical component and SF-36 Mental component.

The association of sleepiness with SNS tone in OSA:

The following 5 references demonstrate that waking muscle sympathetic nerve activity is increased in OSA patients relative to controls, decreases with CPAP use and is correlated with the level of hypersomnolence, measured by mean sleep latency.

13. Carlson, J. T., et al. (1993). "Augmented resting sympathetic activity in awake patients with. obstructive sleep apnea." Chest 103(6): 1763-1768.

Muscle nerve sympathetic activity (MSA) was recorded during wakefulness in 11 patients with obstructive sleep apnea (OSA) and in 9 sex- and age-matched healthy control subjects. MSA as well as circulating plasma norepinephrine was increased in patients with OSA. compared with controls.

14. Narkiewicz, K., et al. (1998). "Sympathetic activity in obese subjects with and without obstructive sleep apnea." Circulation 98(8): 772-776.

Waking muscle sympathetic nerve activity (MSNA) in the 9 obese subjects with occult OSA was 61+/-8 bursts per 100 heartbeats, which was higher than MSNA in normal-weight subjects without sleep apnea (P=0.02) and higher than MSNA in obese subjects without sleep apnea (P=0.02). Obesity alone, in the absence of OSA, is not accompanied by increased sympathetic activity to muscle blood vessels.

15. Narkiewicz, K., et al. (1999). "Nocturnal continuous positive airway pressure decreases daytime sympathetic traffic in obstructive sleep apnea." Circulation 100(23): 2332-2335.

Waking muscle sympathetic nerve activiity (MSNA) was measured in 11 normotensive, otherwise healthy patients with OSA who were treated with CPAP. The measurements were obtained at baseline and after 1 month, 6 months, and 1 year of CPAP treatment. MSNA was similar during repeated measurements in an untreated group. By contrast, MSNA decreased significantly over time in patients treated with CPAP. This decrease was evident after both 6 months and 1 year of CPAP treatment (P=0.02 for both).

16. Waradekar, N. V., et al. (1996). "Influence of treatment on muscle sympathetic nerve activity in sleep apnea." Am J Respir Crit Care Med 153(4 Pt 1): 1333-1338.

Muscle sympathetic nerve activity (MSNA) was measured during wakefulness via peroneal microneurography in 7 patients with documented OSA before and at least 1 mo after compliance-monitored nasal CPAP therapy. Before institution of CPAP therapy, MSNA was high in all patients and decreased after CPAP therapy (baseline versus CPAP: 69.4 +/- 15.3 versus 53.9 +/- 10.5 bursts/min, mean +/- SD; p<0.01). However, the decrease in MSNA was limited to the 4 patients with the greatest nightly use of CPAP (> or = 4.5 h/night), whereas it remained unchanged in the 3 patients who were less compliant. There was a direct linear correlation between the decrease in MSNA (bursts/min) and the average hours of CPAP use per night (r = 0.87, p = 0.01).

17. Donadio, V., et al. (2007). "Daytime sympathetic hyperactivity in OSAS is related to excessive daytime sleepiness." J Sleep Res 16(3): 327-332.

The aim of this study was to investigate the relationships among sympathetic hyperactivity, excessive daytime sleepiness (EDS) and hypertension in obstructive sleep apnoea syndrome (OSAS). Ten newly diagnosed OSAS patients with untreated EDS and daytime hypertension underwent polysomnography (PSG) and daytime measurements of plasma noradrenaline (NA), ambulatory blood pressure (BP), muscle sympathetic nerve activity (MSNA) by microneurography and objective assessment of EDS before and during 6 months of compliance-monitored continuous positive airway pressure (CPAP) treatment. One month after the start of CPAP, BP, MSNA and NA were significantly lowered, remaining lower than baseline also after 3 and 6 months of treatment. CPAP use caused a significant improvement of sleep structures, and reduced EDS. A statistical correlation analysis demonstrated that EDS was not correlated with sleep measures obtained from baseline PSG (% sleep stages, apnoea and arousal index, mean oxygen saturation value), whereas daytime sleepiness was significantly correlated with MSNA. Furthermore, MSNA and BP showed no correlation. Our data obtained from selected patients suggest that the mechanisms inducing EDS in OSAS are related to the degree of daytime sympathetic hyperactivity. Additionally, resting MSNA was unrelated to BP suggesting that factors other than adrenergic neural tone make a major contribution to OSAS-related hypertension. The results obtained in this pilot study need, however, to be confirmed in a larger study involving more patients.