Sleep Research Review™

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In this issue:

Abbreviations used in this issue:

AHI = apnoea-hypopnoea index
CPAP = continuous positive airway pressure
EPAP = expiratory positive airway pressure
OSA = obstructive sleep apnoea

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Welcome to the latest issue of Sleep Research Review.

The issue presents evidence that OSA is a risk factor for diabetic retinopathy in type 2 diabetics, and reports an analysis of the Swedish Twin Registry that examined the association between sleep duration, mortality, and heredity. Danish investigators report the benefits of a vibrational sleep position trainer for patients with positional sleep apnoea, a meta-analysis examines the link between sleepiness at the wheel and motor vehicle accidents, and a large cohort study suggests a link between short sleep duration and the development of metabolic disease. Comments for this issue have been provided by Dr Yasmina Serinel (University of Sydney).

We hope you find these and the other selected studies interesting, and look forward to receiving any feedback you may have.

Kind Regards,

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Obstructive sleep apnea and retinopathy in patients with type 2 diabetes

Authors: Altaf Q et al.

Summary: This longitudinal study examined the relationship between OSA and diabetic retinopathy in patients with type 2 diabetes. 230 patients from two diabetes clinics in the UK were included. Retinopathy was assessed using 2-field 45-degree retinal images for each eye and OSA was assessed using a home-based multichannel cardiorespiratory device. Prevalence rates for sight-threatening diabetic retinopathy (STDR) and OSA were 36.1% and 63.9%, respectively. STDR prevalence was higher in patients with OSA than in those without OSA (42.9% vs 24.1%; p=0.004). After a median follow-up of 43 months, patients with OSA were more likely than patients without OSA to develop preproliferative or proliferative diabetic retinopathy (18.4% vs 6.1%; p=0.02). Patients who received CPAP treatment were significantly less likely to develop diabetic retinopathy.

Comment: Multiple cross-sectional studies have shown an association between OSA and type 2 diabetes. Microvascular complications such as peripheral neuropathy and diabetic nephropathy are common in diabetic patients and this research group has previously reported in observational studies that this was partly associated with comorbid OSA. In contrast, randomised trials of OSA therapy in patients with type 2 diabetes have mostly failed to show improvements in glycaemic control – which then questions whether previous associations between OSA and diabetes (and its complications) were causal. This study is noteworthy and novel as it is the first prospective study to observe the longitudinal relationship between OSA and diabetic retinopathy. It demonstrated that OSA is independently associated with the acceleration of background retinopathy over a 4-year period. Moreover, there was a dose-response relationship independent of confounders. This makes biological sense, given that the same pathophysiological processes of oxidative stress, inflammation and endothelial dysfunction underpin both conditions. In short, this study suggests that OSA may be an independent risk factor for diabetic retinopathy. However, future trials will need to confirm whether OSA treatment slows the progression of retinopathy independent of any improvements in glycaemic control.

Reference: Am J Respir Crit Care Med 2017;196(7):892-900

Abstract

Sleep duration, mortality, and heredity – a prospective twin study

Authors: Åkerstedt T et al.

Summary: This analysis of data from the Swedish Twin Registry investigated the influence of heredity on the association between sleep duration and mortality. Data for 14,267 twins were analysed. A Cox proportional hazards regression analysis (adjusted for confounding factors) found a clear U-shaped association between sleep duration and mortality. Hazard ratios were 1.34 for sleep duration ≤6.5h and 1.18 for sleep duration ≥9.5h compared with a reference value of 7.0h. A co-twin analysis of 1942 twins discordant on mortality showed a hazard ratio of 2.66 for long (≥9.5h) sleep in monozygotic twins and 0.66 for short (<6.5h) sleep. The heritability for mortality was 28% for the whole cohort, 86% for short sleepers and 42% for long sleepers.

Comment: The beauty of twin studies lies in the ability to study both genetic and environmental effects on various outcomes such as mortality. As sleep duration is not thought to be correlated between identical twins, this study sought to quantify the effects of heredity on sleep duration and mortality. Studies as far back as 1964 have demonstrated the association between short and long sleep duration and increased mortality in a U-shaped curve however most studies are fraught with methodological problems related to unreliable self-reported sleep duration. Unfortunately, this study also relied on self-reported sleep duration but its novelty rests in the exploration of the role of heredity in sleep duration and mortality. Ultimately, the unexpected results suggest that genetics may be involved in short sleepers and their mortality but not in the case of long sleepers. If this is indeed the case, then it raises the question of whether environmental factors that potentiate long sleep and their mortality can be identified and by extension whether they can be altered to decrease risk.

Reference: Sleep 2017;40(10):zsx135
Abstract

Treating chronic hypoventilation with automatic adjustable versus fixed EPAP intelligent volume-assured positive airway pressure support (iVAPS)

Authors: McArdle N et al.

Summary: This Australian study investigated whether automatically determined EPAP (AutoEPAP) is non-inferior to FixedEPAP for the control of OSA during intelligent volume-assured pressure support (iVAPS) treatment of chronic hypoventilation. 25 patients with chronic hypoventilation and OSA used iVAPS with AutoEPAP or FixedEPAP on two separate nights in a crossover design. AutoEPAP was found to be noninferior to FixedEPAP for the primary outcome measure of AHI (median 2.7 vs 2.4 events/h; p=NS). There were no significant between-mode differences in sleep breathing and sleep quality, or self-reported sleep quality, device comfort, and patient preference.

Comment: Non-invasive ventilation machines are getting fancier (and more expensive) by the day but newer technologies don't always translate to better patient outcomes. Well-conducted studies from Australia like this one are incredibly important as they provide an evidence base for the use of newer technologies. This study was a non-inferiority trial that essentially demonstrated that the Resmed iVAPS AutoEPAP function was equivalent to FixedEPAP as titrated by an in-lab polysomnogram in reducing AHI in patients with both chronic hypoventilation and OSA. Limitations are that it was only a small study with a heterogeneous group of patients (obesity hypoventilation syndrome, chronic obstructive pulmonary disease, and neuromuscular disease). Furthermore, as acknowledged by the authors, patients were stable and not naïve to treatment and it is unclear whether unstable patients or never-treated patients would also respond favourably. Finally, it should be highlighted that the basis for non-inferiority trials is not only to introduce alternative therapies with similar therapeutic effectiveness but potentially to also demonstrate some advantages over the established gold standard therapies already available. In this context, it remains to be demonstrated what aspect of AutoEPAP iVPAPS would make it a potentially favourable alternative to FixedEPAP.

Reference: Sleep 2017;40(10):zsx136
Abstract

A sleep position trainer for positional sleep apnea

Authors: Laub R et al.

Summary: This Danish study examined the efficacy of a vibrational sleep position trainer in patients with positional sleep apnoea. 101 patients were randomised to use the sleep position trainer or no trainer for 2 months, and then all of the patients used the sleep position trainer for a further 4 months. Participants were assessed by polysomnography at baseline, and after 2 and 6 months. Mean supine sleep time decreased from 47% at baseline to 17% at 2 months in the sleep position trainer group and from 48% to 39% in the control group. Mean AHI decreased from 18 events/h at baseline to 10 events/h (p<0.001) at 2 months in the sleep position trainer group, and from 20 events/h to18 events/h (p=NS) in the control group. The positive effect of the sleep position trainer was maintained at 6 months. Compliance with the sleep position trainer device (>4h per night) was 75.5% and the discontinuation rate was 49.4% at 6 months.

Comment: This was an independent investigator-initiated study of a novel positional device. As clinicians, we always like to offer the most non-invasive and simplest therapeutic intervention to our patients with symptomatic OSA. Patients with positional OSA are often healthy younger males with lower body mass index, to whom CPAP is not an attractive long term option. Studies like these ones are important because they allow us to build an evidence base for their use. What was surprising to me was the very high drop-out rate of 50% comparable to that of CPAP. Although intention-to-treat analysis was used, this study could have benefited from a matched device placebo. Ultimately, patients who continued to use the positional device, however, had significant reductions in their AHIs, used it all night long, and had significant symptomatic benefit.

Reference: J Sleep Res 2017;26(5):641-50
Abstract

Risk of motor vehicle accidents related to sleepiness at the wheel

Authors: Bioulac S et al.

Summary: This systematic review and meta-analysis quantified the relationship between sleepiness at the wheel and motor vehicle accidents. A search of Medline, Scopus, and ISI Web of Science identified 10 cross-sectional studies (n=51,520), 6 case-control studies (n=4904), and 1 cohort study (n=13,674) that were suitable for inclusion. Meta-analysis of the data found that sleepiness at the wheel was associated with an increased risk of motor vehicle accidents (pooled odds ratio, 2.51).

Comment: Although multiple smaller studies have shown that sleepiness at the wheel increases the risk of motor vehicle accidents (this would seem intuitive), this paper is the first systematic review of these observational studies and serves an important role in approaching this public health issue. The study demonstrated a greater than 2-fold risk of motor vehicle accidents in sleepy drivers. Interestingly, half of the patients reported being sleepy predominantly whilst driving and not in other sedentary activities. Additionally, the Epworth Sleepiness Scale (ESS) was not associated with accident risk – probably because the ESS considers patients in times of low levels of alertness whereas driving is a high alertness activity. This highlights the value for clinicians to specifically ask about sleepiness behind the wheel rather than sleepiness in general. Ultimately, we still have a long way to go in discovering a reliable yet simple clinical tool to determine which drivers are at risk – a task that has and continues to prove difficult in those with OSA.

Reference: Sleep 2017;40(10):zsx134
Abstract

Suvorexant for the treatment of primary insomnia

Authors: Kuriyama A & Tabata H

Summary: This systematic review and meta-analysis assessed the efficacy and safety of the dual orexin receptor agonist suvorexant in patients with primary insomnia. A search of PubMed, EMBASE, the Cochrane central register of controlled trials and unpublished data identified 4 randomised trials (n=3076) that were suitable for inclusion. Meta-analysis of the data found that suvorexant significantly improved subjective time to sleep onset, subjective total sleep time, and subjective quality of sleep at 1 and 3 months. The most common adverse effects were somnolence, fatigue, and abnormal dreams.

Comment: Suvorexant is the first orexin antagonist approved for use in Australia for insomnia. Orexins play an important role in maintaining wakefulness and it is the loss of orexin neurons that underpins the pathophysiology of narcolepsy. Hence, blocking orexin neurons should promote sleep. Suvorexant is meant to be taken 30 minutes before bedtime, 7 hours before resuming daily activities, and has a longish half-life of 12 hours. This meta-analysis consisted of 4 randomised controlled trials with over 3000 participants. The chosen primary outcomes were subjective measures of sleep. Suvorexant reduced subjective time to sleep onset significantly (by 9–10 min), increased total subjective total sleep time significantly (18–20 min) and improved subjective quality of sleep. The most common adverse events in comparison with placebo were somnolence, fatigue, abnormal dreams and dry mouth. Suvorexant is a safe and effective medication for use in primary insomnia, although exactly how it compares to current hypnotics is yet to be elucidated.

Reference: Sleep Med Rev 2017;35:1-7
Abstract

Stratification of cardiovascular risk in patients with atrial fibrillation and obstructive sleep apnea – validity of the 2MACE score

Authors: Platek A et al.

Summary: This study determined whether patients with atrial fibrillation (AF) and concomitant OSA have a higher predicted cardiovascular risk than those without sleep-disordered breathing. 211 consecutive AF patients underwent overnight polysomnography for assessment of OSA and had their 2MACE score of cardiovascular risk calculated. 48 patients (22.7%) were found to have OSA (AHI ≥15 events/h). Patients with OSA were at higher risk for cardiovascular disease (29.2% vs 8.1%; p<0.0001), and had a higher mean 2MACE score (2.1 vs 1.4; p<0.0001) than non-OSA patients.

Comment: This observational, cross-sectional study examined whether patients with both AF and comorbid OSA had a higher 2MACE score, a validated tool in the prediction of cardiovascular risk. Previous studies have shown that patients with AF have a higher prevalence of OSA, and patients with OSA have higher rates of AF. Additionally, patients with OSA are more likely to experience recurrent AF after catheter ablation. What are still missing are large randomised controlled trials designed specifically to determine whether treatment of OSA will reduce the incidence or recurrence of AF. This question continues to have significant clinical equipoise. The SAVE trial examined for new-onset AF as a secondary outcome and found similar rates of incidence in both CPAP and non-CPAP arms but absolute numbers were too small to make any conclusions. The present study found an OSA prevalence of 23%, and that those with OSA had a higher cardiovascular risk as defined by a 2MACE score ≥3. Although this study is limited by its cross-sectional design and its quantification of cardiovascular risk, it serves to highlight the potential importance of OSA as a comorbidity in those with AF.

Reference: Sleep Breath 2017; published online Feb 2
Abstract

Gene-by-environment interactions of the *CLOCK*, *PEMT*, and *GHRELIN* loci with average sleep duration in relation to obesity traits using a cohort of 643 New Zealand European children

Authors: Krishnan M et al., on behalf of the SCOPE Study Group

Summary: This NZ study examined genetic influences on the relationship between sleep duration and obesity traits. 643 European children born to participants in the NZ centre of the international SCOPE study were included. Ten genes directly involved in circadian rhythm and a further 20 genes hypothesised to be driven by cyclic oscillations were evaluated. Multivariable regression was used to test the interaction between gene variants and sleep duration, in relation to obesity traits (body mass index [BMI] z-scores and percentage body fat [PBF]). There was no association between mean sleep duration and BMI z-scores or PBF. Uncorrected genotype associations were detected between *STAT-rs8069645* and *ADIPOQ-rs266729* with differences in mean sleep duration. Evidence for uncorrected gene-by-sleep interactions of *CLOCK-rs4864548*, *PEMT-936108* and *GHRELIN-rs696217* were found in relation to BMI z-scores but not PBF.

Comment: Although the fundamental principle underpinning weight gain is a function of "energy in" and "energy out," we have come a long way in understanding the complexity of the determinants of each of these processes. For instance, in adults, studies have shown that sleep restriction can alter glucose metabolism and insulin sensitivity, cause changes in hunger and satiety hormones such as ghrelin and leptin, and can result in changes in our food choices and physical activity. Further evidence is available to suggest that circadian clock gene transcription may be altered as well by short sleep. In children, a meta-analysis of prospective cohort studies found that those with the shortest sleep had a higher risk of being overweight/obese. Given these findings, the authors of this study set out to find out, in children, how an individual's biological clock genes may interact with sleep to determine obesity. Although the results did not find an association between sleep duration (as measured by actigraphy) and BMI, they found some uncorrected associations between certain clock genes and sleep length and BMI. Studies like these are important in our ongoing quest to understand the complex link between energy balance and sleep.

Reference: Sleep Med 2017;37:19-26
Abstract

Short sleep duration increases metabolic impact in healthy adults

Authors: Deng H-B et al.

Summary: This population-based cohort study investigated the metabolic impact of inadequate sleep in healthy adults. 162,121 healthy adults aged 20–80 years were followed up from 1996 to 2014. Cox proportional hazard ratios (HRs) for metabolic syndrome and its components were calculated for 3 sleep duration categories: <6 h/day (short), 6–8 h/day (regular), and >8 h/day (long). Compared with regular sleep duration, short sleep significantly increased the risk of central obesity by 12%, elevated fasting glucose by 6%, high blood pressure by 8%, low high-density lipoprotein cholesterol by 7%, hypertriglyceridemia by 9%, and metabolic syndrome by 9%. Long sleep decreased the risk of hypertriglyceridemia by 11% and metabolic syndrome by 7%.

Comment: These investigators followed up 162,121 healthy individuals over a 20-year period and found that the short sleepers had a higher incidence of developing metabolic syndrome and its components regardless of the presence or absence of insomnia. More than half a million participants underwent screening to exclude those with comorbid conditions, such that they were able to have a "clean" sample of patients without pre-existing conditions. This is probably the largest cohort study to date to suggest a link between short sleep duration and the development of metabolic disease. As with all of these studies, however, self-reported sleep duration is still a significant source of bias.

Reference: Sleep 2017;40(10):zsx130
Abstract

A systematic review of the literature on disorders of sleep and wakefulness in Parkinson's disease from 2005 to 2015

Authors: Chahine L et al.

Summary: Sleep disorders are a common non-motor manifestation in Parkinson disease (PD) and have a significant negative impact on quality of life. This systematic review of literature published in 2005–2015 examined a number of disorders of sleep and wakefulness in PD: rapid eye movement (REM) sleep behaviour disorder, insomnia, nocturia, restless legs syndrome and periodic limb movements, sleep disordered breathing, excessive daytime sleepiness, and circadian rhythm disorders. The influence of PD medications on sleep was also discussed.

Comment: As the awareness of the importance of non-motor manifestations of PD increases amongst GPs and neurologists, so too will the referrals to sleep clinicians for the management of them. This qualitative systematic review is hence timely, relevant and valuable. It provides an excellent review of the literature to date across several important domains and serves as an excellent reference. An important point made by the authors is that although sleep-disordered breathing is not necessarily more common in patients with PD, they also do not necessarily present with classic symptomatology, and hence should have a low threshold for further investigation with polysomnogram. The review also outlines priorities for future research which highlights the scale of what remains to be understood. Patients with PD are complex, and carefully teasing out their symptoms in order to institute the correct treatment is paramount for improving quality of life.

Reference: Sleep Med Rev 2017;35:33-50
Abstract

Independent commentary by Dr Yasmina Serinel BSC, MBBS, FRACP

Dr Yasmina Serinel is a Respiratory and Sleep Physician currently completing her PhD at the University of Sydney. Her research work in hypertension and sleep apnoea has been funded through an NMHRC postgraduate scholarship and has led to awards such as The New Investigator Award at the ASA, the Sydney University Medical School Deans Publication Prize, and the International Trainee Scholarship Award at the American Thoracic Society. She has first-author publications in *Thorax* and has written a book chapter in Cardiovascular Complications in OSA. Whilst completing her PhD, Yasmina works as a Consultant at Nepean Hospital, and runs a Sleep Clinic at the Woolcock Clinic.

