A submission in relation to the Draft National Obesity Prevention Strategy from the Sleep Health Foundation

The importance of sleep and circadian disturbance as risk factors for overweight and obesity

Practice points:

- Short sleep increases the risk for obesity
- Sleep loss creates an obesogenic environment promoting weight gain
- Weight loss is more difficult to achieve in individuals who report short sleep times
- Sleep loss combined with inappropriate timing of eating inhibits weight loss
- Increasing sleep time facilitates weight loss
- Shift work involving rotating night work causes sleep and circadian disturbance which increases the risk for obesity
- Obesity is the main risk factor for Obstructive Sleep Apnoea (OSA)
- OSA may also be obesogenic and independent of obesity, may promote cardiometabolic disease
- OSA may also hinder weight loss efforts in the obese

INTRODUCTION

Sleep that is of good quality and of adequate duration and a circadian rhythm that is robust and well-aligned with the 24-hour sleep/wake and feeding fasting cycles are both fundamental for human health. In contrast, poor and/or insufficient sleep and circadian disturbance have both been causatively linked to an increased risk for multiple adverse health conditions including cancers[1], dementias[2] and cardiometabolic diseases[3]. The link with cardiometabolic diseases is, in turn, strongly coupled with the development of obesity. In this submission from the Sleep Health Foundation, we highlight the epidemiology and mechanistic research linking sleep and circadian disturbance with obesity and its cardiometabolic complications. We propose that understanding and addressing sleep and circadian disturbance be an important component of the national obesity strategy framework for action to reduce overweight and obesity and its consequences amongst Australians.

SHORT SLEEP AND OBESITY

Sleep time has decreased in recent decades around the world,[4-6] due in part to changing work schedules, increasing sedentary work and also the dispersion of cities increasing travel times.[7] Over the same period obesity has been increasing (https://www.abs.gov.au/statistics/health/health-conditions-and-risks/national-health-survey-first-results/latest-release). Furthermore, a relationship has been found by many studies between self-reported short sleep duration (<7 hours daily) and the development of obesity.[8-12] Mechanisms suggested to explain the relationship include changes to the key hormones that regulate food intake - ghrelin and leptin, which lead to increased hunger and appetite and reduced satiety.[13,14] Neuroimaging studies[15,16] have also shown that sleep changes brain processes increasing activity in reward-processing areas, such as the anterior cingulate cortex, ventral striatum, and insula. This could lead to food seeking as a reward behaviour.[17] Additionally, less sleep time and greater wake time allows more time to eat[18] including eating late into the night. Food is metabolized less effectively at night[19] creating an obesogenic state. Sleep loss also increases fatigue[20]

which promotes a sedentary lifestyle, reducing the motivation to exercise and make healthy food choices.[21] All of these factors together could contribute to the relationship between obesity and short sleep. A systematic review and metanalysis[22] published in 2021 synthesized all the data and confirmed the association between self-reported short sleep and development of obesity. The metanalysis found that the chances of developing obesity increased when self-reported sleep duration decreased (OR 1.38 for <5 hours sleep duration, OR 1.14 for 5-5.9 hours sleep duration and OR 1.16 for 6-7 hours sleep duration).[22]

SHIFTWORK AND OBESITY

It is estimated that about 15-20% of the total work force in industrialised nations engages in shift work that involves night work. The prevalence is above 30% in notable industries such as mining and healthcare.[23] In Australia in 2019, 15.6% of the workforce were engaged in shift (https://www.abs.gov.au/statistics/labour/earnings-and-work-hours/working-arrangements). Of concern is the growing evidence (including from Australia) that shift work may predispose individuals to obesity.[24,25] In parallel, shift work has been strongly linked with obesity related cardio-metabolic disease. For example, a recent meta-analysis found that shift work, independent of other risk factors, accounted for a high population-attributable risk for cardiovascular events.[26] Intermediate markers of cardiovascular risk are also increased amongst shift workers. For example, shift work is consistently associated with the metabolic syndrome and its components (central obesity, hypertension, triglyceridemia, hyperglycaemia & low HDL cholesterol)[27-29]. A prospective study also showed an overall increased risk for developing metabolic syndrome in shift work (RR=1.5-5)[30].

It is well known that workers who rotate to night work suffer fragmented and often shortened daytime sleep as well as circadian disruption and misalignment, and this is the likely pathophysiological mechanism that drives obesity and cardio-metabolic disease. These changes with sleep restriction may be related concomitant increases in food/energy intake.[31,32] For example, in a study where sleep was restricted for just 5 days, energy intake increased, particularly at night, to levels that exceeded those needed to maintain wakefulness and this resulted in a weight gain of 0.82kg.[33] Artificial sleep restriction has also been shown to impair glucose tolerance[34], as well as cause sympathetic activation and endothelial dysfunction.[35] However, there are even worse effects when sleep restriction is combined with circadian misalignment and nocturnal food ingestion reflecting conditions during a rotation from dayshift to nightshift. A landmark study found that 12 hours of circadian misalignment (gradually achieved over 10 days) reduced sleep, increased blood pressure and in some volunteers, postprandial glucose responses during the circadian night reached a pre-diabetic range.[36] These data are supported by evidence in mice which demonstrates that circadian disruption leads to insulin resistance and obesity.[37]

Interventions which alter the timing of meals or reduce the window of food consumption time during the day have successfully improved glucose metabolism and weight loss. Time restricted feeding is a meal pattern which involves restricting food intake to a short period of time, ranging from as little as 4 hours to 13 hours.[38] A recent study compared eating meals only during the day versus spreading meals over the day and night during four simulated night shifts in a laboratory environment. It was found that the group that ate only during the day, in alignment with their normal biological rhythms, prevented a deterioration in glucose metabolism over the simulated night work period. In contrast,

the group who ate throughout the day and night showed a deterioration in glucose metabolism with simulated night work.[39] These data suggest that avoiding eating in the night and reducing the window of eating time (increasing the window of fasting) are useful strategies to help prevent metabolic disease in those who are exposed circadian and sleep disruption such as shift workers. This time-restricted feeding is a strategy that is likely to prevent weight gain and, also potentially promote weight loss in shift workers.

OBSTRUCTIVE SLEEP APNOEA (OSA) AND OBESITY

OSA is a common disorder characterised by repetitive periods of obstructed breathing during sleep, causing sleep fragmentation and often, daytime sleepiness and elevated blood pressure. The global prevalence of moderate-severe OSA, defined by a count of breathing pauses during sleep (the apnoea hypopnea index (AHI) ≥ 15) was recently estimated to be 425 million in adults aged 30-69 years.[40] Although age and male gender are pre-disposing risk factors for OSA, obesity is the primary causative factor[41] with population studies suggesting that nearly 60% of all cases of this severity category are attributable to being overweight.[42] Over the 20 years from 1993 to 2013, the ~50% increased prevalence of moderate-severe OSA in the community was predominantly due to escalating obesity rates.[43] Given that the obesity epidemic is continuing unabated, there is a high likelihood that the disease burden of OSA will escalate in the coming decades. From a mechanistic perspective, obesity predisposes to excess deposition of fatty tissue within the upper airway walls and tongue which acts to narrow the airway lumen making it more prone to collapse during sleep. Additionally, central obesity with excess abdominal fat alters respiratory mechanics which is hypothesised to induce a change in tracheal traction and airway diameter, predisposing to upper airway collapse.[41] More recently, another potential pathway by which obesity promotes OSA is via obesity related leptin resistance which has been shown to alter the activity of respiratory motoneurons.[44] The cardiometabolic consequences of OSA are well studied. OSA has been implicated as an independent risk factor for coronary heart disease, heart failure, stroke and atrial fibrillation.[45] There is also evidence that OSA is causatively linked to the metabolic syndrome and its components[46] and to incident type 2 diabetes.[47,48]

Continuous Positive Airway Pressure (CPAP) has been the gold standard mechanical treatment for Obstructive Sleep Apnoea (OSA) for more than 25 years. CPAP therapy which requires breathing pressurised air through a nose mask is highly effective at preventing the collapse of the upper airway during sleep that typifies OSA. Level 1 evidence shows that OSA treatment with CPAP reduces sleepiness in symptomatic patients, improves sleep-related quality of life and modestly reduces blood pressure (BP).[49] However the overall benefit of CPAP on cardiovascular mortality is unclear[50] and the conclusion from randomised trials in the OSA-Type 2 diabetes population is that there is no positive effect of CPAP treatment on glucose metabolism.[51] Similar results have been shown in unselected OSA patients without type 2 diabetes.[52] However, in most trials, sub-optimal CPAP adherence may have been a contributing factor to the negative findings. CPAP attrition amongst prescribed patients in clinical populations has been estimated at 50%[53] and amongst those who continue to use CPAP, sub-optimal nightly compliance is also common with many patients routinely abandoning treatment for large parts of their sleep. In this context, some trials have shown beneficial effects on glucose metabolism in OSA patients with *uncontrolled* type 2 diabetes[54] and with enforced all-night use in

obese OSA patients with *pre-diabetes*.[55] These findings are consistent with meta-analyses suggesting that CPAP treatment does improve insulin resistance[56] and with trials showing improvements in post-prandial lipidemia.[57] However further adequately powered clinical trials are required to strengthen the evidence base. Such trials will be crucial for powering larger phase 1/2 diabetes and metabolic syndrome prevention trials.

Given the above limitations and uncertainty with CPAP, it follows that there has been increased efforts to explore the utility of weight reduction as a viable treatment option for OSA using surgical, dietary, and pharmacological approaches. All approaches appear to confer a dose response relationship between weight loss and OSA alleviation although there is a great deal of intra-individual variability in response[58], irrespective of the approach used. On average, bariatric surgery in OSA patients with a pre-intervention BMI of 51.3kg/m^2 produces a reduction of 14kg/m^2 and 29 events/hr in AHI. In contrast, non-surgical weight loss therapy with a pre-intervention BMI of 38.3 kg/m^2 produces a reduction in BMI and AHI of 3.1 kg/m^2 and 11 events/hour respectively.[59]

Despite obesity being a major pathophysiological factor for OSA, several lines of evidence also suggest a reverse causal pathway - that OSA is not simply an epiphenomenon of obesity but may actually contribute to obesity and cardio-metabolic dysfunction.[60] From a mechanistic perspective, OSA may promote *weight gain* through imbalances in anabolic, appetite and satiety hormones as well as through reduced motivation to exercise. These factors may collectively act to reduce fat oxidation (burning) and increase food consumption.[61,62] In support of this, a large cohort study found that the severity of OSA was positively associated with the subsequent five-year increase in BMI after adjustment for known confounders.[63] Several studies also suggest that OSA may impede *weight loss*. For example, a long-term weight loss study in men with visceral abdominal obesity (a major risk factor for diabetes) showed that those with OSA lost less weight and had smaller reductions in waist circumference and circulating lipid concentrations compared to men without OSA. Furthermore, individuals with greater severity of baseline hypoxemia (a measure of OSA severity) had less loss of visceral abdominal fat and total fat and lesser improvements in glucose/insulin homeostasis at 1 year.[64] Finally, in a cohort study of bariatric surgery, patients with OSA who continued to use CPAP postoperatively to treat OSA, also continued to lose weight at 7 years follow-up, whereas non-CPAP treated patients gained 6.8kg.[65] However in other studies that have not specifically incorporated a weight loss intervention, CPAP has not been shown to passively cause weight or abdominal fat loss.[52,66] Collectively, these studies highlight the importance of weight management in OSA as an adjunctive approach, with CPAP and other OSA therapies, to reduce the severity of this disorder. In this context, weight loss that is tailored to individual patient preferences is now recommended in practice guidelines as part of the OSA treatment strategy for those who are overweight or obese.[67]

In summary, there appears to be a bi-directional relationship between OSA and obesity. When both conditions co-exist, the evidence suggests that their optimal management is best achieved by treating both the OSA and the excess weight using OSA therapy and effective weight loss strategies. Obesity experts should understand that for many patients, weight loss in isolation will likely not cure OSA and that detecting and managing OSA will likely enhance weight loss and the benefits on health outcomes derived from weight loss treatments.

CONCLUSION

Sleep is one of the three pillars of good health. Recognising and treating sleep disturbances such as those related to OSA, shift work and short sleep will likely aid in the prevention of obesity and improve its management.

Associate Professor Craig L Phillips PhD,
Faculty of Medicine and Health,
University of Sydney and
Woolcock Institute of Medical Research
On behalf of Sleep Health Foundation
L1, 5 George Street, North Strathfield NSW 2137

Professor Siobhan Banks PhD,
Research Professor and Director:
Behaviour-Brain-Body Research Centre
University of South Australia
On behalf of Sleep Health Foundation
L1, 5 George Street, North Strathfield NSW 2137

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