Proposed mechanisms between sleep and metabolism

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There has been considerable interest in the negative metabolic impact of sleep deprivation, sleep disturbance, and circadian desynchronisation. Observational studies have paved the way for more rigorous investigation into glycaemic regulation, appetite, and energy expenditure, making it possible to construct credible theories regarding these associations. There are, however, experimental limitations due to numerous confounding factors, artificial laboratory environments, and varying study protocols, making comparison of results problematic; these should be considered when extrapolating results to populations. This article explores these proposed mechanisms for metabolic alteration as described in a recent review by Schmid and colleagues and considers whether interventional strategies would be useful.

What is normal sleep?
Sleep is an active state with cycles of varying levels of brain activity and is affected by multiple external and internal factors (see Table 1). It is generally accepted that a normal sleep period is 7–8 hours for an adult, although there is individual variation and a possible natural tendency for a two-sleep pattern separated by a waking interval of 1–3 hours. Rapid eye movement (REM) sleep has similar brain wave activity to wakefulness, whereas non-rapid eye movement (NREM) sleep reflects stages of progressively reducing brain wave frequency with the lowest signifying deep sleep. The role of NREM sleep is thought important to consolidate new memories and is theorised to allow restoration of cerebral glycogen stores.

Observational data
Large population surveys have associated sleep patterns with metabolic risk. Self-reported short (<7 hours) and long (>8 hours) sleepers versus normal sleepers have significantly greater prevalence of metabolic syndrome, type 2 diabetes, obesity, hypertension, and cardiovascular disease. These findings have been reproduced when using objective measures of sleep quantity in selected groups. Obesity rates in children (when considering normal sleep periods of 10 hours) follow a similar pattern. Self-reported impaired sleep quality, as well as quantity, is also associated with metabolic syndrome independently of obesity or sleep-disordered breathing. Interestingly, however, for shift workers, whose sleep rhythm is regularly disrupted, higher metabolic syndrome prevalence is not universal as in-flight workers do not have the same propensity, possibly reflecting the influence of education and health behaviours.

What are the proposed mechanisms for sleep disturbance altering metabolism?
Laboratory studies have provided potential explanations for these associations involving disruptions in glucose metabolism, appetite, and energy expenditure. Due to small numbers of subjects, studies have typically used a cross-over design to measure the impact of sleep manipulation.

Increased insulin resistance
Insulin resistance reflects elevated insulin requirements to maintain normal glucose homeostasis. Sleep restriction to 4 or 4.5 hours per night has been shown to significantly impair insulin sensitivity and glucose utilisation in the order of 20–30% through a reduction in non-insulin dependent glucose uptake and reduced acute insulin response. These findings have been replicated for varying days of consecutive sleep deprivation including even a single night of sleep reduction.

The cause for these changes in glucose regulation is unclear. Reduced glucagon concentrations lead to increased hepatic gluconeogenesis, and this has been reported following a single night of sleep restriction, but whether this persists after more prolonged sleep disturbance is not yet known. Four nights of consecutive sleep deprivation have been shown to increase evening cortisol and sympathetic activation, while reducing thyroid stimulating hormone, and potentially reflects more extensive hormonal disarray contributing to altered glucose disposal in skeletal muscle, peripheral insulin resistance, and gluconeogenesis. However, findings for both beta-cell insulin secretion and stress hormone secretion (i.e. cortisol and catecholamines) are inconsistent, exposing the problems in comparing small studies with differing protocols and periods of sleep restriction.

Type of sleep disturbed may also play a role, as interruption of NREM but not REM sleep through acoustic stimulation linked to electroencephalogram activity has been shown to increase insulin resistance without a compensatory increase in insulin secretion. The mechanism for this remains uncertain, but as the brain is a major site of glucose disposal, it is feasible that major changes in neural activity may impact on glucose tolerance.

Impaired glucose clearance also appears to occur in circadian rhythm desynchrony, in which there is normal sleep outside habitual sleeping times. This has demonstrated increased average blood glucose by 6% despite...
higher increases in insulin concentrations, implying a reduction in insulin sensitivity with insufficient beta-cell compensation. Intriguingly, a further study that combined circadian desynchrony with sleep restriction to under 6 hours, found increased fasting and postprandial glucose with reduced insulin concentrations, possibly suggesting different coping pathways for shorter- and longer-term sleep restriction. It is likely, however, that any disruption of sleep desynchronisation would impact on sleep quantity and quality and this should be taken into consideration, in addition to the small subject group. Full recovery of beta-cell secretory function was observed following a period of recovery.

**Appetite and food intake**

Several studies have shown changes in food intake following sleep reduction to 4 hours for periods of one to 14 days. This includes increased food intake of around 680 kcal per day, larger meal portions and snacks, and consumption of higher glycaemic index foods. Of particular interest, a study of overweight subjects on a calorie restricting diet for 14 days compared sleep opportunity of 5.5 to 8.5 hours and found equivalent total weight loss but an average of 55% higher lean body mass loss with sleep restriction.

Proposed mechanisms for these changes relate to variation in two hormonal neuropeptides: ghrelin, from gastrointestinal origin, that promotes hunger; and leptin, from adipose cells, that increases satiety. Both hormones affect pancreatic insulin secretion. However, as before, results between various studies have been conflicting, with exaggerated, reduced and unchanged patterns of secretion in response to sleep duration. Leptin responses are difficult to measure due to normal diurnal variation in secretion, with the highest levels during the first part of sleep. This necessitates 24-hour profiles for full assessment and hampers the practicality of assessment. Furthermore, leptin levels are influenced by obesity, gender, dietary intake and exercise, parameters that are rarely controlled for and hamper comparison of results. However, well-conducted studies that minimise these variables and measure 24-hour profiles appear to demonstrate a more consistent association between sleep restriction and circadian desynchrony with impaired leptin secretion, maintaining the plausibility of a mechanistic relationship. Ghrelin secretion is similarly linked to food intake and exercise, highlighting the complexity of measurement and study comparison, and leaving equivocal conclusions.

Brain wave activity may be important. Neuroimaging studies assessing neuronal activity in response to high-calorie versus low-calorie food images following sleep restriction have demonstrated changes in activity levels within the anterior cingulate cortex, increased activity in the putamen and nucleus accumbens, and reduced activity in the ventromedial prefrontal cortex. These areas respectively influence appetite evaluation of foods according to their calorific value, exaggerate food reward, and compromise inhibitory control over food intake, promoting food foraging behaviours. Further research is required to assess whether sleep stages are influential in this.

**Physical activity and energy expenditure**

Physical activity is simple to measure objectively using accelerometers. Following a single night of partial sleep restriction a 13% fall in physical activity has been reported, with a further decline by almost a third after a full week. However, here once again, there is inconsistency between studies, with some reporting higher activity levels, and others no changes even after prolonged sleep restriction.

**Sleep duration as an intervention**

Despite the positive associations reported in observational studies and laboratory analyses of healthy young subjects, ‘real-world’ studies of weight management and sleep duration have been inconclusive. Hart et al. studied 12 overweight and obese women and compared two nights of 5 hours versus two nights of 9 hours of time in bed and found no difference in total energy intake or measured fasting hormones, although there was an increase in proportional protein intake. McNeil et al. compared self-reported sleep quality and duration with visual analogue scales for appetite sensation and self-reported food records for 78 overweight and obese men. They found lower mean satiety quotients in short duration sleepers but no difference in energy intake. O’Brien et al. studied 316 overweight and obese women receiving behavioural weight loss education. Treatment was equally successful regardless of self-reported sleep time at baseline and failed to support a significant relationship between total sleep time or time in bed with weight loss success. The outcome of a study focusing on sleep increase as an intervention for weight management will be of real interest to the field, and there are plans to monitor endocrine, metabolic and psychological effects of sleep duration on study subjects.

Whether sleep recovery for people with established features relating to metabolic syndrome will lead to health improvement is uncertain, and, although benefits of treating sleep-related breathing problems and apnoeas have been demonstrated, mechanisms cannot be considered the same. Perhaps more importantly, subjective well-being including satisfaction with life and positivity has been linked to sleep quality and duration.

One of the uncertainties of sleep intervention as a potential therapeutic target for metabolic dysregulation is whether it will have an impact on indices of morbidity. A systematic review of published trials of psychological and behavioural treatments for persistent insomnia – including stimulus control therapy, relaxation, paradoxical intention, sleep restriction, and cognitive behaviour therapy – concluded that, while reliable changes in sleep parameters could be both achieved and sustained over time, the evidence for improvements in daytime fatigue or other aspects of health was lacking. It appears that an important factor for predicting the success of self-reported sleep improvement is greater confidence in ability to sleep at pre-treatment, suggesting yet another psychological hurdle to overcome in the management of obese patients. Additionally, behaviour therapy, for sleep disturbance in cancer patients, has shown that despite documented improvements in sleep quality, perception of sleep quality and symptoms of fatigue did not consistently follow this.
Conclusions
There is difficulty in drawing conclusive guidance from the studies conducted so far, given the frequency of conflicting results, challenges of generalisation between studies due to multiple confounding factors, small numbers of study subjects, and publication bias. Additionally, experimental studies frequently restrict sleep so significantly that it must be questioned whether results can be extrapolated to chronically restricted sleep patterns. And, finally, the large number of people with normal sleep duration and metabolic syndrome, or any of its component features, highlights that this is not a single solution to restoring population health. However, the growing volume of research does support a relationship between sleep and metabolism, possibly reflective of adaptive changes to increase energy availability for extended wakefulness. Mechanisms are likely to be multifactorial and complex and, given the easy access to calories and increased sedentary nature of our society, these responses may contribute to adverse health outcomes.

Further studies are required to understand more clearly the mechanisms through which sleep and metabolism are linked, to appreciate individual variability in sleep requirements, and to realise whether normalising sleep duration and recovery sleep as an intervention is beneficial to metabolic processes. Until that time, inquiring whether patients allow adequate provision for sleep when they are at risk of or have already developed features of the metabolic syndrome should be considered, even as a marker of general well-being. Where required, management strategies include sleep education and cognitive behavioural therapies.

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Declaration of interests
There are no conflicts of interest declared.

References

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