

The metabolic burden of sleep loss

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In parallel with the increasing prevalence of obesity and type 2 diabetes, sleep loss has become common in modern societies. An increasing number of epidemiological studies show an association between short sleep duration, sleep disturbances, and circadian desynchronisation of sleep with adverse metabolic traits, in particular obesity and type 2 diabetes. Furthermore, experimental studies point to distinct mechanisms by which insufficient sleep adversely affects metabolic health. Changes in the activity of neuroendocrine systems seem to be major mediators of the detrimental metabolic effects of insufficient sleep, through favouring neurobehavioural outcomes such as increased appetite, enhanced sensitivity to food stimuli, and, ultimately, a surplus in energy intake. The effect of curtailed sleep on physical activity and energy expenditure is less clear, but changes are unlikely to outweigh increases in food intake. Although long-term interventional studies proving a cause and effect association are still scarce, sleep loss seems to be an appealing target for the prevention, and probably treatment, of metabolic disease.

Introduction

Metabolic health is, in addition to genetic predisposition, largely dependent on behavioural factors such as dietary habits and physical activity. In the past few years, sleep loss as a disorder characterising the 24 h lifestyle of modern societies has increasingly been shown to represent an additional behavioural factor adversely affecting metabolic health.^{1–3} Specifically, short sleep duration,⁴ impaired sleep quality,⁵ and irregular sleep–wake patterns⁶ have been associated with adverse metabolic traits such as obesity and disturbed glucose metabolism, which are features of the metabolic syndrome. In accordance with these observations, findings from experimental studies have emphasised distinct mechanisms by which sleep loss might provoke the development of metabolic diseases. In particular, central nervous neuroendocrine pathways controlling energy homeostasis^{7,8} and food intake^{9–11} probably play an important part. Peripheral pathways, such as those regulating adipocyte function,¹² also seem to be sensitive to the disturbing effect of insufficient sleep.

In this Review we summarise the existing evidence for a causal link between sleep loss and adverse metabolic traits characterising the metabolic syndrome. We place particular emphasis on potential underlying pathophysiological mechanisms, because they might point to new targets and strategies for the prevention and treatment of metabolic disease.

Observational studies linking sleep loss to adverse metabolic traits

The metabolic syndrome

Although an unequivocal definition of the metabolic syndrome does not exist, it is usually defined as a cluster of metabolic disturbances including visceral obesity, impaired glucose metabolism, dyslipidaemia, and high blood pressure, all of which increase the risk of cardiovascular morbidity and mortality.¹³ Several observational studies^{4,14,15} have investigated the association between short sleep duration and prevalence of the metabolic syndrome. For example, a cross-sectional analysis of data of the Adult Health and Behaviour

Project registry, including 1214 Americans aged 30–54 years, showed a clear association between short sleep duration and an increased prevalence of the metabolic syndrome.⁴ Whereas prevalence of the metabolic syndrome in the entire cohort was 22%, prevalence rates increased to 48% in short sleepers (6–7 h vs 7–8 h per night, odds ratio [OR] 1.48, 95% CI 1.05–2.10) and to 83% in very short sleepers (<6 h per night 1.83, 1.19–2.80). Notably, long sleep duration of (>8 h per night) was also associated with an increased prevalence of the metabolic syndrome (OR 1.81, 95% CI 1.04–3.15). Similarly, analysis of data from the US National Health Interview Survey, including more than 56 000 adults, showed that short (<7 h per night) and long (>8 h per night) sleep duration is associated with an increased probability of obesity, type 2 diabetes, hypertension, and cardiovascular disease.¹⁶

Observational evidence suggests that both sleep duration and sleep quality are linked to metabolic health. In a multiethnic cohort of women aged 46–57 years,¹⁴ poor nocturnal sleep efficiency—ie, a long cumulative time of being awake during night time—was independently associated with the prevalence of the metabolic syndrome (OR 1.40, 95% CI 1.04–1.89). Additionally, reduced sleep depth and sleep-related breathing disorders were associated with the metabolic syndrome (1.45, 1.08–1.95 and 1.73, 1.26–2.37, respectively). Whereas in this study sleep quality was objectively assessed by polysomnographic recordings, other studies have investigated the effects of subjective sleep quality on metabolic traits. For example, with the Pittsburgh Sleep Quality Index (PSQI), one study¹⁵ showed an association between poor subjective sleep quality and presence of the metabolic syndrome—ie, an increase of 2.6 points in the PSQI was associated with a 44% (OR 1.44, 95% CI 1.01–2.06) increase in the presence of the metabolic syndrome.

Irregular sleep–wake cycles and circadian desynchronisation as a consequence of shift work might be particularly harmful for metabolic health. Large cohort studies have shown a clear association between shift work and adverse metabolic traits. In a study of

1811 employees of an airline company, the prevalence of metabolic syndrome was 2.13 (95% CI 1.35–3.37) times higher in shift workers than in regular daytime workers.¹⁷ Furthermore, analyses of a dataset from 26463 retired Chinese workers¹⁸ showed that previous shift work is associated with an increased risk of development of hypertension (OR 1.05, 95% CI 1.01–1.09) and type 2 diabetes (1.10, 1.03–1.17), and with poor self-reported sleep quality (1.18, 1.09–1.27). These findings suggest that shift work and resulting sleep problems exert a long-lasting adverse effect on metabolic health.

Increased bodyweight and obesity

The observational evidence for a link between short sleep duration and increased bodyweight and obesity was summarised in a meta-analysis of 17 cross-sectional studies.¹⁹ This analysis comprised 22 population samples with more than 600 000 adults worldwide. Results clearly show an increased likelihood of obesity (BMI >30 kg/m²) in short sleepers (≤ 5 h per night) compared with regular sleepers (OR 1.55, 95% CI 1.43–1.68). Moreover, the average hours of nocturnal sleep correlated negatively with BMI pooled across all included studies ($\beta -0.35$ units of BMI per h of sleep; 95% CI -0.57 to -0.12). Similar results were obtained when data from 12 studies (13 population samples) including more than 30 000 children were analysed. Again, short sleep duration (≤ 10 h per night) was associated with childhood obesity (BMI >95th percentile), with a pooled OR of 1.89 (95% CI 1.46–2.43).

Type 2 diabetes

Evidence for a link between short sleep duration and increased risk of type 2 diabetes is even stronger than that for the association with obesity, because both cross-sectional and many longitudinal, albeit observational, studies showing a link. We previously systematically summarised evidence from such longitudinal studies up to 2005.³ Thereafter, results of the first National Health and Nutrition Examination Survey (NHANES I) of 9000 Americans with a follow-up time of roughly 10 years provided even stronger evidence for an independent association between short sleep duration and the development of type 2 diabetes than did preceding studies.²⁰ In that study, a sleep duration of less than 5 h per night was associated with an increase of 57% (OR 1.57, 95% CI 1.11–2.22) in risk for development of type 2 diabetes during the follow-up period, even after adjustment for various covariates, including physical activity, depression, alcohol consumption, ethnic origin, education, marital status, and age.

A meta-analysis²¹ confirmed the independent association of short sleep duration (5–6 h per night) with an increased risk of type 2 diabetes (relative risk [RR] 1.28, 95% CI 1.03–1.60), and showed that difficulty in sleep initiation (1.57, 1.25–1.97) and maintenance (1.84, 1.39–2.43) are associated with an even greater risk.

Dyslipidaemia

Few cross-sectional studies have reported on an association between short sleep duration and dyslipidaemia, which is characterised by increased concentrations of LDL cholesterol and low concentrations of HDL cholesterol.^{22,23} Up to now, the only prospective observational study about this issue is the National Longitudinal Study of Adolescent Health, which included more than 14 000 young Americans aged 11–21 years.²⁴ After adjustment for various covariates, results showed that each hour of additional sleep was associated with a decrease in the OR for diagnosis of hypercholesterolaemia in early adulthood (OR 0.87, 95% CI 0.79–0.96). The beneficial effect of longer sleep duration was more pronounced in women (0.85, 0.75–0.96) than men (0.91, 0.79–1.05).

Hypertension

The strongest evidence for a link between short sleep duration and hypertension is from analyses of the datasets of the Nurses Health Studies I and II, in which investigators assessed data from more than 70 000 women, obtained in 1986, 2000, and 2001.²⁵ Cross-sectional results showed that self-reported short sleep duration (< 5 h per night) is associated with an increased likelihood of hypertension (OR 1.19, 95% CI 1.14–1.25). Findings from prospective analyses showed that a sleep duration of less than 5 h per night, compared with a regular duration of 7 h per night, is associated with a higher incidence of hypertension (hazard ratio [HR] 1.20, 95% CI 1.09–1.31), with this association being particularly pronounced in younger women (< 50 years). However, multivariate analyses showed that the association between short sleep duration and development of hypertension was largely mediated by increased rates of obesity. A meta-analysis²⁶ including 11 prospective studies concluded that the risk of hypertension was increased by short sleep duration (RR 1.21, 95% CI 1.05–1.40), disturbance in sleep continuity (1.20, 1.06–1.36), early-morning awakening (1.14, 1.07–1.20), and combined symptoms of insomnia (1.05, 1.01–1.08).

Mortality

Given that the metabolic syndrome and each of its components are associated with an increased risk for premature death, sleep loss is likely to also be associated with increased mortality. Indeed, a meta-analysis²⁷ including 16 prospective studies (27 independent cohorts) and 1 382 999 participants showed that less than 7 h of sleep per night was associated with an increased risk of death (RR 1.12, 95% CI 1.06–1.18). However, more than 8 h per night was likewise associated with an increased risk of death (1.30, 1.22–1.38). A more complete overview of this issue is provided in a previous comprehensive review²⁸ that summarises available evidence, elaborates on potential mechanisms, and suggests a social-ecological framework to explain the association between short sleep duration and mortality.

Experimental studies of mechanisms linking sleep loss to adverse metabolic traits

Glucose metabolism

Karine Spiegel and colleagues²⁹ did the first thorough investigation of the effects of sleep loss on glucose metabolism in 11 healthy young men (aged 18–27 years) whose sleep was restricted to 4 h for six consecutive nights, with a subsequent recovery period of six nights with 12 h of sleep opportunity. During an intravenous glucose tolerance test, sleep restriction versus subsequent sleep extension was associated with impaired glucose tolerance, as shown by a 40% reduction in the glucose disposal rate caused by reduced glucose effectiveness (ie, non-insulin-dependent glucose uptake), and with a reduced acute insulin response. Reanalyses of these data also showed a significant decrease in insulin sensitivity after sleep loss.³⁰ Furthermore, the peak blood glucose response to a breakfast meal was increased by 0.8 mmol/L after the nights of sleep restriction. These results were corroborated and extended in several methodologically sound laboratory studies in healthy men and women, which showed decreases in glucose tolerance and insulin sensitivity after sleep restriction to roughly 4 h per night for periods between one night and 14 days,^{31–34} and after sleep fragmentation for two nights.³⁵ Increased markers of insulin resistance have also been noted in adolescents after their sleep was restricted to 4 h for three consecutive nights.³⁶

Although an impairing effect of short sleep duration on insulin sensitivity, as shown by increased hepatic glucose production²⁸ and reduced peripheral glucose disposal,^{30,33–36} was recorded fairly consistently in all the studies mentioned above, results on the effect of sleep loss on β -cell insulin secretion are much less consistent. Here, fasting insulin concentrations representing basal

secretion of the hormone were unchanged^{31–33} or even increased after sleep loss.³⁶ The insulin response to an intravenous glucose challenge was reduced after sleep loss in one study,²⁹ whereas the response to an oral glucose challenge was unchanged^{29,32,34} or even enhanced in other studies.³³ However, given that glucose tolerance was decreased in all studies,^{29,32–34} as shown by raised postprandial glucose levels, β -cell function was clearly not sufficient to compensate for the reduced insulin sensitivity in the state of sleep deprivation (figure 1). Of note, some evidence exists to show that acute sleep loss reduces circulating concentrations of glucagon,^{33,37} suggesting an inhibitory effect on pancreatic α -cell function.

A study by Nedeltcheva and colleagues³⁸ has provided the first evidence of a modulating effect of dietary intake on the consequences of sleep loss on glucose metabolism. In this study of overweight or obese patients on a hypocaloric weight-loss regimen, 14 days of sleep restriction to 5.5 h, compared with 8.5 h of sleep opportunity, reduced 24 h serum insulin concentrations with no effect on glucose homeostasis. This finding suggests that sleep restriction results in a state of increased insulin economy under hypocaloric conditions.

Circadian rhythm desynchrony—ie, sleeping out of phase of habitual sleeping times—has likewise been shown to adversely affect glucose metabolism. In a carefully designed experimental study,³⁹ healthy adults underwent a 10 day laboratory protocol that required them to eat and sleep at all phases of the circadian cycle, which was achieved by scheduling of a recurring 28 h day. In the test session taking place during the final period of circadian misalignment, average blood glucose concentrations increased by 6%, despite a concurrent 22% increase in circulating insulin concentrations.

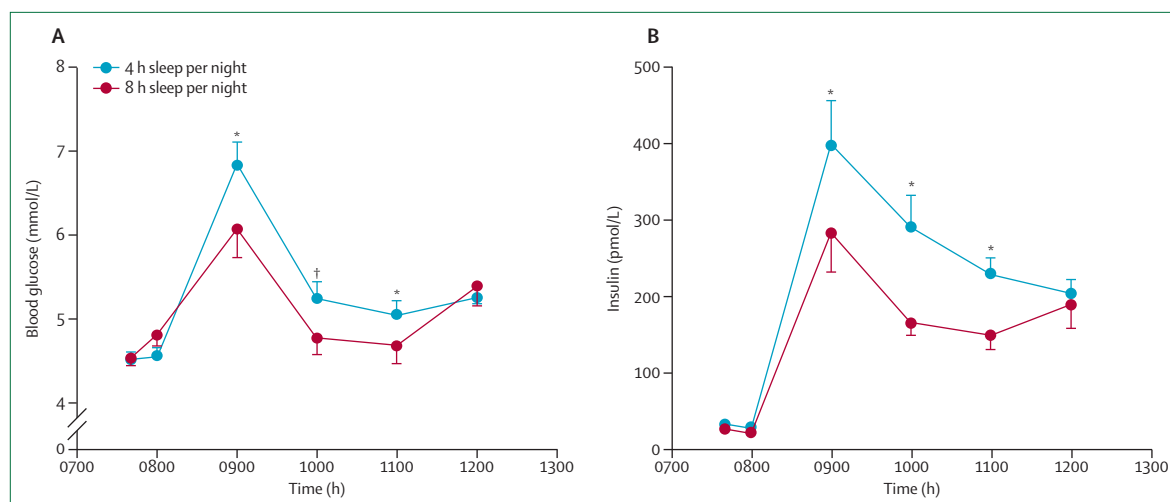


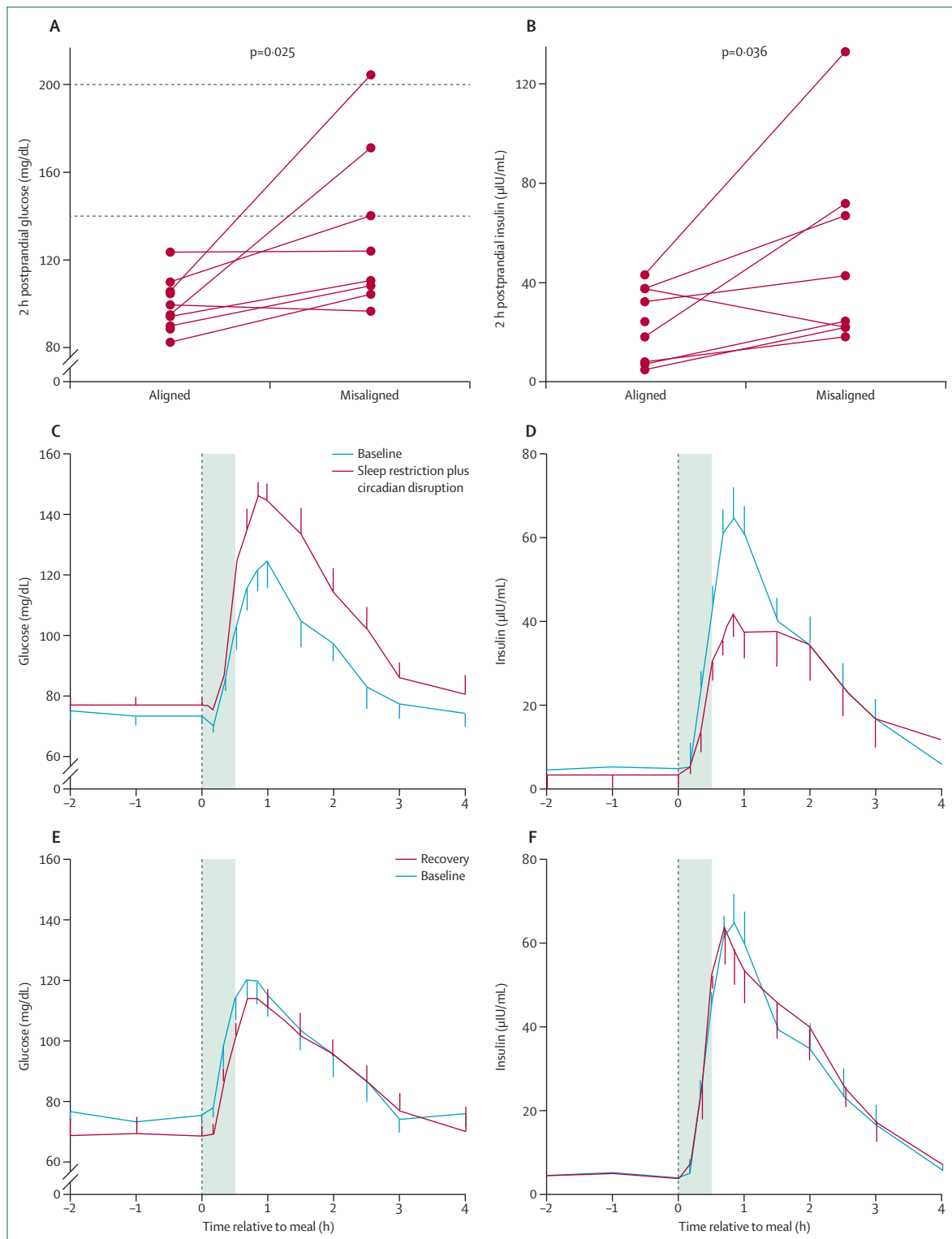
Figure 1: Effect of sleep restriction on glucose and insulin responses to a breakfast meal

Mean (SE) concentrations of plasma glucose (A) and serum insulin (B) before, during, and after breakfast. 15 healthy men were presented with an ad-libitum breakfast buffet from 0800 to 1100 h after 2 nights of sleep restricted to about 4 h (0245–0700 h) and of regular 8 h sleep (2245–0700 h), respectively. Breakfast intake was similar between conditions for total calorie intake (6159 [SE 507] vs 6272 [532] kJ) and composition. * $p < 0.05$. † $p < 0.10$. Modified from reference 33, by permission of the American Academy of Sleep Medicine.

Respective changes were most pronounced in the postprandial state and clearly showed reductions in glucose tolerance and insulin sensitivity that could not be compensated for by increased β -cell insulin secretion

(figure 2). In a comprehensive study⁴⁰ of the metabolic consequences of a combination of imposed circadian desynchrony and sleep restriction, 11 young (aged roughly 23 years) and ten older (roughly 60 years) men

Figure 2: Changes in glucose homeostasis during circadian misalignment (A, B) and after circadian misalignment combined with sleep restriction (C, D)
 Error bars show SE. Plasma concentrations of glucose (A) and insulin (B) 2 h after breakfast (of roughly 670 kcal) in ten healthy adult men and women (n=5 of each) during normal circadian alignment and in the final of four 28 h periods of circadian misalignment (shown are participants with sufficient available data). Dotted lines mark 140 mg/dL and 200 mg/dL 2 h postprandial glucose concentrations, above which concentrations are considered pre-diabetic and diabetic, respectively. Glucose (C, E) and insulin (D, F) responses to an identical standardised breakfast (bar at time 0 h) in 11 young healthy subjects (five women) under conditions of baseline sleep (≥ 10 h time in bed per 24 h), after a 3 week history of prolonged sleep restriction combined with circadian disruption (5.6 h time in bed per 24 h [C, D]), and after 9 days of stable circadian re-entrainment and recovery sleep (10 h time in bed per 24 h [E, F]). Adapted from reference 39, by permission of the National Academy of Sciences of the United States of America (A, B), and from reference 40, by permission of the American Association for the Advancement of Science (C-F).



and women spent 39 days in the laboratory on a programme of 3 weeks of 5·6 h sleep every 24 h, spread across the circadian cycle. In both age groups, this protocol led to substantially increased fasting and postprandial plasma glucose concentrations alongside concurrently decreased plasma insulin concentrations measured after the intervention (figure 2). In conjunction with the results of the previous study,³⁹ which applied a circadian desynchrony protocol without sleep loss, these findings suggest that superimposing circadian desynchrony with sleep restriction leads to a decompensation of β -cell function characterised by severely impaired insulin secretion. Fortunately, β -cell function seemed to be completely restored after a subsequent 10 days of circadian re-entrainment and sleep recovery.⁴⁰

The particular relevance of slow-wave sleep for the maintenance of glucose homeostasis has been suggested by sophisticated experiments in healthy adults in whom slow-wave sleep was strongly suppressed by selective acoustic stimulation for three consecutive nights.⁴¹ Following suppression, glucose tolerance and insulin sensitivity were greatly reduced without compensatory increased insulin secretion. A similar study confirmed these results and additionally showed that glucose metabolism remains unaffected after one night of suppression of rapid eye movement (REM) sleep.⁴² Although these results emphasise the role of slow-wave sleep in the regulation of glucose homeostasis, detrimental effects on glucose metabolism have also been shown in experiments in which sleep duration was restricted with no effect on the amount of slow-wave sleep.^{32–34,36}

Loss of sleep, especially slow-wave sleep, has been suggested to exert adverse effects on glucose homeostasis by stimulation of the hypothalamus-pituitary-adrenal (HPA) axis^{29,32,34,35,43} and sympathetic activity^{29,32,34,35,41,43} to meet the brain's increased need for glucose during wakefulness compared with during sleep.⁴⁴ However, some studies have not shown corresponding changes in HPA-axis activity^{31,33} and others have failed to detect an association between sleep-loss-induced increases in HPA axis and sympathetic activity and decreased insulin sensitivity;³⁴ as such, more work is needed to substantiate this hypothesis.

Appetite and food intake

Evidence for the assumption that the inverse association between sleep duration and bodyweight is due to food intake-stimulating effects of short sleep duration has been obtained in several laboratory studies.^{45,46} Experimental sleep restriction to about 4 h for periods ranging between 1 and 14 days has been shown to result in increased calorie consumption in most studies.^{47–50} Experiments by our group showed no difference in food intake after 2 nights of sleep restriction compared with regular sleep, arguably because unlimited access to calories led to overeating in both conditions.⁷ Increased

food intake in the laboratory setting irrespective of sleep manipulation has likewise been reported in another study⁵¹ when participants were first exposed to a regular sleep condition or to sleep restriction. Notably, here the sleep-loss intervention was followed by a compensatory reduction in calorie consumption during the subsequent period of sleep recovery. Some have argued⁷ that advancement of the time of awakening,^{48–50} compared with keeping it identical between conditions,⁷ is a prerequisite for the orexigenic effect of sleep loss to emerge. However, this assumption is not supported by findings from a study in which 1 week of sleep restriction to two-thirds of the usual time in bed, with wake-up times identical to those of the control condition, resulted in a net increase in food intake of around 680 kcal per day (albeit against a background of slightly decreased pre-intervention energy intake in the sleep-deprivation group compared with the control group).⁵²

In a study in adolescents who slept at home and participated in weekly interviews including 24 h diet recall, sleep curtailment to 6·3 h in comparison to 8·9 h for 1 week led to the consumption of foods with a higher glycaemic index and of more sweets and desserts, resulting in a trend towards increased energy intake.⁵³ Similarly, experiments from a Swedish group showed that after total sleep deprivation for one night, healthy men tend to choose large meal portions and more snacks in a computer-based task.⁵⁴ The conclusion that the potentially anabolic effect of sleep loss noted in these and other studies might favour weight gain and obesity has received experimental support in participants with unlimited access to food.^{47,55} Another study⁵⁶ exposed overweight participants aged 35–49 years to a caloric restriction diet over 14 days and concurrently provided them with a nocturnal sleep opportunity of either 5·5 h or 8·5 h. Results showed that absolute weight loss was similar in both conditions, but that sleep curtailment reduced the 1·4 kg loss of body fat achieved in the regular sleep control condition by 55%, with increases in the concurrent loss in lean body mass (figure 3). This intriguing effect of sleep restriction on body composition has been suggested to be mediated by reduced fat oxidation due to increased circulating concentrations of ghrelin.^{57,58}

Increases in ghrelin concentrations—a likely mediator of increased food intake⁵⁹—induced by sleep loss have been noted in some,^{9,10,40,54,56} but not all, studies of sleep restriction.^{7,47,49,51,52,60} Likewise, a decrease in serum concentrations of leptin, an adipokine that provides the brain with negative feedback on body fat stores,⁶¹ might increase caloric intake after sleep loss.^{9,40,43} However, many studies have reported unchanged^{7,10,49,52,56,60} or even increased concentrations of leptin^{47,51,62–65} after varying degrees of sleep restriction. These conflicting findings could result from differences in experimental protocols regarding inpatient versus outpatient design, access to food, physical activity, and the sex ratio of the sample studied. Moreover, the effect of sleep loss on the ratio of ghrelin to leptin

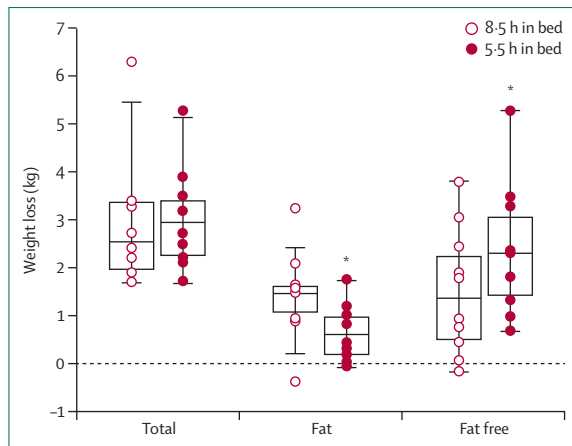


Figure 3: Changes in bodyweight and composition during dietary intervention with and without concomitant sleep restriction

Box plots show loss in bodyweight, fat, and fat-free mass in ten overweight participants (three women, mean BMI 27.4 kg/m² (SD 2.0) during 14 days of calorie restriction (to 90% of the individual resting metabolic rate at screening) accompanied by sleep restriction to 5.5 h and regular sleep of 8.5 h (time in bed; the habitual going-to-bed and getting-out-of-bed times were moved proportionally). Significant difference in loss of fat ($p=0.043$) and fat-free body mass ($p=0.002$) between conditions after study period (initial vs crossover) and pre-treatment body composition were controlled for. Adapted from reference 56, by permission of the American College of Physicians.

might mainly be present in fasted participants and therefore could represent an amplification of the regular neuroendocrine response to energy depletion.⁶⁶

The relevance of specific sleep stages for sleep-loss-induced changes in food intake has not been systematically assessed so far. Slow-wave sleep was preserved in some studies,⁴⁹ and increased in others⁵⁰ that reported increased calorie consumption after sleep loss. Furthermore, slow-wave sleep might have been unchanged in studies restricting sleep to roughly 4–5 h that did not report sleep architecture, because slow-wave sleep is usually restricted to the first half of nocturnal sleep. Divergent data exist for the role of REM sleep on control of food intake;^{67,68} future interventional studies should focus on discernible sleep stages.

The effect of restricted sleep on the brain's response to food stimuli has been examined in a series of neuroimaging experiments. Surprisingly, total sleep deprivation for one night can either reduce⁶⁹ or increase¹¹ neuronal activation in the anterior cingulate cortex, an area that is associated with appetitive evaluation processes, in response to images of high-calorie food items. These inconclusive results leave open the question as to whether sleep loss increases energy intake by enhancement or blunting of the ability to assess available food items according to their caloric value. A generally enhanced sensitivity to food stimuli of brain regions that process the rewarding quality of foods, including the putamen and nucleus accumbens, was noted after 6 nights of sleep restriction to 4 h.⁷⁰ Intriguingly, this effect of sleep loss seems to be greatest for unhealthy as

opposed to healthy food items.⁷¹ However, in behavioural studies reporting increased food intake after partial sleep deprivation, participants did not show any changes in perceived pleasantness of food or their desire to eat.⁴⁸ Daytime sleepiness is positively associated with reduced activation in the ventromedial prefrontal cortex in response to high-calorie versus low-calorie food images,⁷² suggesting that sleep debt might compromise the ability to exert inhibitory control over food intake.⁷³ Noteworthy in this context, individuals with a behavioural predisposition to disinhibited eating who sleep 6 h per night or less seem to be particularly at risk to gains in bodyweight.⁷⁴ Taken together, these observations suggest that energy depletion due to sleep loss might trigger adaptive central nervous mechanisms that favour food foraging. Future studies investigating whether these effects are more pronounced in obese individuals will be of interest.

Physical activity and energy expenditure

The effect of sleep loss on energy expenditure and on physical activity has been the subject of several different experimental approaches in healthy individuals. In accordance with previous findings that activity in the laboratory is reduced after one night of complete sleep restriction,⁷⁵ physical activity (measured with wrist-worn accelerometers) in free-living conditions was decreased by 13% after one night of partial sleep deprivation, with a concurrent shift from intensive to sedentary activities (figure 4).⁷ In line with this finding, in healthy men and women with a parental history of type 2 diabetes, 1 week of 5.5 h sleep opportunity reduced total activity counts by 31% per 24 h, and resulted in an increase in sedentary behaviour of 21 min per 24 h (figure 4).⁷⁶ Additionally, habitually short sleep (<6 h per night) is associated with a 27% decrease in levels of total body movements,⁷⁷ suggesting that insufficient sleep duration might interfere with the well-known protective effect of physical activity on metabolic health.⁷⁸ By contrast with these findings, physical activity (measured with waist accelerometry) was increased in the afternoon after one night of 4 h sleep.⁴⁸ Likewise, physical activity (measured by radar sensor) was shown to be increased in adolescent men after 3 days of 4 h sleep.⁷⁹ Other studies, which applied distinct methods to measure physical activity, did not detect any changes after restriction of sleep duration for 4–8 days.^{47,50,52} These inconsistent results call for further investigations into the effect of sleep loss on physical activity.

The effects of sleep loss on whole-body energy expenditure seem to be mainly dependent on the severity of acute sleep debt. 4 nights of incremental sleep restriction,⁴⁷ 5 nights of 4 h sleep,⁵² or 7 nights of 5 h sleep³⁴ did not change resting energy expenditure, as measured by indirect calorimetry. Likewise, total energy expenditure, assessed by the doubly-labelled-water method, was unaffected by curtailment of sleep to 4 h for 5 nights⁵⁰ or to 5.5 h for 14 days.⁴⁹ An increase in 24 h

energy expenditure of about 92 kcal (roughly 5%), measured by whole-room indirect calorimetry, was reported for women subjected to 3 nights of 4 h sleep compared with 8 h sleep.⁸⁰ By contrast with these negative or very modest effects of partial sleep loss, findings from another study⁸ showed decreases in fasting and postprandial thermogenesis of 5% and 20%, respectively, after 1 night of total sleep deprivation. Supplemental analyses in this study suggested that the reported rise in energy expenditure was a compensatory response to an increase in core body temperature during preceding nocturnal wakefulness. Another study⁸¹ reported a 7% increase in total energy expenditure, as measured in a respiratory chamber, during a 24 h period of total sleep deprivation. Importantly, this period was followed by a 5% reduction during the subsequent day and recovery sleep. Taken together, these findings suggest that compensatory mechanisms act to offset sleep loss-induced changes in whole-body energy expenditure.⁸²

Sleep loss: a challenge to the restorative function of sleep for brain and periphery?

The evidence outlined above shows that sleep loss seems to compromise whole-body energy homeostasis by impairment of glucose metabolism and the control of food intake. Experimental sleep restriction to 4.5 h for 4 days not only reduced total body insulin sensitivity by 16%, but also decreased insulin sensitivity of subcutaneous adipocytes harvested during a post-intervention biopsy by 30%.¹² A roughly similar regimen of sleep restriction for 1 week resulted in marked changes in the human blood transcriptome, affecting genes associated with circadian rhythmicity, sleep homeostasis, and metabolism.⁸³ The involvement of sleep-loss-induced genetic changes in the deterioration of metabolic control is also suggested by the upregulation of gene expression in the striatal opioid system noted after 10 days of sleep deprivation in rats.⁸⁴ Such an effect on reward-processing brain structures might contribute to the increased snacking⁴⁹ and food foraging⁵⁴ shown in sleep-deprived human beings. The stimulation of food-intake behaviour in sleep-deprived individuals might further be mediated by upregulation of the activity of the central nervous hypocretin system^{85,86} and changes in neuroendocrine factors like ghrelin and leptin, as described above.

The anabolic shift in metabolic control triggered by sleep loss via changes in central nervous and neuroendocrine pathways (figure 5) has been suggested to compensate for the additional energy need associated with extended wakefulness. However, this compensation might impose the risk of excessive weight gain in the obesigenic environment that now exists in many countries.^{51,87,46,66} Indeed, provision of additional energy in the form of continuous nocturnal glucose infusion to healthy individuals during 1 night of complete sleep deprivation completely abolishes the sleep-loss-induced

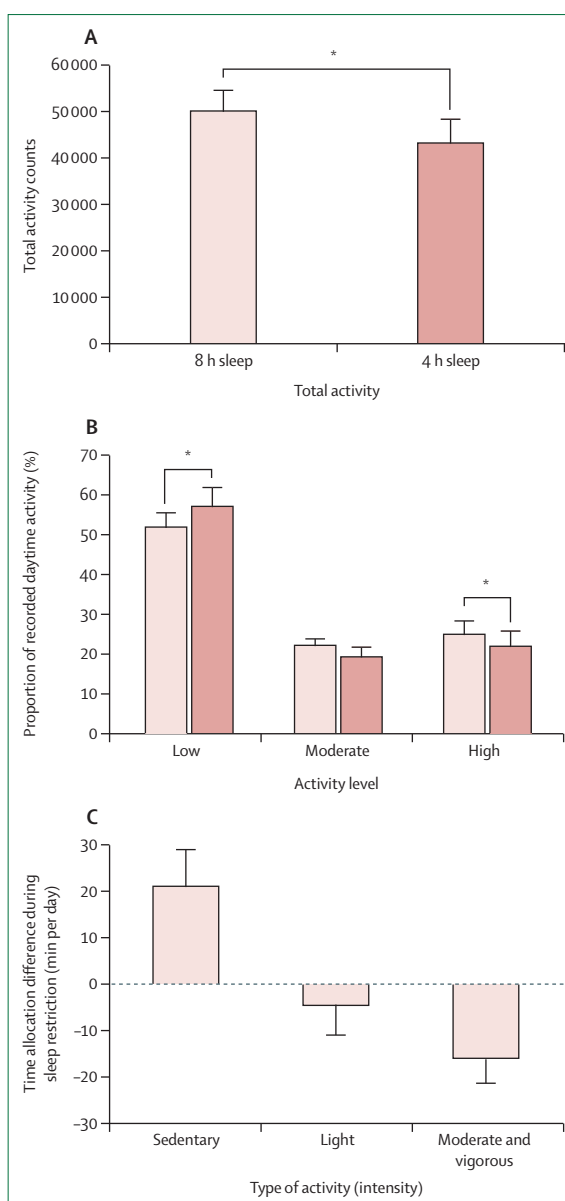


Figure 4: Effects of sleep restriction on physical activity

Mean (SE) total activity counts (A) and distribution of activity intensities (0800 h–2000 h; B) measured by wrist-worn accelerometer under free-living conditions in 15 healthy men after 1 night of sleep restricted to roughly 4 h (right bars) and another time after 1 night of regular 8 h sleep (left bars). Panel C shows mean (SE) difference in time (min per day) allocation to distinct physical activity intensities during 7 days of 5.5 h versus 2 weeks of 8.5 h of night-time sleep opportunity in 18 healthy men and women (n=9 of each) with a parental history of type 2 diabetes. Physical activity was measured by wrist and waist accelerometry. * $p < 0.05$. Modified from reference 7, by permission of the American Society for Nutrition (A, B), and from reference 76, by permission of the American Academy of Sleep Medicine (C).

increase in breakfast intake.⁸⁷ By contrast, glucose infusion to sleeping individuals does not affect subsequent food intake, suggesting that additional energy supply is well tolerated by the sleeping brain.⁸⁷ Sleep can now be safely assumed to not only have a restorative role, but also to

actively support plastic central nervous processes, such as memory consolidation.^{88,89} Thus, impairments in sleep quantity and quality might result in compensatory changes in metabolic control, not least because such impairments challenge the fine-tuned balancing of sleep-related brain activity and its energy supply.

Sleep loss as a target for the prevention and treatment of the metabolic syndrome

On the basis of the findings outlined above, sleep loss seems to be a promising target for the prevention, and probably the treatment, of the metabolic syndrome and its components. For example, treatment of obstructive sleep apnea, a disease that frequently leads to severe sleep fragmentation, with continuous positive airway pressure substantially improves metabolic traits such as glucose homeostasis, dyslipidaemia, hypertension, and obesity.⁹⁰ However, this observation should probably not be taken as a proof for the notion that treatment of sleep disturbances generally improves metabolic health,

because sleep apnoea leads not only to poor sleep quality, but also to hypoxia, which per se is associated with adverse metabolic traits^{91,92} and, likewise, is improved by treatment with continuous positive airway pressure.

Much more common than defined sleep disturbances is voluntary sleep curtailment associated with modern leisure activities, such as the use of technical devices for gaming, online shopping, social networking, or watching television.⁹³ Here, programmes of sleep education and cognitive behavioural therapies focusing on improved sleep hygiene might represent promising approaches to induce behavioural changes. Of note, several randomised, controlled clinical trials are being done of the effectiveness of such interventions to improve metabolic outcomes (NCT01717352, NCT01881724, NCT01135342). If such interventions prove to be effective, the findings will have broad public health implications.

Overall, however, the complete prevention of states of sleep loss and circadian desynchrony in globalised 24 h societies hardly seems feasible. Rather, with increasing knowledge about the physiological and behavioural consequences of such states, development of optimised working schedules (eg, for shift workers) that exert a less impairing effect on metabolic health might be possible. Improvement of environmental conditions—eg, by avoidance of noise and light, and adjustments of external zeitgebers to sleep times—might also be an effective approach to increase sleep quality and thereby its restorative function. This notion has gained strong support from a study⁹⁴ showing that nocturnal exposure to light of more than 3 lux, compared with lower intensities, is associated with adverse metabolic traits such as obesity (OR 1.89, 95% CI 1.18–3.04) and dyslipidemia (1.72, 1.11–2.68). Several rodent studies have shown that light exposure at night increases bodyweight and impairs a wide range of metabolic functions.^{95–98}

Systematic manipulation of sleep quality (eg, by enhancement of slow-wave sleep), which is of particular importance for maintenance of glucose homeostasis, might be another approach to counteract insufficient sleep. Apart from pharmacological interventions,⁹⁹ a recently introduced auditory closed-loop stimulation instrument¹⁰⁰ might be most promising in this regard. This non-invasive technology effectively enhances not only the slow oscillation rhythm of slow-wave sleep, but also its functional effectiveness with regard to memory formation. Findings from future studies examining the effects of such sleep manipulations on metabolic traits will be of interest.

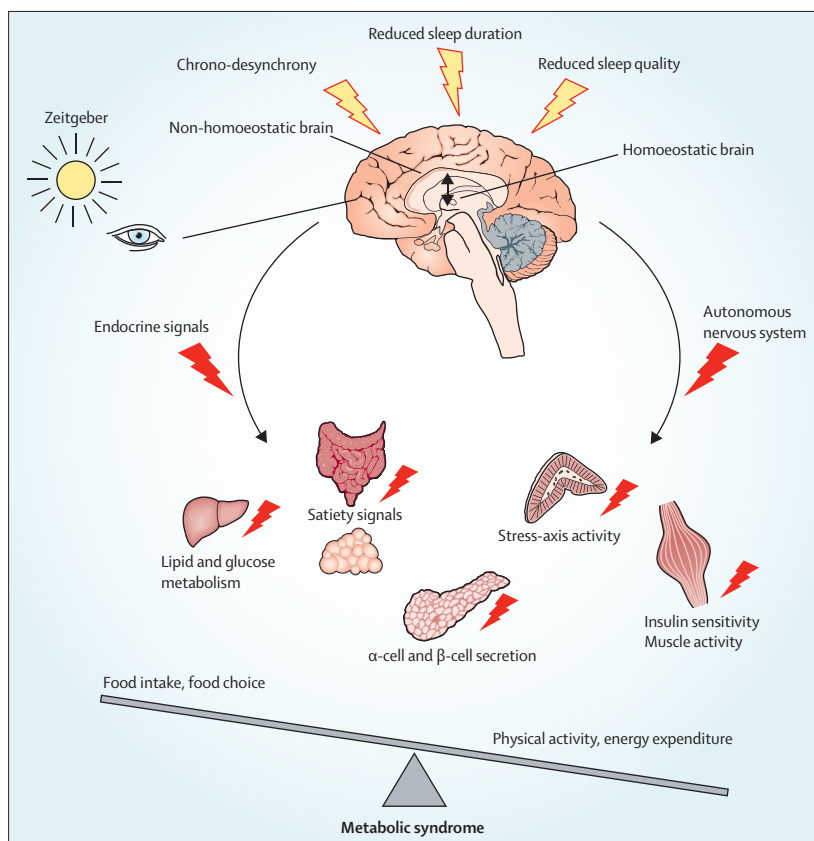


Figure 5: Schematic diagram showing how sleep loss can cause adverse metabolic traits
Reduced sleep duration and sleep quality, and circadian desynchronisation of the sleep–wake cycle (chronodesynchrony) lead via neuroendocrine efferences and modulation of autonomous nervous system activity to increased hepatic glucose production and reduced peripheral glucose uptake (eg, in muscles), changes in pancreatic α -cell and β -cell function, increased stress axis activity (eg, enhanced adrenal cortisol and catecholamine release), and change in secretion of appetite-regulating hormone (eg, ghrelin, leptin) from the gastrointestinal tract and adipose tissue, promoting food intake. These changes in conjunction with a putatively reduced physical activity and energy expenditure, eventually result in positive energy balance and cumulate in adverse metabolic traits, as observed in the metabolic syndrome.

Conclusion

In summary, observational studies have provided strong evidence for a link between sleep loss and adverse metabolic traits. A cause–effect association is suggested by a growing number of experiments that also point to distinct pathophysiological mechanisms underlying the putatively impairing effect of sleep loss on metabolic

Search strategy and selection criteria

We comprehensively searched PubMed from Jan 1, 1998, to Sept 31, 2013, for peer-reviewed articles with the search terms “sleep loss” and “sleep restriction” combined with “metabolic syndrome”, “metabolism”, “food intake”, “body weight”, “energy homeostasis”, “energy expenditure”, “obesity”, “diabetes”, “dyslipidemia”, and “hypertension”. The search focused on reports written in English. We also screened the reference lists of relevant papers for pivotal findings on the basis of design and findings. With regard to epidemiological studies, whenever possible we gave priority to meta-analyses. Because of space constraints, we could not cite every paper of potential relevance and the reader is advised to consult the reference lists of the cited in-depth reviews for additional literature.

health. These findings open up new strategies for targeted interventions aimed at the present epidemic of the metabolic syndrome and related diseases. Ongoing and future studies will show whether interventions to improve sleep duration and quality can prevent or even reverse adverse metabolic traits. Meanwhile, on the basis of existing evidence, health care professionals can be safely recommended to motivate their patients to enjoy sufficient sleep at the right time of day.

Contributors

SMS, MH, BS conceptualised the Review; did the literature research; arranged the figures; and wrote, revised, and approved the manuscript.

Declaration of interests

We declare that we have no competing interests.

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