# Sleep, Health, and Society

## From Aetiology to Public Health

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Chapter 6

# Sleep and metabolic disease

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## Introduction

Metabolic diseases include diabetes and obesity, both of which are associated with reduced quality of life (QOL), decreased life expectancy, and increased economic burden on both the individual and on society (Solomon and Manson, 1997; Wolf and Colditz, 1998; Ettaro et al., 2004; Franco et al., 2007). Rates of obesity in the United States have doubled since 1980 (Flegal et al., 1998, 2002) and the age-adjusted percentage of persons with diagnosed diabetes has also nearly doubled in the United States between 1980 and 2006 (Ioannou et al., 2007; Centers for Disease Control, 2006; Gregg et al., 2004) (see Fig. 6.1). The epidemics of obesity and diabetes are not limited to the United States, however. Rates of both conditions are increasing rapidly worldwide (Wild et al., 2004). Obesity and diabetes, and their consequences, are truly a global problem.

Due to the potentially devastating consequences of these metabolic diseases, it is imperative that modifiable causes of both diabetes and obesity be identified as potential areas of intervention. Because this increase in prevalence was so rapid, occurring over a mere 20- to 30-year period, changes in the genetic composition of the population cannot be blamed. Therefore, environmental and/or behavioural factors must be responsible for the increased rates of obesity and diabetes in the United States and worldwide. Although changes in diet and exercise have played an important role, another possible explanation for the epidemic is reduced sleep duration and quality. There is some evidence that average sleep duration in the United States has declined over the same time period as the increase in obesity and diabetes (Gallup Organization, 1995, 1979; Breslau et al., 1997; Kripke et al., 1979; National Sleep Foundation, 2001). For example, a report from the National Health Interview Survey indicated the percentage of adults reporting sleeping 6 hours or less increased by approximately 5–6% between 1985 and 2004 (National Center for Health Statistics, 2005). Sleep loss may be the result of either a voluntary restriction of time spent in bed or as a result of a sleep disorder, particularly obstructive sleep apnoea (OSA), the prevalence of which has increased in association with the increase in obesity. This chapter will explore the evidence for an association between metabolic diseases and sleep duration and quality.

Three potential pathways leading from insufficient or disturbed sleep to diabetes and obesity are presented in Fig. 6.2. First, short or disturbed sleep may impair glucose metabolism thereby increasing the risk of developing insulin resistance and diabetes independently of changes in weight. Second, short or disturbed sleep may lead to an increase in appetite, which would increase the risk of weight gain if food intake increased without a compensatory increase in energy expenditure. If the weight gain is substantial, it could lead to the development of obesity, which is a major risk factor for the development of insulin resistance and type 2 diabetes. Finally, the third pathway would involve a reduction in energy expenditure after sleep loss, which could also increase the risk of weight gain. This third pathway, however, remains understudied and is only proposed here as a possibility.

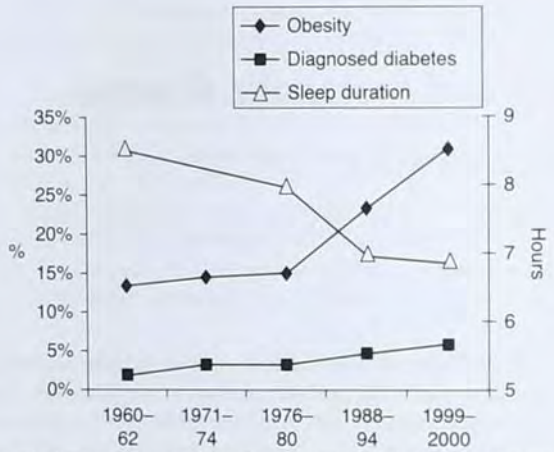


**Fig. 6.1** Prevalence of obesity (BMI > 30 kg/m$^2$), prevalence of diabetes and average self-reported sleep duration in the US between 1960 and 2000 (Gallup Organization, 1979,1995; Kripke et al., 1979; Breslau et al., 1997; Flegal et al., 1998; National Sleep Foundation, 2001; Flegal et al., 2002; Gregg et al., 2004).

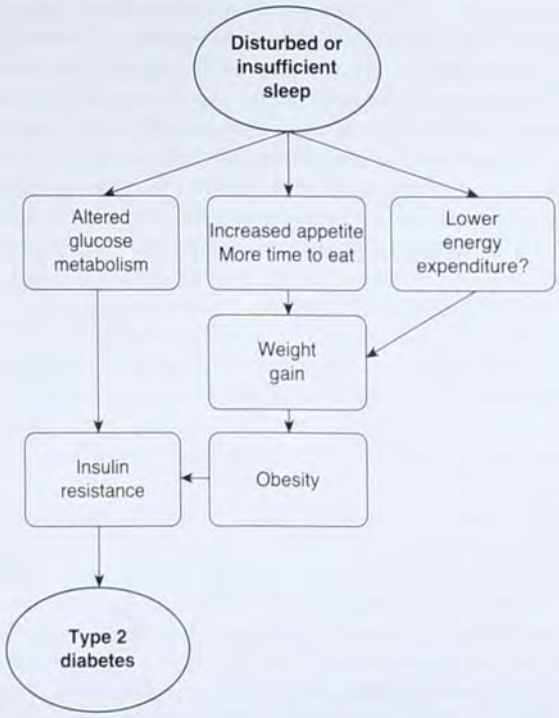


**Fig. 6.2** Potential pathways linking disturbed or insufficient sleep to the development of obesity and diabetes.

## Sleep and glucose metabolism—an overview

In healthy individuals, glucose levels in the blood are tightly regulated through a balance between glucose production (either from the liver or from nutrient-derived glucose in the gut) and glucose utilization by tissues. Insulin plays a key role in this process by inhibiting glucose production in the liver and by stimulating glucose uptake by insulin-sensitive tissues (i.e. muscle, liver, and fat cells). Glucose tolerance refers to the ability of the body's tissues to absorb exogenous glucose from the blood and return blood glucose levels to baseline values. Glucose tolerance is assessed in response to either oral glucose administration, intravenous glucose administration, or meals containing carbohydrates. Insulin sensitivity (SI) and insulin resistance refer to the ability of insulin to exert its effects in target cells and is the best predictor of future development of diabetes. The cellular response elicited by insulin depends on the cell type involved. For example, following a meal, there is an increase in blood glucose, which leads to insulin secretion by pancreatic beta (β)-cells. Insulin binding to its receptor in muscle cells leads to glucose uptake by the muscle to be used as immediate energy or stored as glycogen for use by the muscle cell during times of fasting. When muscle cells become insulin resistant, the same amount of secreted insulin does not induce glucose uptake into the cell, and therefore glucose remains in the blood at elevated concentrations.

In the liver, insulin signalling suppresses gluconeogenesis, which is the production of *de novo* glucose from precursor molecules and is unnecessary in the face of glucose ingestion. Insulin resistance in this tissue results in a lack of inhibition of gluconeogenesis, leading to further elevations of blood glucose. Reduced muscle glucose uptake and increased liver glucose production both contribute to elevated blood glucose levels and decreased insulin action. High blood glucose can have a number of deleterious health consequences, including blood vessel damage, kidney disease, glaucoma, and nerve damage if not controlled. An inadequate reduction of blood glucose then leads to additional insulin secretion by the pancreas, a phenomenon known as β-cell compensation. In this situation, only a higher amount of insulin will result in the desired amount of glucose clearance. Muscle, kidney, and liver account for ~75–85% of glucose disposal. Brain glucose uptake has been reported to use up to ~15–20% of ingested glucose, resulting in at least 90% of glucose disposal accounted for by liver, muscle, brain, and kidney (Meyer et al., 2002) thus even small changes in these tissues' sensitivity to insulin signalling could robustly affect global energy metabolism.

Another important insulin sensitive tissue is the adipose tissue, in which the main function of insulin is to inhibit the mobilization and release of triglycerides into the blood stream (lipolysis). Adipose tissue can account for 2–10% of glucose uptake (Marin et al., 1992), which is partially metabolized to triglyceride precursors for storage and subsequent release into circulation when necessary. The critical role of adipose tissue is as a lipid storage depot. Insulin resistance in these cells impairs the ability of insulin to inhibit lipolysis, which leads to elevated blood fatty acid levels. Fatty acids in the blood can result in the inappropriate accumulation in other tissues, such as muscle and liver. The presence of fatty acids in these areas further impairs insulin action through various mechanisms. In the fed state, insulin acts on adipocytes (fat cells) to inhibit lipolysis and adipocytes respond to glucose uptake by secreting leptin, an adipocyte-derived satiety hormone which signals to the hypothalamus to inhibit feeding in the presence of adequate energy intake. The characterization of leptin as an adipocyte-derived factor was the pivotal discovery that established adipose tissue as not just a lipid storage depot, but an entire endocrine organ responsible for secreting a variety of adipokines, which are important regulators of energy balance and metabolism. Adipokines can affect feeding through proximal signalling to nearby tissues as well as more distal signalling in the hypothalamus

of the brain. This will be further discussed in a later section regarding appetite regulation and the effects of sleep on these functions.

## Glucose metabolism in relation to normal sleep

During normal sleep, glucose tolerance is highest in the morning and lowest in the middle of the night (Van Cauter et al., 1997). This fluctuation appears to be related to reduced SI combined with reduced insulin secretion, resulting in elevated glucose levels in the middle of the sleep period. Optimal glucose tolerance is observed in the morning and decreases throughout the day and into the sleep period.

Exogenous glucose injection will inhibit glucose production by the liver. Therefore, changes in plasma glucose levels during constant glucose infusion reflect changes in glucose effectiveness, which is the ability of glucose to mediate its own disposal independently of insulin. In these studies, higher plasma levels of glucose would indicate reduced glucose effectiveness. In one such study, during 8 hours of nocturnal sleep, plasma glucose levels rose at the beginning of the sleep period, peaked around midsleep, and then declined back to pre-sleep levels (Scheen et al., 1996), indicating reduced glucose effectiveness during sleep. The insulin secretory rate (ISR) followed a very similar pattern to the plasma glucose levels, except that these changes occurred approximately 9 minutes after the changes in glucose levels (Scheen et al., 1996). When subjects were allowed to sleep in the daytime after a night of total sleep deprivation, plasma glucose levels increased abruptly (Scheen et al., 1996). The glucose increase during sleep was positively correlated with stages 2–4 of non-rapid eye movement (NREM) sleep, while glucose levels declined during periods of prolonged wakefulness (Scheen et al., 1996). Rapid eye movement (REM) sleep did not appear to impact glucose levels since they remained stable during REM. Thus, the pattern of glucose levels observed during sleep reflects the pattern of sleep stages during the night: greater NREM sleep in the early part of the night and greater wake and less NREM sleep during the later part of the night. Results from positron emission tomography (PET) demonstrated that whole-brain glucose metabolism declined significantly from wake to NREM sleep (Nofzinger et al., 2002). Since the brain glucose utilization is not mediated by insulin, this decline in brain glucose utilization would result in reduced glucose effectiveness. The increase in glucose levels during sleep may also partly reflect decreased glucose utilization by peripheral tissues. Glucose regulation is thus markedly affected by the sleep-wake cycle.

## Glucose metabolism in response to experimental manipulations of sleep

The effects of acute total sleep deprivation over one night have been examined using constant glucose infusion. The typical pattern of plasma glucose levels during sleep (described above) was not observed during total sleep deprivation. During total sleep deprivation, plasma glucose levels do not exhibit the large increase that is observed during sleep (Scheen et al., 1996). Also, plasma glucose levels were higher in the morning after sleep deprivation than after a night of sleep despite similar insulin levels, suggesting that total sleep deprivation may impair insulin action. The pattern of glucose secretion during nocturnal sleep deprivation may be partly due to the absence of slow wave sleep (SWS) and growth hormone (GH) secretion at the beginning of the night. The effects of total sleep deprivation on metabolism or endocrine profiles are not the same as the effects of partial sleep deprivation (Knutson et al., 2007).

Total sleep deprivation can only be maintained for a brief period of time and does not reflect typical real-world behaviour. Chronic partial sleep restriction, on the other hand, is practiced by many people throughout the United States and the world. Recent estimates from the National

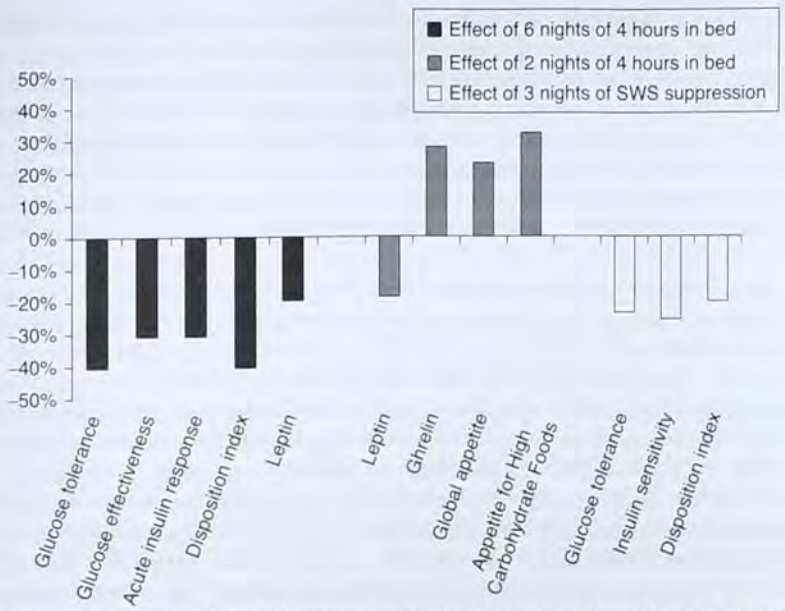


**Fig. 6.3** Summary of results from 3 laboratory studies that manipulated sleep (Spiegel et al., 1999; Spiegel et al., 2004; Tasali et al., 2008).

Sleep Foundation indicate that 16% of adults who work at least 30 hours per week report sleeping less than 6 hours per night on weekdays (National Sleep Foundation, 2008). The first detailed laboratory study of the effects of partial sleep deprivation on glucose metabolism subjected healthy young men to 6 nights of 4 hours in bed followed by 7 nights of 12 hours in bed (Spiegel et al., 1999). On the last 2 days of each condition, the subjects ate identical carbohydrate-rich meals and were at continuous bed rest. Subjects had an intravenous glucose tolerance test (ivGTT) in the morning after the fifth night of each condition followed by 24 hours of blood sampling at 10- to 30-minutes interval (Spiegel et al., 1999). Glucose tolerance was 40% lower, glucose effectiveness was 30% lower, and the acute insulin response to glucose ($AIR_G$) was also 30% lower (Fig. 6.3). SI was lower after sleep restriction but it was not statistically significant. Comparison of the glucose tolerance values observed in this study to values obtained in different subject populations using the same ivGTT protocol indicated that the glucose tolerance values observed after 5 days of sleep restriction were similar to those observed in older adults with impaired glucose tolerance (Garcia et al., 1997), while the values observed after sleep recovery were, as expected, in the range typical of healthy young subjects (Prigeon et al., 1995). The disposition index (DI) is a marker of diabetes risk and is the product of $AIR_G \times SI$, which will remain constant in healthy individuals because β-cell function is able to compensate for insulin resistance with increased insulin release (Bergman et al., 2002). Type 2 diabetes occurs when the pancreatic β-cells are not able to compensate for insulin resistance, resulting in hyperglycaemia. Thus, lower DI values represent a higher risk of type 2 diabetes. DI values of 2,000 and above are typical of subjects with normal glucose tolerance, while DI values under 1,000 have been reported in populations at high risk for type 2 diabetes (Xiang et al., 2006). After sleep restriction, the DI was 40% lower than after sleep extension and 3 of the 11 subjects had DI values under 1,000. These results suggest that a few days of bedtimes restricted to 4 hours in bed could increase the risk of developing impaired glucose tolerance or diabetes.

One limitation to this study was that there may have been an order effect since sleep extension always followed sleep restriction (Youngstedt and Kripke, 2004). A second study compared the effect of 4 hours in bed per night for 2 nights to the effect of 10 hours in bed per night for 2 nights using a randomized cross-over design in healthy lean young subjects. After the second night of both conditions participants underwent constant glucose infusion and blood samples were collected every 20 minutes from 8:00 to 21:00 hours. These results were similar to the findings of the previous sleep restriction study. Between 9:00 and 11:00 hours, glucose levels were higher and insulin levels were lower after 2 days of 4-hour bedtimes than after 2 days of 10-hour bedtimes (Spiegel et al., 2005).

Recently, the effects of an experimental reduction in SWS on glucose metabolism in nine healthy, lean subjects aged 20–31 years were examined. Investigators in this study used noise to inhibit the transition to the SWS stages (stages 3 and 4), resulting an overall reduction in sleep *quality*, rather than quantity. Glucose metabolism after three nights of SWS suppression was compared to glucose metabolism after two nights of undisturbed sleep. Both conditions allowed for 7.5 hours in bed and total sleep time did not differ significantly between the two conditions. Suppression of SWS was associated with 23% reduction in glucose tolerance, 25% reduction in SI, and 20% reduction in the DI (Fig. 6.3) (Tasali et al., 2005). The results of this study suggest that sleep quality, in addition to sleep duration, may play an important role in glucose metabolism.

A second study of healthy, non-obese men aged 20–35 years examined the effects of sleep restricted to 5 hours per night for 7 days compared to 13 days of 10 hours in bed (Buxton et al., 2008). This study used a euglycaemic hyperinsulinaemic clamp technique, which involves measuring the amount of glucose infusion required to maintain constant blood glucose levels in the face of increased insulin administration. A higher rate of glucose infusion indicates greater SI. In this study, SI was reduced by approximately 11% after sleep restriction. This experimental study that involved less severe sleep loss further supports the hypothesis that sleep restriction, at least for one week or less, can impair glucose regulation.

Another recent study attempted to examine the effects of restricting bedtimes of elderly long sleepers on glucose metabolism (Zielinski et al., 2008). They enrolled 40 adults, 50–70 years old who reported that they slept an average of 9.5 hours or more per day. Actigraphic recordings in these individuals indicated that they averaged in fact only 7.5–7.9 hours per night. Subjects were randomly assigned to one of two groups: (1) the experimental group where bedtime was restricted by 90 minutes and (2) the control group who maintained a fixed bedtime schedule. At the end of the intervention, participants in the bedtime restriction averaged 6.55 hours of sleep per night and participants in the control group averaged 6.82 hours per night, a difference of approximately 16 minutes. Fasting glucose increased by 1% in the experimental group and decreased by 4% in the control group, which resulted in a statistically significant post-treatment effect. Pre-treatment SI, which was derived from fasting glucose and fasting insulin levels, was significantly higher in the restriction group, which suggests that randomization did not successfully lead to similar groups at baseline. Nonetheless, the results of these studies suggest that sleep restricted to 6.5 hours per night in older adults does not impair glucose metabolism. Another important finding from this study is that self-reported long sleepers may not, in fact, be long sleepers, but rather be suffering from poor sleep efficiency. Additional research is required to understand the increased morbidity and mortality risk associated with self-reported long sleep (see also Chapter 4).

## Sleep and appetite regulation—an overview

As discussed above, adipokines secreted from fat cells can affect feeding in a variety of ways, including proximal signalling to nearby tissues, as well as more distal signalling in the hypothalamus

of the brain. The arcuate nucleus of the hypothalamus is considered the feeding area of the brain and exerts potent effects on appetite, energy expenditure, and glucose homeostasis. Neurons in this nucleus are regulated by input from a variety of locations in the periphery, including adiposity signals (leptin), gut-derived signals (ghrelin and peptide YY [PYY]), and nutrient-derived signals (free fatty acids) (Schwartz and Porte, 2005). As with most biological systems, the arcuate nucleus contains opposing sets of neuronal circuitry: appetite simulating and appetite-inhibiting neurons (Gale et al., 2004). Ghrelin and PYY, both produced in the gut, have opposing effects on energy balance via an impact on neuronal activity in the arcuate nucleus. Ghrelin, secreted by gastric cells, stimulates appetite, whereas PYY, secreted by intestinal cells, inhibits feeding. Both leptin, produced in adipose tissue, and insulin, secreted by the pancreas in response to a meal, inhibit orexigenic neurons and activate anorexigenic neurons, leading to a decrease in feeding behaviour (Schwartz and Porte, 2005; Porte et al., 2005). Many of these hormones have been implicated as targets of sleep deprivation, specifically leptin.

Leptin is primarily a starvation signal from peripheral tissues to the hypothalamic region of the brain to indicate inadequate energy reserves (Flier, 2004). A decrease in leptin leads to a subsequent increase in feeding. The regulation of leptin is complex and is not entirely understood, however, it is known that leptin secretion is stimulated directly in response to glucose uptake. Leptin secretion requires both insulin signalling, as well as the stimulated uptake of glucose into the adipocyte. When glucose uptake and/or metabolism are impaired, leptin secretion is reduced and appetite is increased (Mueller et al., 1998). Conversely, exogenous leptin treatment inhibits feeding in animals and leptin-deficient humans (Farooqi, 2002).

## Appetite regulation in response to experimental manipulations of sleep

Several laboratory studies have examined the effects of sleep restriction on one or more hormones involved in appetite regulation. The laboratory study discussed above that involved 6 nights of 4-hour bedtimes followed by 6 nights of 12-hour bedtimes reported that mean leptin levels were 19% lower during sleep restriction (Fig. 6.3) (Spiegel et al., 2004a). These changes in leptin levels occurred despite identical caloric intake and physical activity and no change in weight (Spiegel et al., 2004a). The maximal leptin level during sleep restriction was on average 1.7 ng/mL lower, which is somewhat larger than the decrease in leptin reported in young adults after 3 days of dietary intake restricted to 70% of energy requirements (Spiegel et al., 2005; Chin-Chance et al., 2000). Another group recruited eight healthy men aged 18–25 years to compare the effects of 7 days with 4-hour bedtimes to a 3-day recovery period with one night of *ad libitum* sleep followed by 2 nights with 7.5 hours in bed. They found that leptin levels were approximately 33% lower after sleep restriction ($P < .001$) (Guilleminault et al., 2003).

The impact of 2 days of 4-hour bedtimes versus 2 days of 10-hour bedtimes on leptin, ghrelin, and subjective appetite was examined in the laboratory study discussed above that used a randomized cross-over design (Fig. 6.3). Again, this study involved constant glucose infusion after the 2 nights of sleep restriction or extension and 20-minute blood sampling (Spiegel et al., 2004b). Mean leptin levels were 18% lower and mean ghrelin levels were 28% higher in the sleep restriction condition relative to sleep extension (Spiegel et al., 2004b). Appetite was measured using visual analogue scales and was 23% higher during sleep restriction. Furthermore, the increase in appetite for high calorie, carbohydrate-rich foods (including sweets, salty snacks, and starchy foods) was greater than for other food types (Spiegel et al., 2004b). Finally, the change in the ratio of ghrelin-to-leptin between the two conditions was strongly correlated to the change in hunger ratings ($r = 0.87$; $P = 0.01$), suggesting that the changes observed in these appetite hormones was

partially responsible for the increase in subjective appetite. These observed changes would suggest that these subjects would have increased their food intake if they had been allowed *ad libitum* food, and a more recent study has confirmed this. Ten young lean subjects underwent two nights of baseline sleep with 8.5 hours in bed and four nights of 4.5 hours in bed in a randomized order (Tasali et al., 2009). At the end of each condition, subjects had access to a buffet lunch, buffet dinner, and unrestricted snacks. Caloric intake after sleep restriction was increased by approximately 460 kcal ($P = 0.04$), and was particularly increased for carbohydrate-rich foods (Tasali et al., 2009).

A separate laboratory study enrolled 11 sedentary men and women aged 34–49 years who were overweight (body mass index [BMI] between 24 and 29 kg/m$^2$) to examine the effects of more mild sleep restriction (Nedeltcheva et al., 2009). These subjects completed two 14-day periods consisting of either 5.5 hours or 8.5 hours in bed in a randomized order. Average daily caloric consumption from meals across the 14 days did not differ significantly between the two conditions, however, caloric intake from snacks was significantly increased in the sleep restriction condition (Nedeltcheva et al., 2009). Average 24-hour leptin and total ghrelin levels as well as energy expenditure did not differ significantly between the two conditions. Subjects in both conditions gained an average of 2 kg of weight, reflecting the obesogenic environment of the laboratory that included sedentary activity combined with unlimited palatable food. The absence of an effect of sleep restriction on leptin and ghrelin may reflect differences in the effects of this more mild sleep restriction on overweight individuals. Alternatively, the effects of the obesogenic environment and subsequent weight gain may have been so large that they masked any potential effects of mild sleep restriction.

## Potential mechanisms

The deleterious effects of sleep perturbations on health outcomes are unlikely to be attributed to an alteration of a single metabolic variable. Rather these effects are more likely due to a constellation of changes that in their gestalt result in an increased risk of diabetes and obesity if the behaviour should become chronic. It has been postulated that the increase in blood glucose levels in studies of subjects undergoing total sleep deprivation is a result of decreased brain glucose utilization, as seen in studies using PET (Thomas et al., 2000). The reductions observed in insulin-independent glucose disposal in studies of restricted sleep are consistent with this hypothesis since, as mentioned above, brain glucose uptake is a non–insulin-mediated phenomenon.

Another mechanism by which sleep restriction increases the risk of obesity and subsequently diabetes is the observed increase in hunger and appetite in the laboratory studies. It has been suggested that this subjective increase in hunger may be a result of decreased inhibition of hypothalamic activity following sleep restriction. A loss of inhibition on orexigenic neurons in the hypothalamus would result in increased hunger and decreased ability to control that hunger (Gautier et al., 2001; Thomas et al., 2000).

Additionally, 6 days of sleep restriction were associated with an extended duration of elevated nighttime GH concentrations (Spiegel et al., 2000) and with an increase in evening cortisol levels (Spiegel et al., 1999), both of which could exacerbate already deleterious alterations in glucose regulation. For example, elevated evening cortisol concentrations are likely to result in reduced SI on the following morning, leading to an additional increase in blood glucose following sleep restriction (Van Cauter et al., 1997). Increased levels of GH can lead to an induction of a transient insulin resistance in muscle cells, resulting in decreased glucose uptake, elevated blood glucose levels, and subsequent increases in insulin resistance in other tissues. Finally, acute total sleep loss or even a 2-hour reduction of sleep per night for 1 week is associated with increased levels of proinflammatory cytokines and low grade inflammation, a condition known to predispose to insulin resistance and diabetes (Vgontzas et al., 1999, 2004) (see also Chapter 11).

Lastly, increased sympathetic nervous activity is a likely contributor to the increased risk of diabetes and obesity following chronic partial sleep restriction. Increased sympathetic nervous activity at the level of the pancreas could result in a reduction of insulin secretion from pancreatic β-cells. In both laboratory studies of sleep restriction described above, cardiac sympatho-vagal balance, derived from estimations of heart rate variability, was elevated (likely reflecting an increased influence of sympathetic tone) when sleep was restricted (Spiegel et al., 1999, 2004a). However, sympatho-vagal balance at the level of the pancreas has not yet been assessed in any study, but the findings mentioned above would suggest an alteration at this site as well.

## Observational studies of sleep and metabolic disease

Laboratory studies of sleep restriction provide essential insight into potential mechanisms because they are typically conducted in well-controlled environments and involve detailed physiological measurements. One limitation, however, is that laboratory studies can only be short term, lasting a few weeks at most. This leads to the question of whether the associations observed in the laboratory persist in the real world when sleep restriction becomes chronic. Observational studies, especially large population-based epidemiological studies, can provide some insight into the associations between sleep and health outside of the laboratory.

Several large observational studies have reported associations between sleep duration or quality and the presence of diabetes (see also Chapter 5). The Sleep Heart Health Study is a large multicentre cohort study that has performed an overnight in-home polysomnography (PSG) in approximately 6,000 adults 40 years of age and older to determine the cardiovascular and other consequences of sleep-disordered breathing (SDB) (Quan et al., 1997). Results from this study indicated that the odds of having diabetes was significantly higher in those reporting sleeping 5 hours or less (odds ratio [OR]: 2.51; 95% confidence interval [CI]: 1.57–4.02), 6 hours (OR: 1.66; 95% CI: 1.15–2.39), and 9 or more hours (OR: 1.79; 95% CI: 1.08–2.96) compared to 7–8 hours per night (Gottlieb et al., 2005). The OR of having impaired glucose tolerance was significantly higher in those sleeping 6 hours (OR: 1.58; 95% CI: 1.15–2.18) or 9 or more hours (OR: 1.88; 95% CI: 1.21–2.91) compared to 7–8 hours (Gottlieb et al., 2005). Another study of over 1,200 American adults aged 34–54 years also found a U-shaped association between self-reported sleep duration and diabetes (Hall et al., 2008). Adults who reported sleeping less than 6 hours (OR: 1.74; 95% CI: 1.18–2.55) or more than 8 hours (OR: 1.70; 95% CI: 1.04–2.80) per night were more likely to have diabetes than those reporting 7–8 hours per night. Results from the Quebec Family Study in Canada also found a U-shaped association between self-reported sleep duration and the prevalence of type 2 diabetes or impaired glucose tolerance in both men and women (Chaput et al., 2007a). A smaller study in the United States among 210 adults aged 30–54 years used the Pittsburgh Sleep Quality Index (PSQI), which is a validated questionnaire that assesses sleep quality, and found that worse sleep quality was significantly associated with higher serum insulin and glucose levels after adjustment for age and sex (Jennings et al., 2007). The PSQI was completed in another US study of healthy men and women, and the results indicated that frequent problems falling asleep was associated with higher insulin levels in women but not in men (Suarez, 2008).

Similar studies have been conducted in Asia and Europe as well. A study in Korea of over 4,000 adults did not find a significant association between self-reported sleep duration and hyperglycaemia (fasting blood glucose ≥ 5.6 mmol/L) in adults less than 60 years old, however, there was a trend ($P = 0.07$) for higher glucose with increasing sleep duration in those aged 60 years and older (Choi et al., 2008). A Japanese study that used homeostasis model assessment-estimated insulin resistance (HOMA-IR) reported that the OR of having elevated insulin resistance (HOMA-IR > 2.0) was higher among those reporting sleeping less than 6 hours per night compared to those sleeping

6 or more hours per night (OR: 2.17; 95% CI: 1.10–4.26). After adjustment for self-reported sleep quality, only long sleep duration (≥8 hours) predicted high fasting plasma glucose (>125 mg/dL) in over 1,000 adults aged 20 years or older from rural Japan, however, the prevalence of high haemoglobin A1c (HbA1c) (≥6.5%) was significantly higher in those sleeping less than 6 hours (OR: 4.96; 95% CI: 1.03–23.96), 8to <9 hours (OR: 2.92; 95% CI: 1.03–8.27), and ≥9 hours (OR: 4.96; 95% CI: 1.70–14.50) compared to 7 to <8 hours per night (Nakajima et al., 2008). Two studies, one from India and one from Sweden, found greater difficulty initiating sleep, maintaining sleep, and excessive daytime sleepiness among patients with diabetes compared to healthy controls (Sridhar and Madhu, 1994; Gislason and Almqvist, 1987), however, a study in Finland found no difference in self-reported sleep time or sleep complaints between patients with type 2 diabetes and controls (Hyyppa and Kronholm, 1989). Sex differences in the association between sleep duration and prevalent diabetes were observed in a Finnish study (Tuomilehto et al., 2008). Prevalence of type 2 diabetes was significantly higher in women who were short (≤6 hours) and long (≥8 hours) sleepers compared to women who slept 7 hours per night after adjustment for many covariates including BMI and probability of sleep apnoea among others, however, there was no association in men (Tuomilehto et al., 2008). One limitation to these studies is that they used self-reported sleep duration and quality, but one study used wrist activity monitoring to estimate habitual sleep duration and quality (Trento et al., 2008). They observed greater sleep fragmentation and movement time in those with type 2 diabetes as compared to healthy controls (Trento et al., 2008). A study in children also examined the association between sleep and markers of glucose metabolism. These investigators reviewed clinical charts of 40 obese children aged 3.5–18.5 years without diabetes who had one night of PSG in the sleep clinic and found that only age, total sleep time, and percent of REM sleep were significant predictors of insulin resistance as estimated by the HOMA-IR method, but apnoea-hypopnoea index (AHI), SWS, BMI, and measures of oxygen desaturation were not significant (Flint et al., 2007). The results of these studies suggest a cross-sectional association between diabetes and short sleep duration or poor sleep quality, however, the causal direction cannot be determined. Poor or insufficient sleep may increase the risk of developing diabetes, as the laboratory studies suggest, or having diabetes may impair one's sleep.

Several prospective epidemiological studies conducted in the United States have examined the association between sleep duration or disturbance and incident diabetes. The Nurses Health Study, which recruited married female nurses aged 30–55 years in 1976, found an increased risk of diabetes over 10 years among those reporting sleeping less than 6 hours or 9 or more hours per night relative to 7–8 hours, after controlling for many covariates such as shift-work, hypertension, exercise, and depression (Ayas et al., 2003). Adjusting for BMI resulted in a significant risk of incident diabetes for the long sleepers only (Ayas et al., 2003), suggesting that BMI may be on the causal pathway between short sleep and the development of diabetes. When predicting only those cases of diabetes that had symptoms, which included itching, coma, frequent urination, hunger, weight loss, and thirst, sleeping ≤5 hours (OR: 1.37; 95% CI: 1.07–1.77) and sleeping 9 or more hours (OR: 1.36; 95% CI: 1.04–1.73) were associated with a significant increase in incident symptomatic diabetes compared to sleeping 7–8 hours even after adjustment for covariates including BMI (Ayas et al., 2003). Analysis of data from the National Health and Nutrition Examination Survey also demonstrated that diabetes incidence was significantly higher in those reporting sleeping ≤5 hours (OR: 1.47; 95% CI: 1.03–2.09) and those reporting sleeping 9 or more hours (OR: 1.52; 95% CI: 1.06–2.17) compared to those reporting sleeping 7 hours per night after adjusting for covariates including physical activity, depression, alcohol, ethnicity, education, marital status, age, overweight/obesity, and hypertension (Gangwisch et al., 2007). The Massachusetts Male Aging Study recruited men aged 40–70 years in 1987–1989 and examined

them again in 1995–1997 and 2002–2004 (Yaggi et al., 2006). Among men without diabetes at baseline, the odds of developing diabetes were higher among those who reported sleeping 5 hours or less (OR: 1.95; 95% CI: 0.85–4.01), 6 hours (OR: 1.95; 95% CI: 1.06–3.58), and >8 hours (OR: 3.12; 95% CI: 1.53–6.37) per night compared to 7 hours per night after adjustment for covariates such as age, hypertension, smoking, self-rated health, waist circumference, and education (Yaggi et al., 2006). All of these studies suggest a U-shaped association between self-reported sleep duration and incident diabetes in the United States.

Prospective studies of sleep and diabetes are not limited to the United States. A prospective study of adult men in Japan reported that men with either a high frequency of difficulty initiating sleep or difficulty maintaining sleep had two to three times the odds of developing type 2 diabetes over an 8-year period compared to those with a low frequency of these sleep disturbances (Kawakami et al., 2004). Another prospective study in Japan followed 6,500 men and women aged 19–69 years for an average of 4.2 years and found that difficulty initiating sleep, but not sleep duration, was significantly associated with incident diabetes (Hayashino et al., 2007). Over 6,500 Swedish men were followed for 7–22 years and an increased odds of incident diabetes was observed among those who reported difficulty falling asleep or use of sleeping pills (OR: 1.52; 95% CI: 1.05–2.20) after controlling for numerous covariates including age, BMI at baseline, physical activity, smoking, and family history of diabetes (Nilsson et al., 2004). A second prospective study conducted in Sweden followed men and women for 12 years, and found that men who reported difficulty maintaining sleep (OR: 4.8, 95% CI: 1.9–12.5) or who reported sleep duration of 5 hours or less (OR: 2.8, 95% CI: 1.1–7.3) had a significantly greater odds of developing diabetes (Mallon et al., 2005). Sleep duration or disturbances did not significantly predict incident diabetes in women in this sample. A third prospective study from Sweden followed over 1,000 women for 32 years and observed no association between self-reported sleep problems, sleep medication use or sleep duration at baseline, and the incidence of diabetes (Bjorkelund et al., 2005). A prospective study in Germany followed 8,269 men and women aged 25–74 years for an average of 7.5 years and found a significant increased odds of incident type 2 diabetes for those who reported difficulty maintaining sleep at baseline in both men (OR: 1.60; 95% CI: 1.05–2.45) and women (OR: 1.98; 95% CI: 1.20–3.29), even after adjustment for numerous covariates (Meisinger et al., 2005). These studies suggest that self-reported sleep problems and short sleep may increase the risk of developing diabetes, particularly in men.

Since short sleep may lead to the development of diabetes, some investigators questioned whether sleep is associated with glycaemic control among individuals who already have diabetes. In a study of 50 patients with type 2 diabetes from Brazil, a higher percentage of those with poor sleep quality (PSQI score >5) had elevated HbA1c (>7%) (Cunha et al., 2008). Haemoglobin A1c (HbA1c) is a measure of glycaemic control and higher values indicate worse glycaemic control. A study in the United States of 38 patients with type 2 diabetes (18 of whom had restless legs syndrome) observed a significant unadjusted correlation between the Epworth Sleepiness Score and HbA1c ($r = 0.36$), but HbA1c was not associated with PSQI score (Cuellar and Ratcliffe, 2008). Another US study found that 71% of the participants were classified as having poor quality sleep (PSQI score >5) (Knutson et al., 2006). In patients without diabetic complications, HbA1c was associated with perceived sleep debt (self-reported preferred sleep duration minus self-reported actual sleep duration) but in patients with at least one complication, HbA1c level was associated with PSQI score (Knutson et al., 2006). In the study that used wrist activity monitoring to measure sleep in patients with type 2 diabetes, higher HbA1c levels were associated with lower sleep efficiency ($r = -0.29$, $P = 0.057$) (Trento et al., 2008).

Several observational studies have examined the association between sleep duration and obesity or BMI. Table 6.1 summarizes results from studies conducted in adults and Table 6.2 summarizes

**Table 6.1** Summary of published articles examining the association between sleep and BMI or obesity in adults*

| Reference | Sleep measure | Sample | Association with higher BMI or overweight/obesity | | | Country |
|---|---|---|---|---|---|---|
| | | | Short sleep | Long sleep | No significant association | |
| **Cross-sectional studies** | | | | | | |
| Vioque et al. (2000) | Self-report | $n$ = 1,772 men and women<br>Aged >15 years | ✓ | | | Spain |
| Shigeta et al. (2001) | Self-report | $n$ = 453 men and women<br>Age not reported | ✓ | | | Japan |
| Kripke et al. (2002) | Self-report | $n$ = 636,095 men and women<br>Aged 30–02 years | ✓<br>(men and women) | ✓<br>(women) | | US |
| Taheri et al. (2004) | Sleep diary | $n$ = 1,040 men and women<br>Aged 30–60 years | ✓ | ✓ | | US |
| Patel et al. (2004) | Self-report | $n$ = 82,969 women<br>Aged 40–65 years | ✓ | ✓ | | US |
| Cournot et al. (2004) | Self-report | $n$ = 3,236 men and women;<br>Aged 32–62 years | ✓<br>(women) | | ✓<br>(men) | France |
| Vorona et al. (2005) | Self-report | $n$ = 924 men and women<br>Aged 18–91 years | ✓ | | | US |
| Singh et al. (2005) | Self-report | $n$ = 3,158 men and women<br>Aged 18–65 years | ✓ | | | US |
| Kohatsu et al. (2006) | Self-report | $n$ = 990 employed men and women<br>Mean age 48.3 ± 13.0 years | ✓ | | | Rural US |
| Gortmaker et al. (1990) | Self-report | $n$ = 712 men and women<br>Age not reported | | | ✓ | US |
| Heslop et al. (2002) | Self-report | $n$ = 5,819 men <65 years; $n$ = 978 women <60 years | ✓ | | | UK |
| Tamakoshi and Ohno (2004) | Self-report | $n$ = 110,792 men and women<br>Aged 40–79 years | | | ✓ | Japan |
| Amagai et al. (2004) | Self-report | $n$ = 11,325 men and women<br>Aged 19–93 years | | | ✓ | Japan |

**Table 6.1** (continued) Summary of published articles examining the association between sleep and BMI or obesity in adults*

| Reference | Sleep measure | Sample | Association with higher BMI or overweight/obesity | | | Country |
|---|---|---|---|---|---|---|
| | | | Short sleep | Long sleep | No significant association | |
| Ohayon (2004) | Self-report | $n$ = 8,091 men and women Aged 55–101 years | | | ✓ | Europe |
| Bjorkelund et al. (2005) | Self-report | $n$ = 1,447 women Aged 38–60 years | | | | Sweden |
| Ohayon and Vecchierini (2005) | Self-report | $n$ = 1,026 men and women Aged ≥60 years | ✓ | | | France |
| Gottlieb et al. (2006) | Self-report | $n$ = 5,910 men and women Aged 40–100 years | ✓ | ✓ | | US |
| Lauderdale et al. (2006) | Actigraphy | $n$ = 612 men and women Aged 35–50 years | ✓ | | | US |
| Moreno et al. (2006) | Self-report | $n$ = 4,878 men (truck drivers)Mean age 40 ± 10 SD years | ✓ | | | Brazil |
| Chaput et al. (2007a) | Self-report | $n$ = 740 men and women Aged 21–64 years | ✓ | | | Canada |
| Ko et al. (2007) | Self-report | $n$ = 4,793 men and women Aged 17–83 years | ✓ | | | China |
| Rontoyanni et al. (2007) | Self-report | $n$ = 30 women Aged 30–60 years | ✓ | | | Greece |
| Bjorvatn et al. (2007) | Self-report | $n$ = 8,860 men and women Aged 40–45 years | ✓ | | | Norway |
| Asplund and Aberg (2001) | Self-report | $n$ = 3,712 women Aged 40–64 years | | | | Sweden |
| Jennings et al. (2007) | Self-report (PSQI) | $n$ = 210 men and women Aged 30–54 years | | | | US |
| Stamatakis and Brownson (2008) | Self-report | $n$ = 1,258 men and women Aged 20–92 years | ✓ | ✓ | | Rural US |
| Patel et al. (2008) | Actigraphy | $n$ = 3,135 men ≥65 years $n$ = 3,219 women ≥65 years | ✓(obesity and body fat %) | ✓(body fat %) | | US |

**Table 6.1** (continued) Summary of published articles examining the association between sleep and BMI or obesity in adults*

| Reference | Sleep measure | Sample | Association with higher BMI or overweight/obesity | | | Country |
|---|---|---|---|---|---|---|
| | | | Short sleep | Long sleep | No significant association | |
| Choi et al. (2008) | Self-report | *n* = 4,222 men and women<br>Aged >20 years | ✓(<60 years) | ✓(<60 years) | ✓(>60 years) | Korea |
| Buscemi et al. (2007) | Self-report | *n* = 199 men and women (internal medicine patients)<br>Aged 18–89 years | ✓(women) | ✓(women) | ✓(men) | US |
| Chaput et al. (2007b) | Self-report | *n* = 90 women<br>Aged 60–75 years | | | ✓ | Quebec |
| Hall et al. (2008) | Self-report | *n* = 1,295 men and women<br>Aged 30–54 years | ✓ | | | US |
| Fogelholm et al. (2007) | Self-report | *n* = 7,641 men and women<br>Aged ≥30 years | ✓(men) | | ✓(women) | Finland |
| Park et al. (2009) | Self-report | *n* = 8,717 men and women<br>Aged ≥20 years | ✓ | | | Korea |
| Gangwisch et al. (2005) | Self-report | *n* = 9,588 men and women<br>Aged 32–86 years | ✓(32–49 years) | | ✓(≥50 years) | US |
| Lopez-Garcia et al. (2008) | Self-report | *n* = 4,008 men and women<br>Aged ≥60 years | ✓ | ✓ | | Spain |
| Stranges et al. (2008) | Self-report | *n* = 10,308 men and women<br>Aged 44–65 years | ✓ | | | UK |
| **Prospective studies** | | | | | | |
| Gangwisch et al. (2005) | Self-report | *n* = 9,588 men and women<br>Aged 32–86 years | | | ✓ | US |
| Lopez-Garcia et al. (2008) | Self-report | *n* = 3,235 men and women<br>Aged ≥60 years | ✓ | ✓ | | Spain |
| Stranges et al. (2008) | Self-report | *n* = 10,308 men and women<br>Aged 44–65 years | | | ✓ | UK |
| Patel et al. (2006) | Self-report | *n* = 68,183 women<br>Aged 39–65 years | ✓ | | | US |

**Table 6.1** (continued) Summary of published articles examining the association between sleep and BMI or obesity in adults*

| Reference | Sleep measure | Sample | Association with higher BMI or overweight/obesity | | | Country |
|---|---|---|---|---|---|---|
| | | | Short sleep | Long sleep | No significant association | |
| Chaput et al. (2008) | Self-report | $n$ = 276 men and women<br>Aged 21–64 years | ✓ | | | Canada |
| Gunderson et al. (2008) | Self-report | $n$ = 940 women<br>Mean age 33.0 (SD 4.7) years | ✓ | | | US |
| Hasler et al. (2004) | Self-report | $n$ = 496 men and women<br>Aged 19 years at baseline | ✓ | | | Switzerland |
| Littman et al. (2006) | Self-report | $n$ = 173 women<br>Aged 50–75 years | | | ✓ | US |
| Lauderdale et al. (2006) | Actigraphy | $n$ = 612 men and women<br>Aged 35–50 years | | | ✓ | US |
| **Total** | | | **34** | **10** | **13** | |

*A check indicates a significant association between higher BMI or prevalence of overweight/obesity and either short sleep, long sleep, or no significant association. Groups in parentheses indicate that the associations were significant only for that group or outcome measure.

**Table 6.2** Summary of published articles examining the association between sleep and BMI or obesity in children*

| Reference | Sleep measure | Sample | Association with higher BMI or overweight/obesity | | | Country |
|---|---|---|---|---|---|---|
| | | | Short sleep | Long sleep | No significant association | |
| **Cross-sectional studies** | | | | | | |
| Locard et al. (1992) | Parental report | $n$ = 327 obese boys and girls, $n$ = 704 non-obese boys and girls<br>Aged 5 years | ✓ | | | France |
| Gupta et al. (2002) | Actigraphy | $n$ = 383 boys and girls<br>Aged 11–16 years | ✓ | | | US |
| von Kries et al. (2002) | Parental report | $n$ = 6,862 boys and girls<br>Aged 5–6 years | ✓ | | | Germany |
| Sekine et al. (2002) | Parental report | $n$ = 8,274 boys and girls<br>Aged 6–7 years | ✓ | | | Japan |

**Table 6.2** (continued) Summary of published articles examining the association between sleep and BMI or obesity in children*

| Reference | Sleep measure | Sample | Association with higher BMI or overweight/obesity | | | Country |
|---|---|---|---|---|---|---|
| | | | Shortsleep | Long sleep | No significant association | |
| Chaput et al. (2006) | Parental report | $n$ = 422 boys and girls Aged 5–10 years | ✓ | | | Canada |
| Knutson (2005) | Self-report | $n$ = 4,555 boys and girls Aged 11–21 years | ✓(boys) | | ✓(girls) | US |
| Ben Slama et al. (2002) | Parental report | $n$ = 3,148 boys Aged 6–10 years | ✓ | | | Tunisia |
| Benefice et al. (2004) | Actigraphy | $n$ = 40 girls Aged 13–14 years | ✓ | | | Senegal |
| Giugliano and Carneiro (2004) | Parental report | $n$ = 452 boys and girls Aged 6–10 years | ✓(overweight children only) | | | Brazil |
| Padez et al. (2009) | Parental report | $n$ = 4,511 boys and girls Aged 7–9 years | ✓ | | | Portugal |
| Chen et al. (2006) | Self-report | $n$ = 656 boys and girls Aged 13–18 years | ✓ | | | Taiwan |
| Nixon et al. (2008) | Waist Actigraphy | $n$ = 519 boys and girls Aged 7 years | ✓ | | | New Zealand |
| Yu et al. (2007) | Self-report | $n$ = 500 boys and girls (twins) Aged 10–20 years | ✓(girls) | ✓(boys) | | China |
| Kohyama et al. (2002) | Parental report | $n$ = 1,105 boys and girls Aged 3–3.8 years | | | ✓ | Japan |
| Kuriyan et al. (2007) | Parental/ self-report | $n$ = 598 boys and girls Aged 6–16 years | ✓ | | | India |
| Eisenmann et al. (2006) | Self-report | $n$ = 6,324 boys and girls Aged 7–15 years | ✓(boys) | | ✓(girls) | Australia |
| Liu et al. (2008) | 3 nights PSG | $n$ = 335 boys and girls Aged 7–17 years | ✓ | | | US |
| Seicean et al. (2007) | Self-report | $n$ = 529 boys and girls Aged 14–18 years | ✓ | | | US |
| Dieu et al. (2007) | Parental report | $n$ = 670 boys and girls Aged 4–5 years | ✓ | | | Vietnam |
| Hitze et al. (2008) | Parental/self-report | $n$ = 414 boys and girls Aged 6–20 years | ✓ | | | Germany |
| Beebe et al. (2006) | Actigraphy | $n$ = 60 overweight boys and girls<br>$n$ = 22 healthy controls boys and girls<br>Aged 10–17 years | ✓ | | | US |

**Table 6.2** (continued) Summary of published articles examining the association between sleep and BMI or obesity in children*

| Reference | Sleep measure | Sample | Association with higher BMI or overweight/obesity | | | Country |
|---|---|---|---|---|---|---|
| | | | Shortsleep | Long sleep | No significant association | |
| Wells et al. (2008) | Self-report | $n$ = 4,452 boys and girls Aged 11–12 years | ✓(BMI) | | ✓(obesity) | Brazil |
| Lumeng et al. (2007) | Maternal report | $n$ = 785 boys and girls Aged 11–12 years (6th grade) | ✓ | | | US |
| **Prospective studies** | | | | | | |
| Lumeng et al. (2007) | Maternal report | $n$ = 785 boys and girls Aged 9–10 years (3rd grade) and 11–12 years (6th grade) | ✓ | | | US |
| Agras et al. (2004) | Parental report | $n$ = 150 boys and girls Sleep measured at 3–5 years Weight measured at 9.5 years | ✓ | | | US |
| Reilly et al. (2005) | Parental report | $n$ = 7,758 boys and girls Sleep measured at 38 months Obesity measured at 7 years | ✓ | | | UK |
| Taveras et al. (2008) | Parental report | $n$ = 915 boys and girls Sleep measured at 6 months, 1 year and 2 years; BMI z-score measured at 3 years | ✓ | | | US |
| Touchette et al. (2008) | Parental report | $n$ = 1,138 boys and girls Sleep duration reported yearly from 2.5–6 years and BMI measured at 2.5 and 6 years | ✓ | | | Quebec |
| Sugimori et al. (2004) | Self-report | $n$ = 8,170 boys and girls Sleep and BMI measured at ages 3 and 6 years | ✓(boys) | | ✓(girls) | Japan |
| Snell et al. (2007) | Time diaries | $n$ = 2,281 boys and girls Aged 3–12 years at baseline | ✓(3–8 year olds) | | | US |
| **Total** | | | **29** | **1** | **5** | |

*A check indicates a significant association between higher BMI or prevalence of overweight/obesity and either short sleep, long sleep, or no significant association. Groups in parentheses indicate that the associations were significant only for that group or outcome measure.

results from studies in children. Many studies have reported a significant cross-sectional association between short sleep duration and increased prevalence of obesity or higher BMI in both adults and children. Some of these studies also observed higher BMI and obesity associated with longer sleep durations as well, and this U-shaped association between sleep and morbidity has yet to be fully explained. Other studies examined self-reported measures of sleep quality and their association with BMI or obesity. A Swedish study found differences between ages in the association between obesity and sleep problems (Asplund and Aberg, 2001). In 40- to 49-year olds, obesity (≥30 kg/m$^2$) was associated with worse sleep quality, while in 60- to 64-year olds, underweight (<20 kg/m$^2$) was associated with worse sleep quality. A US study that administered the PSQI found that worse sleep quality was associated with higher waist circumference, BMI, and body fat percentage (Jennings et al., 2007). Of note, many studies have reported differences in these associations by gender, by age group, or by outcome measures. In particular, the effect of sleep on BMI appears stronger at younger ages, and fewer studies in children have reported a U-shaped association (Table 6.2). Although we need to consider that the study methodology, sample demographics, and the analytical methods vary between these studies, most have found a cross-sectional association between sleep and BMI. There have also been a few prospective studies of sleep and weight gain (see Tables 6.1 and 6.2), however, these results are more mixed and the effects of sleep have been generally small or non-significant.

Two recent meta-analyses have examined data from studies on the cross-sectional association between sleep and BMI or obesity. Cappuccio et al. (2008) analyzed data from 17 studies including 22 different population samples in adults. Short sleep duration (<5 hours) significantly predicted obesity in 17 of the 22 population samples, and the pooled OR was 1.55 (95% CI: 1.43–1.68). Sleep duration as a continuous variable was significantly associated with BMI in all seven studies for which these data were available, and the pooled regression coefficient was -0.35 kg/m$^2$ change in BMI for every hour more sleep. Cappuccio et al. (2008) also identified 13 different population samples in children Short sleep duration (<10 hours) in children significantly predicted obesity (BMI > 95th percentile) in 7 of the 11 studies and the pooled OR was 1.89 (95% CI: 1.46–2.43). A second meta-analysis also examined sleep and obesity in children (Chen et al., 2008). They identified 17 observational studies in children and the pooled OR predicting obesity from short sleep duration was 1.58 (95% CI: 1.26–1.98). Thus, both meta-analyses found a significant overall association between short sleep duration and increased likelihood of being obese (see also Chapter 5).

A few observational studies have also examined the association between habitual sleep and levels of leptin and/or ghrelin. The Wisconsin Sleep Cohort Study was a population-based study that enrolled Wisconsin State employees aged 30–60 years (Taheri et al., 2004). Investigators collected sleep diaries to assess habitual sleep, conducted one night of PSG in the laboratory, and in the morning following the PSG, a single blood sample was obtained. The results indicated that total sleep time from PSG was negatively associated with ghrelin levels (β coefficient = -0.69, $P$ = 0.008), while average habitual sleep duration was positively associated with leptin levels independently of BMI (β coefficient = 0.11; $P$ = 0.01) (Taheri et al., 2004). Data from the Quebec Family Study of 740 men and women aged 21–64 years found that leptin levels in 5–6 hours were approximately 15–17% lower than expected based on fat mass in both men and women (Chaput et al., 2007b). Two studies in women, however, did not observe similar associations. The Nurses Health Study, which asked participants to mail back a blood sample, did not observe a significant association between self-reported sleep duration and leptin levels (Williams et al., 2007). A randomized trial of moderate-intensity exercise among obese, sedentary post-menopausal women aged 50–74 found no cross-sectional associations between self-reported sleep duration and leptin or total ghrelin levels at baseline nor any significant associations between change in sleep duration

and changes in leptin or ghrelin (Littman et al., 2006). The lack of significant associations may reflect differences in the effects of sleep on appetite regulation in women, particularly obese older women, or may be due to methodological issues such as self-reported sleep duration or sample collection.

Although there are some consistent findings among the numerous observational studies described above, we must consider the methodological limitations of these studies. First, the vast majority of these studies relied on a self-reported measure of sleep duration, which may not be very accurate. Recent analysis comparing actigraphically recorded sleep to self-reported sleep in a sample of over 600 middle-aged adults indicated only moderate agreement between these measures ($r = 0.47$) (Lauderdale et al., 2008). In addition, there may be important confounders that are not taken into account in these analyses, including race, socioeconomic status, physical activity, alcohol and caffeine consumption, and psychological disorders (Lauderdale et al., 2008; Magee et al., 2008). Future studies need to incorporate objective measures of sleep and include detailed measures of potential confounding variables.

The result of these studies, which originated from different countries and cultures, generally agreed that short or poor sleep may increase the risk of developing type 2 diabetes, which is consistent with the findings from the laboratory studies. However, some studies did find differences by sex such that associations were not always observed in women. Furthermore, many studies found that self-reported long sleep (>8 or 9 hours) was associated with diabetes or obesity, and the mechanisms underlying this association need to be determined. Additional prospective and intervention studies that use objective measures of sleep are required to determine if sleep loss is on the causal pathway to the development of diabetes and obesity.

## Obstructive sleep apnoea and metabolic disease

Reduced sleep duration and quality can also be a consequence of a sleep disorder, and one such disorder that has been associated with metabolic disturbances is OSA. OSA is characterized by SDB and involves an obstruction in the upper airway that leads to repeated episodes of increased breathing effort and a reduction (hypopnoea) or complete cessation (apnoea) of air flow (Thorpy, 2009). These episodes are often associated with reduced blood oxygen saturation and sleep fragmentation, and, in some, excessive daytime sleepiness. A diagnosis of OSA requires a minimum of five apnoeas or hypopnoeas per hour of sleep (the AHI). OSA is most common in people aged 40–65 years, and is also more common in men, although post-menopausal women appear to have similar risk of OSA as men of similar ages. A major risk factor for OSA is obesity and the current obesity epidemic has likely led to an increase in the prevalence of OSA. Estimates of the prevalence of SDB (defined as AHI > 5 events per hour) among 30- to 60-year olds in the United States in the early 1990s was 9% for women and 24% for men and the prevalence of OSA (defined as AHI > 5 events per hour plus daytime sleepiness) was 2% for women and 4% for men (Young et al., 1993). Approximately 26% of obese men and women (BMI > 30 kg/m$^2$) have AHI >15 events per hour and 60% have an AHI >5 events per hour (Gami et al., 2003).

Numerous studies have reported a close association between the presence of OSA and the presence of type 2 diabetes. For example, the Wisconsin Sleep Cohort Study found that almost 15% of participants who had an AHI of 15 events per hour or more had diagnosed diabetes compared to only 3% of those with an AHI <5 events per hour (Reichmuth et al., 2005). Another report found that 48% of patients with type 2 diabetes had an AHI of 10 events per hour or higher and 29% had an AHI of 20 events per hour or higher (Einhorn et al., 2007). In fact, the International Diabetes Federation Taskforce on Epidemiology and Prevention recently recommended that patients with either diabetes or SDB be examined for the other condition (Shaw et al., 2008).

The potential mechanisms linking OSA to metabolic disturbances include reduced sleep duration and quality. The impact of short or disturbed sleep on glucose metabolism and appetite regulation discussed previously could also contribute to impaired metabolism in patients with OSA. A few studies have examined glucose metabolism in relation to the presence and severity of SDB. The Sleep Heart Health Study reported that compared to those without SDB (AHI < 5 events per hour), adults with moderate-to-severe SDB (AHI ≥ 15 events per hour) were more likely to have glucose intolerance based on both a fasting blood sample and the 2-hour post-glucose ingestion sample from an oral glucose tolerance test (Punjabi et al., 2004). Furthermore, both a greater degree and a longer duration of oxyhaemoglobin desaturation were associated with glucose intolerance (Punjabi et al., 2004), suggesting that hypoxia may play a role in the disturbances in glucose metabolism. The Wisconsin Sleep Cohort Study also observed a significant cross-sectional association where increasing severity of SDB was associated with a greater prevalence of diabetes, but they did not observe a significant association between the presence of SDB and the development of diabetes over a 4-year period (Reichmuth et al., 2005). These results do not support a causal connection between SDB and impaired glucose metabolism, however, it is possible that a follow-up period of 4 years is not long enough to detect an association. Another study among approximately 2,500 adults without diagnosed diabetes found a significant cross-sectional association between increased SDB and the prevalence of impaired fasting glucose, impaired glucose tolerance, and occult diabetes even after adjustment for age, sex, race, BMI, and waist circumference (Seicean et al., 2008). In a study of 118 non-diabetic adults, SI, DI, and glucose effectiveness all decreased with increasing SDB, particularly in the moderate-to-severe SDB groups (Punjabi and Beamer, 2009). The reduction in SI compared to those without SDB ranged from 26.7% in those with mild SDB (AHI of 5–15 events per hour) to 43.7% in those with severe SDB (AHI of 30 or greater events per hour) independent of age, sex, race, and percent body fat (Punjabi and Beamer, 2009). The decreases in the DI and SI were associated with the average degree of oxyhaemoglobin desaturation (Punjabi and Beamer, 2009). Typically, a hypopnoea is defined as a reduction in airflow that is accompanied by an oxyhaemoglobin desaturation of at least 4%, however, investigators from the Sleep Heart Health Study examined whether a more mild oxyhaemoglobin desaturation was associated with metabolic measures. They reported that greater SDB associated with oxyhaemoglobin desaturation as low as 2% was associated with increased fasting glucose levels (Stamatakis and Brownson, 2008). Of particular concern is that these associations are not found only in adults. Two studies among children found that severity of OSA was associated with greater insulin resistance (Flint et al., 2007) and higher fasting insulin levels (de la Eva et al., 2002). Together these studies suggest an association between SDB or OSA and the prevalence of impaired glucose metabolism or diabetes, however, a causal link remains to be established.

Continuous positive airway pressure (CPAP) is a commonly used treatment for OSA. While sleeping, patients wear a mask that delivers continuous air flow at a pressure sufficient to keep the airways open. Several studies have examined the effects of CPAP treatment on glucose metabolism and appetite regulation in patients with OSA. In patients who have both type 2 diabetes and OSA, most studies observed an improvement in glucose regulation after CPAP (Dawson et al., 2008; Hassaballa et al., 2005; Babu et al., 2005; Schahin et al., 2008; Harsch et al., 2004a; Brooks et al., 1994), but one did not (West et al., 2007). In OSA patients without diabetes, the results are more mixed. Several studies have seen improvements in insulin sensitivity after CPAP use in patients with SDB (Harsch et al., 2004b; Lindberg et al., 2006; Dorkova et al., 2008). Other studies, did not observe an effect of CPAP on measures of glucose regulation (Vgontzas et al., 2008; Smurra et al., 2001; Coughlin et al., 2007; Trenell et al., 2007; Saarelainen et al., 1997). Patients with OSA typically have both higher ghrelin and higher leptin levels compared to BMI-matched controls without OSA (Takahashi et al., 2008; Phillips et al., 2000; Harsch et al., 2003; Ip et al., 2000). The higher levels of leptin are not consistent with the laboratory models of sleep loss, and may in fact reflect greater

leptin resistance among OSA patients. Most studies that examined the effect of CPAP use on either leptin or ghrelin levels have observed a decline in these hormones (Saarelainen et al., 1997; Trenell et al., 2007; Takahashi et al., 2008; Harsch et al., 2003; Ip et al., 2000; Sanner et al., 2004; Chin et al., 1999), but some studies saw no change in leptin levels after CPAP use (Harsch et al., 2004b; Drummond et al., 2008; Rubinsztajn et al., 2006). Finally, OSA is also often associated with recent weight gain (Phillips et al., 1999) and greater visceral adiposity (Vgontzas et al., 2008) compared to BMI-matched controls, however studies that examined the effects of CPAP use on weight loss are also inconclusive. One study observed that those who used CPAP for at least 4 hours per night for 6 months were more likely to lose more than 4.5 kg of weight compared to those who did not meet this minimum use criterion for CPAP compliance (Loube et al., 1997). Two other studies reported a significant reduction in visceral adiposity after CPAP use (Trenell et al., 2007; Chin et al., 1999), but other studies saw no effect of CPAP on weight loss or visceral adiposity (Redenius et al., 2008; Vgontzas et al., 2008; Kajaste et al., 2004). One problem with these studies is the length of time that CPAP is used each night can be quite low. In fact, many of these studies defined compliance as use of CPAP for at least 4 hours, which probably does not allow the patients to achieve a sufficient amount of good quality sleep. In fact, one of the laboratory studies discussed above saw significant deleterious effects on glucose metabolism and appetite regulation when bedtimes were restricted to only 4 hours. Future research is still required to determine if a minimum number of hours of CPAP use can ameliorate metabolic disturbances among patients with OSA.

## Summary

The accumulated evidence from both laboratory and observational studies suggest that insufficient or impaired sleep may play a role in the development of metabolic diseases such as diabetes and obesity. We have discussed the pathways through which sleep could lead to the development of obesity and diabetes. In particular, these pathways involve impairments in both glucose metabolism and appetite regulation, however, sleep's potential impact on energy expenditure warrants further examination.

Despite the large number of studies published to date in support of a link between sleep and metabolic disease, we must keep in mind some of the limitations of these studies. The primary limitation of the laboratory studies is the necessarily short duration of the sleep restriction, which can last a few weeks at most. These studies leave one wondering whether the effects of sleep restriction observed in the laboratory will persist if sleep restriction becomes chronic, or whether one's physiology can adapt to the sleep restriction. The evidence from the observational and large epidemiological studies suggest that one does not adapt to sleep durations less than 6 hours per night. There are, however, limitations to the epidemiological evidence as well. The majority of these studies relied on self-reported sleep duration, which may not be an accurate measure of actual sleep duration. Furthermore, most of the observational studies were cross-sectional so causality cannot be determined. In order to verify the importance of sleep's role in metabolism, future studies need to be designed to address these limitations. Prospective epidemiological studies need to include objective measures of habitual sleep duration and quality and consider important confounders. Finally, intervention studies that test the impact of sleep extension on metabolic health are critical for determining the causal link between sleep and metabolism.

Given the enormous impact obesity and diabetes have on QOL, life expectancy, and economic burden, it is very important to understand what factors influence the development of one or both of these conditions. Evidence reviewed here suggest that sleep duration or quality may play a role, thus future research into the causes and consequences of metabolic disease should include an examination of the impact of impaired or insufficient sleep. If sleep extension is an effective intervention, it would be an inexpensive behavioural modification that may be amenable to many at-risk people.

## Summary box

- Sleep plays an important role in the release of many hormones, including glucose and cortisol. Sleep disturbances can therefore disrupt endocrine function.
- Laboratory studies have observed that sleep restriction is associated with impairments in glucose metabolism and appetite regulation. Sleep restriction is associated with decreased glucose tolerance, lower leptin levels (an appetite suppressant), higher ghrelin levels (an appetite stimulant), and increased subjective appetite.
- Epidemiological studies have found significant associations between shorter self-reported sleep durations and increased diabetes prevalence and higher body mass indices or increased obesity prevalence. Most of these studies have been cross-sectional, however a few longitudinal studies have reported increased weight gain among short sleepers.
- Potential mechanisms underlying these associations include increased sympathetic nervous activity, alterations in GH and cortisol profiles, and decreased inhibition of hypothalamic activity.
- OSA is a sleep disorder that is associated with obesity and appears to increase the risk of impaired glucose metabolism and diabetes. It is not yet known whether this increased risk is due to sleep loss, sleep fragmentation, and/or hypoxia, all of which characterize OSA.
- Future research needs to be conducted to fully understand sleep's role in obesity and diabetes risk. In particular, future studies should be prospective, include objective, detailed measures of habitual sleep, and an examination of energy expenditure. Intervention studies that involve extending or improving sleep are especially important.

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