The Connection Between Sleep Loss, Obesity, and Type 2 Diabetes

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Silvana Pannain, Guglielmo Beccuti, and Eve Van Cauter

Abstract

In this review, evidence is presented to support the hypothesis that reduced sleep duration may be part of the behavioral modifications that played a role in the development of the current epidemic of obesity and diabetes. An important consideration when trying to explain the epidemiologic link between sleep loss and metabolic risk is that it is not clear whether the physiological effects of sleep restriction observed under laboratory conditions over a period of a few days can be translated to chronic sleep restriction as it occurs in free-living individuals. Also, when comparing different laboratory studies of sleep restriction, differences in the "dose" of sleep loss relative to the physiological need of the individual are often ignored. While the body of evidence suggestive of an interaction between sleep loss and the epidemics of obesity and diabetes continues to build at a rapid pace, much remains to be discovered as far as mechanisms and the transition from short-term laboratory conditions to chronic partial sleep deprivation in real life. Intervention studies extending sleep in habitual short sleepers and examining the impact on metabolic outcomes are needed to further address the direction of causality of the association between insufficient sleep, obesity, and diabetes and the potential clinical implications.

Secular Trends in Sleep Duration and the Prevalence of Obesity and Diabetes

In the past few decades, the prevalence of obesity and, consequently, of type 2 diabetes mellitus (T2DM) have increased alarmingly worldwide. Such a rapid increase cannot be explained by an alteration in the genetic pool; it is more likely due to environmental, socioeconomic, behavioral, and demographic factors and the interaction between genetics and these factors. Food marketing practices with increased portion size and widespread availability of high caloric fast food are often cited as a major culprit, alongside reduced physical activity. In recent years, there has been an increased interest in nontraditional behavioral and environmental factors that could also contribute to the epidemic of obesity and

S. Pannain, MD • G. Beccuti, MD • E. Van Cauter, PhD (✉)
Department of Medicine, University of Chicago,
5841 S. Maryland Avenue, Chicago, IL 60637, USA
e-mail: evcauter@medicine.bsd.uchicago.edu

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diabetes [1]. Among these, one novel behavior that seems to have developed during the past few decades and has become highly prevalent is chronic partial sleep curtailment.

Secular trends in sleep duration are poorly documented, but a comparison of surveys conducted in the 1960s and 1970s to those conducted after 2000 suggests a marked decrease in sleep duration. For example, in 1960, a survey study conducted by the American Cancer Society found the modal sleep duration to be 8.0–8.9 h [2] and, in 1975, more than 85% of the participants in the Older Finnish Twin Cohort reported sleeping more than 7 h per night [3]. In contrast, the "Sleep in America" poll conducted by the National Sleep Foundation in 2008 revealed that the average number of hours of sleep on workdays was 6 h 40 min, with an extension to 7 h 25 min on non-workdays [4]. A report from the National Health Interview Survey indicated that the percentage of adults between the ages of 30 and 65 years who report sleeping 6 h or less increased by approximately 5–6% between 1985 and 2004, such that in 2004, more than 30% of men and women in this age group reported sleeping 6 h or less [5]. According to recent polls from the US Centers for Disease Control and Prevention (CDC), approximately 29% of US adults report sleeping less than 7 h per night, and 50–70 million have chronic sleep and wakefulness disorders [6]. When sleep duration is measured objectively (using wrist actigraphy) rather than self-reported, the findings are not less alarming. For example, the Coronary Artery Risk Development in Young Adults (CARDIA) Sleep Study measured the sleep of adults aged 38–50 years for 3 consecutive days on two occasions spaced approximately 1 year apart. The mean sleep duration was 6.1 (± 1.2) h, and it varied across race–gender groups from 6.7 (± 0.9) h for white women to only 5.1 (± 1.3) h for African-American men [7].

Insufficient sleep may be due to a voluntary restriction of time spent in bed or may be the result of a sleep disorder, such as insomnia or obstructive sleep apnea (OSA). Unfortunately, the vast majority of epidemiologic studies that addressed the relationship between sleep duration and the risk of obesity or diabetes did not distinguish between voluntary sleep curtailment and sleep loss due to a pathological condition. Chronic partial sleep loss in contemporary society is certainly partly self-imposed. Our 24-h society involves demands and opportunities to extend the waking period for evening and nighttime work and leisure activities, and consequently a sacrifice of hours available for sleep. These relatively novel behaviors have had a major impact on bedtime duration and duration of dark exposure, resulting in later bedtimes, reduced total sleep time, and the opportunity to be active and ingest food during the natural night.

The function of sleep is most frequently described as a restorative process for the brain, but there is now abundant evidence that sleep is a healthy behavior that is also important for the rest of the body, consistent with the important modulatory effects of sleep on neuroendocrine function and glucose metabolism [8]. The decrease in sleep duration (and the associated increase in sleep complaints) in modern society [9] may be considered as a sleep disorder because it produces both daytime and nighttime alterations of neurobehavioral and physiological systems and raises concerns for a negative impact on health in general, not only mental health.

The gold standard method for assessing sleep is polysomnography (PSG), which combines an all night recording of the EEG with measures of muscle tone and eye movements and allows for the scoring of sleep in stages I, II, III, IV, REM, and Wake. A single night of PSG does not generally provide a good estimation of habitual sleep duration. Objective estimations of sleep duration and sleep fragmentation may be obtained under ambulatory conditions by wrist actigraphy monitoring (WAM). WAM has been validated against PSG, demonstrating a correlation for sleep duration between 0.82 in insomniacs and 0.97 in healthy subjects [10]. Lastly, a number of validated questionnaires to assess subjective sleep duration and quality have been developed. Subjective sleep duration often overestimates the actual sleep duration [11].

Short Sleep Duration and Obesity: Epidemiologic Evidence

According to recent estimates, the worldwide prevalence of obesity has doubled since 1980 [12]. This obesity epidemic has been mirrored in modern society by a secular trend for reduced sleep duration [9]. Figure 10.1 represents the trends in sleep duration and obesity prevalence from 1960 to the first decade of the twenty-first century. Growing evidence suggests that short sleep duration (SSD) may have played a role in the increased prevalence of obesity [14–17]. This section will summarize the literature examining the link between sleep loss and obesity, focusing on studies in adults.

Of note, a number of studies have reported a U-shaped relationship between sleep duration and obesity, where both SSD (generally ≤ 6 h) and long sleep duration (generally > 8 h) were associated with higher body mass index (BMI). There is a general consensus that the mechanisms linking long sleep to obesity are not likely to involve the same pathways linking short sleep and obesity [16, 18–20]. The majority of studies reporting a significant association between long sleep and obesity were based on self-reported sleep duration, and it has been argued that long sleepers may be spending more time in bed without obtaining more sleep. Another putative explanation could be that a subset of obese individuals suffer from fatigue associated with a subclinical condition and spend more time in bed. A further possible explanation is that long sleep may be associated with reduced physical activity and that therefore the association between long sleep and obesity would not persist when adjusting for physical activity. The present chapter focuses on the findings relating short sleep, obesity, and diabetes.

To date, more than 60 epidemiological studies from different geographical regions have examined the association between sleep duration and obesity in adults. In cross-sectional approaches, the vast majority of studies found a significant association between SSD (generally < 6 h per night) and BMI or prevalence of obesity and/or overweight. A systematic review of prospective studies provides similar, albeit not as consistent results, revealing an association with being a short sleeper at baseline and weight gain or the incidence of obesity during the follow-up period.

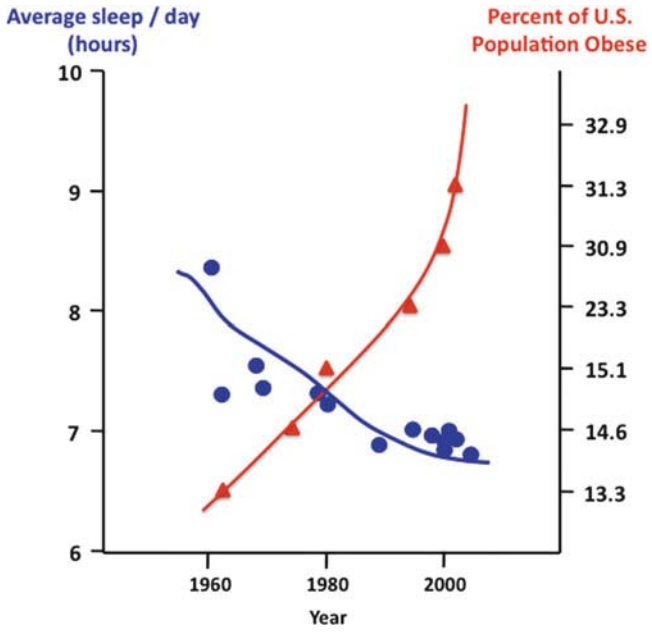

Fig. 10.1 Trends of sleep duration and obesity prevalence in the US population from 1960 to the first decade of the twenty-first century. The sleep duration estimates have been derived from McAllister et al. [13]. US obesity prevalence is from Centers for Disease Control and Prevention (http://www.cdc.gov/obesity/)

A meta-analysis published in 2008 combined data from 18 cross-sectional studies including 604,509 adults from 12 different countries and demonstrated a pooled obesity odds ratio (OR) of 1.55 (CI: 1.43–1.68; $p < 0.0001$) for sleep durations <5 h as compared to 7–8 h [21]. A dose–response effect became apparent such that for each additional hour of sleep, the BMI decreased by 0.35 kg/m^2 (95% confidence interval – CI: −0.57 to −0.12), which would translate to a 1.4 kg decrease in weight in an individual of 178 cm of height. This study represents the first systematic review and meta-analysis of the population-based studies published up to 2008 and demonstrates a consistent association between sleep duration and obesity in different populations around the world. Direction of causality cannot be inferred from these cross-sectional studies. Table 10.1 summarizes the prospective and cross-sectional epidemiologic studies published since 2008, which were not included in the meta-analysis by Cappuccio et al. [21]. We were able to identify 31 such studies, of which 10 involved a longitudinal analysis. Only one of the ten prospective studies had negative findings [46]. In the cross-sectional studies, all but one study found a significant association between short sleep and obesity, although significance was not always found for subsets of subjects (e.g., in men vs. women or conversely). The studies originated from all over the world and involve diverse adult populations.

In sum, the number of concordant studies lends strong support to the hypothesis that SSD may indeed represent a risk factor for obesity. One caveat is that the vast majority of studies have assessed sleep duration by self-report with only five studies so far using objective assessment by WAM and/or PSG. Further, in the majority of studies, there was no information regarding the cause for short sleep, i.e., voluntary bedtime curtailment or biologic inability to obtain more sleep. As shown later in this chapter, laboratory studies where sleep was restricted experimentally in healthy lean volunteers and appetite regulation and/or food intake were examined offer some indication regarding the direction of causality. Intervention studies involving sleep extension in short sleepers will be important to further support a causative role for short sleep on the risk of obesity. A National Institute of Health (NIH)-funded randomized control trial [53] has enrolled 150 US short sleeper adults (< 6.5 h per night) to examine the feasibility of increasing sleep duration to a healthy length (approximately 7.5 h) and to determine the effect of sleep extension on body weight. The findings have not yet been published.

In the subsequent subsections, we discuss the findings of the studies that have used objective assessments of sleep duration and then summarize the state of knowledge regarding the possibility of sex differences in the relationship between sleep and obesity. We then briefly discuss studies that have addressed the impact of genetics and race/ethnicity. Lastly, we review the few studies that have examined the contribution of dietary habits to the relationship between SSD and obesity risk.

Studies Using Objective Measurements of Sleep Duration

When examining epidemiologic studies, one concern is that comparative studies have shown that self-reported sleep duration correlates only moderately with more objective estimations of sleep duration such as those derived from WAM or PSG, and that self-report may overestimate the amount of sleep [11, 54]. A discrepancy between self-report and sleep duration derived from WAM has been confirmed in the Rotterdam Study, a population-based cohort of elderly adults [32]. In that cohort, men overestimated sleep duration by self-report by 0.61 h, while the difference between self-reported and measured sleep durations was only 0.14 h for women. The possibility of a systematic bias in the estimation of the relationship between sleep duration and obesity was suggested by Lauderdale et al. who noted that obese persons tend to report shorter sleep duration for the same amount of objectively assessed sleep than non-obese individuals [26].

To date, only five studies have used objective methods to assess sleep duration in population

Table 10.1 Summary of recent epidemiologic studies (published after 2007 and not included in the meta-analysis by Cappuccio et al. [21]) examining the association between short sleep duration and obesity in adults. The association between sleep duration and obesity is expressed as higher probability, prevalence, or adjusted odds ratio (AOR) of obesity (BMI > 30 kg/m^2) or increased waist circumference

Author	Description and data source	Cohort	Sleep assessment	Results	
Prospective studies					
Gunderson et al. [22]	1-year follow-up Project Viva cohort (US)	940 women postpartum Age 33.0 ± 4.7 yrs	Self-report	≤5 h	OR of SPPWR 3.08 (CI: 1.76–5.38; $p < 0.001$) at 6 months postpartum; OR of SPPWR 3.38 (CI: 1.66–6.86; $p = 0.011$) at 1 year postpartum
				5–≤6 h	NS at 6 months and 1 year postpartum
				7–<8 h	Reference category
Chaput et al. [23]	6-year follow-up Quebec Family Study (Canada)	276 men and women Age 21–64 yrs	Self-report	5–6 h	Increased body weight (+1.98 kg; CI 1.16–2.82) and risk of obesity (+27%)
				7–8 h	Reference category
Lopez-Garcia et al. [24]	2-year follow-up of older adults (age ≥ 60 yrs) (Spain)	1,064 men (age 71.0 ± 8.0 yrs), 1,271 women (age 72.1 ± 7.6 yrs)	Self-report	*In women:*	
				≤5 h	AOR of 5-kg weight gain 3.41 (CI: 1.34–8.69; $p < 0.02$)
				6 h	NS
				7 h	Reference category
				In men: no significant association	
Chaput et al. [25]	6-year follow-up Quebec Family Study (Canada)	283 men and women Age 18–64 yrs	Self-report	<6 h	35% higher probability of ≥5 kg weight gain ($p < 0.01$)
Lauderdale et al. [26]	5-year follow-up Coronary Artery Risk Development in Young Adults (CARDIA) Study	612 men and women Approximate mean age 45 yrs	WAM	No longitudinal association between sleep measurements and change in BMI	
Watanabe et al. [27]	1-year follow-up of employees of an electric power company (Japan)	31,477 men Age 40 ± 9 yrs 3,770 women Age 38 ± 9 yrs	Self-report	*In men:*	
				<5 h	AOR of obesity 1.91 (CI: 1.36–2.67; $p < 0.001$)
				5–5.9 h	AOR of obesity 1.5 (CI: 1.25–1.8; $p < 0.001$)
				7–8 h	Reference category
				In women: no significant association	
Nishiura et al. [28]	4-year follow-up of employees of a gas company (Japan)	2,362 men Age 40–59 yrs	Self-report	<6 h	AOR of obesity 2.46 (CI: 1.41–4.31; $p = 0.011$)
				7–7.9 h	Reference category

(continued)

Table 10.1 (continued)

Author	Description and data source	Cohort	Sleep assessment	Results	
Hairston et al. [29]	5-year follow-up Insulin Resistance Stherosclerosis Study (IRAS) Family Study (US)	322 African-American men and women and 775 Hispanic-American men and women Age 18–81 yrs	Self-report	*Age < 40 yrs:*	
				≤5 h	Increase in BMI (+1.8 kg/m^2, $p<0.001$), SAT (+41 cm^2, $p<0.0001$), and VAT (+13 cm^2, $p<0.01$)
				6–7 h	Reference category—≤ 8 h
				≥8 h	Increase in BMI (+0.8 kg/m^2, $p<0.001$), SAT (+20 cm^2, $p<0.01$), and VAT (+6 cm^2, $p<0.05$)
				Age > 40 yrs: no significant association	
Bo et al. [30]	6-year follow-up Patients from Local Health Units (Italy)	1,597 men and women Age 45–64 yrs	Self-report	Each hour increase in total sleep time	30% Reduction in incident obesity (AOR 0.7/h; CI: 0.57–0.86; $p<0.001$)
Chaput et al. [31]	6-year follow-up Quebec Family Study (Canada)	216 men and women Age 18–64 yrs	Self-report	Maintained short sleep (≤6 h)	Increase in BMI (+1.1 ± 0.36 kg/m^2, $p<0.05$), and fat mass (+2.4 ± 0.64 kg, $p<0.05$) vs. control group
				Increased sleep to 7–8 h	NS vs. control group
				Control (7–8 h)	Reference category
Cross-sectional studies					
Van den Berg et al. [32]	Rotterdam Study (Netherlands)	471 men, 512 women Age 57–97 yrs	WAM and self-report	<5 h	AOR of obesity 2.76 (CI: 1.38–5.49) [NS after adjusting for fragmentation index]
				5–6 h	AOR of obesity 1.97 (CI: 1.26–3.08) [NS after adjusting for fragmentation index]
				6–7 h	NS
				7 h	Reference category
Patel et al. [55]	Osteoporotic Fractures in Men Study (MrOS) and Study of Osteoporotic Fractures (SOF) (US)	3,055 men Age 67–96 yrs 3,052 women Age 70–99 yrs	WAM in all; PSG in 2,862 men and 455 women	*In men:*	
				<5 h	AOR of obesity 3.70 (CI: 2.72–5.04)
				5–7 h	AOR of obesity 1.51 (CI: 1.18–1.93)
				7–8 h	Reference category
				In women:	
				<5 h	AOR of obesity 2.26 (CI: 1.64–3.13)
				5–7 h	AOR of obesity 1.51 (CI: 1.18–1.93)
				7–8 h	Reference category

Vgontzas et al. [33]	Penn State Cohort (US)	561 men Age 50.8 ± 12.6 yrs 739 women Age 54.9 ± 13.6 yrs	Self-report	Compared to the group of subjects who slept > 6 and ≤ 7 h, BMI decreased proportionally to increased sleep for those who slept less ($p < 0.05$). BMI remained similar for those who slept more (NS).	
Hall et al. [34]	Adult Health and Behavior Project registry (US)	568 men, 646 women 83.7% Non-Hispanic Caucasian Age 45 ± 7 yrs	Self-report	< 6 h	AOR of central adiposity 1.73 (CI: 1.21–2.57)
				6–7 h	AOR of central adiposity 1.64 (CI: 1.22–2.20)
				7–8 h	Reference category
Choi et al. [35]	2001 Korean National Health and Nutrition Survey (KNHNS) (Korea)	1,822 men, 2,400 women Age 44.1 ± 0.4 yrs	Self-report	≤ 5 h	Prevalence of abdominal obesity 41.4% (CI: 35.9–47.2)
				6 h	Prevalence of abdominal obesity 31.5% (CI: 28.4–34.8)
				7 h	Prevalence of abdominal obesity 29.2% (CI: 26.5–32.2)
Lopez-Garcia et al. [24]	Older adults (age ≥ 60 yrs) from Spain	1,739 men, 2,269 women Age 71.6 ± 7.7 yrs	Self-report	≤ 5 h	AOR of obesity 1.33 (CI: 1.00–1.77; $p < 0.005$) and severe obesity 2.08 (CI: 1.31–3.32; $p < 0.004$)
				6 h	NS
				7 h	Reference category
Park et al. [36]	2001 and 2005 KNHNS (Korea)	3,723 men, 4,994 women Age 20–65 yrs	Self-report	≤ 5 h	AOR of general obesity 1.24 (CI: 1.05–1.47) and abdominal obesity 1.22 (CI: 1.01–1.47)
				6 h	AOR of general obesity 1.16 (CI: 1.02–1.31) and abdominal obesity NS
				7 h	Reference category
Chaput et al. [25]	Quebec Family Study (Canada)	Cross-sectional analysis: 537 men and women Age 18–64 yrs	Self-report	< 6 h	6% non-obese vs. 30.1% overweight/obese, OR 4.66 (CI: 2.98–6.48), $p < 0.01$
				≥ 7 h	NS
Lauderdale et al. [26]	CARDIA Study (USA)	612 men and women Approximate mean age 45 yrs	WAM	With increasing category of sleep duration (< 4.5 h, 4.5–6 h, 6–7.5 h, ≥ 7.5 h), there was a 0.78 kg/m^2 decrease in BMI	
St Onge et al. [37]	CARDIA study (USA)	3,473 men and women Age 33–45 yrs	Self-report	No associations between sleep measurements and BMI when controlled for physical activity.	
Adamkova et al. [38]	Adults from Czech Republic	2,038 men, 1,932 women Age 18–65 yrs	Self-report	4–6 h	BMI 27.46 ± 4.919
				7 h	BMI 25.40 ± 4.201 $p < 0.001$ for trend
				8–11	BMI 25.18 ± 4.868
Di Milia et al. [39]	Employees in coal industry and university (Australia)	292 men, 59 women Age 41 ± 11 yrs	Self-report	AOR of obesity 2.05 (CI: 1.03–3.55, p 0.05) for < 6 h sleep	

(continued)

Table 10.1 (continued)

Author	Description and data source	Cohort	Sleep assessment	Results	
Thomas et al. [40]	EADS/Augsburg cohort study (Germany)	1,047 men, 116 women Age 39 ± 11 yrs	Self-report	Significant association between sleep duration and BMI ($\beta_{st} = -0.06$, $p = 0.04$) when demographic, health behavior, and work status variables were included	
Watson et al. [41]	University of Washington Twin Registry (US)	1,224 twins: 423 monozygotic, 143 dizygotic, and 46 pairs of unknown zygocity Mean age 36.9 yrs	Self-report	*Dizygotic pairs discordant for sleep duration* ($n = 57$): no BMI difference. *Monozygotic pairs discordant for sleep duration* ($n = 167$):	
				<7 h	Higher mean BMI ($p < 0.02$)
				7–8.9 h	Reference category
Buxton et al. [42]	National Health Interview Survey (US)	56,507 men and women Age 18–85 yrs	Self-report	<7 h	6% Higher probability of obesity
				7–8 h	Reference category
Magee et al. [43]	"45 and UP Study" (Australia)	40,834 men and women Age 45–65 yrs	Self-report	*In men:*	
				<6 h	AOR of obesity 1.72 (CI: 1.34–2.20; $p < 0.017$)
				6 h	AOR of obesity 1.51 (CI: 1.32–1.73; $p < 0.017$)
				7 h	Reference category
				In women:	
				<6 h	AOR of obesity 1.42 (CI: 1.16–1.75; $p < 0.017$)
				6 h	AOR of obesity 1.35 (CI: 1.19–1.52; $p < 0.017$)
				7 h	Reference category
Magee et al. [44]	"45 and UP Study" (Australia)	45,325 men and women Age 55–95 yrs	Self-report	*Age 55–64 yrs:*	
				<6 h	AOR obesity 1.52 (CI: 1.21–1.89; $p < 0.001$)
				6 h	AOR obesity 1.42 (CI: 1.26–1.61; $p < 0.001$)
				7 h	Reference category
				Age > 65 yrs: no significant association	
Magee et al. [45]	"45 and UP Study" (Australia)	16,951 men and women, full time workers Age 45–65 yrs	Self-report	Inverse association between sleep duration and BMI ($p < 0.001$)	
Anic et al. [46]	Collaborative Breast Cancer Study (US)	5,549 women Age 20–75 yrs	Self-report	<6 h	AOR obesity 1.89 (CI: 1.45–2.47; $p < 0.0001$); AOR extreme obesity 3.12 (CI: 1.70–5.75; $p = 0.0003$)
				6–6.9 h	AOR obesity 1.52 (CI: 1.23–1.89; $p = 0.0003$); AOR extreme obesity 2.22 (CI: 1.27–3.87; $p = 0.0003$)
				7–7.9 h	Reference category

Theorell-Haglöw et al. [47]	"Sleep and Health in woman" study (Sweden)	400 women Age 29–70 yrs	Ambulatory PSG	Inverse association between sleep duration and both waist circumference (Adj. β −1.22 cm/h; $p=0.016$) and sagittal abdominal diameter (Adj. β −0.46 cm/h; $p=0.001$).
Knutson [48]	1982–1984 Hispanic Health and Nutrition Examination Survey (HHANES) (US)	889 Cuban-Americans 3,520 Mexican-Americans 1,316 Puerto Ricans Age 36–44 yrs	Self-report	Association between SSD and BMI only significant in Mexican-Americans (β −0.03; CI: −0.06 to −0.004)
Baron et al. [49]	Adults from US	27 men, 25 women Age 18–71 yrs	WAM	Higher BMI was associated with shorter sleep, later sleep timing, caloric consumption after 8 p.m., and fast food consumption
Kim et al. [50]	Adults from US and Puerto Rico	27,983 women Age 35–74 yrs	Self-report	Decreased eating at conventional times among women sleeping <6 h and >10 h vs. 7–7.9 h
Liu et al. [51]	Twin cohort, (China)	854 men and 640 women Age 20–70 yrs	Self-report	In women, but not in men, sleep duration <7 h was associated with higher insulin resistance (HOMA-IR) than sleep duration >7 h but ≤8 h, even after adjustment for BMI or % trunk fat
Wheaton et al. [52]	2008 Behavioral Risk Factor Surveillance System (BRFSS) (US)	384,541 men and women Age 18 to >65 yrs	Self-reported insufficient sleep	Number of days of insufficient rest or sleep strongly correlated with BMI. The relationship was found in all ethnic groups

Adj. β adjusted beta coefficient, *CI* 95% confidence interval, *NS* not significant, *WAM* wrist activity monitor, *PSG* polysomnography, *SAT* subcutaneous adipose tissue, *SPPWR* substantial postpartum weight retention, *VAT* visceral adipose tissue, *yrs* years

studies. A 2008 study by Van den Berg et al. recorded sleep by WAM in 983 participant of the Rotterdam Study of Aging and found that both short sleepers and long sleepers were more likely to be obese, compared to participants who slept 7 to < 8 h [32]. BMI also increased with sleep fragmentation. After adjustment for sleep fragmentation, the relationship between short sleep and BMI was no longer significant whereas it remained significant for long sleep. Of note, in this cohort of elderly participants, self-reported habitual sleep duration was not associated with BMI or obesity, further suggesting that self-reported sleep duration may not correctly estimate actual sleep duration. The largest study based on objective sleep assessments was published by Patel et al. who analyzed WAM recordings from a cohort of elderly men ($n = 3{,}055$; age: 67–96 years) and women ($n = 3{,}052$; age: 70–99 years) participating in the Osteoporotic Fracture Study [55]. As summarized in Table 10.1, the study had positive findings in both men and women. The special interest of this cross-sectional study is that a subgroup of 2,862 men and 455 women also underwent a PSG study to assess the presence and severity of sleep apnea. Compared to those sleeping an average of 7–8 h per night, sleep duration (based on WAM) < 5 h was associated with a BMI on average 2.5 kg/m^2 greater in men and 1.8 kg/m^2 greater in women. Additionally the odds of obesity were 3.7-fold greater in men and 2.3-fold greater in women who slept < 5 h. These associations persisted after adjusting for the severity of sleep apnea as assessed by the Apnea Hypopnea Index (AHI), insomnia and daytime sleepiness. This remarkable study was the first to demonstrate that the association between sleep duration and obesity is in part dependent on the presence and severity of sleep apnea but persists after controlling for AHI or when limiting the analysis to participants without significant sleep apnea. While the findings suggest that the association between short sleep and obesity may be stronger in men, a direct comparison is not possible as the women were nearly a decade older than the men. An additional unique contribution of this study is the demonstration that the impact of reduced sleep times (assessed objectively) on obesity risk is also present in older populations. This is in contrast with other reports that assessed sleep duration by self-report and indicated that short sleep may not be relevant to obesity risk in older populations [29, 44, 56]. The CARDIA Sleep Study assessed sleep by WAM for 6 days and involved both a cross-sectional and a longitudinal analysis [26]. The cross-sectional analysis confirmed the association between SSD and higher BMI reported in previous studies (0.78 kg/m^2 decrease in BMI for each increasing sleep duration category). Greater sleep fragmentation was also associated with higher BMI. The presence of snoring (by self-report) significantly affected the cross-sectional association such that the sleep duration-BMI association observed across the entire sample was stronger among the participants who reported snoring. This finding suggests that obesity-related comorbidities such as OSA may affect sleep duration or conversely that OSA has an independent effect on obesity risk. The prospective analysis did not find an association between sleep duration and weight change over the 5-year follow-up [26]. A small actigraphy-based study by Baron et al. [49] was innovative as it looked not only at sleep duration but also sleep timing. Sleep duration was a significant predictor of BMI while sleep timing did not predict BMI after controlling for sleep duration. Calories consumed after 8 p.m. predicted BMI after controlling for sleep timing and duration, suggesting that evening eating may promote obesity risk, consistent with findings from animal models. Lastly, a study by Theorell-Haglöw et al. performed a PSG in 400 women (aged 29–70 years) participants in the Sleep and Health in Women Study [47]. Sleep duration was inversely related to waist circumference, after adjusting for multiple confounders, including AHI. This study is consistent with the findings of Patel et al. [55] who found that the association between short sleep and obesity is not entirely dependent on the presence and severity of OSA.

Sex Differences in the Relationship Between Sleep and Obesity Risk

Sex differences in sleep duration and quality have been well documented. Women have more sleep complaints, particularly insomnia, but are much less likely to have OSA than men. Somewhat paradoxically, objective sleep duration and the amount and intensity of non-REM sleep are higher in women than in men. There are also well-established sex differences in eating behavior. It is therefore logical that the relationship between sleep duration and obesity risk may be sex-dependent. So far, the studies that have addressed this issue have had contradictory or inconclusive results. Of note, all these studies assessed sleep duration by self-report.

Two prospective studies [24, 27] and three cross-sectional studies [45, 51, 55] have explicitly addressed sex differences. A few additional studies have included women only.

A prospective study conducted in Spain reported that women reporting sleeping <5 h per night had increased odds of gaining 5 kg or more over the following 2 years compared to those who reported sleeping 7 h per night. This association was not found in men [24]. Contrasting with these findings, a Japanese prospective study with a 1-year follow-up showed that the increased risk of obesity for self-described short sleepers was present in men but not in women [27]. In this latter study, the lack of a significant finding in women could be due to the small sample size. Vgontzas et al. in a cross-sectional analysis found a negative linear relationship between hours of sleep duration and BMI. When the analysis was stratified by sex, the association was significant only for men [33]. An analysis of the CARDIA Sleep Study indicated the existence of an inverse relationship between reported sleep duration and BMI in both sex groups, but in unadjusted analyses, the findings appeared more robust in women than in men [26]. Liu et al. were the first to examine the gender-specific association of sleep duration with body composition as assessed by Dual-emission X-ray absorptiometry (DXA) [51]. To adjust for the decrease of sleep duration with age, age-specific quartiles of sleep duration were considered. Additionally the analysis also considered sleep quality factors such as sleep disturbance and habitual snoring. Women in the lowest quartile of short-sleep duration had higher overall and central adiposity and lower lean body mass when compared to those with moderate sleep duration (second and third quartiles). The association persisted after excluding subjects who reported either habitual snoring or sleep disturbance, suggesting that the sleep duration itself is a potential determinant of increased adiposity. A similar association was not found in men.

Four studies up to date have included only women [22, 46, 47, 50] and all four had positive findings linking short sleep with obesity risk. Gunderson et al. found that women who reported shorter sleep duration (≤ 5 h within a 24-h period) at 6 months postpartum were 2.3 times more likely to retain at 1 year substantial postpartum weight (≥5 kg above pre-pregnancy weight) independent of potential confounders including maternal sociodemographics, pre-pregnancy BMI, gestational weight gain, parity, and postpartum behaviors [22]. Additionally, women who reported a reduction in hours of sleep at 1 year postpartum were two times more likely to have substantial postpartum weight retention. The study from Theorell-Haglöw et al. performed a PSG in 400 participants (aged 29–70 years) in the Sleep and Health in Women Study [47]. Not only sleep duration but also sleep quality, as determined by sleep efficiency and sleep architecture (specifically minutes of SWS, the "deep restorative sleep"), was inversely related to waist circumference, after adjusting for age, level of physical activity, smoking status, alcohol consumption, and AHI. Associations were stronger in age <50 years. In a cohort of 5,549 US adult women of similar age range, Anic et al. confirmed an association between SSD and obesity [46]. The association was stronger in participants with morbid obesity [46]. The analysis explored a possible causal relationship by examining the association between lifetime sleep duration (possibly preceding the onset of obesity) and obesity and found a weaker association than with sleep duration measured during the study. The

authors tentatively concluded that short sleep might have been the consequence of obesity. However, self-reported measures of lifetime sleep duration may be poorly reliable and have never been validated. Lastly, Kim et al. collected information about eating behavior and source of calories and correlated to various sleep categories in a cohort of nearly 28,000 women only [50]. SSD was associated with disrupted eating patterns and poor food choices, and thus potentially to a risk of weight gain and obesity.

Impact of Genetic Factors and Race/Ethnicity

A recent study examined self-reported sleep duration and BMI in 1,224 twins (423 monozygotic, 143 dizygotic, and 46 indeterminate pairs), mean age 36.9 years [41]. In a multivariate adjusted analysis including all twins, the mean BMI was found to be 1.2 kg/m^2 higher in short sleeping twins (< 7 h/night) compared to twins sleeping 7–8.9 h per night. The novelty of this study lies in the within-pair analyses. Even when restricted to monozygotic twins, the short sleeping member of the pair had a significantly elevated BMI by 1.0 kg/m^2 compared to the reference group. The persistence of the association within individuals with an identical genetic background supports the hypothesis that behavioral curtailment of sleep, rather than genetic factors, drives the association. Bivariate analysis revealed little evidence of shared genetics between sleep duration and BMI. Consistent findings were reported in a twin study of a Chinese rural population where heritability of sleep duration appeared to be primarily determined by environmental factors whereas heritability of body composition (assessed by DXA) had a strong genetic component [51].

In a cross-sectional analysis of the CARDIA Sleep Study which by design enrolled similar proportions of middle-aged White and African-American men and women, a significant relationship between objective sleep duration based on WAM and BMI emerged, and this association did not vary by race/sex groups [26]. Another prospective study by Hairston et al. focused on minorities (322 African-Americans and 775 Hispanic Americans men and women) known to be at higher risk of metabolic disorders, and used abdominal computer tomography scans to evaluate visceral and subcutaneous adipose tissue (VAT and SAT, respectively) [29]. After controlling for multiple confounders, short sleep (≤ 5 h) was associated with greater fat accumulation over the 5-year follow-up with increased BMI (+1.8 kg/m^2, $p < 0.001$), SAT (+41 cm^2, $p < 0.0001$), and VAT (+13 cm^2, $p < 0.01$) as compared to > 6–7 h sleepers. There were no significant interactions between sleep duration and race groups, suggesting that the impact of short sleep was similar in African-Americans and Hispanics. The relationship was significant in younger participants only (< 40 years old). Because there is an elevated prevalence of short sleepers in these ethnic minorities, these findings raise the possibility that their increased risk of metabolic disorders may be partly mediated by sleep habits. Knutson et al. explored the impact of ethnicity on the association between sleep and body size measured from BMI, skin folds, arm, and calf circumference using data from the Hispanic Health and Nutrition Examination Survey (HHANES) [48]. In a cross-sectional analysis, SSD was associated with larger body size in Mexican-Americans ($n = 3{,}520$), but not in Cubans-Americans ($n = 889$) or Puerto Ricans ($n = 1{,}316$), indicating that distinct factors (e.g., diet intake vs. physical activity) in different ethnic groups could influence the risk of weight gain. One limitation of this study is that the data analyzed were collected over 25 years ago, which was at the beginning of the obesity epidemic and at the time when the prevalence of short sleepers was very small. In fact only 3–5% of the HHANES ethnic groups reported sleeping less than 6 h per night. It is possible that today the association between sleep duration and body size may be detectable in all Hispanic groups. Most recently, in a large cohort of almost 400,000 US adults, of whom 70% white non-Hispanic, there was a positive-graded relationship between days of perceived insufficient sleep and BMI categories from normal weight through different obesity grades among both men and women and in all ethnic groups [52]. Of note, perceived insufficient sleep does not distinguish between sleep duration and sleep quality.

Role of Dietary Habits in the Relationship Between Short Sleep and Obesity

In 2010 and 2011, four epidemiologic studies examined the contribution of dietary habits to the association between sleep duration and obesity [28, 30, 49, 50]. Nishiura et al. analyzed the dietary patterns of 2,362 non-obese Japanese workers. The increased risk of obesity at 4 years for the short sleepers (AOR 2.46 for < 6 h; CI 1.41–4.31) was slightly attenuated but remained significant after controlling for food preferences and unhealthy behavior such as skipping breakfast, snacking, and eating out [28]. In a prospective study with a 6-year follow-up, Bo et al. showed in an Italian cohort that hours of sleep per night, home temperature, and numbers of restaurant meals were each associated with higher obesity incidence [30]. Kim et al. collected information regarding eating behavior in almost 28,000 women. Short sleep (< 5 h/night) was cross-sectionally associated with an increased tendency for eating at unconventional times and dominance of snacks over meals [50]. These eating patterns were associated with increased caloric intake from sweets and fat and lower intake of fruits and vegetables. The finding suggests that short sleep may promote disrupted eating patterns and unhealthy food choices. Lastly, a small cross-sectional study showed that later sleep time and short sleep were associated with increased BMI, but that the association was mostly due to the increased caloric intake after 8 p.m., suggesting that the relationship between short sleep time and obesity could also be mediated by the opportunity of ingesting food during the natural night [49].

Sleep Duration and Diabetes: Epidemiologic Evidence

As for obesity risk, there is evidence for associations of both short sleep and long sleep with an increased risk of T2DM [57–59]. Very different mechanisms are likely to be involved and the present review will focus on short sleep only and on the recent and best-documented studies (summarized in Table 10.2). Additionally, in the last subsection, we review the relationship between short sleep and gestational diabetes risk.

Prospective Studies

A number of prospective studies have examined the association between SSD and incident diabetes. Ten prospective studies published between 2003 and 2007 are included in a meta-analysis reported in 2010 by Cappuccio et al. [57]. The estimated pooled OR of incident diabetes for short sleep was 1.28 (CI: 1.03–1.6). There was however a significant sex difference. The OR was 2.07 (CI: 1.16–3.72) for men but only 1.07 (CI: 0.90–1.28) for women. Difficulty initiating sleep and difficulty maintaining sleep were also significant predictors of incident diabetes. We will review here the recent prospective epidemiologic studies that were not included in this meta-analysis [57].

In a 2009 article, Chaput et al. examined the predictors of T2DM or impaired glucose tolerance (IGT), as assessed by the oral glucose tolerance test (OGTT), over a 6-year follow-up period in 276 participants of the Quebec Family Study [58]. Sleep was self-reported. After adjusting for multiple confounders, using adults with 7–8 h of sleep as a reference, the adjusted relative risk (RR) for the development of T2DM/IGT was 2.78 (CI: 1.61–4.12) for those with sleep duration ≤ 6 h. The RR was attenuated but remained significant after adjustment for BMI, waist circumference, or percent body fat. The latter finding suggests that obesity could partially mediate the developing of T2DM in short sleepers. Data from a community-based cohort of nondiabetics men and women from the Western New York Health Follow-up Study followed for an average of 6 years were used to examine biomarkers that predicted the incidence of T2DM [61]. Participants who were free of T2DM and cardiovascular disease at baseline (1996–2001) were reexamined in the period 2003–2004. Sleep duration < 6 h was categorized as short sleep and sleep duration of 6–8 h served as the reference. A nested case–control study was used to test the hypothesis that being a short sleeper at baseline is associated

Table 10.2 Summary of the epidemiologic studies (published after April 2009 and not included in the meta-analysis by Cappuccio et al. [57]), examining the association between sleep duration and glucose metabolism in adults. The association is expressed as adjusted odds ratio (AOR), adjusted relative risk (ARR) of diabetes, gestational diabetes mellitus (GDM), impaired fasting glucose (IFG), or prediabetes

Author	Description and data source	Cohort	Sleep assessment	Results	
Prospective studies					
Beihl et al. [60]	5-year follow-up Insulin Resistance Atherosclerosis Study (IRAS) (US)	390 men, 510 women Age 40–69 yrs	Self-report	*Non-Hispanic Whites and Hispanics:*	
				≤ 7 h	AOR of diabetes 2.36 (CI: 1.11–5.00)
				8 h	Reference category
				African-Americans: no significant association	
Chaput et al. [58]	5-year follow-up	276 men and women Age 21–64 yrs	Self-report	≤ 6 h	ARR for diabetes 2.42 (CI: 1.49–3.33)
				7–8 h	Reference category
Rafalson et al. [61]	6-year follow-up Western New York Health Follow-up Study (US)	1,455 men and women 91 cases developed IFG individually matched to 272 controls. Age 35–79 yrs	Self-report	< 6 h	AOR of IFG 3 (CI: 1.05–8.59, $p=0.022$) in model 1, NS in model 2, which includes insulin resistance
				6–8 h	Reference category
Xu et al. [62]	10-year follow-up NIH-AARP Diet and Health cohort (US)	164,399 men and women Age 50–71 yrs	Self-report	< 5 h	AOR of diabetes 1.34 (CI: 1.20–1.50)
				5–6 h	AOR of diabetes 1.06 (CI: 1.01–1.11)
				7–8 h	Reference category
Bo et al. [30]	6-year follow-up Patients from Local Health Units (Italy)	1,597 men and women Age 45–64 yrs	Self-report	No association between sleep duration and incident fasting hyperglycemia at follow-up	
Cross-sectional studies					
Vgontzas et al. [63]	Penn State Cohort (US)	1,741 men and women Age ≥ 20 yrs	PSG	Chronic insomnia but not poor sleep was associated with a higher risk for diabetes. Compared with normal sleeping with ≥ 6 h sleep duration, the highest risk of diabetes was in individuals with insomnia and ≤ 5 h sleep (OR 2.95; CI: 1.2–7.0) and in insomniacs who slept 5–6 h (OR 2.07; CI: 0.68–6.4)	
Kim et al. [64]	2005 Korean National Health and Nutrition Survey (KNHNS) (Korea)	1,652 men Age 20–60 yrs	Self-report	*No abdominal obesity* ($n=1,241$):	
				≤ 5 h	AOR of obesity 2.40 (CI: 1.18–4.91)
				5 h	NS
				6 h	NS
				7 h	Reference category
				Abdominal obesity ($n=411$): no significant association	

Shankar et al. [65]	2008 Behavioral Risk Factor Surveillance System (BRFSS) (US)	372,144 men and women Age > 20 yrs	Self-reported perception of insufficient rest or sleep	0 days of insufficient rest/sleep	Reference category
				14–29 days of insufficient rest/sleep	AOR of diabetes 1.15 (CI: 1.07–1.23)
				30 days of insufficient rest/sleep	AOR of diabetes 1.31 (CI: 1.21–1.41)
Knutson et al. [66]	Coronary Artery Risk Development in Young Adults (CARDIA) Study (US)	200 men; 331 women Age 18–30 yrs	WAM	Absence of diabetes	No association between sleep measures and fasting glucose, insulin, or HOMA
				In diabetics: 10% higher sleep fragmentation	Associated with: 9% higher fasting glucose level 30% higher fasting insulin level 43% higher HOMA level
Chao et al. [59]	2006–2007 health examination in Taiwanese University Hospital (Taiwan)	2,145 men, 1,325 women Age >18 yrs	Self-report	< 6 h	AOR of prediabetes NS AOR of diabetes 1.55 (CI: 1.07–2.24, $p = 0.022$)
				6–8.49 h	Reference category
Pregnancy					
Qiu et al. [67]	Cross-sectional study (US)	1,290 women in the 2nd trimester Mean age 33.3 ± 4.4	Self-report	*Lean (BMI < 25 kg/m²): no significant association* *Overweight (BMI ≥ 25 kg/m²):*	
				≤ 7 h	ARR of GDM 9.83 (CI: 1.12–86.32)
				8 h	NS
				≥ 9 h	Reference category
Facco et al. [68]	Prospective study (US) Longest follow-up 34 weeks	189 healthy nulliparous women Mean age 29.7 ± 5.5 yrs	Self-report	< 7 h	Higher oral glucose tolerance value (116 ± 31 mg/dl vs. 105 ± 23; $p = 0.008$). AOR of 1-h OGT ≥ 130 2.4 (CI: 1.1–5.3) AOR of GDM 11.7 (CI: 1.2–114.5)
				> 7 h	Reference category
Reutrakul et al. [69]	Cross-sectional study (US)	169 women in the 2nd trimester Mean age 28.5 ± 5.5 yrs	Self-report	Each hour of sleep reduction was associated with a 4% increase in 1 h glucose during the screening 50-g OGTT	
				OR of GDM 3.4 (CI: 1.3–8.7; $p = 0.01$) if short sleep was associated with being at increased risk for SDB	

Adj. b adjusted beta coefficient, *CI* 95% confidence interval, *HOMA* homeostatic model assessment, *NS* not significant, *OGT* oral glucose tolerance, *SS* short sleep, *SDB* sleep disordered breathing, *yrs* years

with an increased likelihood of developing impaired fasting glucose (IFG) independently of diabetes risk factors and several confounding variables. From their final cohort of approximately 900 individuals, 91 cases progressed from normal fasting glucose to IFG over the 6-year follow-up. Each case was matched with up to three controls (subjects who had normal fasting glucose at both exams, $n=273$) based on sex, race (white vs. other), and duration of follow-up. The average number of hours of weekday sleep duration was 6.8 vs. 7.1 ($p=0.019$) for cases and controls, respectively. Also the HOMA IR, a measure of insulin resistance, was higher in the cases than in the controls. Short sleep was associated with a threefold increased likelihood of developing IFG at 6 years. When HOMA IR was included in the statistical model, the contribution of short sleep was attenuated and no longer statistically significant, suggesting that insulin resistance explains in part the association.

The National Institutes of Health (NIH)-AARP Diet and Health was a large prospective study established in 1995–1996 to examine the relationship between diet and health behaviors and cancer [62]. Six months into the study (1996–1997), a question on hours of day napping and night sleeping was introduced. In 2004–2005, a questionnaire asking to report major chronic diseases including T2DM was mailed to the participants. The final sample included 164,399 participants without diabetes and 10,143 participants with diabetes diagnosed after 2000. [62]. Both SSD (< 5 h) and daytime napping (≥ 1 h) were independently associated with risk of incident T2DM, after controlling for several variables, including health-related and socioeconomic factors, family history of T2DM, and total energy intake. Duration of daytime napping in 1996–1997 was associated with higher risk of diabetes in 2004–2005 in a dose–response manner and in each subgroup of night sleeping duration, after controlling for variable factors, including physical activity. The adjusted RR was moderately attenuated after adjustment for BMI alone or simultaneously with physical activity. The novelty of this study is the prospective examination of daytime napping as an independent risk factor for T2DM. Daytime napping had been previously linked to diabetes in cross-sectional studies, where the direction of causation could not be inferred and the increased napping was interpreted as a consequence rather than a cause of diabetes [70–72]. Daytime napping could be a marker of poor sleep quality or/and of other conditions such as OSA and depression which have been linked to increased risk of diabetes.

Both SSD and T2DM are more prevalent in ethnic/racial minorities than in whites [7, 73, 74], and therefore there may be an interaction between sleep duration and race/ethnicity as predictors of the incidence of diabetes. Beihl et al. evaluated the association between sleep duration and incident T2DM in the Insulin Resistance Atherosclerosis Study (IRAS), a cohort including African-Americans (AA), Hispanic, and non-Hispanic whites (NHW) [60]. They confirmed that sleep duration differed by race/ethnic group with the longest mean sleep duration of 7.1 h in the NHW, 6.8 h per night for Hispanics, and 6.3 h per night for AA. Furthermore, they observed a strong interaction between short sleep and race/ethnicity as predictors of incident diabetes, with a significant association present in NHW and Hispanics but not in African-Americans, after controlling for multiple variables.

In an Italian study of 1,282 patients recruited from the practice of six independent family physicians and studied at baseline and after 6 years of follow-up [30], predictors of incidence of obesity and fasting hyperglycemia (including IFG and diabetes) were examined. A total of 979 subjects had normal fasting glucose levels at baseline. In a multiple logistic regression analysis, after adjusting for sex, education level, alcohol intake, baseline BMI and glucose, and multiple putative risk factors for diabetes, the incidence of obesity but not of fasting hyperglycemia was related to the hours of sleep. It is noteworthy that laboratory studies have been consistent in indicating that post-challenge glucose levels are more readily increased by sleep restriction than fasting values.

Cross-Sectional Studies

Most cross-sectional population studies of the relationship between sleep and metabolism relied on self-reported sleep duration.

A study reported by Vgontzas et al. in 2009 is unique in using PSG to examine in a cohort of 1,741 adults the joint effects of insomnia and objective SSD on diabetes risk [63], while controlling for sleep apnea, a major confounder for both sleep disturbance and risk of T2DM. Complaining of insomnia for 1 year and having the lowest objectively defined sleep duration (≤ 5 h) increased the odds for prevalent diabetes by nearly threefold (OR 2.95; CI 1.24–7.05), compared with the group who had no insomnia/poor sleep complaint and slept for >6 h. The risk did not change after adjusting for PSG variables such as number of awakenings, number of sleep stage changes, percentage of stage 1 sleep, and periodic limb movements. The second highest OR was found in the group of insomniacs who slept 5–6 h, with a near twofold but nonsignificant increase in the risk of diabetes. Finally, objective SSD in the absence of a sleep complaint was associated with a nonsignificant increase in the odds for diabetes, but this subgroup was of relatively small size. Shankar et al. [65] examined the data on 372,144 participants of the Behavioral Risk Factor Surveillance System (BRFSS), a large multiethnic, nationally representative, cross-sectional survey conducted annually by the Center for Disease Control (CDC) in men and women, of all race-ethnicities from all 50 US states, the District of Columbia, and the three territories. A recent report based on this survey found that an estimated 11.1% of Americans reported experiencing insufficient rest or sleep every day for the preceding 30 days and only 30.7% of respondents reported no days of insufficient rest or sleep [6]. The analysis by Shankar et al. focused on cardiovascular disease, diabetes mellitus, and obesity in relationship to days of insufficient rest or sleep. Increasing categories of self-reported insufficient rest/sleep in the previous month were found to be positively associated with all three outcomes. Specifically 13 days of insufficient sleep in 1 month compared to 0 days increased the risk of diabetes by 30%, with a graded relationship to the number of days, after adjustment for a large number of potential confounders. This relationship persisted when men and women were analyzed separately. The strength of this study is the very large size of the cohort and the equal representation of men and women. One caveat is that perceived insufficient rest or sleep is a subjective measure; additionally, it may be related to other factors such as underlying sleep disordered breathing (SDB), psychosocial stress, depressive symptom, endocrine disorders, or the effect of lifestyle choices which all may predispose to diabetes mellitus and cardiovascular disease. An analysis of data of the 2004–2005 US National Health Interview Survey in 56,507 adults, 49% males, age range 18–85 years, showed that both short sleep (< 7 h) and long sleep (>8 h) were positively associated with the risk of obesity, diabetes, hypertension, and cardiovascular disease [42]. The researchers employed a multilevel logistic regression, simultaneously controlling for individual characteristics (e.g., ethno-racial group, gender, age, education), other health behaviors (e.g., exercise, smoking), family environment (e.g., income, size, education), and geographic context (e.g., census region). The CARDIA Sleep Study collected information on objective sleep duration and fragmentation by WAM in more than 600 middle-aged adults. A recent paper from Knutson et al. [66] examined the association between sleep measures and fasting glucose, fasting insulin, and HOMA-IR in participants with and without diabetes. Sleep fragmentation, but not habitual sleep duration, was related to higher fasting glucose, insulin, and estimated insulin resistance in subjects with diabetes but not in those without diabetes. These findings are consistent with a previous survey study from the same group [75] which showed that self-reported sleep disturbances may adversely affect diabetes control.

Kim et al. examined the data from the Third Korean National Health and Nutrition Examination Survey 2005 in 1,652 male adults [64]. SSD (≤ 5 h, self-reported) was significantly associated with an increased prevalence of diabetes among men without abdominal obesity (AOR

of diabetes 2.40; CI: 1.18–4.91) compared to those with sleep duration of 7 h after adjustment of age, smoking, drinking, exercise, education, household income, residential area, hypertension, general obesity, abdominal obesity, high triglyceride, low HDL-C, and high cholesterol. The adjusted OR for diabetes was not significantly elevated in short sleepers with abdominal obesity, suggesting that abdominal obesity may have had a predominant role on diabetes risk. This was the first study that demonstrated an association between sleep duration and diabetes in an Asian population. Chao et al. examined the relationship between sleep duration and prediabetes/newly diagnosed T2DM in a Taiwanese population [59]. After excluding the subjects with a high risk of OSA, those with a positive history of T2DM, and those taking hypnotic drugs, a total of 3,470 adults were recruited. Each subject completed a questionnaire on sleep duration and lifestyle factors. Subjects were classified into short (< 6.0 h), normal (6.0–8.49 h), and long sleepers (≥ 8.5 h). The proportion of subjects with normal glucose tolerance, prediabetes, and newly diagnosed T2DM was 71.9, 22.9, and 5.2%, respectively. There were significant differences in age, sex, weight, education level, BMI, waist to hip ratio, systolic and diastolic blood pressure, alcohol and coffee drinking habits, family history of T2DM, and sleep duration among the three glycemic groups. In a multinomial regression, both short and long sleepers had a higher risk of newly diagnosed T2DM with an OR of 1.55 (CI: 1.07–2.24) and 2.83 (CI: 1.19–6.73), respectively, even after adjustments for age, sex, education level, family history of T2DM, cigarette smoking, alcohol and coffee drinking, and physical exercise. Furthermore, this association remained significant even after controlling for both general and central obesity. Sleep duration was not found to relate to prediabetes.

Studies in Pregnancy

Pregnancy is a condition of increased insulin resistance, and women with risk factors for diabetes such as family history, obesity, and excessive pregnancy-related weight gain may develop hyperglycemia during pregnancy, referred to as gestational diabetes mellitus (GDM). Decreases in both duration and quality of sleep are common in pregnant women [76, 77] as a result of hormonal and physical factors. Based on the epidemiologic data in the general adult population discussed above, it is conceivable that pregnant women with insufficient sleep or poor sleep quality may be at increased risk of GDM. Most epidemiologic studies have not included pregnant women; hence very little is known regarding this question.

We discuss here three studies that have examined the risk of GDM in women with sleep disturbances, including insufficient sleep. In a pilot study, Qiu et al. interviewed 1,290 women during early pregnancy to obtain self-reported measures of habitual sleep duration and snoring behavior [67]. Results from screening and diagnostic testing for GDM were abstracted from medical records. After adjusting for maternal age and race/ethnicity, women who reported sleeping ≤ 4 h per night during early pregnancy had a 5.6-fold increased risk of GDM as compared with those women who reported sleeping 9 h per night (the reference group) (RR = 5.56; CI 1.31–23.69). The positive association remained, although somewhat attenuated, after further adjustment for maternal pre-pregnancy BMI (RR = 4.18; CI 0.94–18.60). Overall, snoring was associated with a nonsignificant 1.86-fold increased risk of GDM (RR = 1.86; CI 0.88–3.94). The risk of GDM was particularly elevated among overweight pregnant women who reported snoring. Compared with lean pregnant women who did not snore, those who were overweight and snored had a 6.9-fold increased risk of GDM (CI 2.87–16.6). Facco et al. conducted a prospective cohort study in a convenience sample of healthy nulliparous women during pregnancy [68]. The women responded to a survey addressing sleep duration and SDB symptoms early and again later in pregnancy. SSD was defined as < 7 h per night. Subjects were asked about snoring and snoring frequency. Frequent snoring, used as a surrogate marker of SDB, was defined as snoring ≥ 3 nights per week. Outcomes in women who reported

SSD or frequent snoring while pregnant (early and/or late pregnancy) were compared to outcomes in women without these sleep complaints. A total of 189 women participated, 48% reported SSD, and 18.5% reported frequent snoring. Impaired glucose tolerance and GDM were more frequent in women with these sleep disturbances. Both SSD (10.2% vs. 1.1%; $p=0.008$) and frequent snoring (14.3% vs. 3.3%; $p=0.009$) were associated with a higher incidence of GDM compared to women without sleep complaints, even after controlling for potential confounders. Reutrakul et al. enrolled pregnant women scheduled to undergo a 50-g OGTT during the second trimester of gestation, according to standard of care [69]. Subjects completed standardized questionnaires assessing daytime sleepiness, SDB risk, sleep quality and duration, and sleep disturbance due to nocturia or other causes. There was an inverse correlation between sleep duration and 1-h glucose values post 50-g OGTT ($r=-0.21$, $p<0.01$) such that each hour of shorter sleep was associated with a 4% glucose increase. They also noted an increased incidence of preterm delivery in short sleepers. In addition, sleep disturbances, including frequent snoring (after adjustment for BMI), increased SDB risk, short sleep, and a combination of increased SDB and short sleep, were associated with a significantly higher risk of developing GDM.

These three studies emphasize the need for more research to characterize the impact of sleep disturbances on the risk of GDM and on pregnancy outcomes as well as the need for intervention studies to examine the possible beneficial effects of optimizing sleep duration and quality during pregnancy.

Impact of Sleep Restriction on Obesity Risk: Laboratory Studies

While a large body of epidemiologic evidence has pointed to an association between sleep loss and the increased risk of obesity, the direction of causality and the underlying mechanisms are still unclear. Theoretically, sleep loss could affect energy balance via a decrease in energy expenditure or an increase in energy intake. To date, laboratory studies examining the impact of experimental sleep deprivation have mainly focused on energy intake and/or the hormonal signals known to regulate hunger and appetite (e.g., leptin, ghrelin, PYY). The potential impact of sleep loss on energy expenditure has been much less explored.

Studies of acute total sleep deprivation (TSD) (as compared to normal nighttime sleep) conducted more than two decades ago demonstrated unequivocally that the presence or absence of sleep has a major impact on pituitary-dependent hormonal regulation and glucose metabolism [78]. In the first part of this section, we review the findings from laboratory studies that have used protocols of TSD to examine the role of sleep and circadian rhythmicity in the 24-h profiles of hormones involved in the neuroendocrine regulation of appetite (first part of Table 10.3). To date, such studies have focused only on leptin and ghrelin. We then summarize the results from a growing number of laboratory studies that have explored the effects of partial sleep deprivation (PSD) on caloric intake, weight gain, hunger, and appetite and the levels of hormones known to affect energy metabolism (second part of Table 10.3).

TSD Studies: Impact on Leptin and Ghrelin

Leptin, a hormone secreted by the adipocytes, provides information about energy status to the neural networks regulating homeostatic feeding in the hypothalamus [99, 100]. In humans acute caloric shortage or surplus leads to decreased or increased circulating leptin levels, respectively [100, 101]. These changes in leptin concentrations have been associated with reciprocal changes in hunger [101]. The 24-h leptin profile is not only dependent on the timing and amount of food intake, but appears to be also modulated by sleep and circadian rhythmicity. In a landmark study, when bedtimes were shifted by 8 h and the impact of meal intake was eliminated by administering continuous enteral nutrition to healthy lean young volunteers, a leptin elevation was

Table 10.3 Summary of the laboratory studies examining possible mechanisms linking sleep duration and obesity in adults

Total sleep deprivation				
Author	Intervention – time in bed	Subjects	Caloric intake	Changes with sleep deprivation
Simon et al. [79]	8 h×1 night (23:00–7:00) 24 h sleep deprivation (8 h shift of sleep) 8 h daytime recovery	7 men Age 21–25 yrs BMI 22.2±0.6 kg/m^2	24 h continuous enteral nutrition (50% carbohydrate, 35% fat, and 15% protein; 378 kilojoules/h)	Weight: n/a Leptin was increased during both the night of total sleep deprivation and daytime recovery sleep. A circadian elevation of leptin independent of sleep was also observed. Ghrelin: n/a Hunger: n/a Food intake: n/a
Mullington et al. [80]	8 h×3 nights (23:30–7.30) 88 h sleep deprivation Either 7 h or 14 h×3 nights of recovery	10 men Age 22–37 yrs BMI 20–34.5 kg/m^2	Three meals/24 h+optional evening snack during baseline and recovery vs. three meals+scheduled late evening snack during sleep deprivation	Weight: unchanged Leptin: decreased during night Ghrelin: n/a Hunger: n/a Food intake: n/a
Dzaja et al. [81]	8 h×1 night (23:00–7:00) 1 night sleep deprivation	10 men Age 28±3.1 yrs BMI 20.5–29.5 kg/m^2	Matched standardized meals (1,800 kcal/24 h; 30% fat, 60% carbohydrates, and 10% protein)	Weight: n/a Leptin: n/a Ghrelin: decreased during night Hunger: n/a Food intake: n/a
Schmid et al. [82]	7 h×1 night (22:00–6:00) 1 night sleep deprivation	10 men Age 20–40 yrs BMI 20.7–25 kg/m^2	No food from 21:00 to hypoglycemic clamp (at 7:30)	Weight: n/a Leptin: n/a Ghrelin: n/a Hunger: increased Food intake: n/a
Pejovic et al. [41]	8 h×4 nights (22:30–6:30) 40 h sleep deprivation 8 h×2 nights of recovery	21 men and women Age 18–30 yrs Divided in 2 groups: BMI 23.2±2.8 and 25.0±2.1 kg/m^2	Uncontrolled food intake	Weight: n/a Leptin (24 h profile): increased Ghrelin: n/a Hunger: unchanged Food intake: unchanged
Partial sleep deprivation				
Guilleminault et al. [83]	8.5 h×2 nights (22:30–7.00) 4 h×7 nights (first group 22:30–02:30; second group 2:15–06:15) 1 night *ad libitum* and 8.5 h×2 nights of recovery	8 men Age 18–25 yrs BMI 22.9±0.7 kg/m^2	Standardized diet (rich in carbohydrates on the blood-drawing days)	Weight: n/a Leptin: reduced Ghrelin: n/a Hunger: n/a Food intake: n/a

Spiegel et al. [84]	8 h×3 nights (23:00–7:00) 4 h×6 nights (1:00–5:00) 12 h×7 nights (21:00–9:00)	11 men Age 22±1 yrs BMI 23.4±0.5 kg/m^2	Weight-maintenance meals on the day preceding and on the day of blood sampling	Weight: unchanged Leptin: reduced Ghrelin: n/a Hunger: n/a Food intake: n/a
Spiegel et al. [85].	10 h×2 nights (22:00–8:00) 4 h×2 nights (1:00–5:00)	12 men Age 22±2 yrs BMI 23.6±2 kg/m^2	Matched dinner on the second night Matched glucose infusion during blood sampling	Weight: unchanged Leptin: reduced Ghrelin: increased Hunger: increased Food intake: n/a
Schmid et al. [86]	7 h×1 night (1st session) 4.5 h×1 night (2nd session) 1 night of sleep deprivation (3rd session)	9 men Age 20–40 yrs BMI 20.7–25.0 kg/m^2	No food from 21:00 to single morning blood draw	Weight: n/a Leptin: unchanged Ghrelin: increased Hunger: increased Food intake: n/a
Bosy-Westphal et al. [87]	>8 h×2 nights Four nights of consecutively increasing sleep curtailment (7 h, 6 h, 6 h, 4 h) >8 h×2 nights of recovery	14 women Age 23–38 yrs BMI 20–36.6 kg/m^2	*Ad libitum* diet prior to OGTT	Weight: increased (+0.4 kg) Leptin: increased Ghrelin: unchanged Hunger: unchanged Food intake: increased (+20% by dietary records) Resting metabolic rate and total energy expenditure: unchanged
Schmid et al. [88]	7 h×1 night (22.30–6.30) 4.5 h×1 night (22.30–3.00)	10 men Age 20–40 yrs BMI 20.7–25.0 kg/m^2	No food from 21:00 to hypoglycemic clamp	Weight: n/a Leptin: n/a Ghrelin: n/a Hunger: unchanged Food intake: n/a
Schmid et al. [89]	8 h 15 min×2 nights (22.45–7.00) 4 h 15 min (2.45–7.00)×2 nights	15 men Age 20–40 yrs BMI 22.9±0.3 kg/m^2	Uncontrolled food intake until the morning of the 2nd night when blood sampling was initiated and *ad libitum* food offered	Weight: n/a Leptin: unchanged Ghrelin: unchanged Hunger: unchanged Food intake: increased in both sleep conditions (60% excess in energy intake vs. their estimated daily energy demand) Physical activity: decreased during the daytime under free-living and shifted toward lower intensity levels

(continued)

Table 10.3 (continued)

Total sleep deprivation

Author	Intervention – time in bed	Subjects	Caloric intake	Changes with sleep deprivation
Magee et al. [90]	8 h × 1 night (22.30–6.30) 5 h × 2 nights (1.30–6.30) 8–10 h × 1 night of recovery	10 men Age 19–23 yrs Non-obese	Standardized evening meal (1,546–1,992 KJ)	Weight: n/a Leptin: unchanged Ghrelin: unchanged Hunger: unchanged but significant reduction in satiety Caloric intake: n/a
Tasali et al. [91]	8.5 h × 4 nights 4.5 h × 4 nights	10 men and women Age 18–28 yrs BMI 20–25 kg/m^2	Matched meals. *Ad libitum* buffet at the end	Weight: unchanged Leptin (single AM assessment): increased Ghrelin: n/a Hunger: n/a Caloric intake: increased by >400 Kcal
Nedeltcheva et al. [92]	8.5 h × 14 nights 5.5 h × 14 nights	6 men, 5 women Age 34–49 yrs BMI 24–29 kg/m^2	*Ad libitum* diet. Identical meals on the blood sampling day	Weight: similar increase in both sleep conditions Leptin: unchanged Ghrelin: unchanged Hunger: n/a Caloric intake: increased snacks
Omisade et al. [93]	10 h × 2 nights (22.00–8.00) 3 h × 1 night (5.00–8.00)	15 women Age 18–25 yrs BMI 18.3–51.9 kg/m^2	Matched meals	Weight: n/a Leptin (AM and PM assessment): increased Ghrelin: n/a Hunger: unchanged Caloric intake: n/a
van Leeuwen et al. [94]	8 h × 2 nights (23.00–7.00) 4 h × 5 nights (3.00–7.00) 8 h × 3 nights (23.00–7.00) of recovery	15 men Age 19–29 yrs BMI 23.3 ± 2.7 kg/m^2	Matched meals and snacks + one more snack (fruit; 50 kcal) at 0:30 during sleep restriction	Weight: n/a Leptin: increased Ghrelin: n/a Hunger: unchanged Food intake: n/a
Simpson et al. [95]	10 h × 2 nights (22.00–8.00) 4 h × 5 nights (3.00–8.00)	136 men and women Age 22–45 yrs BMI 17.7–32.6 kg/m^2	*Ad libitum* food access	Weight: n/a Leptin (single AM assessment): increased Ghrelin: n/a Hunger: n/a Caloric intake: n/a

Nedeltcheva et al. [96]	7 h×2 nights 5.5 h×14 nights 8.5 h×14 nights	10 men and women Mean age 41 ± 5 yrs Mean BMI 27.4 ± 2 kg/m^2	Caloric content restricted to 90% of resting metabolic rate	5.5 h (vs. 8.5): Same weight loss, but decreased fat mass loss and increased fat-free mass loss Leptin (24 h profile): unchanged Acylated ghrelin (24 h profile): increased Hunger: increased
Brondel et al. [97]	8 h×2 nights (00.00–8.00) 4 h×1 night (2.00–6.00)	12 men Age 18–29 yrs BMI 19–24.6 kg/m^2	*Ad libitum* food intake after sleep restriction.	Weight: n/a Leptin: n/a Ghrelin: n/a Hunger: increased before breakfast and dinner Caloric intake: increases of 560 kcal Physical activity: increased by 48 kcl Positive 24 h energy balance of 510 kcal
St Onge et al. [98]	9 h×5 nights 4 h×5 nights	15 men and 15 women Age 30–45 yrs BMI 22–26 kg/m^2	Food intake controlled during first 4 days, then *ad libitum*	Weight: n/a Leptin: n/a Ghrelin: n/a Hunger: increased before breakfast and dinner Caloric intake: increased Resting metabolic rate and total energy expenditure: unchanged

yrs years, *OGTT* oral glucose tolerance test

observed when sleep was allowed during the daytime after the night of TSD [79], suggesting that the sleep state, irrespective of time of day, affects leptin release. The possibility that sleep may promote the release of leptin and thus the control of satiety was further supported by the demonstration that prolonged TSD resulted in a decreased amplitude of the leptin diurnal variation and that sleep recovery restores the normal circadian variation [80]. While the two previous studies [79, 80] included only men, more recent work by Pejovic et al. involving both men and women confirmed a dampening of the 24-h circadian rhythm of leptin following a night of TSD but the flattening of the rhythm was due to higher daytime, rather than lower nighttime, levels [102]. Hunger ratings were unchanged but caloric intake and meal composition were not strictly controlled.

Ghrelin, a peptide produced predominantly by the stomach, is also involved in energy homeostasis, but, in contrast to leptin, ghrelin stimulates appetite [103]. The 24-h profile of ghrelin levels shows a marked nocturnal rise, which reflects at least partly the rebound of ghrelin following suppression by the evening meal. The nocturnal rebound is eventually attenuated as the night progresses, suggesting the inhibitory effects of sleep on ghrelin secretion, and therefore on the hunger-promoting effects of ghrelin [104]. The impact of TSD on the nocturnal ghrelin profile has been examined in only one study in which the nocturnal ghrelin elevation was paradoxically dampened when subjects were sleep deprived [81]. More recently, Schmid et al. reported that a single night of TSD resulted in increased subjective hunger the following morning [82] but neither leptin nor ghrelin levels were assessed.

PSD Studies: Impact on Leptin and Ghrelin

The pioneer "sleep debt study" of Spiegel et al. looked at the impact of recurrent PSD (bedtime restricted to 4 h per night for 6 nights, as compared to a fully rested condition) in healthy young men and demonstrated a robust decrease of leptin levels throughout the 24-h cycle, despite identical amounts of caloric intake, similar sedentary conditions, and stable weight [84]. The magnitude of the decrease was comparable to that observed in a similar subject population after 3 days of underfeeding by approximately 900 cal/day [105]. These observations confirmed preliminary findings by Guilleminault et al. [83] who reported that 7 nights of sleep restriction to 5-h bedtimes led to a reduction in peak nocturnal leptin levels. In the "sleep debt study," the reduction in leptin levels in the debt condition was paralleled by an increase in peripheral sympathetic nervous activity, measured via an analysis of heart rate variability. The findings suggested that repeated PSD could result in a reduced ability of leptin to accurately sense energy balance. The findings suggested that if exposed to *ad libitum* food, the subjects, under sleep restriction, would have increased their food intake and possibly gained weight. This initial demonstration of an adverse impact of sleep loss on appetite regulation was confirmed and extended in a follow-up randomized crossover design study examining the impact of 2 nights of 4 h as compared to 8 h in bed on leptin, ghrelin, and hunger and appetite [85]. Relative to the rested condition, sleep restriction was associated with an 18% decrease in leptin levels, a 28% increase in ghrelin, and more than 70% increase in the ghrelin:leptin ratio [85]. Hunger showed a 23% increase and appetite for nutrients with high carbohydrate content (such as sweets, salty snacks, and starchy foods) was increased by more than 30% [85]. Importantly, there was a remarkable correlation between the increase in subjective hunger ratings and the increase in the ghrelin:leptin ratio.

Based on these initial findings, subsequent PSD studies examined measures of caloric intake. A preliminary study in 10 healthy young adults estimated that after 4 nights of restricted sleep to 4.5 h in bed, participants ingested on average an excess of more than 400 kcal from an *ad libitum* buffet relative to when they were allowed 8.5 h bedtimes. This nearly 14% increase in caloric intake was achieved mainly by excess intake of carbohydrate-rich nutrients [91]. Confirming and extending these findings, a recent

randomized crossover study comparing 5 nights of 4 h in bed to 5 nights of 9 h in bed in 15 men and 15 women found that when presented with ad lib food on the fifth day of each condition, the subjects consumed nearly 300 more Kcal when sleep restricted [98]. There was no significant impact of sex on this increase in caloric intake. Of note, in these two studies involving *ad libitum* conditions, caloric intake was controlled and kept identical under both sleep conditions prior to access to *ad libitum* food. In another study, 14 young women were exposed to an *ad libitum* diet during an 8-day at home protocol including 2 days of bedtimes > 8 h, followed by 4 days of bedtime progressively decreased to 7 h, 6 h, 6 h, and 4 h (for a total of 9 h of bedtime loss over a 4-day period relative to 8 h in bed). Sleep was not recorded and caloric intake was self-reported. The women reported on average a 20% increase in food consumption over the 4 days of sleep restriction and 11 of the 14 participants experienced weight gain (mean: +0.4 kg) [87]. A randomized crossover design study of 14 nights of sleep restriction or extension by ±1.5 h per night in overweight middle-aged adults who had *ad libitum* access to palatable food throughout the study demonstrated an increased consumption of carbohydrates and calories mostly from snacks, particularly in the evening and overnight, in the restricted sleep condition [92]. In this study, significant weight gain was observed under both sleep conditions because the participants consumed excessive amounts of calories in the "obesigenic" sedentary environment of the laboratory.

When interpreting the findings regarding the neuroendocrine regulation of appetite from studies that provided *ad libitum* access to food, one must keep in mind that weight gain may obliterate or obscure the impact of sleep loss on leptin and/or ghrelin since the release of both hormones is readily affected by changes in adiposity. A recent study in a large sample ($n = 136$) observed an increase in morning leptin levels after five to 7 nights of bedtime restriction to 4 h per night [95]. This increase in leptin levels was larger in women than in men and also larger in those with higher baseline BMI. The findings are suggestive of increased food intake and consequent weight gain following sleep restriction. However, neither food intake nor changes in body weight across the study period were evaluated.

Infrequent sampling for leptin and/or ghrelin (both hormones are secreted in a pulsatile fashion, and are modulated by circadian rhythmicity) may also complicate data interpretation. For example, in a study involving a single assessment of satiety and leptin levels at 7:30 a.m. after 5 nights of 4 h in bed (bedtimes from 3 a.m. to 7 a.m.) and after five nights of habitual sleep (bedtimes from 11 p.m. to 7 a.m.), no effect of bedtime restriction on satiety could be detected and leptin levels were elevated, rather than decreased [94]. However, bedtime restriction was achieved by delaying the timing of lights off, a condition that usually results in a phase delay of the central circadian pacemaker. As the nocturnal elevation in leptin levels is influenced by circadian rhythmicity [79], the elevated morning leptin level is likely to reflect a phase delay of the nocturnal rise in leptin.

Short-term studies involving one or two nights of bedtime restriction as compared to normal sleep have had variable results. A 2010 study comparing one night of 8 h in bed vs. one night of 4 h in bed in a randomized crossover design conducted in 12 young lean men observed a large increase in caloric intake (+22% or nearly 560 Kcal) and an increase in hunger ratings before breakfast and dinner [97]. In a subsequent study comparing 2 nights of 4 h 15 bedtimes vs. 2 nights of 8 h 15 bedtimes, appetite ratings, daytime levels of leptin and ghrelin, hunger, and calories consumed were similar after both sleep conditions. Of note, the first experimental day was spent under ambulatory conditions and food intake was not controlled [89]. A recent report where bedtimes were restricted to 3 h for only one night and leptin levels were measured in saliva at two isolated time points during the following day did not find significant changes in hunger or craving scores, while morning leptin levels were elevated after short sleep [93].

Lastly, a recent report has examined for the first time the response of PYY levels of sleep restriction. PYY is a peptide secreted by the neuroendocrine

L cells in the ileum and colon in response to a meal. The postprandial release of PYY appears to be involved in meal-related satiety and to contribute to meal termination. Similarly, glucagon-like peptide-1 (GLP-1) is secreted by the same L cells in response to a meal and has multiple actions, mostly related to glucose homeostasis, and decreases food intake by increasing satiety via central nervous system (CNS) mechanisms. Adiponectin, released by adipose tissues, promotes insulin sensitivity. Levels of adiponectin are reduced in obese and diabetic subjects. The study with PYY determinations involved 2 nights of 5 h in bed as compared to a fully rested night (8–10 h in bed) and examined peripheral levels of PYY, ghrelin, adiponectin, and leptin in young healthy men [90]. Satiety was reduced and levels of PYY were lower in the sleep loss condition. The other hormones were not affected. Although hormonal levels were assessed at a single time point upon awakening, this is the first report of decreased PYY levels after sleep restriction in humans, which could represent another mechanism underlying the reduced feeling of satiety consistently reported by sleep-deprived individuals. Lastly, young healthy men and women studied in a forced desynchrony protocol (involving over 1 month of laboratory conditions on a 28-h sleep–wake and dark–light cycle with four isocaloric meals per 28-h cycle) exhibited lower leptin levels when they ate and slept 12 h out of phase from their usual schedule [106]. Sleep efficiency was 67% when circadian disruption was maximal, compared to 84% in conditions of circadian alignment. The findings are consistent with an inhibition of leptin levels by sleep disruption but the relative contributions of circadian misalignment and sleep loss in such a protocol cannot be unambiguously dissected.

Cross-sectional population studies that examined leptin levels in relation to sleep duration have had conflicting findings. In the Wisconsin Sleep Cohort study, 5 h of habitual sleep time as compared to 8 h of sleep and both self-reported habitual sleep duration and PSG were obtained. Short habitual sleep was associated with a 15.5% decrease in morning leptin levels, while short PSG-based sleep duration was associated with 14.9% increase in morning ghrelin levels, after controlling for BMI [19]. In contrast, in a more recent study by Hayes et al. on data from the Cleveland Family Study, for each hour of decreased sleep there was a 6% increase in leptin levels after controlling for obesity and associated comorbidities [107]. A recent paper by Knutson et al. suggests that the data obtained in lean subjects may not be easily extrapolated to individuals with obesity [108]. The authors performed a cross-sectional analyses of data from participants in an ongoing sleep extension study of obese men and women, aged 18–50 years, who report sleeping less than 6.5 h per night on average [53]. Habitual nocturnal sleep duration and quality were also estimated using WAM. SDB was assessed over one night using a portable screening device. Using the baseline data available on 80 participants at the time of the analysis, no significant associations between leptin levels adjusted for the degree of adiposity and any of the sleep measures, including sleep duration, sleep efficiency, and SDB, were found.

In summary, the bulk of the current evidence from laboratory studies of sleep restriction points to a dysregulation of appetite. Inconsistent findings regarding the neurohormonal control of appetite during partial sleep restriction may be attributed to differences in the study design such as the duration of sleep restriction (1–2 vs. multiple days), the circadian timing of the restricted bedtimes, caloric intake and weight changes during the study, and finally the timing and frequency of hormonal measurements. The original finding of a decrease in leptin levels after PSD was obtained under conditions of strictly controlled caloric intake, fixed circadian timing, and BMI was unchanged [84, 85]. When feeding is *ad libitum*, an increase in weight generally occurs and has therefore the opposite effect on leptin levels, which may be more responsive to changes in adiposity than to changes in sleep duration. Ghrelin levels were measured in only one of the six studies. It is possible that the impact of sleep restriction on the neuroendocrine regulation of appetite is more clearly apparent in conditions of weight maintenance caloric intake or in conditions where caloric intake is lower than energy requirements.

If this was the case, sleep restriction could undermine the success of a reduced calorie diet by decreasing the compliance to the dietary regimen and its efficacy. The findings of a recent study [96] support this hypothesis.

Sleep Loss and Energy Expenditure

Beside the changes in neurohormones involved in the regulation of food intake, reduced energy expenditure (EE) is to date a poorly explored pathway that could also link short sleep and the risk of obesity. The amount of total daily energy expenditure (TEE) comprises three components: (1) *Resting metabolic rate* (RMR, 60% of TEE) defined as the energy expenditure of an individual under basal conditions (at rest, after an overnight fast); (2) *Thermic effects of meal* (TEM 10% of TEE), which includes the energy expenditure involved in digestion, absorption metabolism, and storage of food; (3) *Activity-related energy expenditure* (AEE, 30% of TEE), which involves all volitional and non-volitional activities. For most individuals, AEE is not accounted for by physical exercise, but rather by low-moderate intensity activities of daily living such as sitting, standing, walking, and other occupational, volitional, and spontaneous activities, all together referred to as nonexercise activity thermogenesis (NEAT) [109]. AEE is the most variable component of TEE, has a major weight in the energy balance equation, and is critical for long-term weight maintenance.

Subjects with sleep problems and/or excessive daytime sleepiness have reported significant reductions in energy ratings and in levels of physical activity [110, 111], which could reflect both reduced amounts of exercise and reductions in NEAT, and thus an overall decrease in AEE. Subjective sleepiness and fatigue increase immediately and significantly with sleep deprivation [112], however, is not clear if these would affect volitional or non-volitional daily activities or other components of TEE. Prospective data from the Nurses' Health Study showed differences in risk of weight gain in short sleepers but no difference in self-reported levels of voluntary activity in the women sleeping ≤ 6 h per day vs. those sleeping 7 h per day [113]. In the cross-sectional analysis of the CARDIA sleep study, BMI was independently associated with sleep duration and sleep fragmentation in over 600 early-middle-aged adults, and this association was not modified by accounting for self-reported levels of physical activity [26]. In participants in the Third National Health and Nutrition Examination Survey, self-reported fatigue was associated with a higher BMI, higher waist circumference, and a reduced likelihood of getting recommended levels of physical activity [114].

The findings from the five studies that examined the impact of short-term sleep restriction on physical activity have not been entirely consistent. In comparison with a rested night (7 to > 8 h in bed), Schmid et al. demonstrated that sleep restriction to 4 h for 2 nights led to a reduction in physical activity measured by accelerometry under free-living conditions, but there were no significant changes in food intake, hunger and appetite, and levels of leptin and ghrelin [89]. In contrast, Brondel et al., also using accelerometry, observed increased physical activity in the afternoon and evening after one night of PSD [97], but caloric intake increased by 560 kcal with sleep deprivation, likely resulting in a overall positive energy balance. Bosy-Westphal et al. studied 14 healthy lean and obese women after 4 nights of 5.5 h in bed, by indirect calorimetry; compared to the rested condition (9 h sleep for 2 nights), there was no change in resting EE, even when adjusted for fat-free mass or total EE. In a protocol involving a more prolonged sleep restriction (14 nights of 5.5 h vs. 14 nights of 8.5 h in bed) in healthy overweight subjects who remained in the laboratory under sedentary conditions, total EE assessed by the gold standard doubly labeled water method, RMR assessed by indirect calorimetry, and the TEM were not affected by the bedtime condition [87]. The most recent study [98] examined EE by the doubly labeled water method in subjects who participated in a randomized crossover design comparison of 5 nights of 4 h in bed vs. 5 nights of 9 h in bed and did not detect a difference in TEE.

In sum, the bulk of the evidence points at reduced or unchanged energy expenditure in

subjects submitted to repeated partial sleep loss. Of note, a recent study that compared total energy expenditure during a night of sleep and during a night of TSD in subjects who remained in a whole room indirect calorimeter for 3 days found that the energy cost of sustained wakefulness across the night under sedentary conditions was only 134 ± 2 Kcal [115]. The energy cost of sleep restriction by 2–4 h per night is likely to be less, may be as low as 50–70 Kcal, in sharp contrast with 300–600 Kcal increases in energy intake which were observed in several laboratory studies of partial sleep restriction [87, 98].

Impact of Sleep Restriction on Diabetes Risk: Laboratory Studies

Studies in healthy volunteers who underwent experimental sleep restriction have unequivocally demonstrated that insufficient sleep may cause alterations in glucose metabolism and have suggested mechanisms by which sleep loss might increase the risk of diabetes.

Total Sleep Deprivation

Kuhn et al. published in 1969 the very first laboratory study of the effect of prolonged TSD (for 72–126 h) on oral glucose tolerance and showed that TSD leads to a marked increase in glucose levels [116]. These findings were ignored for a long time, most probably because such extended periods of TSD are uncommon in real life. In 1981, another study involving 120 h of TSD demonstrated alterations of glucose metabolism at the level of the muscle consistent with a prediabetic state and increased fasting glucose levels at the end of the sleep deprivation period [117]. In 1993, a study involving 60 h of TSD observed increases in fasting insulin levels, as well as in the insulin response to OGTT, without change in glucose levels, suggesting decreased insulin sensitivity [118]. These important studies may not have had the scientific impact they deserved because TSD is a condition invariably followed by sleep recovery and a correction of metabolic abnormalities. Chronic PSD is much more common and may involve irreversible alterations.

Partial Sleep Deprivation

The first laboratory study of PSD in healthy lean adults [18] found that restricting sleep to 4 h per night for 6 nights resulted in a 40% decrease in glucose tolerance, impaired beta-cell function, reduced noninsulin-dependent glucose utilization, and a trend for decreased insulin sensitivity (SI) as assessed by minimal model analysis of a frequently sampled intravenous glucose tolerance test (ivGTT). The ivGTT is a validated tool that provides assessments of SI, pancreatic beta-cell responsiveness (referred to as "acute insulin response to glucose", AIRg), and glucose effectiveness (SG), a measure of noninsulin-dependent glucose disposal [119]. The SG was 30% lower in the state of sleep debt. AIRg was reduced by more than 30% after sleep restriction despite a trend for decreased SI. The disposition index (DI), i.e., the product of SI and AIRg, is a validated marker of diabetes risk [120]. In the state of sleep debt, the DI was decreased by an average of about 40% as compared to the fully rested state. The glucose tolerance values observed after 5 nights of 4-h bedtimes in the young lean participants were similar to those reported in older adults with impaired glucose tolerance [121]. The metabolic findings in the sleep debt condition were paralleled by an increase in the activity of the sympathetic nervous system. At the end of the recovery phase, glucose tolerance normalized to levels expected for healthy young adults [122]. A criticism of this initial "sleep debt study" is that sleep restriction (6 nights of 4-h bedtimes) was more severe than commonly occurring in real life. Also, the study did not follow a randomized crossover design and therefore the possibility of an order effect (sleep restriction preceded sleep extension) could not be excluded. These issues were addressed in a follow-up study of 2 nights with 10 h in bed vs. 2 nights with 4 h in a randomized crossover design [85]. After the second night of each bedtime condition, caloric intake was replaced by an intravenous glucose

infusion at a constant rate to avoid fluctuations of hunger and appetite related to meal ingestion. Even though sleep duration was restricted for only two nights, glucose tolerance was decreased as observed in the initial study, partly as a result of inadequate insulin secretion [123]. In a recent study in non-obese healthy men, sleep restriction to 5 h per night for 1 week resulted in a significant reduction in SI as assessed by hyperinsulinemic euglycemic clamp, considered the gold standard method for SI determination [124]. The volunteers also underwent an ivGTT on a separate day and again, SI was decreased following sleep restriction, without adequate compensation by insulin release and therefore diabetes risk, as assessed by the DI, was elevated. In a 2008 study involving women only and performed under ambulatory conditions without objective sleep assessment and without control of caloric intake, progressive sleep curtailment over 4 nights (for an average bedtime restriction of 2.5 h per night, relative to 8-h bedtimes) had no impact on oral glucose tolerance [87]. More recently, Nedeltcheva et al. [125] examined the effects of moderate but prolonged sleep curtailment (5.5 h per night for 14 nights) in sedentary middle-aged men and women, and observed a decrease in glucose tolerance due to decreased SI in the absence of adequate beta-cell compensation. In addition, SG was increased. Such recurrent bedtime restriction is closer to the sleep curtailment experienced by many people in everyday life, and in people at risk it may facilitate the development of insulin resistance, reduced glucose tolerance, and ultimately diabetes. Indeed, epidemiologic studies suggest that people who sleep less than 6 h per night are at higher risk of T2DM. Consistent findings were reported by Van Leeuwen et al. who simulated in healthy young men the cumulative sleep debt as it can occur during a regular five working days schedule [94] with bed times restricted to 4 h per night. After the fifth day of sleep restriction, morning fasting glucose levels were unchanged, but fasting insulin concentrations were increased, suggesting reduced insulin sensitivity. After two nights of recovery sleep, fasting glucose was lower than at baseline, while insulin returned to baseline levels. The authors suggested that the effects of one workweek of sleep restriction could be reversed by recovery sleep on weekends. Donga et al. evaluated SI in middle-aged men and women after one single night of partial sleep restriction with the hyperinsulinemic euglycemic clamp and observed a reduction in glucose infusion and disposal rates, indicating a deterioration of glucose tolerance and peripheral insulin sensitivity [126]. They also assessed endogenous hepatic glucose production rate, by continuous infusion of [6,6-$^{2}H_{2}$]-glucose, and found an increase by approximately 22% after sleep restriction. Free fatty acid levels were also increased. These findings point to increased insulin resistance at the level of the liver and adipose tissue, respectively.

Putative Mechanisms and Implication

Multiple pathways are likely to mediate the adverse effects of sleep loss on the risk of obesity and diabetes, and much work is needed to elucidate their respective roles and interactions. Figure 10.2 presents a simplified schematic representation. Among the effects of insufficient sleep that have been documented are alterations of the central neurohormonal control of energy homeostasis and glucose metabolism, a decrease in brain glucose utilization, an increase in sympathetic activity and a decrease in vagal tone, increases in the levels of circulating hormones counter-regulatory to insulin action (cortisol, growth hormone, and catecholamines), a putative decrease in EE, an increase in inflammation, and finally more time to eat.

An upregulation of the activity of orexin neurons, concentrated in the lateral hypothalamus, may be one of the primary mechanisms linking sleep deprivation and some of its adverse metabolic effects. Indeed, the orexin system plays a key role in the interaction between sleeping and feeding. Orexin producing neurons have an extensive and divergent projection system innervating numerous structures in the CNS including all the components of the ascending arousal system and the entire cortex [127]. This system is involved in the regulation of many functions such

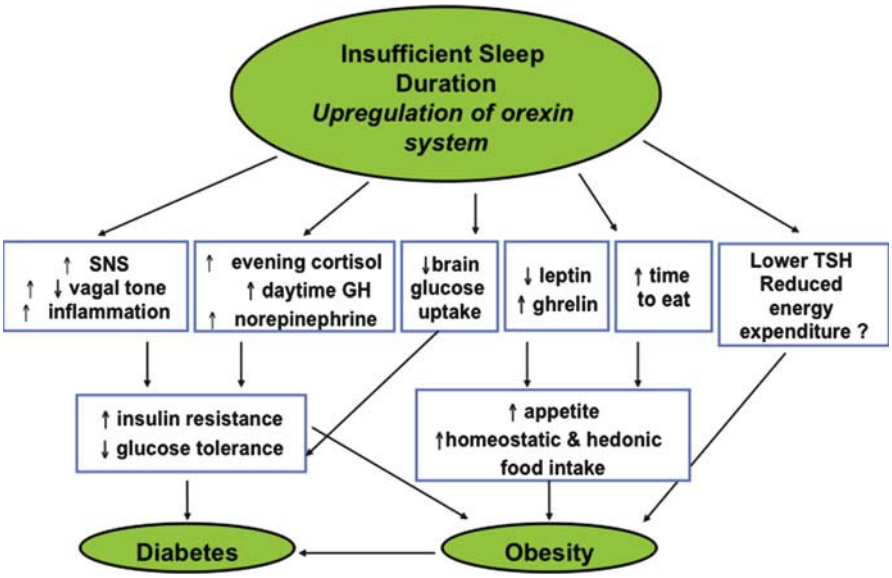

Fig. 10.2 Schematic representation of the multiple pathways likely to mediate the adverse effects of sleep loss on the risk of obesity and diabetes

as sleep–wakefulness, locomotor activity, feeding, thermoregulation, sympatho-vagal balance, and neuroendocrine and cardiovascular control [128]. Orexigenic neurons are firing during the wake period and are inactive during deep non-REM sleep due to a direct inhibition by GABA-ergic hypothalamic neurons [129]. Orexin-containing neurons play a central role in the maintenance of arousal. Deficiencies in the orexin system are associated with sleep disorders that involve chronic excessive daytime sleepiness, including narcolepsy and OSA [130, 131]. In contrast, when sleep deprivation is enforced behaviorally, the orexin system is overactive, most likely to maintain wakefulness against the increased sleep pressure [132–134]. There is evidence that orexins may stimulate food intake, particularly the early part of the usual sleep period, which is when voluntary sleep deprivation most often occurs in humans [130, 135]. Orexigenic neurons regulate the homeostatic feeding center in the hypothalamic arcuate nucleus (ARC), and concurrently affect hedonic feeding mediated by the "reward centers" (ventro-tegmental area and nucleus accumbens) [136, 137]. During starvation, the orexin neurons may be disinhibited by low levels of the anorexigenic hormone leptin and low glucose levels [129], and are excited by the hunger-promoting hormone ghrelin [138]. The peripheral metabolic cues, including insulin, leptin, and ghrelin, directly interact with ARC in the hypothalamus and ultimately indirectly modulate the activity of the orexigenic neurons to regulate food intake [135]. Additionally, the peripheral hormonal signals may influence the activity of orexigenic neurons via vagal afferents to the nucleus of the solitary tract (NST) [139].

As reviewed in this chapter, multiple studies of experimental sleep restriction have shown alterations in the metabolic hormones that are involved in the regulation of energy balance, including elevated evening cortisol levels, extended duration of daytime elevated growth hormone (GH) levels, and reductions in thyroid-stimulating hormone (TSH), lower leptin levels, and higher ghrelin levels [18, 84]. Insufficient sleep also results in elevations of markers of sympathetic nervous activity and in decreases in vagal tone. At the level of the pancreatic beta cell, this altered sympatho-vagal balance is likely to impair the expected compensatory

hyperinsulinemia needed to compensate the reduced insulin sensitivity associated with sleep loss. Furthermore, elevated cortisol levels have been shown to promote increased food intake and the accumulation of visceral fat in humans [140, 141]. Similarly, since TSH normally functions to stimulate basal metabolic rate, the reductions in TSH resulting from sleep restriction [84] may lead to a reduction in EE.

Another important mechanism that may promote hyperglycemia, considering that brain is the major user of glucose, is reduced brain glucose utilization after sleep deprivation, as shown by PET studies [142]. Finally, sleep loss and sleep disturbances have been associated with increased concentrations of C-reactive protein (CRP) [143]. Both partial and total sleep loss, in young, healthy individuals results in elevation of the levels of the inflammatory cytokine Il-6, which will in turn increase CPR production [144, 145]. TSD also increases the plasma levels of TNF-alpha soluble receptor 1 [146]. Low-grade inflammation predispose to both insulin and leptin resistance [147]. Thus, sleep disturbances appear to promote systemic inflammation that could, over time, further contribute to metabolic disturbances and increase the risk of obesity and diabetes. CRP has been recently proposed as a leptin-binding protein, and thus the increase in CRP resulting from sleep restriction may further limit the amount of free leptin that is able to penetrate the blood–brain barrier and inhibit central orexigenic activity.

Conclusion

In sum, the evidence reviewed in this chapter support the hypothesis that reduced sleep duration may be part of the behavioral modifications that played a role in the development of the current epidemics of obesity and diabetes. An important consideration when trying to explain the epidemiologic link between sleep loss and metabolic risk is that it is not clear whether the physiological effects of sleep restriction observed under laboratory conditions over a period of a few days can be translated to chronic sleep restriction as it occurs in free-living individuals. Also, when comparing different laboratory studies of sleep restriction, differences in the "dose" of sleep loss relative to the physiological need of the individual are often ignored. While the body of evidence suggestive of an interaction between sleep loss and the epidemics of obesity and diabetes continues to build at a rapid pace, much remains to discover as far as mechanisms and the transition from short-term laboratory conditions to chronic PSD in real life. Intervention studies extending sleep in habitual short sleepers and examining the impact on metabolic outcomes are needed to further address the direction of causality of the association between insufficient sleep, obesity, and diabetes and the potential clinical implications.

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Editors
Priyattam J. Shiromani
Department of Psychiatry
and Behavioral Science
Ralph H. Johnson VA and Medical
University of South Carolina
Charleston, SC, USA

Susan Redline
Department of Medicine
Harvard Medical School
Brigham and Women's Hospital
and Beth Israel Deaconess
Medical Center
Boston, MA, USA

Tamas Horvath
Section of Comparative Medicine
Yale University School of Medicine
New Haven, CT, USA

Eve Van Cauter
Department of Medicine
University of Chicago
Chicago, IL, USA

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