Chapter 2
Effects of Sleep Deficiency on Hormones, Cytokines, and Metabolism

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Abstract What are the best approaches to reduce the staggering health and economic costs of the diabetes and obesity epidemics? Traditional efforts have centered on diet and exercise, which are key health behaviors during wakefulness. Yet, mounting evidence supports the addition of sleep as a third pillar of health. Increasingly, scientific research suggests insufficient sleep puts Americans at risk for weight gain and impaired glucose regulation. Synthesizing epidemiological studies with clinical experiments enables a more complete understanding of these relationships by tying population-level trends to underlying mechanisms and causes. Although the associations between sleep, obesity, and diabetes and their intertwined

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mechanisms are still emerging, the current "epidemic" of insufficient sleep seems to warrant individual, behavioral, and policy interventions.

Keywords Sleep • Sleep deficiency • Insomnia • Circadian disruption • Cytokines • Hormones • Glucose metabolism • Insulin sensitivity • Obesity • Diabetes

Pressing Public Health Concerns: The Obesity and Diabetes Epidemics

Twin epidemics of obesity and diabetes imperil public health in the United States and worldwide. Identifying and implementing strategies to mitigate these epidemics are critical to improving well-being and reducing healthcare expenditure.

The incidence and prevalence of obesity and diabetes have increased significantly over the past decades. According to 2010 Center for Disease Control data, 33.3 % of American adults are overweight (Body Mass Index (BMI) >25) and an additional 35.7 % are obese (BMI > 30), while 18 % of children over six are obese [1]. Obesity affects over 78 million adults and 12.5 million children in the United States. The prevalence of obesity has more than doubled in children and adults over the past decades, with a projected 33 % rise from today's levels by 2030 [2–4]. This epidemic is not limited to America. World Health Organization data from 2008 indicate that over 1.4 billion adults worldwide were overweight, 500 million of whom were obese [5].

Largely preventable, excess weight poses significant health problems, leading to increased morbidity and mortality [6]. The expense of obesity and overweight is also immense. Finkelstein et al. calculate costs of approximately $147 billion in 2008 or 9 % of annual United States healthcare expenditure [7]. Thorpe et al. conclude that related costs account for 12 % overall and 27 % of per capita healthcare spending growth from 1987 to 2001 [8].

Obesity is associated with a significant increase in different types of cancer and identification of the pathways through which obesity influences cancer risk is critical to primary and secondary prevention. Emerging evidence suggests that insulin resistance and hyperinsulinemic compensation that occurs in response to obesity-related insulin resistance represent an important pathway through which obesity influences cancer risk and disease progression [9]. To provide a better understanding of how sleep deficiency may stimulate cancer cell growth, this chapter will focus on the mechanisms through which sleep deficiency alters exercise, energy expenditure and dietary behavior, as well as insulin secretion, insulin resistance, and glucose metabolism.

Obesity and overweight have significantly contributed to the alarming rise of the diabetes epidemic. Comprising ~95 % of diagnosed cases, type 2 diabetes is primarily responsible for this increased incidence and prevalence [10]. Type 2 diabetes and excessive weight are frequently comorbid. The World Health Organization estimates that excessive weight accounts for 44 % of the global diabetes burden, and the Center

for Disease Control colorfully comments that "we are eating ourselves into a diabetes epidemic" [11]. As of 2010, the Center for Disease Control approximates that 25.8 million or 8.3 % of Americans had type 2 diabetes, a 160 % increase in prevalence since 1980 [12]. Moreover, a Center for Disease Control survey 2005–2008 reveals that about 35 % of Americans were prediabetic by assessing diagnostic measures including fasting blood glucose and hemoglobin A1c samples [12]. Like obesity, the diabetes epidemic is not unique to the United States, and the World Health Organization considers diabetes to be implicated in four million or 9 % of annual global deaths [11]. Since diabetes is often comorbid with obesity and overweight, costs generally reflect the impact from both conditions. In a 2008 study, the American Diabetes Association calculated the direct costs of diabetes and related complications as $116 billion and the associated diminished national productivity as $58 billion [10].

Given the scope and scale of obesity and diabetes, mitigating these epidemics is a prime public health priority.

Reconsidering Public Health Strategies to Combat Obesity and Diabetes: The Role of Insufficient Sleep

Traditional efforts to combat overweight and diabetes have centered on diet and exercise. Nevertheless, increasing scientific evidence suggests that a public health focus should move beyond diet and exercise to include sleep as a third pillar of health and well-being in the fight against obesity and diabetes.

American culture generally fails to recognize the importance of sleep. The introduction of electricity in the late twentieth century has fostered an attitude prioritizing work and leisure over sleep. Televisions, computers, smartphones, and tablets further facilitate 24/7 activity. Moreover, the popularity of coffee and energy drinks has skyrocketed over the past decade. Relying on caffeine and other stimulants to stay awake is only one of many reasons why (and signs that) Americans are not getting sufficient sleep. A workers' inadequate sleep can be related to an unsupportive supervisor in the workplace [13]. Noise and other environmental disturbances, as well as the demands of family life and childcare, compound this problem. Moreover, disorders such as sleep apnea, restless leg syndrome, and insomnia may further interfere with sleep (Figs. 2.1 and 2.2).

Modern lifestyles and work practices also disrupt circadian rhythms, which can be an additional challenge to adequate rest. Working in shifts around the clock, travel across time zones, and the reality of a global economy can profoundly disrupt the natural sleep cycle. Circadian misalignment not only affects the brain's central pacemaker in the suprachiasmatic nucleus [14] but also impacts peripheral organs and tissues that also have their own circadian clocks [15, 16].

Therefore, a range of contributing factors can lead to sleep deficiency, which the strategic planning group of the National Heart Lung and Blood Institute defines as an "insufficient quantity or inadequate quality of sleep obtained relative to that needed for optimal health, performance, and well-being" [17].

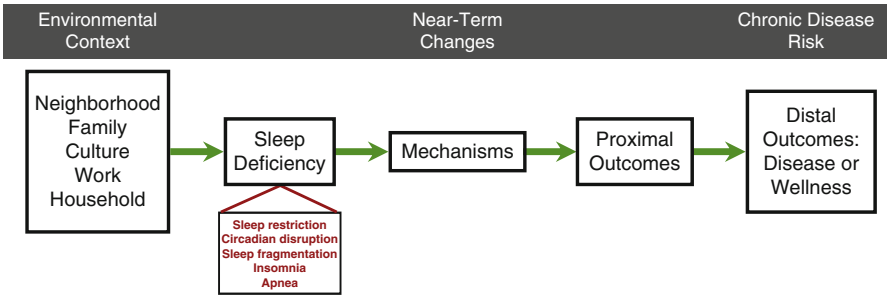

Fig. 2.1 General conceptual framework for evaluating the effects of insufficient sleep on health and wellness

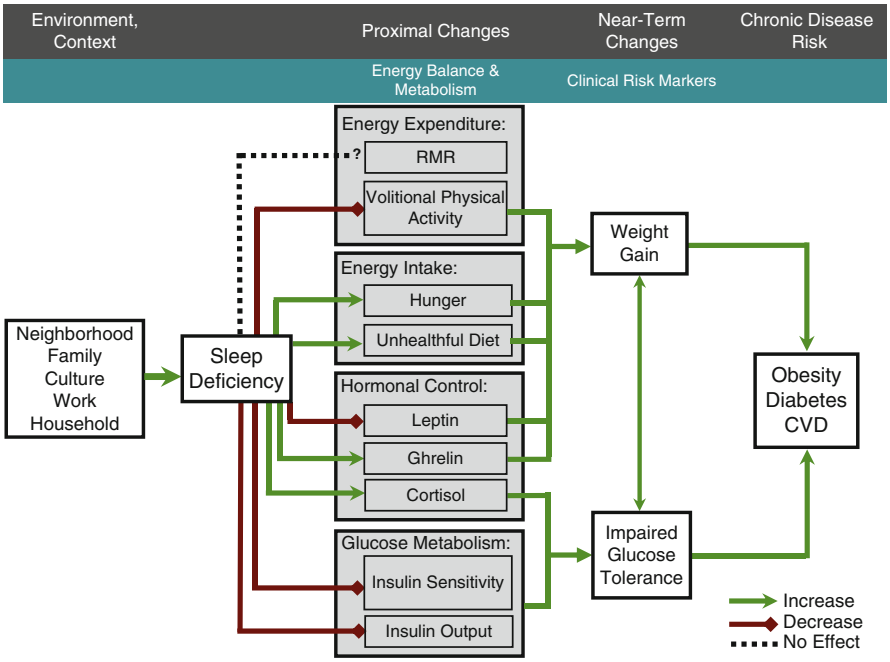

Fig. 2.2 Mechanistic conceptual framework for evaluating the effects of insufficient sleep on diabetes and obesity

Sleep insufficiency is an increasing problem in the United States. Americans report averaging 1.5–2 h less sleep than a century ago [18]. Recent surveys also suggest that more than one-third of American adults sleep less than 6 h each night, well below the recommended 7–9 h [19]. While approximately 30 % of adults report

symptoms of insomnia, many limit their sleep voluntarily to watch TV, surf the Internet, or complete work [20]. Similarly, Owens estimates that about one quarter of children experience sleep difficulties over the course of childhood [21].

Indeed, the Institute of Medicine has recognized sleep deprivation and sleep disorders as unmet public health problems [22].

Sleep and Metabolism: Epidemiological Evidence

From a population-level perspective, scientists have noted parallel increases in obesity, diabetes, and sleep deficiency over the past decades. Within the United States, the similarity in geographical distribution of all three conditions is visually compelling (Fig. 2.3). Given the scale of these conditions, epidemiological studies are valuable for identifying associations and trends in large groups of individuals. Cross-sectional studies examine exposure and disease status at one point in time, while longitudinal cohort trials can identify temporal relationships. Nevertheless, epidemiological observations cannot prove causality. The tendency to focus on sleep duration alone without consideration of quality or circadian shifts can further constrain the conclusions of epidemiological analysis. Within these limitations, cross-sectional and longitudinal studies provide a basis for establishing links between insufficient sleep, diabetes, and obesity.

Epidemiological Evidence in Pediatric and Adult Populations: Associations Among Insufficient Sleep, Overweight, and Obesity

Throughout the life course, insufficient sleep is often associated with overweight and obesity. A prospective study of over 900 infants in the United States found that 6-month-olds sleeping less than 12 h per day are at higher risk for overweight by age three [23]. A prospective study of 150 American children 3–5 years old indicates that sleeping 30 min less each night than recommended was positively correlated with overweight at 9.5 years of age [24, 25]. Similarly, by analyzing wrist actigraphy recordings of 383 American adolescents to assess sleep, Gupta et al. found an 80 % reduction in obesity risk for every hour of sleep gained per night [26] (Fig. 2.4).

While individual studies can be valuable in identifying patterns, reviews and meta-analyses can provide a broader sample size to generalize the relationship between sleep and weight in pediatric populations. Patel and Hu's review of 11 and Cappuccio et al.'s meta-analysis of 12 cross-sectional global pediatric studies show consistent patterns of increased obesity risk with insufficient sleep, particularly short sleep duration [27, 28]. Based on this evidence, Bell et al. speculate, "There is a critical window prior to age five, when nighttime sleep may be important for subsequent obesity status. Insufficient nighttime sleep among infants and preschool-aged

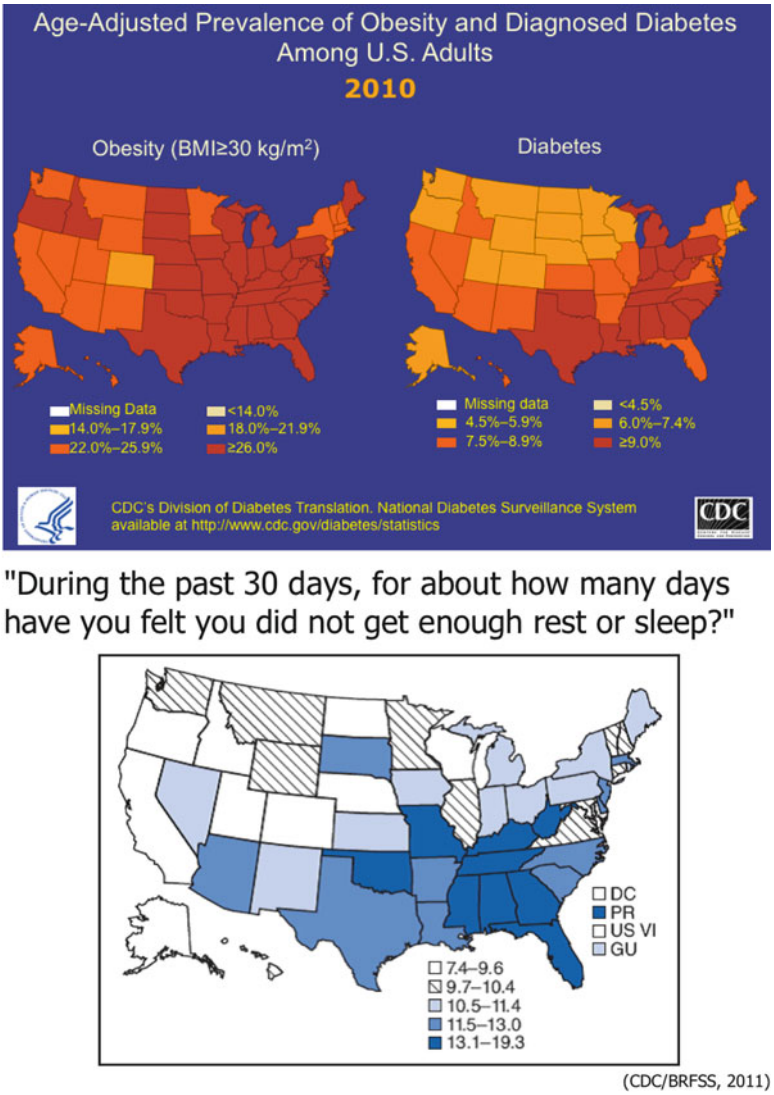

Fig. 2.3 Similarities between the geographic distribution of obesity, diabetes, and reported sleep insufficiency (Sources: CDC Data and Slides (2010–2011)

children appears to be a lasting risk factor for subsequent obesity, while contemporaneous sleep appears important to weight status in adolescents" [3].

Though apparently weaker, this relationship between weight and sleep continues into adulthood [28]. A U-shaped curve exists between sleep duration and weight with the lowest BMIs being associated with the recommended 7–8 h per night. Longitudinal studies surveyed support an independent positive association between

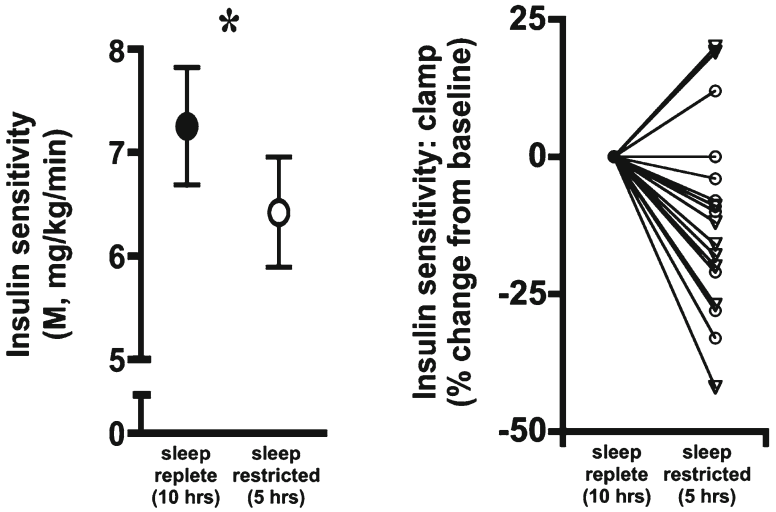

Fig. 2.4 (Insulin sensitivity in young adult men is reduced following 1 week of sleep restriction. Insulin sensitivity was measured using the euglycemic hyperinsulinemic clamp procedure at baseline during a sleep replete condition (10 hrs/night, filled circles) and compared to a sleep restriction condition (5 hours per night for 1 week; open circles). *Left panel*: mean ± SE. *Right panel*: individual values for change with sleep restriction relative to baseline sleep replete (Orfeu Buxton et al. [70])

insufficient sleep and weight gain. A systematic meta-analysis of short sleep duration and obesity in adult populations yields similar results [29]. In a pooled regression, a 0.35 kg/m^2 increase in BMI was associated with each 1 h less sleep per night, compared to a reference of 7 h per night of self-reported sleep.

Epidemiological Evidence in Pediatric and Adult Populations: Associations Between Insufficient Sleep and Diabetes in the Context of Overweight

The overlap between excessive weight and diabetes alone is significant. The American Diabetes Associate notes that "most patients with [type 2] diabetes are obese" [10], while overweight confers greater risk of insulin resistance. The concomitance of diabetes and excess weight is observed throughout the life course. In a survey of 3,953 diabetic and 7,666 nondiabetic youth (3–19 years) from diverse ethnic and racial backgrounds, the prevalence of overweight and obesity in subjects with type 2 diabetes was 10.4 % and 79.4 %, respectively [30]. It is, therefore, plausible that sleep insufficiency could increase risk for type 2 diabetes by predisposing children and adults to weight gain.

Many studies, however, report that sleep independently relates to diabetes risk, even after controlling for the confounding effects of obesity and overweight. A 2012 cross-sectional study of black and white adolescents by Matthews et al. reports

that short sleep duration correlates with higher insulin resistance independent of adiposity and other confounding factors [31]. Adolescents with greater sleep fragmentation, which may indicate poor sleep quality, tended to have higher glucose levels, another risk for diabetes [31]. A similar effect for short sleep duration and insulin resistance was observed in the Cleveland Sleep and Health Study of black and white adolescents, although results disappeared when the investigators adjusted for central adiposity [32]. Differences in sample characteristics likely contributed to these somewhat conflicting results; fewer adolescents in the Cleveland sample were obese and a greater proportion of these adolescents were long sleepers.

Again, meta-analyses and reviews are useful to gauge systematic trends. Cappuccio et al. [29] analyzed ten prospective studies with a pool of over 100,000 adults to ascertain the association of type 2 diabetes with sleep duration and quality. After controlling for BMI, age, and other confounding factors, they found results similar to those from their "Meta-Analysis of Short Sleep Duration and Obesity in Children and Adults" [27]. Specifically, sleeping less than 6 h per night conferred an RR of 1.28 in predicting the incidence of type 2 diabetes, and prolonged duration (>8–9 h) had a higher RR of 1.48. As for sleep quality, Cappuccio et al. found that difficulty falling and staying asleep were highly correlated with type 2 diabetes risk with RRs of 1.48 and 1.84, respectively. Knutson et al.'s review connects insufficient sleep with poor glucose control and type 2 diabetes, particularly in men [19]. Although some studies do not find a significant association between sleep and diabetes in women [33], a 10-year American Nurses Health Study [34] of exclusively female subjects found increased diabetes risk after controlling for confounding variables such as BMI, shift work, hypertension, exercise, and depression.

Buxton and Marcelli's study of data from the US National Health Interview Survey (2004–2005) also links insufficient sleep, diabetes, and obesity [35]. Using a range of four classes of predictors, the investigators employ a socio-geographic model to expand upon prior conceptual frameworks and detect often neglected social and behavioral effects on chronic diseases. As with prior cross-sectional analyses, the Buxton and Marcelli study reveals that short and long sleep duration are both directly and independently associated with increased risk for obesity and diabetes in a representative sample of the American adult population. Obtaining 7–8 h sleep per night was associated with the lowest risk profile for the adults surveyed. The analysis also indicates indirect relationships such as a significant association of diabetes, obesity, and hypertension with cardiovascular disease. Buxton and Marcelli's framework suggests that sleep is more strongly linked to obesity, diabetes, and cardiovascular disease than other sociodemographic or health behavior covariates.

Epidemiological Evidence: Associations Between Insufficient Sleep and Mortality

Given these associations with excess weight and diabetes, it is not surprising that insufficient sleep is also linked to higher mortality rates in epidemiological studies. Cappuccio's meta-analysis of 16 prospective studies including 27 independent

cohorts found that both short and long duration of sleep are significant predictors for all-cause mortality [36]. For individuals averaging less than 7 h of sleep per night, the risk of death increased by 12 %. As a result, epidemiological evidence suggests that insufficient sleep is associated with the more proximal outcomes of excessive weight and diabetes, as well as with the distal outcome of mortality [37].

Associations Between Insufficient Sleep and Obesity: Energy Intake and Hormones

Energy balance influences weight regulation and may explain associations between insufficient sleep and the current obesity and overweight epidemics. Positive balance suggests weight gain, while negative balance can lead to loss. Perceived hunger versus satiety, dietary selection, and calories ingested all influence energy intake. While sleep itself is an energy-conserving state, short duration can encourage weight gain by allowing more time to eat. But it is more complex than simply having more time to eat—many population and laboratory studies demonstrate that insufficient sleep affects physiological energy balance, resulting in weight gain.

Moreover, a spectrum of hormones and other signaling pathways influence caloric intake and utilization. Providing potential physiological links between short sleep and overweight, ghrelin, leptin, peptide YY, cortisol, and Glucagon-like peptide-1 (GLP-1) vary under different sleep conditions. The hormone leptin [38], produced by adipose cells; the peptide YY (PYY) [39], released by neuroendocrine cells in the ileum and colon after eating; and GLP-1 all signal satiety and reduce appetite. On the other hand, the hormone ghrelin, primarily produced by the gastric fundus, stimulates appetite [38]. Longer-acting cortisol, which has a wide range of effects throughout the body and is secreted by the adrenal cortex, is also linked to increased hunger and visceral adiposity [39]. Since these hormones may impact eating behavior and dietary preference, variations in levels may underlie energy balance changes observed during sleep insufficiency.

Epidemiological Evidence: Discerning Relationships Between Energy Intake and Sleep

Epidemiological research suggests that insufficient sleep may effect changes in energy balance that lead to excess weight but cannot prove causality. In the HELENA study, Garaulet et al. review the relationship between short sleep duration, physical activity, and dietary habits in 3,311 adolescents from nine European countries [40]. After adjusting for BMI, physical activity levels as measured by hip accelerometers were significantly reduced in adolescents with chronic partial sleep deprivation (<8 h/night). Short sleepers were more likely to consume unhealthy diets with more servings of junk and snack foods but fewer servings of fruits, vegetables, and dairy.

Epidemiological studies yield similar findings in adults. In a population of 542 male freight workers, Buxton et al. use a multivariable model to demonstrate that sleep adequacy, perceiving to usually getting enough sleep, is a mediator of healthful food selection [41]. Professional drivers typically experience more job strain, as well as disruption of sleep and mealtime schedules, than other freight workers because of lengthy and irregular work shifts. Compared to drivers who felt fatigued, those reporting adequate rest consumed more vegetables and fruit with less sugary drinks and snacks. This cross-sectional analysis was constrained by self-reported data, an exclusively male population, and a lack of information regarding stimulant use other than nicotine. Nevertheless, the study points to the possible role of adequate sleep, independent of other workplace factors, in maintaining a healthful diet.

Other cross-sectional studies reveal associations between sleep and hormones that may influence energy intake. Analysis of a Wisconsin Sleep Cohort Study of 1,024 adults found that short sleep was associated with lower leptin and higher ghrelin levels [42]. Comparing subjects averaging 5 h versus 8 h of sleep per night predicted 15.5 % lower leptin and 14.9 % higher ghrelin levels, respectively. The Québec Family Study, which includes 740 men and women, supports these observations regarding leptin and also reports lower physical activity levels in obese short sleepers [43]. Therefore, epidemiological studies suggest a range of possible interfaces between both sleep and energy balance.

Laboratory Evidence: Insufficient Sleep and Energy Intake

Controlled experiments can point to causality and reduce the influence of confounding factors. However, inconsistencies exist between various studies, which rely on data from small sample sizes and employ different protocols. It is especially important to consider differences in food availability. For example, Raynor and Wing report that doubling portion size of snack foods can increase consumption by 81 % [44]. Differences in study design include restrictive versus ad libitum feeding, trial duration, and the range of outcomes measured.

Laboratory studies of insufficient sleep vary with respect to observed effects on subjects' satiety, diet composition, and caloric consumption. Chapman et al.'s meta-analysis of five controlled trials found a cumulative effect of sleep insufficiency on food intake (Cohen's $d = 0.49$) [45]. Individual studies provide further detail. After one night of 4-h sleep curtailment, Brondel et al. found a 22 % increase in ad libitum energy intake in 12 subjects and increased preprandial hunger without particular predilections in food type [46]. On the other hand, Schmid et al.'s acute 4-h sleep restriction study does not indicate changes in ad libitum energy intake or hunger in 15 men over 2 days [47]. Participants in this trial exceeded their estimated required caloric needs by ~60 % and increased fat consumption on average. In a longer experiment comparing 5 days of 4-h sleep restriction to 9-h sleep in 30 adults, subjects showed a 15 % increase in ad libitum energy intake and a 39 % increase in dietary and saturated fat consumption, especially in women [48]. Differing effects

of sleep loss on energy intake with respect to gender, age, and phases of the menstrual cycle are areas for further investigation [48].

Studies over a longer duration indicate a similar spectrum of negative results for chronic partial sleep restriction. Nedeltcheva et al. report increased snacking activity generated higher energy intake for 11 participants during a 2-week trial of 5.5 h of sleep per night compared to 8.5 h [49]. The sleep-restricted state was associated with a 54 % increase in the consumption of high-carbohydrate snacks especially at night, while average energy intake from meals remained constant. It is important to note that again under ad libitum conditions, caloric intake of adequately rested subjects sometimes exceeded physiological requirements, likely reflecting non-homeostatic mechanisms [49].

On the other hand, in a natural environment outside the laboratory, Beebe et al.'s study of 41 adolescents (14–16 years old) also indicates that chronic partial sleep restriction (<6.5 h per night) affects dietary intake [50]. During sleep curtailment, participants preferred and consumed diets of higher glycemic load but did not alter fat and protein consumption on average. Beebe et al. note significantly increased sweet consumption with decreased sleep duration. Laboratory studies of both chronic and acute partial sleep restriction indicate that insufficient sleep can lead to increased hunger and caloric intake.

Laboratory Evidence: Total Sleep Deprivation, as well as Acute and Chronic Partial Sleep Restriction, May Alter Hormonal Regulation and Lead to Changes in Energy Intake

Hormonal regulation may play a role in observed changes in diet and appetite with insufficient sleep. Leptin and ghrelin both have 24-h profiles that interact with sleep, as shown by trials using total sleep deprivation to eliminate the confounding effects of meal response. Simon et al.'s study of subjects receiving continuous enteral nutrition demonstrates that leptin levels are independently related to sleep after one night of total sleep deprivation and a resulting 8-h circadian shift [51]. In subsequent research, Mullington et al. note a decrease in the diurnal amplitude of leptin variation in ten healthy men during 88 h of total sleep deprivation [52]. Insufficient sleep also seems to affect ghrelin levels. Dzaja et al. found a dampening of nocturnal ghrelin elevation during 24-h total sleep deprivation [53].

While these extreme sleep restrictions are necessary to establish definitive links between sleep and hormonal profiles, evaluating states of partial and acute sleep restriction can yield results that more closely match real-life conditions. Spiegel, Leproult, et al. limited 11 healthy young men to 4 h of sleep per night for six nights and found significant decreases in mean and maximum leptin levels compared to the rested state [54, 55]. Possible negative influences on these levels include elevated cortisol levels and autonomic dysfunction, as indicated by decreased heart rate variability. Since caloric intake was tightly controlled, the authors postulate that approximately 3 days of dietary restriction at 70 % of energy requirements would have

been necessary to cause this observed reduction in leptin. In sleep-restricted participants, the rhythm amplitude of leptin profiles was 20 % lower and acrophase occurred 2 h later on average, despite typical diurnal variation. Although they did not assess subjective hunger, these physiological changes could be expected to increase appetite because of leptin's role in signaling satiety [56].

In another study of 12 healthy young men, Spiegel, Tasali, et al. measured a broader range of variables that link acute restricted sleep to energy intake [57]. After two nights with 4-h sleep duration, leptin levels decreased by 18 % and ghrelin levels rose by 28 %. In this experiment, the investigators also assessed appetite by a visual analogue scale and found a 24 % increase in subjective hunger during short sleep duration. Like the participants in Nedeltcheva et al.'s study [49], sleep-restricted participants' desire for high-carbohydrate, calorie-dense foods intensified disproportionately. The strong correlation between increased hunger and ghrelin-to-leptin ratio further suggests an underlying physiological process that links insufficient sleep to energy balance via hormonal control.

In a study of 11 young and 12 older adults, Buxton et al. also found evidence of hormonal changes that could affect energy intake under chronic conditions of short sleep duration in conjunction with circadian desynchrony [58]. Endogenous rhythms are synchronized to 24-h days, and disruptions of oscillators have been shown to alter hormone secretion and regulation [14]. Buxton et al. administered a strictly controlled eucaloric diet in the laboratory setting and collected blood samples over a wide range of circadian phases. During a study of partial sleep restriction (5.6 h per 24 h) combined with experimenter-controlled 28-h "days" over a period of 3 weeks, leptin and ghrelin profiles were slightly lower and higher, respectively, when compared to baseline. Unlike Spiegel et al. [57], the investigators noticed less pronounced changes in these two hormones, possibly indicating that circadian disruption and short sleep duration together produce a different response than short sleep duration alone [58]. With respect to the two age groups, Buxton et al. found significant interactions between subject age and time. Specifically, there were higher levels of leptin and free ghrelin in younger compared to older subjects during sleep times. This result indicates that the effect of sleep on energy balance may change over the life course.

Since healthy, young lean men are the participants of most research evaluating the effects of acute and chronic partial sleep restriction, Omisade et al. conducted a study of acute short sleep in healthy young women to determine whether effects were gender specific [59]. After one night of a 10-h sleep opportunity, 15 participants in the follicular phase of the menstrual cycle were restricted to 3 h of sleep the following night. Sleep-restricted women had significant elevations in morning leptin levels without reported changes in subjective hunger. Therefore, acute short sleep duration seems to affect hormonal regulation in healthy young women as well.

It is important to note that several studies of chronic and acute sleep curtailment do not record changes in leptin and ghrelin profiles, even with altered appetite. For example, Nedeltcheva et al. did not observe changes in either leptin or ghrelin levels of subjects after 2 weeks of short sleep (5.5 h per night) despite increased

hunger and caloric consumption [60]. An ad libitum feeding study design may explain this and similar results because hormonal responses after eating can mask changes in ghrelin and leptin profiles on a controlled eucaloric, or negative energy balance, diet [58].

However, even studies without ad libitum eating sometimes reveal mixed results. St-Onge et al. conducted an experiment under strict laboratory conditions of partial sleep restriction and controlled diet with fixed meal times [61]. Four days of 4 h of sleep per night produced no effect on participants' leptin or peptide YY levels compared to the rested state. Underestimation of energy requirements using the Harris-Benedict equation, however, created a condition of slightly negative energy balance that could have influenced hormone levels [61]. Short sleep, however, induced significant gender-specific effects in the hormones GLP-1 and ghrelin. The authors postulate that different hormonal mechanisms may regulate appetite in women and men because male, but not female, participants exhibited increased fasting, morning, and total ghrelin levels. Women, but not men, showed lower afternoon levels of GLP-1. Unlike St-Onge et al. [61], Magee et al. found a statistically significant reduction in PYY levels and a corresponding decrease in subjective satiety following two nights of acute short sleep duration [62]. Diet and activity, however, were not stringently controlled, and the participants were limited to healthy young men. Given the wide range of experiment designs and findings, studies with analogous conditions would be needed to more accurately assess hormone regulation of energy intake on a broader scale.

Laboratory Evidence: Insufficient Sleep May Affect Neural Reactions to Food Stimuli and Promote Energy Intake

Altered brain response to food stimuli is another possible mechanism for increased energy intake and unhealthy diet during insufficient sleep [63]. In an effort to identify brain regions vital to these behaviors, Benedict et al. used functional magnetic resonance imaging in 12 male subjects to assess responses to food stimuli after total sleep deprivation [63]. When presented with pictures of food, subjects with one night of total sleep deprivation exhibited increased activation of the right anterior cingulate cortex. This response was positively correlated to subjective hunger ratings despite unchanged fasting glucose levels. In a larger study of 30 partially sleep-restricted men and women, St-Onge et al. also used functional magnetic resonance imaging to evaluate brain activation in response to food stimuli [64]. After a 6-day trial of 4 h per night in bed, participants demonstrated increased activation in the cingulate gyrus and other areas associated with reward systems in response to food images. Not only does sleep deficiency appear to increase the desirability of food by activating central reward systems, but it may also induce impairments in self-control. A study by Barber et al., using a multiple-mediator model to assess the effect of sleep on work engagement, suggests that decreased sleep quality and duration predicts poor self-control and ability to resist temptation [65].

Laboratory Evidence: Various Levels of Insufficient Sleep Link to Energy Expenditure

On the other side of the energy balance equation, sleep may also affect energy expenditure. Total energy expenditure (TEE) includes basal resting metabolic rate (RMR), the thermic effect of meals (TEM), and volitional activity-based energy expenditure (AEE) [66]. Studies indicate that short sleep has mixed effects on RMR and TEM, which account for about 60 % and 10 % of expenditure, respectively [66, 67]. Benedict et al. using indirect calorimetry found that one night of total sleep deprivation in healthy young men reduced resting and postprandial energy expenditure [68].

In chronic partial sleep restriction studies, Nedeltcheva et al. [60] did not find a similar impact on total energy expenditure as observed in Benedict et al. [68]. To study the effects of insufficient sleep on weight loss, Nedeltcheva et al. observed ten overweight adults subjected to caloric restriction during 2 weeks of 8.5 versus 5.5 h sleep duration [60]. Although shorter sleep duration reduced weight loss by 55 % in sleep-restricted subjects, the investigators did not observe changes in total energy expenditure. In order to determine caloric output, Nedeltcheva et al. used doubly labeled water to gauge metabolic rate. In a subsequent report, Nedeltcheva et al. [69] found comparable weight loss in overweight and obese subjects with hypocaloric intake under conditions of short and adequate sleep. Indicating a metabolic difference between sleep conditions, subjects' respiratory quotients were elevated with 2 weeks of short sleep restriction (5.5 h per night) compared to the rested state (8.5 h). The authors postulate that this increase in respiratory quotient during the trial signaled the utilization of more carbohydrate energy. Under conditions of short sleep, overweight and obese participants did not preferentially burn fat but used carbohydrates instead. Although weight loss was comparable in sleep-restricted participants, fat again contributed much less to the weight loss (25 %) than in the rested state (56 %) as the subjects disproportionately lost muscle.

Buxton et al. found that fasting RMR remained unchanged from baseline in subjects provided with an isocaloric and nutrient-controlled diet under conditions of partial sleep restriction for 1 week and controlled activity [70]. In contrast, after adding circadian rhythm disruption to a prolonged restricted sleep challenge, Buxton et al. found that RMR decreased by 8 % [58]. Circadian desynchrony may have interfered with food metabolism and caused nutrients to be excreted unchanged [60]. Circadian misalignment of central and peripheral oscillators may have desynchronized metabolic signals, which, along with altered hormone levels and glucose metabolism, could have caused the decrease in RMR and energy expenditure.

Therefore, sleep deficiency may contribute to the current rise in overweight and obesity by inducing positive energy balance that leads to weight gain.

Explaining Associations Between Insufficient Sleep and Diabetes: Glucose Homeostasis and Hormonal Regulation

Laboratory studies may also help explain the relationship between insufficient sleep and diabetes. Trials of sleep restriction demonstrate adverse effects on glucose homeostasis, insulin sensitivity, and pancreatic secretion [19]. Again, hormones may underpin these very proximal sleep restriction outcomes. A wide range of tests are available to assess the effects of insufficient sleep on glucose homeostasis (Table 2.1).

Laboratory Evidence: The Impact of Total Sleep Deprivation on Glucose Homeostasis

In an early experiment to assess the effects of sleep deprivation on glucose homeostasis, Kuhn et al. found that 72–126 h of total sleep deprivation induced higher levels of plasma glucose in response to an OGTT [71, 72]. Similarly, Benedict et al.'s trial of one night of total sleep deprivation in young healthy male participants with strictly controlled dietary intake reveals elevated post-breakfast plasma glucose concentrations [68]. Increased insulin levels did not accompany the significantly higher glucose values, indicating reduced pancreatic beta-cell responsiveness [68]. Although disturbances induced by total sleep deprivation trials generally correct quickly, abnormalities sometimes persist beyond recovery periods [19].

Laboratory Evidence: The Impact of Recurring Partial Sleep Restriction on Glucose Homeostasis

Spiegel et al. investigated the impact of recurrent short sleep on metabolism and endocrine function [73]. After a trial of 4 h of sleep for six consecutive nights, healthy young men exhibited impaired glucose tolerance in response to a tolbutamide-modified IVGTT and controlled carbohydrate-rich meals. Relative to the recovery state, sleep-deficient subjects cleared an intravenous bolus of glucose at a 40 % slower rate, which was similar to that of older adults with impaired glucose tolerance. Minimal model analysis demonstrates a 30 % decrease in glucose effectiveness and acute insulin response to glucose. Since glucose effectiveness is a measure of non-insulin-dependent glucose utilization, a lower level can indicate decreased uptake of glucose by the brain, whose metabolism does not require insulin [73]. The authors postulate that decreased cerebral glucose uptake may have caused the subjective sleepiness reported on the fifth day of the short sleep trial.

Table 2.1 An overview of tests used to evaluate glucose homeostasis

Type	Test	Test description	Interpretation	Op. Cit.
Retrospective, cumulative measurement of chronic glycemia	Hemoglobin A1c	The percent of glycated hemoglobin in a blood sample	Historical indication of blood sugar regulation over the prior 2 months. Diagnostic of diabetes Normal: <5/6 % Prediabetic: 5.6–6.5 % Diabetic ≥6.5 %	ADA, *Diabetes Care* January 2012; Broussard et al., *AIM* 2012 [82, 87]
Glycemic response to fasting: indicative of hormonal control	Fasting plasma glucose	Plasma glucose levels after a ≥8 h fast	Fasting lowers blood glucose levels, stimulating glucagon release which elevates blood glucose. Insufficient release of and/or sensitivity to insulin results in hyperglycemia Prediabetic: 100–125 mg/dL Diabetic ≥126 mg/dL	ADA, *Diabetes Care* January 2012; Spiegel and Lancet, 1999; Matthews et al., *Sleep* 2012; Broussard et al., *AIM* 2012 [31, 73, 80, 85]
Hormonal response to fasting	Fasting insulin	Serum insulin (and c-peptide) levels after an ≥8 h fast	Insulin production is elevated in response to fasting which causes the release of glucagon to raise blood glucose levels Hyperinsulinemia: >20 uU/mL insulin and >4.6 ng.mL c-peptide	Buxton et al., *STM* 2012; Nedeltcheva et al., *JCEM* Sept 2009; Buxton, *Diabetes* 2012 [58, 70, 80]
Mathematical approximation	HOMA (homeostasis model assessment index)	HOMA-IR = (Fasting Insulin*Fasting Glucose)/22.5	Mathematical model that approximates steady-state insulin sensitivity and beta-cell function based on fasting insulin and glucose levels	Spiegel et al., *JCEM* 2004 [55]
		HOMA-Beta = (20*Insulin)/(Glucose−3.5) %	Useful in larger-scale clinical studies	

Response to standardized challenge	OGTT (oral glucose tolerance test)	Standard 75 g oral glucose dose administered after an 8–12 h fast. Blood glucose and insulin levels tested at time intervals after ingestion	After 2 h: normal (<140 mg/dL diabetic) Indicates the effectiveness of glucose removal from the bloodstream. Insulin resistance can be gauged from calculating glucose-AUC (Muniyappa)	Nedeltcheva et al. JCEM 2009; Broussard AIM 2012; Pamidi et al., *Diabetes Care* 2012 [80, 82, 88]
Response to a more ecologically valid challenge	Meal response	Standard meal administered, sometimes after an 8–12 h fast. Blood glucose and insulin levels tested at time intervals and after ingestion	After 2 h: normal (<140 mg/dL diabetic) Indicates the effectiveness of glucose removal from the bloodstream in response to a more ecologically accurate glucose challenge. Insulin response can be gauged from calculating glucose-AUC (Muniyappa)	Buxton et al., *STM* 2012 [58]
Response to precise, high-dose challenge	IV glucose tolerance test	IV glucose (.3 g/kg) bolus administered after an 8–12 h fast. Blood samples for plasma glucose and insulin levels tested frequently after injection up to 180 min	Minimal model analyses (MINMOD) indicate insulin sensitivity (Si) and glucose effectiveness. *Glucose tolerance is the slope of the natural log of glucose values from minute 5 to 19 after dose*	Buxton et al., *Diabetes* 2010; Spiegel and Lancet, 1999; Broussard et al., *AIM* 2012 [70, 73, 82]
Gold standard	Hyperinsulinemic euglycemic clamp	IV insulin is infused at a high and then lower steady rate to maintain euglycemia (90 mg/dL). At steady state, the glucose infusion rate in mg/kg body weight • min is recorded	The rate of glucose infused every minute per kg of patient body weight needed to maintain euglycemic measures the rate of peripheral glucose utilization and indicates tissue insulin sensitivity	Buxton et al., *Diabetes* 2010 [70]

The sleep-restricted participants' lower acute insulin response, an early marker of diabetes, was in the range seen in older adults and gestational diabetes. There was no significant difference in insulin sensitivity between the short sleep and recovery intervals in the trial.

Concordant with the impaired glucose tolerance indicated by the IVGTT, sleep-restricted participants showed higher post-breakfast glucose levels than in the sleep-replete state [73]. In a subsequent experiment in 2004, Spiegel et al. examine the effects of recurrent partial sleep debt on glucose homeostasis after a carbohydrate-rich breakfast [57]. They use the HOMA model as an indication of beta-cell function and as an integrated measure of the glucose and insulin responses to meals, rather than an index of insulin sensitivity. As in the 1999 experiment, post-breakfast glucose levels were elevated with short sleep, and insulin concentrations were higher but not significantly so when compared to the sleep-replete condition (a week of 10-h time in bed). Sleep-restricted participants showed a 56 % increase in HOMA values over the adequately rested state.

Buxton et al.'s double-blind, randomized study further demonstrates short sleep's negative effect on insulin sensitivity in healthy young men [70]. The investigators used an IVGTT to provide an accurate measure of insulin sensitivity and also employed a euglycemic hyperinsulinemic clamp technique, considered the gold standard for insulin sensitivity assessment. The conditions of this experiment include a confirmed baseline sleep-replete state, confinement to the laboratory setting, eucaloric controlled diets, and monitored minimal activity.

After 1 week of 5 h of sleep per night, results of both the IVGTT and euglycemic hyperinsulinemic clamp evaluations correlated with each other, revealing significantly reduced insulin sensitivity compared to the rested state [70]. Minimal model analysis of IVGTT data showed a decrease in mean insulin sensitivity, although the acute insulin response did not significantly change across conditions. Sleep-restricted subjects had a reduced disposition index, indicating increased diabetes risk, and glucose tolerance was significantly decreased. Moreover, decreased insulin sensitivity was not offset by increased pancreatic insulin secretion.

These results were essentially similar to Spiegel et al.'s findings which, on later reexamination, revealed indices of HOMA levels and glucose disposition that indicated insulin resistance during conditions of short sleep [73]. As Buxton et al. note, this finding also concurs with data from Nedeltcheva et al.'s study which demonstrate increased insulin resistance and impaired glucose tolerance in sleep-restricted subjects under conditions of high caloric consumption and sedentary activity [60]. In a randomized crossover investigation conducted in a laboratory setting, Nedeltcheva et al. assessed the effects of chronic partial sleep restriction (5.5 h per night for a 2 week period) on male and female middle-aged adults. Participants were given ad libitum access to food, while activity was maintained at a low level. It is important to note that this increase in insulin resistance occurred under laboratory protocols more analogous to real-life conditions.

Laboratory Evidence: The Impact of Various Levels of Insufficient Sleep on Inflammatory Markers

Pro-inflammatory cytokines are also increased by sleep restriction. For example, 24-h levels of IL-6 are increased by sleep restriction in men and women [74, 75], whereas TNF alpha has been shown to increase with sleep restriction only in men [75]. CRP levels have been shown to be elevated in one study of both acute total sleep deprivation and 10 days of partial sleep restriction to 4.2 h/night [76] but have not always replicated, for example, in a study of 4 h/night of sleep restriction [74]. More recently CRP has been associated in NHANES with extremes of sleep duration (short or long), but this effect varies by both gender and ethno-racial categories and is not present in all categories [77]. Far more work is needed to understand the role of inflammation due to sleep loss and its subsequent effects on glucose homeostasis.

Epidemiological and Laboratory Evidence: The Impact of Chronic Partial Sleep Restriction Combined with Circadian Disruption on Glucose Homeostasis

Given the evidence for impaired glucose homeostasis during total sleep deprivation and chronic short sleep duration, Buxton et al. investigated the consequences of prolonged sleep restriction combined with circadian disruption [58]. This study is important because cross-sectional and prospective epidemiological evidence indicate an increased risk of obesity and diabetes in shift workers whose schedules disrupt circadian rhythms. These disruptions usually diminish the duration and quality of sleep because the central circadian pacemaker makes it difficult to maintain sleep during the day when it exerts its greatest homeostatic drive for alertness [14]. Increased noise from routine daily activities can also disturb daytime sleep, as Buxton et al. document in a study of hospital sounds' impact on sleep [78]. In light of these endogenous and external factors interfering with daytime sleep, it is not surprising that jobs which disrupt circadian rhythms predispose at-risk populations to adverse health effects. Indeed, a 3-year prospective study shows that of workers with prediabetic indices, such as elevated fasting glucose, night-shift workers are at fivefold risk for developing overt diabetes compared to day workers [79].

To test these epidemiological observations in a controlled laboratory setting, Buxton et al. employed a forced desynchrony protocol that manipulates light/dark, feeding/fasting conditions to allow participants' biological pacemakers to oscillate according to inherent circadian rhythms [14]. Forced desynchrony permits the separation of endogenous homeostatic mechanisms from the "sleep-wake" and "fasting-feeding cycles" [58]. In order to avoid the possibility of entrainment,

the investigators imposed a 28-h "day" for the trial, and sleep times were equivalent to 5.6 h per night in a 24-h day. Buxton et al. hypothesized that circadian disruption would augment the relationships of short sleep duration to impaired glucose tolerance.

After 3 weeks of sleep restriction combined with circadian disruption, participants exhibited fasting and post-breakfast peak plasma glucose concentrations that were significantly elevated compared to the rested state [58]. Three of 21 participants exhibited postprandial glucose concentrations in the prediabetic range. Despite this hyperglycemia, fasting plasma and integrated insulin levels were significantly lower, and postprandial insulin secretion was reduced by 32 %. Prior studies such as Buxton et al.'s 2010 evaluation [70] of sleep restriction without circadian disruption and Nedeltcheva et al.'s 2009 assessment [80] of short sleep duration under conditions of high caloric consumption and sedentary activity revealed increased peripheral insulin resistance with elevated glucose levels despite slightly elevated or unchanged insulin profiles. Under conditions of recurrent sleep restriction combined with circadian disruption, participants' low insulin levels, concomitant with high plasma glucose, seem to indicate insufficient pancreatic beta-cell secretion of insulin [58]. Signaling that short sleep may lead to even more generalized islet cell dysfunction, Schmid et al. found evidence of impaired alpha-cell glucagon secretion in young healthy men with sleep debt in response to hypoglycemia [81].

In addition to possible pancreatic dysfunction, a recent study by Broussard et al. has shown a direct metabolic tissue dysfunction following sleep loss [82]. In this study, participants underwent an IVGTT followed by fat biopsy after a period of both four nights of 8.5 h in bed and four nights of 4.5 h in bed in a randomized crossover design. Sleep restriction induced a reduction in insulin signaling in the fat cells taken from participants after short sleep, resulting in an overall decrease of cellular insulin sensitivity by 30 % as compared to "normal" sleep. This is in contrast to a whole body insulin sensitivity reduction of 16 %, suggesting that the fat cell, like the pancreatic β-cell, may be a particularly vulnerable cell type to the effects of sleep loss.

Laboratory Evidence: The Impact of Insufficient Sleep on Glucose Homeostasis via Cortisol Regulation

Other studies also demonstrate an impact of insufficient sleep on cortisol in response to range of sleep challenges. Cortisol plays an important role in glucose homeostasis by stimulating gluconeogenesis in the liver to raise blood sugar and by counteracting insulin.

Total sleep deprivation and acute partial sleep restriction elevate cortisol levels. Leproult et al. evaluated the effect of one night of total sleep loss and of partial restriction on healthy young men, whose caloric intake was restricted to a constant intravenous glucose infusion. This protocol disrupted the hypothalamic-pituitary-adrenal axis [83]. Total sleep deprivation raised participants' mean cortisol levels by 45 % on the following day, whereas a short sleep of 4 h yielded a more modest 37 %

increase. The investigators note that increased amplitudes of secretion and a slower rate of cortisol decline may indicate impaired glucocorticoid feedback mechanisms. Omisade et al.'s study in healthy young women shows similar results after one night of 3-h sleep restriction [59]. Afternoon and evening cortisol levels were elevated, resulting in altered 24-h cortisol profiles.

Spiegel et al.'s longer trial of partial sleep restriction of 4 h per night for 6 days also shows changes in cortisol [54, 55]. Nevertheless, 24-h mean cortisol levels were similar in trials of sleep insufficiency and sleep extension. Like Leproult et al. and Omisade et al.'s findings, sleep-restricted participants in Spiegel et al.'s study also demonstrated higher late afternoon and evening cortisol levels with the nadir occurring about 1.5 h later than in the rested state. As in prior studies, they propose that the slower decline in cortisol from the morning acrophase throughout the day resulted in elevated evening values. Buxton et al.'s study of 20 healthy, nonobese men who underwent restricted sleep for 5 h per night over a 1-week period reveals similar changes in cortisol under conditions of controlled diet and activity [70]. In sleep-restricted subjects, late afternoon and evening levels of salivary free cortisol were significantly elevated compared to the sleep-replete condition but did not show linear correlation to insulin sensitivity. The sleep-deficient participants experiencing 28-h "days" in Buxton et al.'s study of prolonged sleep restriction combined with circadian disruption also exhibited higher plasma cortisol levels compared to the rested state [60]. These hormonal changes persisted throughout the 3-week exposure in all circadian phases.

Overall, studies suggest a strong relationship between insufficient sleep and impaired glucose homeostasis and cortisol regulation. These proximal outcomes may explain observed associations between sleep and the diabetes epidemic.

Laboratory Evidence: The Impact of Insufficient Sleep on Glucose Homeostasis via Sympathetic Nervous System Activation

Studies have shown links between increased sympathetic output and obesity, insulin resistance, obstructive sleep apnea, hypertension, and leptin resistance. Many studies also suggest a role of the sympathetic nervous system (SNS) in the alteration of glucose regulation following sleep loss. The SNS is regulated by sleep-wake cycles and its activity is highest during REM sleep and wakefulness and gradually decreases during non-REM sleep [84]. Sleep onset is associated with a significant decline of circulating concentrations of catecholamines, which serve as direct readouts of sympathetic activity. In contrast, nocturnal and morning awakenings are associated with increases in these hormones [85]. One study by Marangou and colleagues administered catecholamines before an IVGTT to test their effects on glucose regulation in healthy humans [86]. Norepinephrine infusion resulted in a significant increase in blood glucose and circulating free fatty acids during the IVGTT, as well

as a marked decrease in insulin sensitivity and disposition index, suggesting a significant increase in diabetes risk with increased levels of catecholamines [86].

Additionally, sleep disturbances have been shown to increase sympathetic output. In a study comparing 5.5 h with 8.5 h of time in bed in 11 healthy middle-aged volunteers, a significant increase was observed in nighttime and 24-h epinephrine levels during sleep restriction [80]. Furthermore, heart rate variability (HRV), a read-out of cardiac sympathetic nervous system activity, has been shown to be impaired during short sleep [55, 73], suggesting an increase in sympathetic drive during sleep restriction.

The relationship suggested between sleep loss and sympathetic nervous system dysfunction proposes another likely mediator of several of the negative metabolic effects of sleep loss and sleep disorders, including insulin resistance, decreased glucose tolerance, and reduced leptin signaling, all of which can predispose an individual to obesity.

Conclusions and Policy Implications

Mounting evidence from both epidemiological and laboratory investigations indicates the deleterious and complex effects of insufficient sleep. In view of the morbidity and mortality associated with the global obesity and diabetes epidemics, the relationships between inadequate sleep, excess weight, and impaired glucose regulation are particularly troubling. The burgeoning "epidemic" of inadequate sleep seems cause for concern. Indeed, rising sleep insufficiency in both pediatric and adult populations has paralleled the surge in obesity and diabetes. These epidemics and associated disorders, such as hypertension, cardiovascular disease, and cancer, generate enormous healthcare and economic burdens. While public policy efforts tend to focus on waking health behaviors such as diet and exercise, it seems crucial to highlight sleep as a third pillar of health and well-being.

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