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Sleep Duration and Diabetes Risk: Population Trends and Potential Mechanisms

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Abstract

Sleep is important for regulating many physiologic functions that relate to metabolism. Because of this, there is substantial evidence to suggest that sleep habits and sleep disorders are related to diabetes risk. In specific, insufficient sleep duration and/or sleep restriction in the laboratory, poor sleep quality, and sleep disorders such as insomnia and sleep apnea have all been associated with diabetes risk. This research spans epidemiologic and laboratory studies. Both physiologic mechanisms such as insulin resistance, decreased leptin, and increased ghrelin and inflammation and behavioral mechanisms such as increased food intake, impaired decision-making, and increased likelihood of other behavioral risk factors such as smoking, sedentary behavior, and alcohol use predispose to both diabetes and obesity, which itself is an important diabetes risk factor. This review describes the evidence linking sleep and diabetes risk at the population and laboratory levels.

Keywords

Sleep; Diabetes; Insomnia; Obesity; Circadian

Introduction

Insufficient sleep duration is recognized as an important unmet public health problem [1] and has been included as a national health priority in Healthy People 2020 [2]. Many previous studies have associated habitual short sleep duration to important adverse cardiometabolic outcomes, including weight gain, obesity, diabetes, cardiovascular disease,

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and stress. A proposed mechanism of these relationships is that insufficient sleep duration triggers dysregulation of metabolism [3–7] and increased immune response [8, 9], resulting in appetite dysregulation and cardiometabolic disease [4, 7].

The pathways between short sleep and diabetes are unclear. Several studies have used partial sleep deprivation protocols to elicit sleep loss and study metabolic consequences. These studies typically involve recruitment of young, healthy volunteers who typically sleep 8–9 h to undergo an acute sleep restriction of 4–6 h over a period of days to weeks. One common finding is that sleep deprivation is associated with insulin resistance and glucose intolerance [10–12], described in more detail below. These findings have come from studies that have employed continuous glucose monitoring [13] as well as challenge paradigms such as glucose tolerance tests [14]. This has led to a large number of studies that have aimed to explore this relationship in more detail and discern potential mechanistic pathways [11, 15–17]. Parallel to these laboratory findings, several epidemiologic studies have examined self-reported short sleepers relative to obesity and diabetes risk [18–22], frequently finding overlapping patterns.

The present review addresses the following issues: (1) population trends linking habitual insufficient sleep with diabetes risk, (2) potential physiologic mechanisms linking sleep loss with diabetes risk, (3) potential behavioral mechanisms linking sleep loss with diabetes risk, (4) increased prevalence of diabetes in obstructive sleep apnea and treatment implications, and (5) importance of circadian control of metabolism in the relationship between sleep and diabetes. We finish with recommendations for future work and conclusions.

Insufficient Sleep and Diabetes Risk: Population Trends

Definition of Insufficient Sleep

Conflicting Definitions and Operationalizations—There are currently hundreds of studies that have examined habitual sleep duration as an independent variable in relation to outcomes such as cardiometabolic disease morbidity and mortality. Although there is an emerging consensus regarding how sleep duration should be defined, there are many ways that sleep duration has been operationalized in population-level studies. First, although the most common approach is to use retrospective self-report survey items as these are most feasible for population-level research, other studies have used prospective self-report, e.g., sleep diaries, single-timepoint objective measures, e.g., polysomnography, and prospective objective measures, e.g., actigraphy. Since there is no direct measure of sleep in humans, all of these estimates assess somewhat different aspects of sleep and there is still no gold standard measure of habitual sleep duration. Because of this, varying study methodologies needs to be considered during evaluation.

Within measurement approaches (e.g., survey items, sleep diary, actigraphy), methods may also vary. For example, some survey measures use time estimates to compute sleep duration, some ask for “typical” or “weekday” (i.e., modal) sleep duration, whereas others ask for “average” (i.e., mean or median) sleep duration; also, some items specifically ask about night-time sleep only and some assess 24-h sleep. There is a lack of consensus on how to operationalize sleep duration as a variable. Some studies evaluate it as a continuous variable,

assuming that effects are continuous and linear. Other studies evaluated sleep duration as a three-level variable (short, normal, and long) to account for nonlinear and potential threshold effects. Still others have used a four-factor approach (very short, short, normal, and long) to further clarify nonlinear effects, while some have used more categories, with a reference in the middle of the distribution. These varying approaches make comparisons across studies difficult. With these qualifications in mind, several important conclusions can be drawn from the existing literature regarding sleep and diabetes risk.

Consensus Recommendations—Recently, a panel convened jointly by the American Academy of Sleep Medicine and Sleep Research Society released recommendations for sleep duration in adults. This recommendation stated that 7 or more hours of sleep was likely necessary to maintain optimal health and functioning [23, 24]. In a companion document [25, 26], it was revealed that for the domain of metabolic health in particular, there was consensus that less than 7 h was inappropriate, that 7–9 h was probably appropriate, but that there was uncertainty of the appropriateness of >9 h of sleep. In a parallel effort by the National Sleep Foundation, a similar consensus panel also recommended at least 7 h of sleep for optimal health, though this group did achieve consensus that more than 9 h was not appropriate [27, 28]. Echoing these recommendations, the American Thoracic Society also released a statement that its consensus panel also warns that insufficient sleep duration (which they define as 6 h or less) is likely associated with poor health, including diabetes [29].

Prevalence of Insufficient Sleep

Population Prevalence Estimates—Based on the consensus statement released by the American Academy of Sleep Medicine and Sleep Research Society, the Centers for Disease Control and Prevention released prevalence data for insufficient sleep using the 2014 Behavioral Risk Factor Surveillance System. This report [30•] suggested that approximately one third of US adults do not get the recommended amount of sleep. Specifically, using the item, “On average, how many hours of sleep do you get in a 24-hour period?,” the distribution of sleep duration of the population is shown in Fig. 1. These estimates are consistent with other studies. For example, Krueger and Friedman [31] used data from the National Health Interview Survey to estimate that the prevalence of <7 h (i.e., ≤6 h since hours were only measured in whole numbers) is 28.3 %. Grandner and colleagues estimated this value to be higher, at 39.92 %, in the 2007–2008 wave of the National Health and Nutrition Examination Survey [32].

Although there are claims made regarding the increased prevalence of sleep duration in society, available evidence suggests that sleep duration has not actually decreased much in recent years. For example, Bin and colleagues investigated global trends in sleep duration across 15 countries since the 1960s [33]. Overall, they found little to no evidence that sleep duration is shortening worldwide, especially in the USA. Among four US-based studies that employed similar methodology, one found a slight increase in sleep time, one found that the proportion of people sleeping 6 h or less decreased, but two found that the proportion has increased. Therefore, although a claim of increased prevalence of short sleep is not well-

supported by the available data, the exceedingly high prevalence of short sleep duration is sufficiently alarming.

Social and Demographic Factors in Sleep Duration—It should be noted that sleep duration is differentially distributed in the population. For example, women are more likely to be short sleepers than men [34]. Also, racial/ethnic minorities—especially African-Americans—are more likely to be short sleepers [34, 35•, 36]. These effects are independent of socioeconomics, though poverty itself is a short sleep risk factor [34, 35•]. These patterns are especially relevant since there are gender, racial/ethnic, and socioeconomic differences in rates of diabetes prevalence, and sleep may be playing a role. In particular, sleep duration may play a role in racial/ethnic disparities in obesity and diabetes [35•, 36]. The social-ecological model of sleep and health (Fig. 2) attempts to bring these factors together to a coherent model that describes the role of sleep at the interface of upstream social-environmental determinants and downstream health consequences.

Epidemiologic Studies of Sleep and Diabetes Risk

Short Sleep Duration and Diabetes

Compared to other traditional diabetes risk factors, such as being overweight, family history of diabetes, and physical inactivity, overwhelming evidence from meta-analyses indicate that curtailed sleep duration, such as <5 h per day (very short sleep) and <6 h per day (short sleep) durations, is equally predictive of diabetes, with relative risks of 1.48 (95 % CI 1.25, 1.76) and 1.18 (95 % CI 1.10, 1.26), respectively [37]. The cardiometabolic consequences of short sleep duration may be stronger in prediabetes, a precursor condition to diabetes characterized by impaired fasting glucose and glucose tolerance, and a blood sugar of 5.6 and 6.9 mmol/L. In one study, researchers found that individuals who reported short sleep duration (≤5 h) had a 2.06 higher odds of prediabetes (95 % CI 1.00–4.22) compared to individuals who reported 7 h of sleep [38].

The relationship between short sleep duration and diabetes and diabetes outcomes is well-established across different contexts and within different groups. Although men and women are affected by the negative effects of short sleep duration on diabetes, it is more pronounced in men [39]. Consistently, racial/ethnic minorities in the USA are another group affected by the negative effects of short sleep duration on diabetes [40]. In a nationally representative sample, Zizi and colleagues found that black and white short sleepers (≤5 h) were 91 % more likely to report a diabetes diagnosis compared to those who slept on average 6–8 h per day [41]. However, Jackson and colleagues found that the relationship between short sleep duration and diabetes was stronger among whites compared to blacks [42]. These two sets of findings highlight that short sleep and its impact on diabetes cut across sociodemographic factors and is a national issue that requires urgent attention. Although the putative association between short sleep and diabetes is well evidenced, the causal mechanisms that undergird this association are not fully understood. Meta-analytical evidence indicate that sleep duration, specifically short sleep duration, is associated with hemoglobin A_1c (HbA_1c), a marker of glucose metabolism [43]. In sum, the aforementioned evidence

indicates that the relationship between short sleep duration and diabetes and diabetes outcomes may be mediated by unhealthy glucose levels and insulin resistance.

Short Sleep Duration and Obesity

Short sleep duration is associated with current and future obesity [44]. Previous evidence indicates that the relationship between short sleep and obesity is mediated by several factors which includes, but is not limited to, increased appetite/dietary intake, physical activity, and/or thermoregulation. A meta-analysis of 16 cross-sectional studies indicates that short sleepers are more likely to have nontraditional eating habits that deviate from the standard three-meals-a-day regimen, generally resulting in eating very high caloric foods at rare periods of the day. Over time, these poor eating and sleeping patterns can lead to chronic health conditions, such as obesity, cardiovascular disease, and cardiometabolic conditions. To address this pattern, it is imperative to understand the causal pathway that leads short sleepers to unhealthy dietary intake behaviors. One possible explanation is the mediating effect of leptin and ghrelin, which are hormones responsible for the physiological drives of satiation and increased appetite, respectively. Short sleepers compared to average sleepers generally have reduced leptin, elevated ghrelin, and increased body mass index [45]. Other possible pathways include increased opportunity to eat, increased fatigue, and altered thermoregulation [46••].

Potential Physiologic Mechanisms Linking Sleep Loss and Diabetes Risk

Insulin Resistance

In a landmark study by Spiegel and colleagues, 11 healthy men were assessed in the laboratory following 12 or 4 h in bed. Insulin and glucose measures were assessed using an intravenous glucose tolerance test at 5 and 10 h after meals. The results showed rather strikingly that the sleep deprivation condition was associated with higher baseline insulin and glucose and, as a result, higher homeostatic model assessment (HOMA) values, an indicator of insulin resistance [14]. This study was followed up by several others, which showed similar findings—that sleep deprivation was associated with increased insulin sensitivity and could potentially lead to insulin resistance [37, 47–49]. These studies have been seen as the strongest evidence physiologically linking sleep loss to the increased rates of diabetes observed in epidemiologic studies. Follow-up studies are examining the role of processes upstream of insulin signaling to better understand mechanisms by which sleep loss may induce insulin resistance. For example, sleep restriction may alter insulin signaling in adipocytes and this may be driving insulin resistance [50].

Leptin and Ghrelin

Several studies have suggested that the metabolic hormones leptin and ghrelin are implicated in the association between sleep and diabetes risk. Leptin is a hormone secreted by adipose tissue that is involved with signaling of feelings of satiety. Sleep laboratory studies have shown that acute sleep deprivation decreases leptin [13, 51], which would presumably result in decreased satiety. Ghrelin, on the other hand, is a hormone that is secreted by the stomach in a pulsatile manner, prior to meals, stimulating hunger. In laboratory studies, acute sleep deprivation has resulted in increased ghrelin, perhaps indicating increase physiologic hunger

[12, 13, 17, 52]. This combination of increased hunger and decreased satiety may increase eating, which may predispose individuals to obesity and diabetes. Studies have shown concomitant changes to energy balance [53, 54] and subjective experiences of hunger [13] that are consistent with this hypothesis. Further, disruptions in leptin and ghrelin may also result in dysregulation of insulin and glucose, which have been explored in a number of other studies relative to sleep loss [17, 50, 55–58].

Leptin was proposed as early as 60 years ago [59] but the specific protein and gene coding regions were discovered via studies of obese mice [60]. Similar to other hormones, its secretion is pulsatile, and it has a distinct circadian rhythm, with elevations in the evening and early morning [61]. Leptin is a hormone that is primarily secreted by white adipose tissue; for this reason, it has been studied as a signal for adiposity [62, 63]. Its primary functions, though, seem to be in signaling to the hypothalamus the level of current energy reserves for the purpose of adjusting food intake and energy expenditure [63, 64]. In the case of depleted energy stores, hypoleptinemia signals activate food intake via upregulation of agouti-related protein and neuropeptide Y in the arcuate nucleus and orexin and melanin-concentrating hormone in the lateral hypothalamus. Hypoleptinemia signals also activate food intake via downregulation of pro-opiomelanocortin and cocaine- and amphetamine-regulated transcript in the arcuate nucleus and brain-derived neurotrophic factor in the ventro-medial hypothalamus [64]. Leptin also acts in the ventrotegmental area to regulate reward experiences of and motivation for feeding, as well as in the brainstem to promote satiety [64].

A study in rats documented the nighttime rise in leptin but did not see alterations due to 5-h sleep restriction, despite showing increases in ghrelin and food intake [65]. Another study in rats, however, did show that sleep restriction lasting up to 4 weeks resulted in consistently lower leptin levels and concominant food intake [66]. Similarly, Rosa Neto and colleagues showed leptin decreases due to sleep deprivation [67], as did Martins and colleagues [68]. A study in rats showed that exogenous leptin suppresses rapid eye movement (REM) but enhances slow wave sleep [69].

Different results are seen in mice. Husse and colleagues found that total sleep deprivation was associated with elevated leptin that persisted after recovery [70]. Further, Laposky and colleagues found that leptin-deficient mice showed marked sleep dysregulation, suggesting a causal relationship between leptin and sleep regulation [71, 72].

In humans, Rasmussen and colleagues [73] studied sleep and leptin levels before and after dramatic weight loss (mean BMI = 41 to 27), compared to a nonobese control group (mean BMI = 23). The nonobese group demonstrated mean polysomnographic sleep of 448 min; the obese group slept less with a mean 360 min, which increased to 385 min following weight loss. Regarding 24-h leptin, the obese group demonstrated higher mean leptin secretion (35 μg/L) compared to the nonobese group (12 μg/L, $p < 0.01$). Following weight loss, leptin decreased significantly, to 17 μg/L, which was no longer significantly different from the nonobese group. Thus, it seems that the reduction in fat mass led to reductions in leptin production, and this effect outweighed any effect related to sleep duration changes.

Spiegel and colleagues studied leptin secretion changes as a result of sleep deprivation to 4 h. They found that sleep deprivation reduced mean levels of leptin by 19 %, reduced maximal levels by 26 %, and reduced rhythm amplitude by 20 % [51]. Similarly, the same group performed another study, where they studied sleep restriction for 2 days [13]. They found an 18 % decrease in leptin levels. Studies by Pejovic and colleagues [74] and Omisade and colleagues [75] both showed increased leptin following one night of sleep deprivation. Mullington and colleagues found reductions in leptin amplitude following sleep restriction [76]. However, one night of sleep deprivation did not lead to alterations in leptin levels in two studies [77, 78]. Similarly, in a study of eight individuals in a sleep restriction protocol that reduced sleep opportunity by one third for 8 days, Calvin and colleagues found no differences in leptin levels versus nine individuals who did not receive sleep restriction [79]. In a study of 11 healthy adults in a 5.5-h sleep deprivation condition, Nedeltcheva and colleagues also did not find a difference in leptin levels, despite showing increased snacking [80]. St-Onge and colleagues found that sleep deprivation to 4 h for 4 days was also not associated with leptin changes [48], while Reynolds and colleagues [55] and Simpson and colleagues [81] found that sleep restriction to 4 h for five nights resulted in increased leptin levels, a finding that was replicated by Markwald and colleagues in a longer protocol [53].

Several studies have evaluated leptin levels associated with habitual sleep duration. In a pediatric sample, Boeke and colleagues [82] found that chronic curtailed sleep was associated with lower leptin levels in girls at age 7, especially in girls with more adiposity. Among adolescents, though, lower leptin was seen among shorter-sleeping males only. No other relationships were found. In a sample of children ages 8–11, Hart and colleagues found that a sleep intervention for 3 weeks reduced energy intake and weight, but demonstrated lower leptin values [83]. In another study of 8–11-year olds, Kjeldsen and colleagues found that less sleep was associated with lower leptin values, but only in analyses adjusted only for body fat; after including other covariates, these relationships were no longer significant [84]. In samples of adolescents, Al-Disi and colleagues [85] and Martinez-Gomez and colleagues [86] found no relationship between sleep duration and leptin, though a study of male university students did show a relationship between sleep and leptin, with slightly higher leptin among short sleepers [87].

An analysis of the Wisconsin Sleep Cohort, which included 1024 adult volunteers, found that polysomnographic sleep was associated with lower leptin levels [45]. Similarly, in a subsample of the Women's Health Initiative, short sleep duration was also associated with lower leptin levels [88]. In a sample of adults in the Quebec Family Study, Chaput and colleagues found that leptin levels were lower than expected among short sleepers, based on predicted values [89]. Charles and colleagues found that police officers sleeping 5–7 h had lower leptin values than those sleeping at least 8 h [90]. Similarly, a population-level study of adults in Brazil found that short sleep was associated with lower leptin levels in normal-weight individuals [91].

In contrast to the studies above reporting lower leptin levels with sleep short sleep duration, a report from the Cleveland Family Study, however, found that shorter sleep duration was associated with higher leptin levels [92], and a study from Taiwan found that hyperleptinemia was associated with shorter sleep duration [93]. Also, both Knutson and

colleagues [94] and Littman and colleagues [95] found no association between sleep and baseline leptin. Further, Littman and colleagues found that those who increased sleep duration over time showed decreased leptin, relative to those that reduced sleep time [95]. One study evaluated baseline leptin levels in subjects with insomnia [96]. The insomnia subjects demonstrated less polysomnographic total sleep time, but no differences in leptin were found. In another study of sleep quality, this time in depressed adults, Hafner and colleagues found that poor sleep quality was associated with lower leptin, but only in normal-weight women over age 59 [97].

Given the circadian patterning of leptin, there may be an interacting role of light exposure. For example, Figueiro and colleagues found that when kept in dim light conditions (<0.5 lx), subjects in a 5-h sleep condition had reduced morning leptin levels relative to an 8-h sleep condition. However, when subjects underwent a 5-h sleep condition but were given 60 lx of either red, green, or blue light, leptin levels were significantly higher [98]. On the other hand, Garaulet and colleagues report on a CLOCK gene variant that predisposes to sleep reduction and metabolic effects, but does not seem to impact leptin values [99].

Laboratory studies have shown that sleep deprivation of normal sleepers results in decreased leptin [92, 100] and elevated ghrelin [101, 102]. Epidemiologic studies have replicated this finding, demonstrating associations between habitual short sleep duration and both decreased leptin and elevated ghrelin [45]. Ghrelin, produced in the stomach and pancreas, regulates hunger. It is a 28-amino acid peptide that was only recently discovered (in 1999) and named because of its potential role in growth hormone function, as the endogenous ligand for growth hormone secretagogue receptor 1-a (GHSR) [103]. It is primarily secreted by the stomach and its actions in the hypothalamus are most relevant to this discussion [103]. Through the GHSR pathway, ghrelin has unique orexigenic and adipogenic effects at the level of the hypothalamus [103–107].

Ghrelin has a well-characterized circadian rhythm, with increased secretion during the day, particularly before mealtimes, and marked suppression at night. Animal studies have shown that this suppression can be attenuated with restricted feeding [65]. Several studies have shown that ghrelin promotes slow wave sleep in humans [108].

Sleep deprivation may increase ghrelin. This has been seen in animal models [68, 109]. In humans, a now classic study by Spiegel and colleagues evaluated the effects of two nights of sleep curtailment to 4 h in bed in 12 healthy, young men. Total ghrelin levels after two nights of 4 h of sleep were 28 % higher, relative to a rested condition [13]. This one finding is frequently cited and has instigated several additional studies of ghrelin in sleep restriction. For example, Benedict and colleagues report that an acute sleep deprivation protocol was associated with significantly increased morning ghrelin concentrations [77]. Other studies, though have not seen changes in ghrelin [79, 80], and one study found that 24-h ghrelin decreased during sleep restriction for 5 days [53]. Sample characteristics may play a role—St-Onge found that sleep restriction was associated with increased ghrelin in men but not women [48, 110]. In contrast to these studies that employed partial sleep deprivation, few studies have been done with total sleep deprivation, but one study found elevated ghrelin levels [111].

A few studies of ghrelin associated with sleep abnormalities have also been conducted. In night eating syndrome patients, ghrelin levels were lower among those with night eating syndrome, relative to controls [112]. Motivala and colleagues found that nighttime ghrelin was lower among insomnia patients versus controls [96].

Age may also play a role. In a study of 8–11-year olds, a reduction in sleep time by 1.5 h did not produce a change in ghrelin [83]. In a study of 14–18-year-old girls, Al-Disi and colleagues found that shorter sleep duration was associated with elevated ghrelin levels [85], especially in the nonobese subsample. In a study of Danish children, Kjeldsen and colleagues, though, found that ghrelin levels were positively associated with higher sleep durations [84]. In a study of Japanese university students, no association between sleep and ghrelin levels was found [87].

In adults in the general population, actigraphically measured sleep was not associated with ghrelin in a Brazilian population sample [91] or a sample of postmenopausal, sedentary, overweight women [95]. In data from the Wisconsin Sleep Cohort Study, which was a prospective cohort study that included middle-aged adults, shorter habitual sleep duration was associated with increased ghrelin [45].

Inflammatory Cytokines

Here we briefly describe the potential role of two inflammatory cytokines in the relationship of sleep deprivation with diabetes—tumor necrosis factor (also referred to as tumor necrosis factor α or TNF-α) and interleukin-6 (IL-6). TNF-α is a cytokine that is produced by activated macrophages. It has many roles as a proinflammatory molecule, including stimulation of the acute phase reaction. It is also involved with systematic inflammation. TNF-α was given its name when it was discovered to induce apoptosis in tumor cells [113]. TNF-α promotes several related immune cell functions [114]. The primary functions of TNF-α involve activation of the nuclear factor kappa (NFk) B and mitogen-activated protein (MAP) kinase pathways. NFkB is a protein complex that controls DNA transcription and is involved in cellular responses to stressors, and MAP kinase is involved in many cellular processes, including response to stressors and gene expression. Taken together, these roles promote immune response and cell regulation.

Although several studies have evaluated relationships between TNF-α and sleep, some of these results are inconclusive. For example, one study found that sleep restriction to 6 h across 12 nights led to elevated 24-h TNF-α levels among men but not women [115]. Another study of one night of sleep restriction found increases in TNF-α messenger RNA expression [116]. Not all studies showed positive findings. In a study where sleep was restricted to two 2-h naps, no elevations in TNF-α were seen [117]. Another study of sleep restriction for 10 days found no changes in the levels of the TNF-α p55 receptor, which is a critical component for many of the functions of TNF-α [118]. It is possible to show increases in TNF-α without increased levels of the receptor, though, as this was seen in one study of total sleep deprivation [119].

Some of the inconsistent findings may in part be due to individual differences in vulnerability to sleep loss and the different receptor types studied [9]. Only one study has

investigated TNF-α in a population setting. In the Cleveland Family Study, shorter polysomnographic sleep (which may not be related to habitual sleep) was associated with elevated TNF-α, such that each hour of sleep was associated with an 8 % increase in TNF-α [120]. Taken together, these studies suggest that sleep may play a regulatory role in TNF-α function.

Like TNF-α, IL-6 is a proinflammatory molecule. It is secreted by T-cells and macrophages, and like TNF-α, it plays an important role in both the acute phase response and chronic inflammation. It also plays a role in body temperature regulation and stimulation of energy utilization in adipose tissue, where 15–30 % of IL-6 is expressed. Interestingly, IL-6 release is 2–3 times greater in visceral, as opposed to subcutaneous, adipose tissue [121]. This may be one reason why IL-6 levels are associated with obesity [122]. It should be noted that IL-6 can have anti-inflammatory processes, since it inhibits TNF-α and IL-1, and promotes IL-10, whic his anti-inflammatory.

IL-6 is characterized by a circadian rhythm. It is highest at night, with a noted elevation around sleep onset [123]. IL-6 is then suppressed by slow wave sleep, which characterizes much of the early parts of sleep [123]. Sleep deprivation delays (pushes back) the nighttime peak of IL-6, which may be the reason for demonstrated undersecretion at night and oversecretion during the day [123]. If IL-6 is administered exogenously, slow wave sleep and REM sleep toward the beginning of the night are suppressed, with a rebound later in the night [123]. Interestingly, even though sleep deprivation in the laboratory may lead to nighttime undersecretion, a study of night shift work showed increased secretion at night [124].

Several laboratory studies have examined the effects of experimental sleep restriction on IL-6. Haack and colleagues found that after 12 days in the laboratory, where sleep was restricted to 4 h (versus 8 h), IL-6 levels were elevated by 62 % [118]. Similarly, in another 12-day laboratory study (this time with sleep restricted to 6 h), IL-6 secretion was again elevated [115]; since 24-h sampling was available, it was shown that differences were found between 18:00 and 24:00, and 3:30 and 6:00. A more recent study found that after five nights of sleep restriction to 4 h in 13 healthy young men, an increase in IL-6 was observed, which did not normalize after a limited recovery opportunity [125].

Several studies have also examined habitual sleep. In the Cleveland Family Study, elevated IL-6 (7 % increase per hour) was associated with self-reported long sleep duration [120]. In a Taiwanese cohort, long sleep duration was also associated with elevated IL-6 [126]. Although these studies did not find associations with short sleep, a study of Alzheimer's caregivers and controls found that actigraphic sleep duration was negatively correlated with IL-6 [127], and a study of mothers found that self-reported short sleep of <5 h was associated with elevated IL-6 at 3 years postpartum [128].

Habitual short sleep duration has been associated with increased risk of cardiovascular disease [4, 7], though mechanisms for this relationship are unknown. Proposed mechanisms involve increased neurobehavioral stress response, increased oxidative stress, and increased inflammation. All of these proposed mechanisms are partially supported by the finding of

increased inflammatory biomarkers associated with short sleep duration. This finding has been seen in the context of laboratory studies of sleep deprivation of normal sleepers, as well as population-based studies of habitual short sleepers [4]. Specifically, elevations in IL-6 and TNF-α associated with short sleep have been demonstrated in both population [120, 128] and laboratory [115, 116, 118, 125] studies, but these have not been evaluated in verified short sleepers.

Potential Behavioral Mechanisms Linking Sleep Loss and Diabetes Risk

In addition to physiologic pathways linking sleep loss and diabetes risk, there are a number of potential indirect pathways by which behavioral mechanisms may be playing a role. Sleep loss may lead to the consumption of more calories during the 24-h period, impaired decision-making that could lead an individual to make more unhealthy food choices, and increased likelihood of other unhealthy behaviors that can increase diabetes risk.

Increased Caloric Intake

Several studies have shown that sleep loss can increase caloric intake across the 24-h period. St-Onge and colleagues showed that otherwise healthy individuals, when restricted to 5 h of sleep opportunity, consumed approximately 500 kcal per day compared to a well-rested condition [54]. This finding was replicated and extended by Markwald and colleagues, who showed that this increase in caloric intake was associated with increased energy expenditure at night during the period where the individual was typically asleep [53]. Also, this study showed that the increased caloric intake occurred exclusively at night, while morning caloric intake was slightly reduced. In a large study by Spaeth and colleagues, this finding was replicated in a more diverse sample [129, 130]. The Spaeth study additionally showed that this increased energy intake was associated with about 1 kg of weight gain across 5 days, though the weight gain was disproportionately experienced by Black/African-American men, followed by non-Hispanic White men and Black/African-American women. Non-Hispanic White women showed the least weight gain. In a separate laboratory study, increased food intake following sleep deprivation was restricted to calorie-dense snacks [80]. Thus, sleep loss may increase energy intake at night, especially from energy-dense sources, resulting in weight gain and increased diabetes risk [131].

Impaired Decision-Making

Unhealthy eating is also a product of unhealthy food choices. Making healthy food choices can be difficult, and this can be even more difficult under conditions of sleep loss. Sleep loss impairs executive function [132–136]. In particular, sleep loss may impair an individual's ability to make healthy choices by limiting their ability to accurately weigh risks and benefits of an action [137] and promote hedonic decision-making [138]. These could lead to an unhealthy eating pattern that may increase risk for diabetes.

Increased Likelihood of Other Unhealthy Behaviors

Habitual short sleep duration is associated with other unhealthy behaviors that may increase diabetes risk. Increased sedentary lifestyle is associated with habitual short sleep duration [139, 140], perceived insufficient sleep [141], and general sleep disturbances [142].

Smoking is also associated with both short sleep duration [140] and poor sleep quality [143]. Individuals with sleep difficulties are also more likely to consume excessive alcohol [144, 145]. Taken together, sleep difficulties such as insufficient sleep duration and poor sleep quality may lead to unhealthy behaviors that are themselves diabetes risk factors.

Diabetes and Obstructive Sleep Apnea

Overlapping Prevalence of Diabetes and Sleep Apnea

Type 2 diabetes mellitus (T2DM) and obstructive sleep apnea (OSA) are very prevalent in the obese population. Combining the data from the five NHANES studies showed that of the three variables age, race, and body mass index (BMI), BMI was the greatest contributor to the prevalence of diabetes [146]. T2DM in obesity is characterized by both insulin resistance and impaired insulin secretion. OSA, independent of obesity, has been shown to induce insulin resistance, although the exact mechanism is unclear [147].

A wide variation exists in the prevalence of OSA in patients with T2DM. This variation stems from the differences in the study population and definitions for respiratory disturbance index (RDI) to measure sleep breathing disorders [148]. Foster et al. noted an 86 % prevalence of OSA in his obese diabetic population [149]. Similarly, Aronsohn et al. reported a 77 % prevalence of OSA in their patients with T2DM. They also noted poorer glycemic controls with increasing severity of OSA [150]. Brooks et al. noted the prevalence of OSA in his diabetic population to be 70 %, although this study was limited by its size and a screening questionnaire of excessive sleepiness and snoring before recruitment [151]. Einhorn et al. noted a slightly lower prevalence of 36 % [152]. Heffner in his retrospective study of 16,066 persons with diabetes noted that only about 18 % of the population was diagnosed with OSA, a number significantly lower than that of the estimated prevalence in the studies mentioned above [153]. Similarly, many cross-sectional and prospective studies have shown a higher prevalence of T2DM in patients with OSA [154–156], confirming this bidirectional relationship of these chronic medical conditions.

Obstructive Sleep Apnea and Obesity

Obesity is one of the strongest risk factors for the development of OSA with a proportionally increasing prevalence with increasing BMI [157]. While the prevalence of OSA in the general population is estimated to be 0.15–0.3 %, the prevalence in the obese population is estimated to be 19–31 % [158]. Increasing BMI alters the upper airway mechanics contributing to the upper airway obstruction. Several mechanisms such as increased pharyngeal fat deposition, airway edema, alterations in the leptin signaling pathways, as well as reduction of the functional residual capacity, have been incriminated as the reasons for the development and progression of OSA [159, 160]; details of the pathophysiology are beyond the scope of this review.

Sleep Apnea and Insulin Resistance

Insulin resistance is characterized by decreased peripheral insulin responsiveness, resulting in decreased glucose uptake and glucose intolerance. Sleep apnea has been shown to be independently associated with increased insulin resistance [161], irrespective of obesity,

body fat distribution, and age [162, 163]. The pathophysiology behind this association is believed to be due to the effects of sleep apnea on sleep, namely intermittent hypoxia (IH) and sleep fragmentation which trigger activation of the sympathetic nervous system, oxidative stress, systemic inflammation, dysregulation of the appetite-regulating hormones, and activation of the hypothalamic-pituitary-adrenal axis. These mechanisms contribute in the progression toward insulin resistance [164].

Activation of the sympathetic nervous system by IH associated with sleep apnea is thought to play a major role in the development of insulin resistance by reducing insulin sensitivity, insulin-mediated glucose uptake, and reduction of insulin secretion. Activation of the sympathetic nervous system could increase cortisol synthesis by activation of the hypothalamic-pituitary-adrenal axis. Cortisol increases glucose production, decreases peripheral glucose uptake, and inhibits insulin secretion from the pancreatic beta cells. Reactive oxygen species (ROS), generated due to oxidative stress secondary to IH, may worsen insulin resistance by inhibiting insulin-induced energy substrate uptake in muscle and adipose tissue. Low levels of appetite regulating hormones such as leptin and adiponectin have been associated with higher insulin resistance. Sleep fragmentation due to sleep apnea, resulting in sleep deprivation and loss of REM sleep, may also contribute to reduced glucose tolerance [164].

Sleep Apnea, Oxidative Stress, and Inflammation

IH associated with sleep apnea may result in oxidative stress and release of ROS, which contributes to a proinflammatory state [164]. ROS may inhibit the uptake of glucose in peripheral tissues and suppress insulin secretion [164]. Oxidative stress has been linked to pancreatic beta cell proliferation and cell death [165]. Treatment with continuous positive airway pressure (CPAP) therapy has been shown to attenuate oxidative stress [166]. Moderate to severe OSA is associated with endothelial dysfunction, increased arterial stiffness, and elevated serum inflammatory markers [167]. A baseline proinflammatory state is seen in diabetic patients as well, with elevated levels of circulating inflammatory cytokines, such as interleukin-6 and tumor necrosis factor alpha, which have been shown to play a role in the pathogenesis of insulin resistance and T2DM [164]. The exact mechanism of action of chronic inflammation in the pathogenesis of insulin resistance in sleep apneic patients is not known.

Treatment of Sleep Apnea

The potential mechanism of CPAP therapy on glycemic control is incompletely understood. Elimination of intermittent hypoxia and sleep fragmentation with CPAP therapy may result in improved glycemic control [168]. Observational studies have shown the beneficial effect of CPAP therapy on insulin resistance in patients with OSA and T2DM [151, 169].There are a limited number of randomized control trials (RCT) to evaluate the effect of CPAP therapy on glucose control in diabetic patients, with inconsistent results due to short-term follow-up and small sample sizes.

Martinez-Ceron and colleagues in a recently concluded RCT to evaluate the effect of CPAP therapy on OSA patients with suboptimally controlled diabetes mellitus showed improved

insulin resistance and glycemic control, measured by HbA_1c, over a period of 24 weeks. These benefits were not limited to patients with severe OSA. This improvement was thought to be secondary to reversal of the proinflammatory status attributed to CPAP therapy [170].

The optimal duration of CPAP therapy lacks clarity as well. It has been reported that glycemic control in T2DM is associated with apneas and hypopneas related to REM sleep rather than nonrapid eye movement (NREM) sleep [171]. Extension of CPAP use for up to 7 h was associated with greater reduction in HbA_1c levels when compared to patients with 4 h of CPAP use [171].

In conclusion, CPAP use is associated with improved insulin sensitivity and glycemic control. These beneficial effects may be related to longer duration of CPAP use and greater compliance with CPAP therapy in patients with suboptimal control of diabetes.

Future Directions

There are several key directions for future research. For epidemiologic studies, perhaps the most pressing issue is a lack of phenotypic clarity regarding sleep habits associated with diabetes risk. Current studies stress the issue of insufficient sleep, yet estimates of insufficient sleep rely on habitual sleep duration. Not only is there a lack of objective, or even validated subjective, measures of sleep duration at the population level, sleep duration does not capture sleep need, which may vary across individuals, as does resilience to sleep loss. Further, the potentially high rate of confounding with insomnia needs to be clarified. In short, although the association between insufficient sleep and diabetes risk is relatively well-established, important characteristics and qualifications still need to be discerned.

From a physiologic standpoint, two main future directions are apparent from the literature. First, laboratory studies need to better operationalize real-world sleep loss so that relevant mechanistic links that increase population risk for diabetes are separated from apparent links that merely reflect an acute reaction to a laboratory setting. Questions remain as to whether pathways such as leptin, ghrelin, insulin, and inflammation reflect real-world causal pathways linking habitual short sleep duration and diabetes. Second, the role of circadian physiology needs to be explored in more detail. Existing basic research is showing that many metabolic processes are under circadian control and that circadian gene transcription patterns can influence insulin signaling and adipocyte function [172••, 173]. Also, in animal models, circadian patterns of food intake differentially impact aspects of weight regulation [173–178]. Currently, though, almost none of these studies have not made the translational step to human research.

Conclusions

Sleep is important for many physiologic processes, and many of these processes are involved in regulation of metabolism. Perhaps because of this, insufficient sleep and sleep disorders have been identified as novel and important risk factors for the development of diabetes. This is particularly alarming since insufficient sleep is experienced by approximately one third of the US population and sleep apnea—a sleep disorder highly prevalent among middle-aged and older adults—is present in three quarters or more of persons with diabetes.

Increased recognition of the importance of sleep in the understanding of and management of diabetes is warranted. Current literature suggests both physiologic and behavioral pathways linking sleep and diabetes risk, which are also related to obesity risk. An overall schematic of this is presented in Fig. 3. Future research is needed to clarify the epidemiologic links between diabetes and specific sleep phenotypes, as well as to discern mechanistic links between sleep and metabolic dysfunction.

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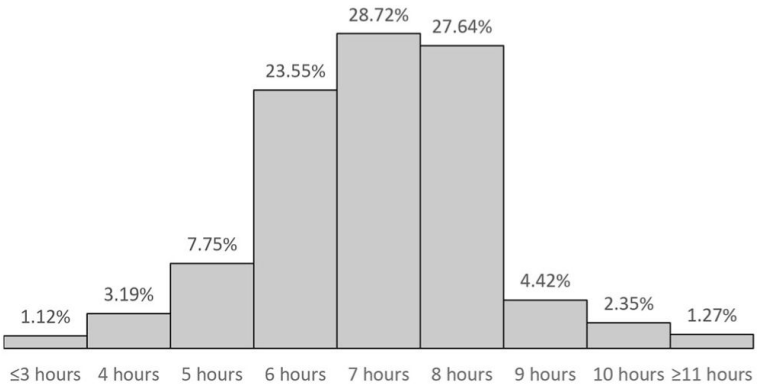

Fig. 1.
Distribution of sleep duration in the USA, using the 2014 BRFSS

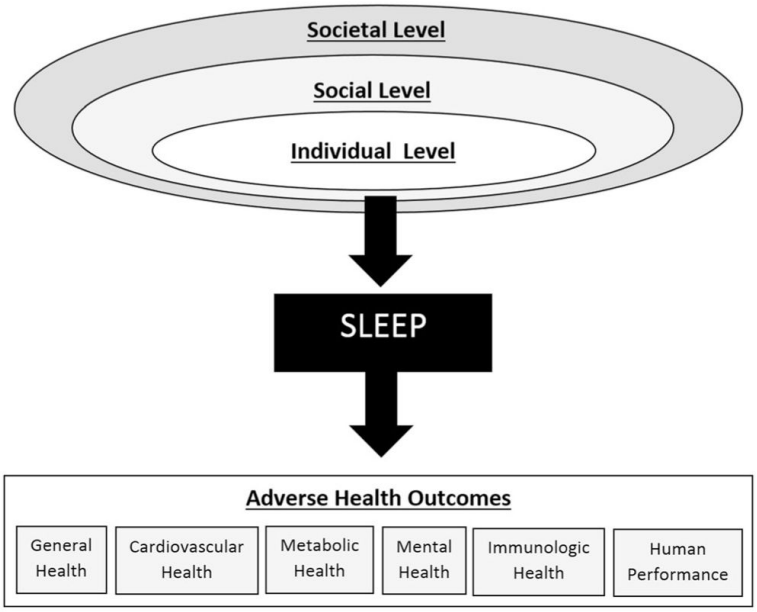

Fig. 2.

Social-ecological model of sleep and health (adapted from Grandner et al. [179], with permission from Elsevier)

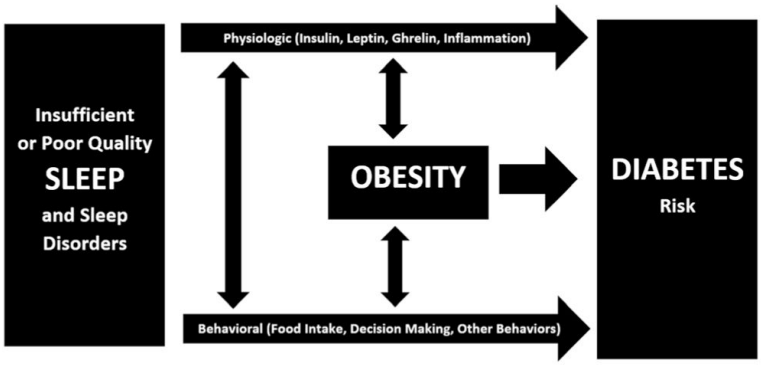

Fig. 3.

The role of physiologic and behavioral pathways and obesity in linking insufficient sleep duration and/or poor sleep quality and sleep disorders to diabetes risk