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Original Article

Association between sleep deficiency and cardiometabolic disease: implications for health disparities

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ABSTRACT

Background: Cardiometabolic diseases, which include obesity, diabetes, hypertension, and cardiovascular disease, are associated with reduced quality of life and reduced life expectancy. Unfortunately, there are racial/ethnic and socioeconomic disparities associated with these diseases such that minority populations, such as African Americans and Hispanics, and those of lower socioeconomic status, experience a greater burden. Several reports have indicated that there are differences in sleep duration and quality that mirror the disparities in cardiometabolic disease. The goal of this paper is to review the association between sleep and cardiometabolic disease risk because of the possibility that suboptimal sleep may partially mediate the cardiometabolic disease disparities.

Methods: We review both experimental studies that have restricted sleep duration or impaired sleep quality and examined biomarkers of cardiometabolic disease risk, including glucose metabolism and insulin sensitivity, appetite regulation and food intake, and immune function. We also review observational studies that have examined the association between habitual sleep duration and quality, and the prevalence or risk of obesity, diabetes, hypertension, and cardiovascular disease.

Conclusion: Many experimental and observational studies do support an association between suboptimal sleep and increased cardiometabolic disease risk.

1. Introduction

Cardiometabolic disease refers to obesity, diabetes, and cardiovascular disease (CVD), which are grouped together because they are related and share risk factors. For example, approximately 70% of total mortality in type 2 diabetes is due to CVD, and individuals with the metabolic syndrome, which is a clustering of risk factors including obesity, dyslipidemia, high blood pressure (BP), and insulin resistance, are at an increased risk of developing type 2 diabetes and CVD [1]. Unfortunately, the prevalence of these diseases is not distributed equally among the different racial/ethnic and socioeconomic groups in the USA. Obesity rates are higher in African Americans (45%) and Mexican Americans (36.8%) compared to whites (30%) [2], and African Americans and Mexican Americans are at a greater risk of developing diabetes compared to non-Hispanic whites [3]. The prevalence of hypertension is also higher among African-American adults compared to non-Hispanic whites [4]. Persons with lower socioeconomic status are also at an increased risk of cardiometabolic disease [5,6]. Cardiometabolic disease is associated with reduced quality of life, decreased life expectancy, and increased economic burden [7–10], and due to the disparities in cardiometabolic disease, minorities and people from lower socioeconomic groups suffer a greater burden.

There are disparities in optimal sleep duration and sleep quality that parallel the disparities in cardiometabolic disease. Minority groups, particularly African Americans, have shorter habitual sleep duration and poorer habitual sleep quality based on objectively measured wrist actigraphy compared to non-Hispanic whites [11,12]. In addition, several studies that used polysomnography (PSG) consistently observed lower amounts of slow-wave sleep (SWS) and reduced sleep efficiency among African Americans compared to non-Hispanic whites [13–16]. A recent meta-analysis of data from 14 studies that enrolled people without suspected sleep disorders and that used either actigraphy or PSG demonstrated that on average African Americans sleep almost 30 min less, take 6 min longer to fall sleep, have a 5% lower sleep efficiency, and have an 8% less SWS than non-Hispanic whites [17]. In addition, sleep disorders such as obstructive sleep apnea (OSA) may be more common, may go undiagnosed more frequently, and may be treated less efficaciously in African-American patients [18,19]. OSA is associated with poor sleep quality and often reduced sleep duration. Papers in this special issue also report sleep disparities.

Thus, cardiometabolic disease disparities and sleep disparities seem to exist, which begs the question of whether suboptimal sleep

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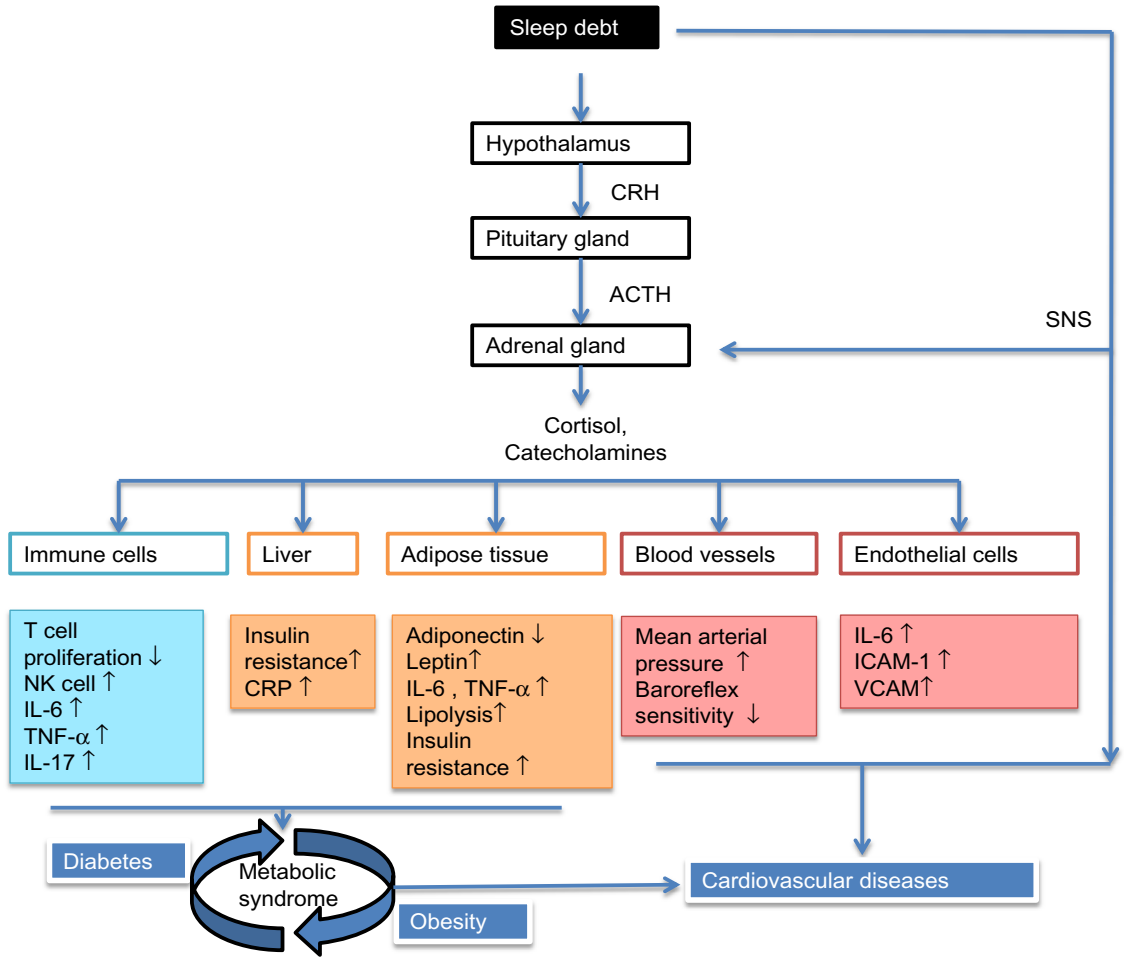

Fig. 1. Contributions of sleep debt in the pathophysiology of cardiometabolic diseases. Suboptimal sleep leads to metabolic dysfunction via the activation of stress–immune axis. Acute sleep loss can trigger metabolic distress in immune cells, hepatocytes, adipocytes, endothelial cells, and blood vessels by disturbing their homeostatic regulation. Prolonged activation along with defective counter-regulatory mechanisms as a consequence of chronic sleep deficiency may lead to the development of cardiometabolic diseases. Abbreviations: Natural killer (NK) cell, interleukin (IL), tumor necrosis factor (TNF), C-reactive protein (CRP), intercellular adhesion molecule (ICAM), vascular cell adhesion molecule (VCAM), corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), sympathetic nervous system (SNS).

may partially mediate the cardiometabolic disease disparities. In order for this to be true, suboptimal sleep needs to be associated with increased cardiometabolic disease risk. Therefore, the aim of this paper is to review the association between sleep duration or sleep quality and cardiometabolic disease risk factors in both experimental and observational studies. Note that OSA, a sleep disorder associated with cardiometabolic diseases, is beyond the scope of this article (see Ref. [20] for a review of this topic). The next step for research would be to explicitly test whether sleep partially mediates cardiometabolic disease disparities.

2. Sleep loss and its role in the development of cardiometabolic disorders: what do experimental studies tell us?

Sleep is an important and complex physiological process that is critical for maintaining metabolic homeostasis. Disturbances in metabolic homeostasis can increase the risk of developing cardiometabolic diseases, such as diabetes, obesity, and heart diseases. Mounting evidence suggests that suboptimal sleep is a possible risk factor in the development of cardiometabolic disease. The effects of experimental sleep manipulation, which includes sleep deprivation or fragmentation, on cardiometabolic measures are discussed in the following paragraphs. It is important to recognize that these effects of sleep are not isolated to any one of these single outcomes. Cardiometabolic diseases often share overlapping and intertwined pathways of sleep-regulated metabolic function, and perturbations in any one pathway may lead to an increased risk of multiple metabolic disorders (see Fig. 1). Controlled laboratory studies of sleep restriction (SR) and/or sleep fragmentation have shown that sleep curtailment under conditions of total sleep deprivation (TSD; continuous wake) or partial sleep deprivation (PSD; reduced sleep period) even for a night impairs metabolic function and homeostasis.

3. Sleep and diabetes

3.1. Glucose metabolism

In healthy individuals, glucose homeostasis is a tightly regulated balance between glucose release into the blood and glucose utilization to maintain a plasma glucose level of approximately 5 mmol/L. A decrease in plasma glucose levels suppresses the release of insulin by pancreatic β-cells, activates the sympathetic nervous system, and triggers the release of pancreatic α-cell glucagon, catecholamines, cortisol, and growth hormone (GH). These changes will collectively inhibit glucose uptake and increase hepatic glucose release into the blood. On the other hand, an increase in plasma

glucose will lead to the stimulation of insulin secretion and suppression of glucagon to restore normal glucose levels. One of the key regulatory factors in glucose metabolism is insulin. Insulin regulates glucose metabolism through both direct actions (binding to insulin receptors in the muscle and adipose tissue to stimulate glucose uptake) and indirect actions [suppression of glucose release from the liver and kidney, inhibition of free fatty acid (FFA) release]. Insulin resistance is the decreased ability of cells to respond to insulin. This generally leads to an abnormal increase in pancreatic insulin secretion to regulate plasma glucose uptake. When this compensation from the pancreatic β-cells becomes insufficient, it leads to type 2 diabetes mellitus (T2DM).

Spiegel et al. demonstrated a direct effect of SR on glucose metabolism [21]. In this study, glucose tolerance measures were taken after one week of PSD of 4 h in bed per night for six nights (sleep debt) and after six nights of 12 h/night in bed (sleep recovery). A 40% decrease in the rate of glucose clearance (glucose tolerance) and a 30% decrease in glucose effectiveness, the ability of glucose to mediate its own disposal independent of insulin, were observed during the sleep-debt condition. This was the first evidence showing that sleep loss can impair glucose metabolism. Subsequent studies further corroborated this finding. Acute partial SR of 4 h in bed for one night when compared to a night of unrestricted sleep showed an increase in endogenous glucose production ($p = 0.017$) and a decrease in glucose disposal rate ($p = 0.009$) from a hyperinsulinemic clamp assessment indicating a decrease in hepatic and peripheral insulin sensitivities [22]. In another study, two nights of sleep curtailment to 4 h in bed per night in healthy men reported a significant decrease in insulin sensitivity compared to two nights of unrestricted sleep [23]. In other studies that enforced PSD (5 h in bed) for 1 week in men [24] and four days of decreasing sleep curtailment (7 h, 6 h, 4 h, and 4 h on consecutive nights) in women [25], decreased insulin sensitivity and glucose tolerance were observed. The chronic effects of sleep loss on alterations in glucose metabolism were further demonstrated by a randomized crossover study comparing 5.5 h in bed per night for two weeks to 8.5 h in bed per night for two weeks in 11 healthy, overweight individuals. This SR period was associated with a reduced oral glucose tolerance and insulin sensitivity [26]. Quality of sleep also affects insulin sensitivity as demonstrated by a study that fragmented sleep across the night [27], and another that suppressed stage N3 [deep non-rapid eye movement (REM) sleep or SWS] [28]. In both of these studies, decreased glucose tolerance and insulin sensitivity were observed. A single night of SWS or REM suppression was compared to a night of uninterrupted sleep in 16 healthy men, and insulin sensitivity was decreased after SWS suppression (−15%, $p < 0.001$) but not after REM suppression [29].

These studies collectively suggest that sleep durations of ≤6 h across multiple consecutive nights and poor sleep quality have profound effects on glucose metabolism and homeostasis.

3.2. Counter-regulatory molecules

Other counter-regulatory hormones coordinate glucose homeostasis, and they are impacted by sleep curtailment, including glucagon [30] and catecholamines [31]. The alterations in the secretory profiles of these molecules may also contribute to the changes in glucose regulation observed after SR. Two crossover studies of a single night of total sleep [32] or partial sleep [30] deprivation showed decreased basal glucagon levels; however, catecholamine levels remained unchanged. In another study of PSD, one night of PSD was associated with significantly increased catecholamine levels [31]. A similar finding was also reported in a crossover study of 14 healthy males during a 24-h continuous wakefulness [33]. They reported an increase in nocturnal and daytime levels of norepinephrine ($p < 0.05$). Another study that included both men and women reported an increase in nocturnal and 24-h epinephrine ($p < 0.05$) and nocturnal norepinephrine ($p < 0.05$) during two weeks of 4.5 h in bed per night compared to 8.5 h in bed per night [26]. Three days of 4 h in bed per night compared to 9 h in bed per night for three days in adolescent boys resulted in an increase in fasting insulin (+59%, $p = 0.001$), fasting C-peptide (+24%, $p < 0.001$), and postprandial C-peptide (+11%, $p = 0.018$), in addition to a 24% decrease in the 24-h epinephrine levels ($p = 0.013$) [34]. The combination of elevated insulin and C-peptide levels, and unchanged glucose and glucagon levels indicates a reduced sensitivity to insulin. These studies point to a suppressive action of sleep loss on pancreatic α-cell glucagon secretion irrespective of the glycemic level. The pancreatic glucose regulation could be partly under the control of the autonomous nervous system.

3.3. Adipokines

In addition to the skeletal muscle and liver, another important insulin-sensitive peripheral tissue is the adipose tissue, which is composed mainly of adipocytes, fibroblasts, immune cells, and other cell types. It secretes various peptides and proteins collectively called adipokines, including leptin, adiponectin, omentin, resistin, tumor necrosis factor (TNF)-α, and interleukin (IL)-6. The white adipose tissue is not only an energy-storage depot but also an endocrine regulator of energy homeostasis. Acute SR of 4.5 h in bed per night for four days was compared to 8.5 h in bed per night for four days in a randomized crossover study [35]. The phosphorylation of Akt is a crucial early step in insulin signaling in the adipocytes, and the effect of increasing doses of insulin on the phosphorylation of Akt was reduced by 30% ($p = 0.01$) after acute sleep deprivation, which indicates a decreased insulin sensitivity in the adipose tissue. There was also a parallel reduction in the total body insulin sensitivity ($p = 0.02$). The actions of insulin through the Akt pathway in the adipose tissue include leptin secretion and fat metabolism, and therefore alterations in the insulin sensitivity of the adipose tissue could have important metabolic consequences.

One of the most-studied adipokines in relation to sleep duration is leptin, which is produced by the adipocytes in proportion to the mass of the adipose tissue. Leptin signals satiety through its interactions with the appetite-regulating centers in the brain; hence, it is called the satiety hormone. Leptin is regulated by insulin through glucose metabolism (ie, by food intake), and it also has a diurnal rhythm that peaks at the nocturnal sleep phase and declines in the morning a few hours after a rise in levels of another adipokine called adiponectin [36,37]. Continuous TSD for 88 h in healthy men [body mass index (BMI) range: 20–34.5 kg/m^2] decreased the nocturnal amplitude of leptin ($p < 0.001$) [38]. Similarly, 4 h in bed per night for 6 days significantly decreased leptin's amplitude by 20% when compared to 12 h in bed per night for six nights in 11 lean men [39]. PSD of 4 h in bed for two days also decreased leptin levels (−18%, $p = 0.04$) in 12 healthy men (BMI: 23.6 ± 2.0 kg/m^2) [40]. The effects of SR on leptin levels in subsequent studies have been mixed, with some studies reporting an increase in leptin [25,41–45], while others reported no significant difference [33,46–51] after SR. Among the studies that did find an increase in leptin levels, one measured the energy balance of the subjects and found the energy balance to be positive during sleep loss in comparison to after habitual sleep [25]. Leptin increased in parallel with an increase in energy intake and energy expenditure (EE) [25], while other studies either reported no significant differences in energy intake [42,45,52] or did not evaluate EE [44]. Among the studies that reported no significant difference in leptin, some did not assess energy intake or controlled calorie intake [33,46,51], while others reported an increase in calorie intake without any changes in EE [47,49,50]. Finally, a recent study of SR observed decreased leptin levels, consistent with the Spiegel et al. study described above [53]. In this study, 19 healthy

men were sleep-restricted by 1.5 h each night for three weeks [53]. In the sleep-restricted group, the morning leptin levels after 3 weeks of SR were reduced ($p = 0.023$) compared to baseline. The subjects were allowed to eat ad libitum, but no documentation of caloric intake during those three weeks was reported. Interpreting the discrepant results regarding SR and leptin levels is further complicated by the dynamic relationship between leptin, food intake, and body fat changes, and these three components are not always measured and/or controlled.

Adiponectin is another adipocyte-derived hormone that has been known to have anti-inflammatory properties. Decreased plasma levels of adiponectin have been associated with an increased insulin resistance. Like leptin, adiponectin has an internal circadian rhythm that peaks late in the morning and decreases during nocturnal sleep [37]. In one study, 74 healthy adults were allowed 4 h in bed per night for five days (SR) after two nights of 10 h in bed (baseline) [52]. A decrease in plasma adiponectin levels after SR compared to baseline was observed among Caucasian women ($p = 0.028$), but an increase in adiponectin after SR compared to baseline was observed among African-American women ($p = 0.006$) despite similar adiponectin levels at baseline in both racial groups. No significant alterations of adiponectin were observed among men [52]. An increase in leptin under conditions of leptin resistance and a decrease in adiponectin contribute to the pathogenesis of insulin resistance and diabetes in overweight or obese individuals. Other adipokines that are altered under controlled conditions of sleep loss are TNF-α and IL-6, which are discussed in the section "Sleep and Immune System."

In conclusion, sleep loss has a deleterious effect on insulin sensitivity and overall glucose homeostasis through alterations in several key metabolic hormones, including insulin, leptin, and other adipokines.

4. Sleep and obesity

Experimental studies of SR have demonstrated an effect of short sleep on markers of positive energy balance such as decreased EE, increased feelings of hunger and appetite, increased food intake, and changes in appetite-regulating hormones. The effects of acute sleep curtailment on energy homeostasis could lead to weight gain overtime if sleep loss is extended for longer periods.

Studies have examined the effects of SR on hunger and food intake. For example, a single night of TSD or PSD (4.5 h in bed/night) leads to a significant increase in hunger [51]. Partial SR of 4 h in bed per night for two consecutive days induced an increase in hunger and appetite (+23–24%, $p < 0.01$) especially for foods with high carbohydrate content such as sweets and salty snacks ($p < 0.02$) [40]. In 14 healthy women (BMI: 20.0–36.6 kg/m^2), four nights of consecutively increasing sleep curtailment (7 h, 6 h, 6 h, and 4 h sleep/night) with an ad libitum diet had a profound effect on the total energy intake (+20%, $p < 0.05$) with no changes in EE [25]. A single night of 4 h in bed, when compared to 8 h in bed, increased the total calorie intake by 22% ($p < 0.01$) [54]. This increase in food consumption was mostly during breakfast and dinner, particularly under free-living conditions, and this was preceded by a greater sensation of hunger. A significantly higher preference for fatty foods was also noted on the day after SR, particularly at dinner. In another study, participants were restricted to two-thirds of their habitual sleep time for eight days, and their caloric consumption was measured [47]. The wake time for all participants was constant, and ad libitum food intake was allowed. Under these conditions, caloric intake increased by 677 kcal/day ($p = 0.014$) in the sleep-deprived state. Mimicking a typical workweek, 31 participants in another study were allowed to sleep for 4 h/night for five days, and a control group of six participants were allowed 10 h in bed [55]. Sleep-restricted subjects consumed more calories (+30% of daily caloric requirement, $p = 0.003$) during days with restricted bedtime compared to control subjects during corresponding days. In a study that limited time in bed to 5.5 h/night for two weeks with ad libitum access to food and snacks, no changes were observed in caloric intake during meals or EE, but calories from snacks increased ($p < 0.04$) [26]. In another study, 15 men and 15 women were restricted to 4 h in bed per night for 5 days after 9 h in bed per night for five days [56]. The diet on the first four days was controlled, while ad libitum food intake was allowed on the last day. Participants consumed more energy on day five after short sleep (2813.6 ± 593.0 kcal) than after 9 h in bed (2517.7 ± 593.0 kcal; $p = 0.023$). This effect was mostly due to an increased consumption of fat ($p = 0.01$), notably saturated fat ($p = 0.038$) after short sleep. This study also observed differences in energy intake between men and women. Women had a 15.3% increase in energy intake after short sleep relative to habitual sleep ($p = 0.07$), while men had a 9.2% increase ($p = 0.14$). The increase in the consumption of fatty foods also varied between women (+39%, $p = 0.007$) and men (+10.3%, $p = 0.32$). When comparing these studies, the different effects on food intake could be attributed to differences in the study design such as availability of types of food, snacks, and participant characteristics such as age, gender, and BMI. These studies bolster the notion that sleep loss could lead to an increased appetite, particularly for unhealthy foods, and it could promote weight gain.

Specific sleep stages may be related to hunger and appetite. Specifically, inverse associations between REM sleep duration and hunger ($p < 0.031$) and between stage 2 sleep and appetite for sweet ($p < 0.015$) and salty ($p < 0.046$) foods were detected in one study [57]. This study also observed that stage 2 sleep percentage was inversely related to energy consumed ($p < 0.024$), and the percentages of stage 2 sleep ($p < 0.005$), SWS ($p < 0.008$), and REM sleep ($p < 0.048$) were inversely related to fat intake, while SWS ($p < 0.040$) and REM sleep durations ($p < 0.050$) were inversely related to carbohydrate intake. Thus, more REM and more SWS were associated with less fat and carbohydrate intake. In another study that used PSG, a night of fragmented sleep in male subjects resulted in a decrease in REM ($p < 0.05$) and an increase in the post-dinner desire-to-eat ratings ($p < 0.05$) the following day [46]. Thus, specific sleep stages, such as REM and SWS, may be particularly important in appetite regulation.

A few studies noted differences in EE under conditions of sleep deprivation. One study of 5 h in bed per night for five days showed an increase in 24-h EE (+5%, $p < 0.01$) when compared with 9 h in bed per night for five days [41]. A parallel increase in food intake (+6%, $p < 0.05$) was observed. Post-dinner snacking increased with a greater preference for carbohydrates. This may be attributed to the increased energy required to stay awake during periods of wakefulness and ad libitum availability of food. The study participants had an overall positive energy balance with an average yet statistically insignificant increase in weight gain in the 5-h/night sleep condition. Other studies have shown a decrease in EE following sleep loss. In 14 normal-weight men in the morning after 24 h of continuous wakefulness, both resting and postprandial EE were assessed along with hunger ratings before the standardized breakfast. The resting (–5%, $p < 0.05$) and postprandial (–20%, $p < 0.001$) EE were significantly reduced after one night of TSD with a significant increase in hunger ratings, while no changes in ad libitum food intake in the afternoon were observed [33]. One night of TSD in seven healthy participants increased EE by 32% during the night of TSD and then decreased by 4% during the recovery night when compared to baseline [58]. Some studies also showed that SR decreased physical activity, which may contribute to lower EE during sleep debt. In 15 healthy men, spontaneous physical activity was recorded by accelerometer during a 15-h daytime period after two nights of restricted bedtime (4.5 h in bed per night) [49]. Sleep deprivation significantly decreased physical activity ($p = 0.008$), and

it also shifted the physical activity toward a lower intensity activity ($p < 0.05$) without any changes in energy intake. Another study of a single night of sleep restricted to 4 h in bed per night resulted in a 22% increase in caloric intake ($p < 0.01$) with a significant increase in physical activity recorded by an actimeter despite an increase in sleepiness [54]. The latter study allowed ad libitum food intake, and that may be reflected in the increased caloric intake with an increased physical activity. The data summarized above suggest that an increased food intake during insufficient sleep is a physiological adaptation to provide energy needed to sustain additional wakefulness; yet, when food is easily accessible, intake surpasses need. The increase in appetite and food intake coinciding with decreases in physical activity and EE under sleep-deprived conditions could result in overeating.

In addition to the homeostatic system, the hedonic system also plays an important role in regulating food intake. After one night of TSD, 16 healthy normal-weight men choose larger food portions (+14%, $p = 0.02$) in correspondence with an increased hunger status [59]. The portions of snacks consumed after breakfast also increased (+16%, $p = 0.02$). TSD [60] and PSD [61] lead to greater stimulation of brain regions in response to hedonic food stimuli. The overall neuronal activity measured by functional magnetic resonance imaging (fMRI) in response to food stimuli was greater after SR than after habitual sleep. The areas of the brain with an increased neuronal activity after sleep deprivation were associated with reward centers. Another study showed that sleep loss decreases activity in the appetite evaluation regions within the human frontal cortex and the insular cortex during food desirability choices combined with an increase or amplification of activity within the amygdala promoting a desire for high-calorie foods [62].

SR is also known to alter the hormonal profile of appetite-regulating hormones: anorexigenic leptin (discussed previously) and orexigenic ghrelin. While ghrelin and leptin levels remain unchanged in some studies [46,47,49,50], a few others have shown significant changes after sleep deprivation. A randomized crossover study of 16 healthy normal-weight men resulted in an increase in hunger ratings parallel to an increase in morning plasma ghrelin levels (+13%, $p = 0.04$) after one night of TSD when compared to 8 h in bed sleep opportunity [59]. A similar study with 14 men also showed elevations in morning ghrelin levels ($p < 0.02$) following the night after TSD [33]. In yet another study with nine healthy normal-weight men, the plasma ghrelin levels were 22% higher after the total standard deviation (SD) than after 7 h of sleep ($p < 0.05$) [51]. Feelings of hunger were elevated, whereas morning leptin concentrations remained unaffected. In a randomized crossover study of 12 healthy normal-weight men, two consecutive nights of PSD (4 h in bed) were compared with two consecutive nights of 10 h in bed [40]. Ghrelin levels were elevated (+28%, $p < 0.04$), along with an increase in the subjective hunger and appetite ($p < 0.01$). In another study of 27 normal-weight men and women, three nights of 4 h in bed (PSD) were compared to 9 h in bed under conditions of controlled calorie intake [48]. The total morning ghrelin increased ($p < 0.05$) in men but not in women. On the contrary, in a study of 16 healthy normal-weight adults (eight men and eight women), the 24-h ghrelin levels decreased after a night of PSD (5 h in bed) in comparison to baseline (–30%, $p < 0.001$), while the 24-h leptin levels increased (+22%, $p < 0.05$) under the same conditions [41]. Although the changes in hormone levels promoted satiety and reduced hunger, there was a significant increase in the overall food intake promoting overeating in this study. Thus, the association between ghrelin and sleep loss is not consistent, which may be due to the duration and severity of SR as well as to the complex association between food intake and regulation of this hormone.

If sleep loss increases appetite and subsequently food intake without a compensatory and equivalent increase in EE, then sleep loss could increase the risk of weight gain and obesity.

5. Sleep and CVDs

5.1. Blood pressure

Circulation of blood by the cardiovascular system is partially mediated through the regulation of BP. Baroreflex modulated by behavioral and physiological changes contributes to the control of arterial BP through the autonomous nervous system and baroreceptors. In a normotensive person, the BP circadian rhythm is characterized by a steep nocturnal/sleep decrease called BP dipping and a rise in the wake-associated elevations of BP. Non-dipping in BP is associated with CVD risk [63], and this has been associated with poor sleep [64]. An increased BP during sleep deprivation could be due to a combination of factors such as an increased sympathetic outflow to the heart or periphery, a decreased baroreflex sensitivity, and a resetting of the baroreflex set point to a higher level.

After a night of TSD in eight healthy men and women, the systolic BP (SBP) ($p = 0.002$) and diastolic BP (DBP) ($p = 0.05$) were significantly higher than after a night of regular sleep. However, the morning plasma catecholamines and heart rate remain unchanged [65]. In another study of six healthy men, TSD increased DBP ($p = 0.02$) and increased the arterial baroreflex set point by 12 mm Hg ($p < 0.05$) [66]. No changes in morning plasma catecholamines, including epinephrine and norepinephrine, dopamine, or cortisol, were recorded. These two studies attribute the effects of sleep deprivation on baroreflex to changes in peripheral and central mechanisms, but they did not observe an increase in their measures of sympathetic nervous activity. This could be due to the subjects resting in a supine position throughout the study [67]. This scenario is unlikely to occur in the real world, as it may be difficult to stay awake recumbently when sleep pressure is high.

A single night of SR in normotensive subjects from 8 h in bed to 5 h in bed was associated with an increase in the morning to mid-afternoon SBP and heart rate ($p < 0.05$) [68]. When the PSD duration was increased to 4 h in bed for six consecutive nights, a significant decrease in heart rate variability (HRV) was observed ($p < 0.02$), which indicates elevated sympathovagal balance [21]. Another study found no significant differences in SBP, DBP, or mean arterial pressure (MAP) after 36 h of continuous sleep deprivation in 18 subjects seated in an upright position while the measurements were taken, but arterial baroreflex sensitivity significantly decreased [69]. This study also observed a significant increase in the sympathetic modulation of BP variability and a reduction in the parasympathetic modulation of HRV, which suggest an increased sympathetic nervous activity. In summary, the above studies demonstrate the effects of acute sleep loss on HRV, BP, and arterial baroreflex sensitivity, and a prolonged effect of sleep loss on these cardiac measures could increase the risk of heart diseases.

5.2. Endothelial dysfunction

The endothelium, a thin layer of cells that forms the inner surface of blood vessels, controls vascular tone, inflammatory response, and coagulation [70]. Endothelial function is clinically assessed as the degree of impaired vasodilation measured in arterial and venous circulation by changes in vessel diameter [71,72]. The impairment of endothelial function is a mechanism in the development of CVD [73], and it is also an independent predictor of CVD risk [74]. In a randomized controlled study of 15 healthy lean participants (10 men and five women), PSD (two-thirds of regular sleep duration) for eight days showed a significant impairment in the arterial endothelial function (–4.4%, $p < 0.01$) when compared to the control group [75]. In another randomized crossover study of 18 healthy male participants, PSD (<5 h) for five days was compared to regular sleep (>7 h), and a significant reduction in the venous endothelial function was

observed [76]. Similarly, acute TSD also altered endothelial-dependent arterial [77] and microvascular activities [78] in healthy participants. Thus, experimental sleep loss appears to impair endothelial function.

Sleep debt impacts many of the risk factors for CVD, including increased BP, insulin resistance, obesity, unhealthy diet, and lower physical activity as suggested by the controlled sleep deprivation studies discussed previously. In addition to these risk factors, cardiometabolic diseases, which are known to be inflammation-associated pathological states, can be exacerbated by the activation of stress and immune systems during prolonged cumulative SR.

6. Potential mechanisms that relate sleep to cardiometabolic disease risk

6.1. Stress response

Several studies have shown an activation of the hypothalamic–pituitary–adrenal (HPA) stress axis in response to SR. The HPA axis is the principal mediator of the neuroendocrine stress system, and it seems to play a central role in sleep-debt-induced metabolic impairment. The activation of HPA axis initiates hypothalamic secretion of corticotropin-releasing hormone (CRH) leading to the secretion of glucocorticoids (cortisol) by the adrenal cortex. Cortisol inhibits the activation of the HPA axis through a negative feedback loop to the hypothalamus and pituitary. The circadian rhythm of the HPA axis is regulated via the suprachiasmatic nuclei (central pacemaker) in the brain. Cortisol rhythmicity is a critical regulatory component of the sleep/wake cycle. In a healthy person with sufficient nocturnal sleep, cortisol levels begin to increase toward the end of their sleep period resulting in a morning surge in cortisol levels that peak shortly after awakening. After this peak, the negative feedback mechanism begins to suppress the HPA axis, leading ultimately to a long quiescent period of low cortisol levels reaching its nadir 1–2 h around sleep onset.

TSD of >24 h [79–81] or partial deprivation of 3–4 h in bed each night for 1–3 days [34,44,82] showed no significant change in morning cortisol levels after sleep deprivation. The same trend was observed for levels of plasma adrenocorticotropic hormone (ACTH), which is produced by the pituitary in response to CRH [83]. In other studies of PSD (3–4 h in bed per night) where bedtimes were either delayed or wake times were advanced, decreased morning cortisol levels were observed in men [84,85] and women [45]. REM sleep has been shown to be positively correlated with morning cortisol levels [86] but inversely associated with afternoon cortisol levels [87], and this could partly explain the decreased morning cortisol levels after SR. It is possible that SR causes a shift in the time of morning cortisol rise and/or the prolonged wake time activates the HPA axis through the night decreasing the amplitude of morning cortisol peak. This in addition to the lack of repeated blood sampling before and after morning wake time suggests the possibility that the actual peak of cortisol may have been missed. Another possibility is that the rate at which the morning cortisol levels decrease following its peak is slower after a night of SR resulting in elevated evening cortisol levels. This was shown in the study of acute SR (3 h in bed for one night) [45] and prolonged SR (4 h in bed per night for five days) [42]. In the first study, a significant reduction in morning cortisol ($p = 0.02$) and an elevation in evening cortisol ($p = 0.04$) as a result of slower decline of daytime cortisol ($p = 0.04$) were observed after SR [42,45]. In the second study, an increase in cortisol ($p = 0.002$) but not ACTH levels was observed after five days of sleep deprivation. Cortisol was 15.5% higher after SR, but decreased during the day due to its internal rhythmicity. An increase in evening cortisol levels was a result of a slower decline of daytime cortisol. The elevation of evening cortisol was recorded in other studies of SR as well [85,88,89]. Cortisol levels also increased after sleep fragmentation when compared to non-fragmented sleep ($p < 0.05$) [46]. This difference is attributed to a lower morning rise in cortisol and a higher evening cortisol level [46]. A controlled study that simulated habitual sleep patterns of a typical week included five days of SR (workweek) followed by two days of extended sleep opportunity (weekends). No changes in the 24-h cortisol were observed when comparing SR to baseline; however, a decrease in the 24-h cortisol levels during sleep extension ($p < 0.05$) was observed [90]. In summary, cortisol levels appear to increase as a result of sleep loss, and these elevated levels could exacerbate sleep disturbances. Higher cortisol levels are associated with higher insulin resistance [91,92], and therefore these could be one mechanism through which sleep loss impairs glucose metabolism. HPA axis activation can also regulate immune cell traffic [93], and it provides another possible link between sleep and chronic-inflammation-based diseases.

An additional or alternative pathway linking sleep, stress, and glucose metabolism involves gene expression. Partial SR for 4 h in bed per night for 5–7 days activated several gene pathways, notably those that were involved in the stress response and apoptosis, as measured by gene microarray [94,95]. A similar differential gene expression was observed after a single day of prolonged wakefulness [96]. These studies elucidate the possibility that a mechanism alternative to cortisol–HPA–stress axis may be activated. Sleep deprivation showed differential expression of stress-related genes particularly those related to endoplasmic reticulum (ER) stress. ER stress can lead to protein misfoldings that activate the unfolded protein response (UPR) pathway. The cell produces heat shock proteins (HSPs) to counter the perturbations caused by ER stress, but when it fails to check the UPR stimulation, it triggers cell apoptosis. For example, the activation of the ER stress pathway in macrophages could lead to apoptosis, which is detrimental in atherosclerotic lesions.

6.2. Sleep and immune system

Chronic inflammation, a risk factor for CVD, is caused by disruption to immune system homeostasis. The immune cells follow the 24-h biological rhythm that is regulated by the central clock, and sleep is partly regulated by proinflammatory cytokines. Some of the key sleep-associated inflammatory measures include cytokines such as TNF-α, IL-1, IL-2, IL-6, and IL-10, and immune cells such as neutrophils, monocytes, and lymphocytes. The mechanism of activation and regulation of this neuroendocrine–immune axis is not entirely known. Sleep deprivation disturbs the circadian rhythm of the immune cells leading to disruptions of the physiological rhythms that could lead to metabolic and endocrine consequences. It has been shown that white blood cells (WBCs) such as neutrophils and natural killer (NK) cells peak during the light phase of the sleep/wake cycle and reach their nadir during the dark cycle, while the circulating monocytes, T and B lymphocytes peak during the early stages of nocturnal sleep and decrease during the day [97]. A circadian rhythm in cytokines has also been observed. TNF-α, IL-1, IL-2, IL-6, and IL-12 (proinflammatory) reach their peaks during the sleep phase, while IL-10 (anti-inflammatory) reaches its maximum levels proceeding wake initiation.

TSD of ≥40 h in humans alters both the cellular and cytokine patterns of immune cells. A delay in the rhythm of lymphocytes and monocytes by 3–6 h was observed in TSD compared to normal sleep. Lymphocytes, monocytes, and NK cells were significantly higher during the night of wakefulness, and they remained high the following day when compared to baseline [81,98]. Two nights of TSD increased neutrophils and leukocytes, but the levels returned to baseline after sleep recovery [99]. On the contrary, the leukocyte numbers measured in the morning after >40 h of TSD showed a decrease in NK cell counts ($p = 0.001$) and an increase in monocytes ($p = 0.017$)

[81]. PSD is a better representation of habitual sleep loss in the population than TSD. Studies that followed a PSD sleep protocol showed variable results in leukocyte count as well. An increase in WBC count ($p = 0.03$) and neutrophils ($p = 0.01$) was observed the morning after three nights of PSD to 4 h in bed per night [100]. No changes in monocytes, lymphocytes, and C-reactive protein (CRP) were reported. The increase in leukocyte numbers persisted even after a night of sleep recovery following acute partial sleep loss [101]. Further analysis showed a significant increase in neutrophil populations. Another study reported a decline in NK cell activity by 30% ($p < 0.01$) after a night of PSD (4 h/night) toward the later part of sleep [102]. This was restored after sleep recovery the following night. PSD during the early part of sleep for one night showed no changes in WBC count across baseline, PSD, and recovery nights [103]. However, granulocyte numbers significantly decreased, while lymphocyte numbers increased the morning after PSD. Recovery night restored the immune cell numbers to baseline values. Simultaneous decrease in NK cell activity ($p < 0.05$) was observed after accounting for fluctuations in NK cell count between baseline and PSD suggesting an impairment in its activity independent of decrements in the number of NK cells. An inhibitory effect of SR on NK cell count and activity was observed. In parallel, a significant reduction in T-helper cell IL-2 (an activator of NK cells) production was observed. This reduction in NK cell activity persisted even after a night of recovery sleep. When T lymphocytes collected after SR were incubated with monocytes after baseline sleep, a decrease in IL-2 production signified the effect of PSD on T-cell function. A night of TSD elevated neutrophil counts, and it altered subpopulations of circulating neutrophils the following morning [104]. An increase in immature cells and CD11b surface marker was observed. The elevation of CD11b and CD35 on neutrophils is observed in chronic inflammatory diseases like asthma. This suggests that nocturnal wakefulness may promote a proinflammatory state of circulating immune cells. The effect of sleep deprivation on WBC numbers has been mixed across studies, and this variation could be explained by differences in blood sampling frequency, time of day, and sample heterogeneity. Changes in immune cell numbers after SD, for the most part, returned to baseline levels after recovery sleep. This could suggest an alteration in their redistribution between the lymphoid organs and the peripheral tissue. This could potentially play a role if sleep activates inflammation in the peripheral tissues like the adipose tissue, and thereby modulating cellular insulin sensitivity.

Effects of sleep loss on cytokine gene and protein expression have also been recorded. The two most commonly assessed cytokines are IL-6 and TNF-α. These proinflammatory cytokines are primarily monocyte-derived, and they are elevated during SWS and reach their nadir in the morning [105]. After a night of TSD, the mean daytime IL-6 values were significantly higher ($p < 0.05$) than baseline, and a nighttime undersecretion ($p < 0.05$) was reported [106]. When compared with a night of continuous wakefulness, sleep elucidated an increase in the concentrations of soluble IL-6 receptors (sIL-6R) but not membrane-bound IL-6R, which negatively regulates IL-6 trans-signaling [107]. No changes in IL-6-producing monocytes were observed. TSD was associated with an increase in proinflammatory IL-1β [108]; however, data on IL-6 have been mixed. Continuous wakefulness resulted in the increase in IL-6 [88,109,110], the decrease in IL-6 [111], or no measurable changes [97,108]. This could in part relate to IL-6 cytokine's dual proinflammatory and anti-inflammatory roles. Continuous wakefulness of 40 h significantly increased TNF-α ($p < 0.01$) but not its receptor, TNFR1 [112]. No changes in IL-6 and CRP levels were documented.

PSD for one night (4 h in bed) showed a significant increase in nocturnal IL-6 levels compared to baseline [113]. Blood was sampled during the nocturnal sleep period. However, daytime IL-6 levels after PSD was not measured. Another study of acute partial restriction of REM sleep across four days showed no changes in cytokines IL-1β, IL-2, IL-4, IL-6, IL-10, TNF-α, and IFN-γ, but it showed a significant increase in T lymphocytes and IgA. However, another study that included a week of PSD from 8 h in bed to 6 h in bed for seven nights showed elevated levels of 24-h IL-6 ($p < 0.01$) and TNF-α ($p < 0.05$), indicating a proinflammatory shift [114]. A similar increase in proinflammatory cytokines IL-1β (137%, $p < 0.05$), IL-6 (163%, $p < 0.05$), and IL-17 (138%, $p < 0.05$) was observed in the stimulated peripheral blood mononuclear cells (PBMC) collected after five nights of PSD to 4 h in bed [115]. A possible difference in results could be attributed to limits in the detection of low concentrations of plasma cytokine levels owing to their short half-life and sensitivity of assay used for its detection. Moreover, the frequency of sampling may vary; some studies include a single morning sample, and local inflammation caused by repeated blood sampling via catheter insertion could also confound the results [116]. Stimulation of PBMC in vitro could detect a low-grade inflammation that may not be captured in plasma samples.

Recently, analysis of the transcriptome of blood cells after sleep deprivation has shed light on the differential expression of several genes, a common thread being the alteration of immune pathways. Whole genome microarrays complemented with pathway and transcription factor analysis of blood samples comparing experimentally induced PSD of 4 h in bed per night for five days to baseline and post-recovery periods revealed that 33% of the 25 most upregulated genes were related to immune function including IL-8 biosynthesis regulation ($p < 0.001$), lymphocyte activation ($p < 0.02$), and nuclear factor-kappa B (NF-kB) signaling ($p < 0.005$) besides several genes related to stress signaling [94]. Among the 25 most downregulated genes, 19 were associated with immune system including NK cell function. Cumulative SR resulted in an increase in IL-8 production along with the activation of toll-like receptors (TLRs), NF-kB, and the activator protein (AP)-1. These pathways point toward the activation of proinflammatory cascade through the innate immune system. This study also showed a shift toward Th2 cell type, while the total number of T cells remained constant. This, along with the gene expression data, suggests that acute SR activates the innate and adaptive immune systems. In addition, one night of TSD significantly decreased the number of pre-mDC-producing IL-12, a main inducer of Th1 response [117]. Compared to a night of sustained wakefulness, sleep suppressed IL-4-producing Th2 cells [118]. The Th1/Th2 balance measured by IFN-γ/IL-4-producing T cells was enhanced by SWS. During the REM phase of sleep, the Th balance reversed. However, the ratio of Th2/Th1 was lower ($p < 0.01$) during sleep than during wakefulness.

Natural regulatory T cells (nT_{reg}) are key regulators of adaptive immune responses that are regulated by IL-2 production. They are known to attenuate activated immune responses and to control systemic immune homeostasis. Following one night of TSD, nT_{regs}, known to exhibit its highest suppressive activity during sleep, was diminished [119]. To put it in context, the increase in proinflammatory cytokines during sleep will consequently lead to subsequent increases in the suppressive activity of nT_{regs} to maintain immune homeostasis. In this study, the levels of IL-2 and T-cell proliferation were sleep-independent; however, the same was not true for nT_{reg} activity. A diminished nT_{reg}-suppressive activity rhythm might be a factor in the aggravation of the immune system post sleep deprivation. PSD during early part of the sleep cycle showed an increase in monocytic IL-6 and TNF-α when compared to uninterrupted sleep [120]. An increase in messenger ribonucleic acid (mRNA) transcripts of IL-6 and TNF-α genes was also observed. Bioinformatic analysis suggested that the inflammatory response was mediated by NF-kB signaling pathway. A significant increase in IL-8 and IL-1β gene transcripts was also observed. The data from the gene array were limited by sample size ($n = 5$). In the morning after a night of PSD to 4 h in bed, the activation of NF-kB was greater than baseline or sleep recovery mornings [121]. Effects of acute SR on blood

transcriptome were accessed at time points distributed across the day following one week of <6 h or 8.5 h of sleep each night [95]. Loss of circadian rhythmicity of genes associated with peripheral circadian clocks, oxidative stress, inflammation, and metabolism was observed after acute SR. Another study collected blood samples the morning after normal sleep, after 48 h of prolonged wakefulness and after 12 h of recovery sleep to study the changes in blood transcriptome [96]. Differentially expressed genes were identified to represent NK cell signaling, ER stress, oxidative phosphorylation, and mTOR signaling, representing a shift toward inflammatory stress response.

In conclusion, sleep loss alters the immune homeostasis and tilts the scales toward proinflammation. Even if recovery sleep has been shown to restore the immune balance, chronic sleep deprivation for weeks, months, and even years could potentially activate a state of chronic low-grade inflammation that could cause metabolic distress.

7. Habitual sleep and the development of cardiometabolic disorders: what do observational studies tell us?

Experimental studies conducted in the controlled environment of the laboratory provide detailed information about physiological changes associated with SR or impairments in sleep quality. These studies, however, are brief, lasting only a few weeks. Chronic conditions like obesity, diabetes, and CVD develop over longer periods of time, and therefore we need to understand whether habitual sleep patterns are also associated with chronic disease risk. Observational, epidemiological studies can shed some light on this area. It is important to keep in mind while interpreting the results these studies that many of these studies had to rely on subjective estimates of sleep duration or sleep quality. Self-reported sleep duration has been only moderately associated with objectively estimated sleep duration [122,123]. Nonetheless, numerous studies have observed consistent associations using subjective sleep assessments that support the findings of the laboratory studies; sleep deficiency appears to be associated with cardiometabolic disease.

8. Habitual sleep and obesity or BMI

A multitude of observational studies have examined the association between sleep and obesity or BMI. Over 60 published articles have reported significant cross-sectional associations between short sleep duration (generally <6 h/night) and an increased prevalence of obesity or higher BMI (see Refs. [124–126] for reviews). These associations have been observed in both adults and children and from a variety of countries, including the USA and countries in Europe and Asia. Many of these studies also observed a higher mean BMI associated with longer sleep durations (generally >8 h/night), indicating a U-shaped association between self-reported sleep duration and BMI where both short and long sleepers have a higher average BMI. In addition to sleep duration, worse subjective sleep quality has also been associated with higher BMI [127,128]. One meta-analyses of data from many of these cross-sectional studies found that short sleep duration (<5 h/night) significantly predicted prevalent obesity in adults [pooled odds ratio (OR) was 1.55, 95% confidence interval (CI): 1.43–1.68] [129]. Thus, most published studies have reported a significant cross-sectional association between inadequate sleep (too short or too long) and higher BMI or the presence of obesity. One important limitation of these studies is that sleep was self-reported. A few studies have examined objectively estimated sleep duration. For example, a study in the USA that collected at least three days of wrist actigraphy in over 600 middle-aged adults found that a shorter average sleep duration was associated with a higher average BMI in cross-sectional analysis [130]. A study in Brazil also collected actigraphy data for at least three days and recorded one night of PSG in 1074 adults, and the study found that obese and overweight subjects had shorter sleep durations based on actigraphy and PSG, and less SWS and REM sleep, although these comparisons were unadjusted [131]. A study of over 2700 older men (≥65 years) in the USA recorded one night of PSG, and found that those with the lowest percentage of SWS had the highest mean BMI and the largest mean waist circumference, but they did not find an association between SWS and percent body fat [132]. Thus, there is some evidence for a cross-sectional association between objectively characterized sleep and body size. Of course, another important limitation of these studies is that they are cross-sectional, and therefore causal direction cannot be inferred. Indeed, the association between sleep and BMI could be bidirectional. It is well known that obesity is a major risk factor for OSA, a sleep disorder that is associated with an increased risk of cardiometabolic diseases (see Refs. [20] and [133] for reviews on OSA).

Some prospective studies examined sleep and change in body size measures in adults (see Table 1 for details on these studies). Four of these studies did not find a statistically significant association between sleep duration and change in body size [130,137,142,144]. Some studies reported a significant association between shorter sleep and weight gain or an increased BMI among adult men and/or women [134–136,138–140,143,145,147], and sleep disturbances and increased weight gain in women [141]. Two studies observed associations between longer sleep durations and an increased weight gain [134,139], and in a weight loss study that compared an exercise program to a stretching program, women who slept less at follow-up lost more weight [146]. In a US study of African-American and Hispanic adults that measured the height and weight as well as the subcutaneous and visceral fat, participants aged 18–39 years who reported sleeping ≤5 h/night experienced a larger increase in BMI, visceral fat, and subcutaneous fat over five years compared to those aged 18–39 years who reported sleeping 6–7 h/night [134]. In this same study, sleep duration was not associated with a change in BMI or body fat among those aged ≥40 years [134]. A few studies reported sex differences in these associations, but which sex demonstrated a significant association was not consistent. For example, one study found an effect in men but not in women [139], while another study saw an effect in women but not in men [141]. Some, but not all, prospective studies found longitudinal associations between short sleep duration and increases in body weight, and some found long sleep associated with a greater weight gain or a lesser weight loss. In addition, some of these studies suggest that there may be important age or gender differences, which require further examination.

9. Habitual sleep, appetite regulation, and dietary behavior

Quite a few observational studies have examined the relationship between habitual sleep characteristics and levels of hormones involved in appetite regulation and/or dietary behavior. For example, in cross-sectional analysis of data from 740 men and women in the Quebec Family Study, leptin levels in those sleeping 5–6 h/night were approximately 15–17% lower than predicted based on body fat alone [148]. The Wisconsin Sleep Cohort Study, which enrolled state employees aged 30–60 years, found that the average habitual sleep duration was positively associated with leptin levels independently of BMI ($\beta = 0.11$, $p = 0.01$) [149]. The Women's Health Initiative prospective Observational Study (WHI-OS), which enrolled postmenopausal women, found that women reporting ≤6 h of sleep per night had lower fasting leptin concentrations than those reporting ≥8 h of sleep per night adjusting for age, race, total body fat mass, and smoking status [150]. A fourth study found the opposite association; shorter sleep was associated with higher leptin levels. Specifically, this study examined fasting leptin levels and self-reported sleep duration in a sample of 254 Taiwanese adults, and the study found that women sleeping <6.5 h/night had an increased

Table 1
Summary of prospective studies that examined the association between habitual sleep and changes in body size.

Authors	Follow-up period	Method of sleep assessment	Sample	Results	Country
Adults					
Hairston et al. Sleep 2010 [134]	5 years	Self-report	Age: 18–81 years $N = 1107$ (IRAS Family Study);	Significant associations were observed in subjects aged 18 to <40 years but not ≥40 years. These associations found that compared to those reporting sleeping 6–7 h/night, those sleeping ≤5 h/night, and those reporting sleeping ≥8 h/night had a larger increase in BMI (LS mean = 2.7 kg/m^2 for ≤5 h, 0.91 kg/m^2 for 6–7 h, and 1.81 kg/m^2 for ≥8 h), a larger increase in subcutaneous fat measured by CT (LS mean = 68.21 cm^2 for ≤5 h, 26.93 cm^2 for 6–7 h, and 47.54 cm^2 for ≥8 h), and a larger increase in the visceral fat measured by CT (LS mean = 11.89 cm^2 for ≤5 h, 1.46 cm^2 for 6–7 h, and 5.64 cm^2 for ≥8 h) adjusting for age, sex, race, and baseline fat.	USA
Hasler et al., 2004 [135]	21 years	Self-report	Age: 19 years at baseline, $n = 496$ (Zurich Cohort Study)	Longitudinal analysis resulted in an odds ratio of 0.50 for sleep duration (in hours) predicting obesity.	Switzerland
Chaput et al., 2008 [136]	6 years	Self-report	Age: 21–64 years, $n = 276$ men and women (Quebec Family Study).	In fully adjusted model, short sleepers gained more weight: 5–6 h/night gained 1.84 (95% CI: 1.08, 2.61) kg compared to those sleeping 7–8 h/night. Long sleepers (9–10 h/night) did not differ from 7–8-h sleepers.	Canada
Gangwisch et al., 2005 [137]	8–10 years	Self-report	Age: 32–86 years, $n = 9588$ men and women (NHANES).	No significant prospective association	USA
Gunderson et al [138].	6 months	Self-report	Age: mean 33.0 (SD 4.7), $n = 940$ postpartum women.	Women who slept ≤5 h/night at 6 months postpartum had increased odds for a substantial weight retention (≥5 kg above pre-pregnancy weight) at follow-up compared to women sleeping 7 h/night (OR: 3.13; 95% CI: 1.42, 6.94).	USA
Lauderdale et al., 2009 [130]	5 years	Actigraphy	Age: 35–50 years at baseline, $n = 612$ men and women (CARDIA).	No significant prospective association	USA
Watanabe et al., 2010 [139]	1 year	Self-report	Age: mean 39.8 years, $N = 34{,}852$ men and women.	Compared to men sleeping 7 to <8 h/night, men who slept <5 h/night, 5 to <6 h/night, or ≥9 h/night had a larger increase in BMI (β: < 5: 0.016; 95% CI: 0.003, 0.146); (5 to <6: 0.013; 95% CI: 0.001, 0.061); (≥9: 0.018, 95% CI: 0.079, 0.34). No significant associations were observed in women.	Japan
Patel et al., 2006 [140]	16 years	Self-report	Age: 39–65 years, $n = 68{,}183$ women (Nurse's Health Study).	Women who slept ≤5 h/night gained 1.14 kg (95% CI: 0.49, 1.79), and those sleeping 6 h/night gained 0.71 kg (95% CI: 0.41, 1.00) more than those sleeping 7 h/night adjusting for age and baseline BMI.	USA
Lyytikainen et al [141].	5–7 years	Self-report	Age: 40–60 years, $N = 7022$ male and female municipal employees (Helsinki Health Study).	After adjusting for age, women with frequent trouble falling asleep (OR: 1.65; 95% CI: 1.22, 2.22), women frequently waking up several times per night (OR: 1.49; 95% CI: 1.22, 1.81), or women reporting trouble staying asleep (OR: 1.41; 95% CI: 1.13, 1.75) were more likely to have gained 5 kg or more than women without such sleep problems. No significant associations were observed in men.	Finland
Stranges, AJE 2008 [142]	5–6 years	Self-report	Age: 44–65 years, $n = 10{,}308$ men and women (Whitehall Study).	No significant prospective association	UK
Nishiura et al., 2010 [143]	4 years	Self-report	Age: mean 47.8 years, $N = 3803$ male white-collar workers.	Men sleeping <5 h/night, as compared to those sleeping 7 h/night, increased their BMI by 0.15 kg/m^2 more over 4 years (95% CI: 0.03, 0.27), after adjustment for age, baseline BMI, lifestyle behavior, and medication.	Japan
Appelhans et al [144].	Average of 4.6 years	Actigraphy	Age: 48–59 years, $N = 310$ women (Study of Women's Health Across the Nation).	No significant prospective association.	USA
Xiao [145]	Average 7.5 years	Self-report	Age: 51–72 years, $n = 83{,}377$ men and women (National Institutes of Health – AARP Diet and Health Study).	Compared with 7–8 h of sleep, shorter sleep (<5 h or 5–6 h) was associated with a greater weight gain (in kilograms; men: for <5 h, β = 0.66, 95% CI: 0.19, 1.13, and for 5–6 h, β = 0.12, 95% CI: −0.02, 0.26; women: for <5 h, β = 0.43, 95% CI: 0.00, 0.86, and for 5–6 h, β = 0.23, 95% CI: 0.08, 0.37). Adjusting for mediators (physical activity level, overall time spent sitting, total caloric intake, and the intake of fruits and vegetables, whole grains, and total fat) diminished associations.	USA
Littman et al. 2006 [146]	1 year	Self-report	Age: 50–75 years, $n = 173$ overweight, sedentary postmenopausal women randomized to an exercise or stretching weight loss program.	Exercisers who slept less at follow-up than at baseline lost more weight than those whose sleep stayed the same or those who slept more. Stretchers who napped less at follow-up gained more weight, and both exercisers and stretchers whose trouble falling asleep increased gained more weight.	USA
Lopez-Garcia AJCN 2008 [147]	2 years	Self-report	Age: ≥ 60 years $n = 3235$ men and women.	In fully adjusted model, the association between sleep duration and odds of gaining ≥5 kg over the follow-up period was significant in women only: ≤ 5 h/night: 3.41 (1.34–8.69); 6 h/night: not significant; 7 h/night referent; 8 h/night: 3.03 (1.29–7.12); 9 h/night 3.77 (1.55–9.17); ≥10 h/night not significant.	Spain

odds of having hyperleptinemia, defined as leptin levels in the upper quartile (OR: 2.15; 95% CI: 0.99, 4.78, $p = 0.055$) compared to women who slept at least 6.5 h/night [151], although statistical significance was not quite reached. In men, there was a similar but not statistically significant association (OR: 4.98; 95% CI: 0.80–42.4, $p = 0.096$). Although most of these epidemiological studies are consistent with the laboratory studies, other studies did not observe a significant association between self-reported sleep duration and leptin levels. Women in the Nurse's Health Study returned a blood sample through the mail for the assessment of leptin, and no association was found between self-reported sleep duration and leptin levels [152]. A study among 173 overweight, sedentary postmenopausal women aged 50–74 years also did not observe a significant cross-sectional association between self-reported sleep duration and fasting leptin or total ghrelin levels [146]. Finally, in a sleep extension study, 80 obese men and premenopausal women aged 18–50 years who were habitual short sleepers, no association was observed between average sleep duration or sleep efficiency from two weeks of wrist actigraphy recordings and fasting levels of leptin [153]. Two studies looked at appetite hormones in relation to sleep measured via PSG. The Wisconsin Sleep Cohort Study found that the total sleep time from one night of PSG was inversely associated with ghrelin levels ($\beta = -0.69$, $p = 0.008$) but was not associated with leptin levels [149]. The Cleveland Family Study in adults (average age was 45 years) recorded one night of PSG with bedtimes at 23:00 and wake times at 6:45 for everyone, and a fasting blood sample was collected the following morning. They found that shorter TST and less REM sleep were associated with higher leptin levels, while SWS was not associated with leptin [154]. Because time in bed was the same for all individuals, it raises the question of how the measurements from one night of PSG are impacted by varying degrees of sleep debt within individuals. In other words, more REM sleep on the PSG could represent a REM rebound due to habitual SR, but habitual sleep duration was not reported or included in the analyses. The discrepant results concerning the association between sleep and leptin among these studies may be due to unmeasured confounding, differences in the association between sleep and appetite regulation in obese versus lean adults, or to methodological issues such as self-reported sleep duration or sample collection.

Recently, many observational studies that have examined cross-sectional associations between habitual sleep duration, sleep quality, or sleep problems and dietary intake or dietary patterns have been published (see Table 2 for details about these studies).

Among studies that relied on self-reported measures of sleep duration, shorter sleep durations were associated with greater total energy intake [150,158,159,164,166,174], greater fat intake [163,164], greater carbohydrate intake, and greater alcohol intake [159,160]. However, one study found lower caloric intake among people with insomnia [165], and two studies did not observe significant associations between habitual sleep and dietary intake [167,168]. Several studies also found an association with optimal sleep (not short sleepers and/or better sleep quality) and healthier eating habits, such as eating breakfast, eating more regular meals, snacking less, eating at home more often, and a greater variety of foods in the diet [156,157,162,169–172]. Sleep disturbances among undergraduate students in Portugal were associated with more bulimic behavior and more social pressure to eat [155]. A study of 459 postmenopausal women used one week of wrist actigraphy to estimate sleep duration, and found that sleep duration was negatively associated with the amount of fat and calories consumed even after adjusting for BMI and physical activity [173]. These data indicate that at a specific level of BMI and physical activity, a woman who sleeps less consumes more calories, particularly from fat, on average than a woman sleeping more does. One study of adult women and men aged 19–45 years examined diet and sleep architecture using PSG, and found that a greater nocturnal (dinner plus any late night snacks) intake of fat was associated with lower sleep efficiency, greater REM latency, higher percentage of Stage 2 NREM, lower percentage of REM, and greater wake after sleep onset (WASO) after adjustment for age, gender, and socioeconomic status [161]. These results indicate that dietary intake can impact sleep, and therefore the sleep–diet relationship may be bidirectional.

Differences in dietary intake could partly explain the association between short sleep duration and weight gain as dietary intake is associated with weight gain [175]. Recently, a meta-analysis compared the effect of alcohol, sleep deprivation, and TV watching on food intake using 23 controlled, laboratory studies in healthy participants, and found that the effect was greatest for alcohol (Cohen's $d = 1.03$; 95% CI: 0.66, 1.4; $P = 0.001$) followed by sleep deprivation (Cohen's $d = 0.49$; 95% CI: 0.11, 0.88; $P = 0.05$) [176]. Thus, habitual sleep loss could result in significant weight gain, and one pathway though which this could happen is increasing energy intake.

10. Habitual sleep and diabetes risk

Several observational studies have reported cross-sectional associations between inadequate sleep and greater prevalence of diabetes or impaired glucose tolerance (see Ref. [177] for another recent review). Sleep quality is generally worse based on both subjective and objective estimates in people with T2DM [178]. Furthermore, among persons with T2DM, poorer glycemic control is associated with worse sleep quality and increased sleep disordered breathing [179–181]. Indeed, OSA seems to be highly prevalent among patients with type 2 diabetes, with estimates ranging from 58% to 86% [20]. Although the results of these studies indicate that inadequate sleep is associated with diabetes, the direction of causality cannot be determined. Insufficient sleep may increase the risk of developing diabetes, as the laboratory studies suggest, or, conversely, having diabetes could impair sleep quality. Still, if inadequate sleep can impair glucose control among patients with T2DM, then we need to better understand how to improve sleep in this population in order to identify whether such interventions can help to improve disease management and to reduce the risk of complications.

A recent cross-sectional study in China simultaneously examined self-reported sleep duration (<6, 6–8, and >8 h) and subjective sleep quality (poor vs. good) in relation to the presence of impaired fasting glucose (IFG) [182]. People with IFG are considered to have "pre-diabetes", and therefore they are at a risk of developing T2DM. Compared to good sleepers who sleep 6–8 h, all other groups had increased odds of having IFG. Poor sleepers who sleep <6 h had the highest odds (OR: 6.37; 95% CI: 4.66–8.67) and good sleepers who sleep >8 h had the second highest odds of IFG (OR: 3.17; 95% CI: 2.29–4.41) [182]. These results highlight the importance of both sleep duration and sleep quality, and underscore the need to understand better the health risks associated with long sleep.

Prospective studies provide stronger evidence for a causal link between inadequate sleep and the development of cardiometabolic diseases. Many studies reported increased odds of diabetes associated with short sleep duration (≤5 h and/or ≤6 h), and some observed a U-shaped association [183–187]. Furthermore, impaired sleep quality, such as difficulty initiating or maintaining sleep, has been associated with increased odds of developing diabetes in multiple studies [188–193]. Note that one study did not find a significant association between sleep and incident diabetes [194], while one study observed a significant association in men only [191]. A meta-analysis of 10 prospective studies examined the association between the incidence of diabetes and either short self-reported sleep duration, long self-reported sleep duration, or subjective sleep disturbances [195]. The estimated pooled OR for short sleep was 1.28 (95% CI: 1.03–1.6); however, there was a significant gender

Table 2
Summary of studies that examined the association between habitual sleep and dietary patterns or behavior.

Study	*n*	Age range or mean (SD) and sex	Sleep measure	Dietary measure	Result summary
Soares et al., 2011 [155]	870	Undergraduate students aged 17–25 years in Portugal	Two questions addressing difficulties initiating sleep (DIS) and difficulties maintaining sleep (DMS). A sleep disturbance index (SDI) was the sum of DIS and DMS scores	Eating Attitudes Test – 40 used to measure: (1) diet concerns (DCs), (2) bulimic behavior (BB), and (3) social pressure to eat (SPE)	In the total sample and in males, BB and SPE dimensions were significantly associated with sleep difficulties (DIS, DMS, and SDI). In females, BB was significantly associated with sleep difficulties (SDI, DIS; $P < 0.01$).
Nakade et al., 2009 [156]	800	Female students aged 18–29 years in Japan	Healthy sleep habits based on self-reported sleep quality, sleep hours, regularity of sleep–wake cycles, and sleep satisfaction	Excert from Examination Eating Habits to assess drinking, smoking, and regularity of meals	Participants with healthier sleep habits were significantly more likely to eat breakfast regularly, and they were less likely to eat "midnight snacks"
Hicks et al., 1986 [157]	31	College students in the USA (age not specified)	Self-report	Meal record for 1 day	Short sleepers (average 6 h/night) were more likely to deviate from the normal three meals/day pattern, and they showed a tendency to eat more small meals or snacks than longer sleepers (≥8 h/night).
Haghighatdoost et al., 2012 [158]	410	Female students aged 18–28 years in Iran	Sleep duration based on physical activity record for 24 h during a weekday and a weekend day	Food frequency questionnaire	Compared to subjects in the highest tertile of sleep duration (>8 h/day), subjects in the lowest tertile of sleep duration (<6 h/day) had a higher intake of energy (2406 ± 825 vs. 2092 ± 700 kcal/day; $P < 0.01$). The mean percentages of protein and carbohydrate intakes were 14% and 58% in the lowest tertile and 19% and 51.6% in the highest tertile, respectively ($P < 0.05$). The intake of fruits, whole grains, beans, niacin, vitamin C, and vitamin B12 was lower among those in the lowest tertile compared to the highest tertile. Note that these differences are adjusted only for total energy intake.
Galli et al., 2013 [159]	118	Obese men and premenopausal women aged 18–50 years who are short sleepers and are enrolled in a sleep extension study in the USA	14 days of wrist actigraphy, and sleep apnea was assessed using a portable screening device	A 3-day food diary	After adjustment for apnea severity, age, gender, BMI, and race/ethnicity, a 30-min shorter sleep duration was associated with 83-kcal greater energy intake on average. RDI was inversely related to carbohydrate intake, and it was positively associated with fat intake. Sleep duration was also inversely associated with alcohol intake after adjusting for age, gender, and BMI or ethnicity/race.
Chaput et al., 2012 [160]	703	Quebec Family Study: men and women aged 18–64 years in Canada	Self-report	A 3-day food record	After adjusting for covariates, short sleep duration (≤7 h/night) was associated with an increase in the odds of exceeding the recommended weekly alcohol intake of 14 drinks for men and seven drinks for women compared to those sleeping between 7 and 8 h (OR: 1.87, 95% CI: 1.03– 3.54, both sexes combined). Long sleepers (≥9 h/night) did not differ from 7 to 8 h sleepers.
Crispim et al., 2011 [161]	52	Women and men aged 19–45 years in Brazil	Nocturnal polysomnography (PSG)	A 3-day food diary immediately prior to the PSG	A greater nocturnal intake (dinner plus any late night snacks) of fat was associated with lower sleep efficiency, greater REM latency, higher percentage of N2, lower percentage of REM, and greater WASO after adjustment for age, gender, and socioeconomic status
Imaki et al. 2002 [162]	12,333	Male employees aged 20–59 years at a chemical plant in Japan	Self-report with three response options: < 6; 6.1–8.9; ≥ 9 h	Dietary habits assessed with seven items: (1) the number of meals per day (one, three times; two, twice; three, irregular); (2) snack between meals (yes or no); (3) eating out (frequently or rarely); (4) daily diet pattern (regular or irregular); (5) intake of vegetables in the diet (ample or none); (6) seasoning of food (strongly salty, conventional or lightly seasoned); (7) oily food items (preferred or not desired much).	Short sleepers (≤6 h/night) were more likely to eat meals irregularly, snack between meals, and eat outside the home than those reporting sleeping between 6.1 and 8.9 h. (Long sleepers were not analyzed because the prevalence was only 1%.)

(*continued on next page*)

Table 2 (*continued*)

Study	*n*	Age range or mean (SD) and sex	Sleep measure	Dietary measure	Result summary
Shi et al., 2008 [163]	2828	Adults ≥20 years old in China	Self-report	3-day food records.	In adjusted models, subjects who slept for <7 h/night had significantly higher percentage of energy intake from fat (1.5% more per day) and significantly lower percentage from carbohydrates (1.8% per day) than those who slept for 7–9 h/day.
Parvaneh et al., 2014 [164]	226	Men and women aged 20–55 years old in Iran	Sleep Habit Heart Questionnaire	Three days of a 24-h dietary recall	Sleep duration showed significant but weak positive correlations with energy intake ($r = 0.174$), carbohydrate intake ($r = 0.154$), and fat intake ($r = 0.141$).
Zadeh et al., 2011 [165]	87	Men and women aged 21–45 years in India	Insomnia Screening Index.	A 3-day food diary	The presence of insomnia was associated with lower caloric intake, lower protein intake, and lower carbohydrate intake compared to normal sleepers.
Patterson et al., 2014 [166]	223	UCLA Energetics Study: African-American and non-Hispanic whites aged 21–69 years in the USA	Self-report	Energy intake = total energy expenditure from doubly labeled water technique	Compared to ≤6 h/day, participants who reported longer sleep consumed fewer total kilocalories per day (–50 kcal/day for 7 h, –41 kcal/day for 8 h, and 187 kcal/day for ≥9 h.
Rontoyanni et al., 2007 [167]	30	Women 30–60 years of age in Greece	Sleep Habits Questionnaire and a 7-day sleep diary	Two 24-h dietary recall	A weak positive association between sleep duration and saturated fat ($r = 0.392$, $P < 0.05$). No significant association between sleep duration and energy intake or a preference for fat or carbohydrate consumption.
Hart et al., 2012 [168]	318	Women in the USA in a clinical weight loss trial who were ≥30 years old, overweight, or obese, and they reported ≥10 urinary incontinent episodes per week	PSQI for time in bed (TIB)	Block Food Frequency Questionnaire	TIB was not associated with any of the dietary composition variables measured on the Block FFQ.
Kim et al., 2011 [169]	27,983	Sisters of women who had breast cancer. Ages 35–74 years.	Self-report	Assessed meal and snack frequencies (days/weeks) via self-report modified Block FFQ	Tendency for eating during conventional hours (from breakfast to dinner) increased with increasing sleep duration up to 7–7.9 h. Dominance of snacking over meals decreased with increasing sleep duration. Women with a long daily sleep duration (≥10 h) were similar to those with less than normal sleep duration (<6 h).
Nishiura et al. 2010 [170]	2632	Male employees aged 40–59 years with a BMI <25 kg/m^2 at a gas company in Japan	Self-report	Dietary patterns: preference for fatty food, skipping breakfast, snacking, and eating out (all yes or no responses)	In unadjusted analysis, the prevalence of a preference for fatty foods, skipping breakfast, and eating out was highest among the shortest sleepers (<6 h).
Grandner et al [171,172].	5587 – sleep duration analysis 4552 – sleep problem analysis	NHANES 2007–2008: men and women with a mean age of 46 years in the USA	Self-reported sleep duration and sleep problems.	A 24-h recall, guided by a structured interview	In adjusted models, the total energy intake did not differ by sleep duration but the number of foods in the diet was significantly lower in the very short (<5 h), short (5–6 h), and long sleep (≥9 h) duration groups compared to those reporting sleeping 7–8 h/night. Very short sleepers also reported eating fewer carbohydrates and less protein than those reporting sleeping 7–8 h/night. Daytime sleepiness was associated with an increased total calorie intake. Difficulty maintaining sleep was associated with less variety in diet. Sleep duration groups and the four sleep difficulty groups were associated with differences in micronutrient intake.
Grandner et al. 2010 [173]	459	Women's Health Initiative: postmenopausal women aged 50–81 years in the USA	7 days of wrist actigraphy	Food Frequency Questionnaire (FFQ)	Nocturnal sleep duration was significantly negatively correlated with the amount of fat ($r = –0.185$, $p = 0.0004$) and calories ($r = –0.162$, $p = 0.002$) consumed after adjusting for age, education, income, exercise, BMI, and total dietary grams
Stern et al., 2014 [150]	769	Women's Health Initiative: postmenopausal women with a median age of 63 years in the USA	Self-report Insomnia Scale	Food Frequency Questionnaire	Women who reported sleeping ≤6 h/night demonstrated a 1% increase in the mean dietary energy intake relative to women who reported sleeping 7 h/night. WHI insomnia scale was not significantly associated with diet quality, dietary energy intake, or the macronutrient composition of dietary energy intake.

difference. The OR was 2.07 (95% CI: 1.16–3.72) for men and 1.07 (95% CI: 0.90–1.28) for women, indicating a stronger association among men. The pooled OR for long sleep was 1.48 (95% CI: 1.13–1.96), indicating that overall there is a significant U-shaped association between self-reported sleep duration and incident diabetes. Finally, both difficulty initiating sleep (pooled OR: 1.57; 95% CI: 1.25–1.97) and difficulty maintaining sleep (pooled OR: 1.84; 95% CI: 1.39–2.43) significantly predicted incident diabetes. Another meta-analysis examined the association between sleep duration and the metabolic syndrome, which is characterized by a combination of abdominal adiposity, dyslipidemia, elevated glucose, and elevated BP [196]. The authors identified 12 cross-sectional studies and three cohort studies, and they estimated for short sleep durations (<5–6 h/night) an OR of 1.27 (95% CI: 1.10, 1.48) in the cross-sectional studies and 1.62 (95% CI: 0.74, 3.55) in the three cohort studies. For long sleep durations (>8–10 h/night), the OR was 1.23 (95% CI: 1.02, 1.49) in the cross-sectional studies and 1.62 (95% CI: 0.86, 3.04) in the cohort studies. Thus, the prospective associations were not significant in this meta-analysis of three studies. Overall, prospective epidemiological studies suggest that subjective short or long sleep duration and poor sleep quality may predict the development of diabetes. Whether or not strategies to improve sleep can help reduce the risk of diabetes or improve glucose control in diabetes patients has yet to be determined.

11. Habitual sleep and CVD risk

Self-reported short sleep and subjectively poor sleep quality have been associated with a higher average BP or a higher prevalence of hypertension in cross-sectional studies [197–203]. Some of these studies also observed a higher BP among long sleepers [198,203], and two of these studies observed a significant association only in women [200,202]. Analysis of the National Health and Nutrition Examination Survey (NHANES) did find that self-reported short sleep duration was associated with both self-reported chronic disease (eg, obesity and hypertension) and objectively measured markers of chronic disease (eg, obesity and hyperlipidemia) [204]. Two studies among elderly adults found no association between habitual sleep duration and BP [205,206], which suggests that associations between sleep and BP may be modified by age. In one study that recorded wrist actigraphy among adults aged 35–50 years, shorter sleep duration and lower sleep quality were both associated with higher BP [207]. A small study among 23 healthy, young adults aged 18–28 years examined sleep efficiency based on wrist actigraphy in relation to nocturnal BP dipping, which is a phenomenon associated with a lower CVD risk. They found that those with an average sleep efficiency <85% had a blunted nocturnal dip in SBP compared to those with a sleep efficiency ≥85% [208]. Thus, cross-sectional studies generally support a relationship between inadequate sleep and higher mean BP, but the causal direction cannot be determined, and the strength of these associations may be modified by gender or age.

Several prospective epidemiological studies have examined various cardiovascular outcomes in relation to habitual sleep. Analysis of the NHANES data in the USA found that short sleepers (≤5 h/night) had increased odds of incident hypertension over 8–10 years (OR: 1.32; 95% CI: 1.02–1.71) compared to those reporting sleeping 7–8 h/night after adjusting for numerous potential confounders [209]. In the study of adults aged 35–50 years that estimated sleep duration using actigraphy, shorter sleep was significantly associated with incident hypertension over five years (OR: 0.72; 95% CI: 0.55, 0.95) [207] and incident coronary artery calcification (OR: 0.67 per h; $p = 0.011$; 95% CI: 0.49–0.91), which is a predictor of the development of coronary heart disease [210]. The Nurses' Health Study found a significantly increased risk of incident coronary heart disease over 10 years associated with a short (≤5 h/night) self-reported sleep duration (risk ratio: 1.45; 95% CI: 1.1–1.92) and a long (≥9 h/night) self-reported sleep duration (risk ratio: 1.38; 95% CI: 1.03–1.86) compared to those sleeping 8 h/night [211]. A few studies have examined CVD mortality in relation to self-reported sleep duration, but none found a significant association in fully adjusted models [212–214]. Poor subjective sleep quality was also associated with increased coronary artery disease mortality in men (RR: 3.1; 95% CI: 1.5–6.3) [212]. A study in the USA of >3400 men and women ≥35 years of age reported a significant increase of CVD events in those who complained of insomnia every day compared to those without any insomnia complaint (RR: 1.78; 95% CI: 1.03–3.08) [214]. Overall, there is some evidence that inadequate sleep is associated with CVD and hypertension, but more rigorous studies are required to fully understand whether inadequate sleep actually leads to CVD.

12. Summary

Experimental studies have found associations between SR or sleep fragmentation and impairments in glucose metabolism, alterations in appetite regulation, and increased inflammation, all of which would increase the risk of developing cardiometabolic disease. Observational studies have reported many cross-sectional associations between self-reported short and/or long sleep durations and prevalent obesity, diabetes, and hypertension. Fewer prospective studies exist, and results are often mixed. Some demonstrated an association between sleep duration and weight gain or incident cardiometabolic disease.

13. Future directions

Future research should focus on novel interventions to modify sleep. These studies could explicitly test whether extending sleep duration in short sleepers, restricting time in bed in long sleepers, improving sleep quality, or treating sleep disorders such as OSA can lead to improvements in cardiometabolic health. Thus, these interventions could be behavioral (changing bed times) or therapeutic [continuous positive airway pressure (CPAP) for OSA; medications for insomnia], depending on the specific sleep problem. Finally, studies should investigate whether sleep deficiency partially mediates cardiometabolic disease disparities between racial/ethnic and socioeconomic groups. If so, these novel interventions and the therapeutics to improve sleep could help to reduce the associated health disparities, but they must be explicitly tested in the disadvantaged groups.

14. Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2015.02.535.

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