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Sleep duration and cardiometabolic risk: A review of the epidemiologic evidence

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Laboratory studies have found that short-term sleep restriction is associated with impairments in glucose metabolism, appetite regulation and blood pressure regulation. This chapter reviews the epidemiologic evidence for an association between habitual sleep duration and quality and risk of cardiometabolic diseases including obesity, diabetes and hypertension. Multiple studies observed a cross-sectional association between short sleep duration (generally <6 h per night) and increased body mass index or obesity, prevalent diabetes and prevalent hypertension. Many studies also reported an association between self-reported long sleep duration (generally >8 h per night) and cardiometabolic disease. There have been a few prospective studies and several, but not all, have found an association between short sleep and incident diabetes, hypertension and markers of cardiovascular disease. Future prospective epidemiologic studies need to include objective measures of sleep, and intervention studies are needed in order to establish a causal link between impaired or insufficient sleep and cardiometabolic disease risk.

Introduction

Cardiometabolic risk has been defined as a cluster of metabolic and cardiovascular abnormalities, including abdominal obesity, insulin resistance, hypertension, dyslipidemia and atherosclerosis, that predispose individuals to cardiovascular disease (CVD) and type 2 diabetes.[1,2] CVD, type 2 diabetes and

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overweight/obesity are closely linked conditions. 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 and insulin resistance, are at increased risk of developing type 2 diabetes and CVD.[3] The prevalence and impact of these cardiometabolic diseases is enormous. The World Health Organization estimates that worldwide in 2004–2005 approximately 1.6 billion adults were overweight, 400 million were obese, over 190 million people had diabetes and 17.1 million people died of cardiovascular disease.[4] In addition to increased mortality risk, CVD, diabetes, and obesity are associated with reduced quality of life and an increased economic burden on both the individual and on society.[5–8] Thus, an important goal of global public health is to reduce cardiometabolic risk.

Efforts to reduce the burden of these diseases require a better understanding of the mechanisms underlying increased cardiometabolic risk. Poor diet and limited physical activity certainly play an important role, but an additional possible explanation for the epidemic of cardiometabolic diseases is reduced sleep duration and quality. There is some evidence in the US that the number of adults obtaining insufficient sleep has increased over the same time period that the prevalence of obesity and diabetes has increased.[9–13] For example, a report from the National Health Interview Survey indicated the percentage of adults report sleeping 6 h or less increased by approximately 5–6% between 1985 and 2004.[14] Sleep loss may be the result of either a voluntary restriction of time spent in bed or as a result of a sleep disorder, such as insomnia and obstructive sleep apnea (OSA). Unfortunately, most epidemiologic studies cannot distinguish between voluntary sleep curtailment and sleep loss due to a pathological condition. Section 4 will discuss the impact of sleep disorders such as OSA on metabolism. Laboratory studies involving experimental restriction of time in bed provided the initial evidence that sleep loss can increase cardiometabolic risk and other papers in this issue will discuss these laboratory studies (see Section 1). One limitation of laboratory studies, however, is that they are short-term, lasting a few weeks at most. This raises the question of whether the associations observed in the laboratory persist in the real world when sleep loss is chronic. Epidemiologic studies provide some insight into the associations between sleep and health outside of the laboratory. This paper will review the epidemiologic evidence linking sleep duration and/or quality to cardiometabolic risk, including the relationship between sleep and body mass index (BMI) or obesity, appetite regulation, type 2 diabetes, hypertension and cardiovascular disease.

Sleep and BMI, obesity and appetite regulation

Several observational studies have examined the association between sleep and obesity or BMI. Over 65 published articles have presented cross-sectional analyses and most found a significant association between short sleep duration (generally $<$6 h per night) and increased prevalence of obesity or higher BMI in both adults and children from various countries (see[15–17] for reviews). Some of these studies also observed higher mean BMI associated with longer sleep durations (generally $>$8 h per night), suggesting a U-shaped association between sleep duration and BMI. Studies that examined self-reported measures of sleep quality have generally found worse sleep quality associated with higher BMI.[18,19] Two recent meta-analyses analyzed data from some of these cross-sectional studies. Cappuccio et al.[20] analyzed data from 17 studies and found that short sleep duration ($<$5 h per night for adults, $<$10 h per night for children) significantly predicted obesity in adults (pooled odds ratio [OR] was 1.55, 95% CI: 1.43–1.68) and in children (pooled OR was 1.89, 95% CI: 1.46–2.43).[20] Sleep duration as a continuous variable was also significantly associated with BMI: the pooled regression indicated that on average BMI was 0.35 kg/m^2 lower for every additional hour of sleep.[20] A second meta-analysis examined sleep and obesity in children and the pooled OR predicting obesity from short sleep duration was 1.58 (95% CI: 1.26–1.98), which means that children who were short sleepers had 58% greater odds of being obese.[21] Thus, both meta-analyses confirmed that short sleep duration increased the odds of being obese. Most cross-sectional studies used self-reported sleep duration, but a few studies have used more objective measures. In a subset ($n = 612$) of the Coronary Artery Risk Development in Young Adults (CARDIA) study in the US, wrist actigraphy was used to estimate sleep duration when participants were approximately 35–50 years old. Participants with shorter average sleep durations had higher BMI than those with longer sleep

durations in cross-sectional analyses.[22] The Osteoporotic Fractures in Men (MrOS) study, which included over 2700 men aged 65 years and older, used polysomnography to determine which characteristics of sleep were associated with measures of body composition.[23] Those with the lowest percentage of slow-wave sleep (SWS) had the highest mean BMI and largest mean waist circumference, but the study did not find an association between SWS and percent body fat. In summary, most studies have reported a significant cross-sectional association where shorter sleep duration and in some studies longer sleep duration were associated with higher BMI or the presence of obesity. Of note, however, is that some studies have reported differences in these associations by age group. In particular, the association between sleep and BMI appears stronger at younger ages, and only one study in children has reported a U-shaped association.[24]

There have also been a few prospective studies of sleep and weight gain in both adults and children (see Table 1). A few of these studies found no statistically significant association between sleep duration and change in body size.[22,25,26]. Many studies, however, did report a significant association. For example, in the Nurse's Health Study women who slept ≤5 h per night gained 1.14 kg (95% CI: 0.49, 1.79) and those sleeping 6 h per night gained 0.71 kg (95% CI: 0.41, 1.00) more weight over 16 years than those sleeping 7 h adjusting for age and baseline BMI.[27] In the Quebec Family Study, those who reported sleeping 5–6 h per night gained approximately 1.84 kg (95% CI 1.08–2.61) more over 6 years than those reporting 7–8 h per night, even after adjustment for numerous potential confounders.[28] A study in Spain also reported that women who reported sleeping ≤5 h per night had increased odds of gaining 5 kg or more over 2 years compared to those who slept 7 h per night (OR 3.41, 95% CI 1.34–8.69).[29] This study also reported increased weight gain among women who reported sleeping 8 h or 9 h per night. No association was seen in men. A study in Japan found that mean BMI among men who were short (<6 h) or long (≥9 h per night) sleepers increased more than in men who slept 7–<8 h per night, however no association was observed among women.[30] A recent study among two minority groups in the US, African-Americans and Hispanic adults, found that among those aged 18–39 years short self-reported sleep (≤5 h per night) was significantly associated with a greater increase in BMI, visceral fat & subcutaneous fat over 5 years compared to those sleeping 6–7 h per night.[31] Of note, the association between short sleep and change in visceral fat was similar to the association between short sleep and change in subcutaneous fat. No association between sleep and change in BMI or fat was observed for those aged 40 years or older.[31] Among children in the UK, the odds of becoming obese between 38 months and 7 years of age was higher for children sleeping <10.5 h per night (OR 1.45, 95% CI: 1.10–1.89) and children sleeping 10.5–11.4 h per night (OR 1.32, 95% CI: 1.02–1.79) relative to children sleeping 12 h per night at 38 months of age.[32] A study that collected time diaries in children also found a small but significant association between sleep duration and 5-year change in BMI (beta = −0.115, $p < 0.01$), however, when stratified by age group, the association was only significant among the younger children who were aged 3–7.9 years at baseline (beta = −0.153, $p < 0.010$).[33] Finally, a study in the US collected parental reports of sleep duration when the children were 6 months, 1-year and 2 years of age and sleep duration was averaged over the three time points.[34] Average sleep duration<12 h per night (versus >12 h) was positively associated with BMI *z* score, sum of skinfolds and odds of being overweight at 3 years of age, even after multiple adjustments.[34] These prospective studies together suggest that sleep duration is associated with changes in body size, which could increase the risk of developing obesity and associated cardiometabolic disease.

Two hormones that are involved in appetite regulation are leptin, a satiety factor, and ghrelin, an appetite stimulant. Previous laboratory studies found that sleep restriction resulted in decreased leptin and increased ghrelin in peripheral blood.[35,36] A few observational studies have also examined levels of leptin and ghrelin in relation to habitual sleep duration. The Wisconsin Sleep Cohort Study, a population-based study that enrolled Wisconsin State employees aged 30–60 years, collected sleep diaries to assess habitual sleep, conducted one night of polysomnography (PSG) in the laboratory, and in the morning following the PSG, obtained a single blood sample.[37] Total sleep time from PSG was inversely associated with ghrelin levels (beta = −0.69, $p = 0.008$) while average habitual sleep duration was positively associated with leptin levels independently of BMI (beta = 0.11, $p = 0.01$).[37] Data from the Quebec Family Study of 740 men and women aged 21–64 years indicated that leptin levels in those sleeping 5–6 h per night were approximately 15–17% lower than predicted based on

Table 1
Summary of prospective observational studies that examine association between sleep and changes in body size.

Authors	Sample	Sleep measure	Follow-up period	Results
Adults				
Hasler et al., 2004[76]	$n = 496$ men & women in Switzerland aged 19 years at baseline.	Self-report	11 years	Adjusted OR for sleep duration predicting obesity was 0.50 ($p < 0.01$).
Gangwisch et al., 2005[25]	$n = 9588$ men & women in US aged 32–86 years.	Self-report	8–10 years	No significant association between sleep duration and BMI change.
Patel et al., 2006[27]	$n = 68,183$ women in US aged 39–65 years.	Self-report	16 years	Those who reported sleeping ≤5 h/night & 6 h/night gained more weight than those sleeping 7 h/night.
Stranges et al., 2008[26]	$n = 10308$ men & women in UK aged 44–65 years	Self-report	5–6 years	No significant association between sleep duration and change in BMI or waist circumference.
Lopez-Garcia et al., 2008[29]	$n = 3235$ men & women in Spain aged ≥60 years.	Self-report	2 years	Increased odds for gaining ≥5 kg associated with sleep ≤5 h/night, 8 h/night and 9 h/night compared to 7 h/night in women only.
Chaput et al., 2008[28]	$n = 276$ men & women in Canada aged 21–64 years.	Self-report	6 years	Short sleepers (5–6 h/night) gained more weight than those sleeping 7–8 h/night.
Gunderson et al., 2008[77]	$n = 940$ post-partum women in US, mean age 33.0 (SD 4.7) years.	Self-report	6 months	Women who slept ≤5 h/night at 6 months post-partum had greater odds of substantial weight gain by 1-year post-partum compared to 7 h/night (OR 3.13, 95% CI 1.42–6.94).
Hairston et al., 2010[31]	$n = 1107$ men & women in the US aged 18–81 years	Self-report	5 years	Among 18–39 years olds, increase in BMI, subcutaneous fat and visceral fat was grater among those sleeping ≤5 h/night compared to 6–7 h/night. No significant associations for those aged ≥40 years.
Children				
Agras et al., 2004[78]	$n = 150$ boys & girls in US aged 3–5 years at baseline.	Parental report	6 years	Mean sleep at ages 3–5 years was 30 min less for those who became overweight compared to those who did not, most of which was daytime sleep.
Sugimori et al., 2004[79]	$n = 8170$ boys & girls in Japan aged 3 years at baseline.	Parental report	3 years	Children obese at both 3 years & 6 years of age had largest % of short sleepers. Association was statistically significant in boys but not girls.
Reilly et al., 2005[32]	$n = 7758$ boys & girls in UK aged 38 months at baseline.	Parental report	4 years	Children sleeping <10.5 h/night and 10.5–11.4 h/night were more likely to be obese at age 7 years than children sleeping ≥12 h per night.
Lumeng et al., 2007[80]	$n = 785$ boys & girls in the US aged 9–10 years at baseline.	Maternal report	3 years	Sleep duration as continuous variable significantly predicted overweight (OR 0.60 per hour, 95% CI 0.36–0.99). Sleep problems were not associated with overweight.
Al Mamun et al., 2007[81]	$n = 2494$ boys & girls in Australia. Sleep assessed at 6 months & 2–4 years of age.	Parental report	Obesity at 21 years of age	Obesity was not associated with sleeping problem at 6 months Increasing sleep problems at 2–4 years of age was associated with increased BMI and overweight/obesity at age 21.
Snell et al., 2007[33]	$n = 1441$ boys & girls in US aged 3–13 years at baseline.	Time diaries	5 years	Statistically significant association between sleep from time diary predicting BMI. Only significant among children aged 3–7.9 at baseline.
Taveras et al., 2008[34]	$n = 915$ boys & girls in US. Sleep assessed at 6 months, 1-year & 2 years of age.	Parental report	BMI at 3 years of age	Average sleep duration <12 (vs >12 h) was positively associated with BMI z score, sum of skinfolds & odds of being overweight, after multiple adjustments.
Touchette et al., 2008[82]	$n = 1138$ boys & girls in Canada. Sleep assessed yearly from 2.5 to 6 years of age.	Parental report	BMI at 6 years of age	Short persistent sleepers (<10 h) had higher risk of overweight/obesity (OR 4.2) compared to 11-h persistent sleepers.

body fat alone.[38] These two studies are consistent with some of the laboratory studies but two other studies in women did not observe similar associations. The Nurse's Health Study, which asked participants to return a blood sample through the mail, did not observe a significant association between self-reported sleep duration and leptin levels.[39] Also, a controlled randomized trial of moderate-intensity exercise among 173 obese, sedentary postmenopausal women aged 50–74 found no cross-sectional associations between self-reported sleep duration and leptin or total ghrelin levels nor any significant associations between change in sleep duration and changes in leptin or ghrelin after the exercise intervention.[40] These discrepant results may be due to differences in the association between sleep and appetite regulation in women, particularly obese older women, or may be due to methodological issues such as self-reported sleep duration, sample collection or assay procedures. Finally, the Women's Health Initiative study examined the relationship between sleep and dietary intake in 459 postmenopausal women aged 50–81 years.[41] Average sleep duration from 1 week of wrist actigraphy was negatively correlated with dietary fat intake and total calories, which suggests that short sleepers have a greater food intake particularly in the form of fat. A study in adolescents did not find an association between hunger ratings and average nocturnal sleep from 7-day sleep diaries, however, those who slept 3 h or more during the daytime reported greater caloric intake and food cravings and this association did not appear to be confounded by nocturnal sleep duration.[42] More research is required to assess whether habitual insufficient sleep is truly associated with greater appetite and greater food intake.

Sleep and diabetes

Several large observational studies have reported cross-sectional associations between short sleep duration or impaired sleep and greater prevalence of diabetes or impaired glucose tolerance (see[17] for a review). Most of these studies found an increased odds of diabetes associated with short sleep durations ($\leq$5 h or $\leq$6 h per night) and some also found an increased odds of diabetes among long sleepers ($\geq$8 or $\geq$9 h). One study found stronger associations in older people [43] and another observed a significant association in women only.[44] Most of these studies relied on self-reported sleep duration and quality, but one study used wrist actigraphy and found greater sleep fragmentation in those with type 2 diabetes compared to healthy controls but no difference in total sleep time.[45] A survey study among African-Americans with type 2 diabetes found a significant association between poor subjective sleep quality or insufficient sleep and worse glycemic control as indicated by higher HbA1c levels.[46] Finally, a study of 60 patients with type 2 diabetes found that 77% of the patients had an apnea-hypopnea index above 5, which indicates sleep-disordered breathing (SDB).[47] Furthermore, a greater degree of SDB was associated with worse glycemic control.[47] The results of these studies suggest an association between diabetes and short sleep duration or poor sleep quality, however, the direction of causality cannot be determined. Poor or insufficient sleep may increase the risk of developing diabetes, as the laboratory studies suggest, or, conversely, having diabetes could impair sleep.

Several prospective studies have examined the association between sleep duration or impaired sleep and incident diabetes. The results are summarized in Table 2. Most of these studies reported increased odds of diabetes associated with short sleep duration ($\leq$5 h and/or $\leq$6 h) and many observed a U-shaped association. Furthermore, impaired sleep, such as difficulty initiating or maintaining sleep, was associated with increased odds of developing diabetes in multiple studies. A meta-analysis of 10 prospective studies examined the association between the incidence of diabetes and either short sleep duration, long sleep duration or sleep disturbances.[48] The estimated pooled OR for short sleep was 1.28 (95% CI: 1.03–1.6), however, there was a significant gender difference. The OR was 2.07 (1.16–3.72) for men and 1.07 (0.90–1.28) for women, indicating a stronger association among men. The pooled OR for long sleep was 1.48 (1.13–1.96), indicating that overall there is a significant U-shaped association between 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. Thus, taken together, prospective epidemiologic studies have suggested that subjective short or long sleep duration and poor sleep quality predict the development of diabetes.

Table 2
Summary of prospective observational studies that examine association between sleep and incident diabetes.

Authors	Sample	Sleep measure	Follow-up period	Results
Ayas et al., 2003[83]	$n = 70{,}026$ women in the US aged 30–55 years at baseline.	Self-report	10 years	When adjusting for BMI, only those reporting sleeping 9 h/night or more had significantly higher odds of incident diabetes compared to those sleeping 8 h/night (OR 1.29, 95% CI 1.05–1.59). When predicting incident symptomatic diabetes, both those reporting sleeping $\leq$5 h/night (OR 1.37, 95% CI 1.07–1.77) and those reporting $\geq$9 h/night (OR 1.36, 95% CI 1.04–1.73) had significantly higher odds than those sleeping 8 h/night.
Kawakami et al., 2004[84]	$n = 2649$ men in Japan aged 18–53 years at baseline.	Self-report	8 years	Difficulty initiating sleep (OR 2.98, 95% CI 1.36–6.53) and difficulty maintaining sleep (OR 2.23, 95% CI 1.08–4.61) both predicted incident diabetes.
Nilsson et al., 2004[85]	$n = 6599$ men in Sweden aged 35–51 years at baseline.	Self-report	Mean 14.8 years	Increased odds of incident diabetes among those who reported difficulty falling asleep or use of sleeping pills (OR 1.52, 95% CI 1.05, 2.20).
Meisinger et al., 2005[86]	$n = 8269$ men & women in Germany aged 24–74 years at baseline.	Self-report	Mean 7.5 years	Difficulty maintaining sleep predicted incident diabetes in both men (OR 1.60, 95% CI 1.05–2.45) and women (OR 1.98, 95% CI 1.20–3.29). Difficulty initiating sleep was not associated with incident diabetes.
Mallon et al., 2005.[87]	$n = 1244$ men & women in Sweden aged 45–65 years at baseline.	Self-report	12 years	In men, difficulty maintaining sleep (OR 4.8, 95% CI 1.9–12.5) and sleeping $\leq$5 h (OR 2.8, 95% CI 1.1–7.3) predicted incident diabetes. There were no significant associations between sleep and diabetes in women.
Bjorkelund et al., 2005[88]	$n = 1447$ women in Sweden aged 38–60 years at baseline.	Self-report	32 years	No association between incident diabetes & sleep problems or sleep duration.
Yaggi et al., 2006[89]	$n = 1139$ men in US aged 40–70 years at baseline	Self-report	15–17 years	Odds of incident diabetes were higher for those reporting sleeping 6 h/night (OR 1.95, 95% CI 1.06–3.58) and 9 h (OR 3.12, 95% CI 1.53–6.37) compared to those sleeping 7 h/night.
Gangwisch et al., 2007[90]	$n = 8992$ men & women aged 32–86 years.	Self-report	8–10 years	Odds of incident diabetes was higher for those reporting sleeping $\leq$5 h (OR 1.47, 95% CI 1.03–2.09) and $\geq$9 h (OR 1.52, 95% CI 1.06–2.17) compared to those sleeping 7 h/night.
Hayashino et al., 2007[91]	$n = 6509$ men & women aged 19–69 years.	Self-report	Median 4.2 years	Odds of incident diabetes was higher for those reporting difficulty initiating sleep "sometimes" (OR 1.39, 95% CI 1.04–1.88) and "often" (OR 1.63, 95% CI 1.04–2.59) compared to those with no difficulty. Sleep duration and difficulty maintaining sleep were not related to incident diabetes.
Chaput et al., 2009[92]	$n = 276$ men & women in Canada aged 21–64 years.	Self-report	Mean 6 years	Odds of incident impaired glucose tolerance/type 2 diabetes (combined) were higher for those reporting sleeping $\leq$6 h (OR 2.42, 95% CI 1.49–3.33) and $\geq$9 h (OR 2.31, 95% CI 1.41–3.15) compared to those reporting sleeping 7–8 h/night.
Biehl et al., 2009[93]	$n = 900$ men & women in US aged 40–69 years at baseline.	Self-report	5 years	Among non-Hispanic whites and Hispanics (combined), odds for incident diabetes were higher among those reporting sleeping $\leq$7 h (OR 2.36, 95% CI 1.11–5.00) compared to those sleeping 8 h/night. No association between sleep duration and incident diabetes was observed in African-Americans.
Xu et al., 2010[94]	$n = 174{,}542$ men & women in US aged 50–71 years age baseline.	Self-report	3–10 years	Odds of incident diabetes was higher in those reporting sleeping <5 h (OR 1.46, 95% CI 1.31–1.63) and 5–6 h (OR 1.11, 95% CI 1.06–1.16) compared to those sleeping 7–8 h/night. Longer day napping was also associated with increased odds of incident diabetes.

Sleep and cardiovascular disease

Sleep duration and quality have also been associated with blood pressure in epidemiologic studies.[49–54] Cross-sectional studies have generally found that self-reported short sleep durations or subjectively poor sleep quality are associated with higher blood pressure or higher prevalence of hypertension.[43,49,51–53,55,56] Some of these studies also observed higher blood pressure among long sleepers.[43,49] Two of these studies observed a significant association in women but not men.[53,56] A few studies found no association between sleep and blood pressure, including two among elderly adults[57,58] and one among children aged 3–10 years[59], which suggests that associations between sleep and blood pressure may be modified by age. Two studies used wrist actigraphy, an objective measure, to estimate sleep duration and quality. One of these studies was conducted among 238 adolescents and found that low sleep efficiency, but not sleep duration, was significantly associated with prevalent prehypertension.[60] In a subset of participants in the CARDIA study, sleep duration and quality was estimated from 3 to 6 days of wrist actigraphy when participants were approximately 35–50 years old.[61] Shorter sleep duration and lower sleep maintenance (the percentage of time between sleep onset and sleep end that was spent sleeping) were both associated cross-sectionally with higher blood pressure. Thus, cross-sectional studies generally support a relationship between disturbed or insufficient sleep and higher blood pressure, but the causal direction cannot be determined and the strength of these associations may vary by gender and age.

Several prospective epidemiologic studies have examined cardiovascular outcomes in relation to sleep duration. Analysis of over 4500 adults who participated in the National Health and Nutrition Examination Survey (NHANES) in the US found that those who reported sleeping $\leq$5 h per night had increased odds of incident hypertension (OR 1.32, 95% CI: 1.02–1.71) compared to those reporting sleeping 7–8 h per night after adjusting for numerous potential confounders.[50] In the CARDIA study of adults aged 35–50 years, sleep duration estimated from 3 to 6 days of wrist actigraphy was significantly associated with incident hypertension over five years.[61] The odds ratio for shorter average sleep duration predicting hypertension was 1.37 (95% CI: 1.05–1.78), which means for every hour less sleep there is a 37% higher odds of incident hypertension. The CARDIA study also examined incident coronary artery calcification (CAC), which is a predictor of the development of coronary heart disease. Results indicated a significant negative association between sleep duration and incidence of CAC. Longer measured sleep duration was associated with a decreased adjusted odds of incident calcification over 5 years (OR = 0.67 per hour, $p = 0.011$; 95% CI: 0.49–0.91), which means every extra hour of sleep was associated with a 33% lower odds of CAC.[62] The Nurses' Health Study examined incident coronary heart disease (CHD) over 10 years and found a U-shaped association with self-reported sleep duration.[63] The risk ratio (RR) was 1.45 (95% CI: 1.1–1.92) for those reporting $\leq$5 h sleep per night and 1.38 (95% CI: 1.03–1.86) for those reporting $\geq$9 h per night compared to those sleeping 8 h per night. A few studies have examined cardiovascular disease mortality in relation to sleep duration, but none found an association in fully adjusted models.[64–66] Subjective insomnia or insomnia symptoms have been associated with increased cardiovascular disease events or mortality. For example, a study in Sweden reported that coronary artery disease mortality was higher for men reporting difficulty initiating sleep (RR: 3.1, 95% CI: 1.5–6.3), but no association was observed in women[64] A study in the US of over 3400 men and women 35 years of age or older reported a significant increase of a cardiovascular disease event in those who complained of insomnia every day compared to those without any insomnia complaint (RR: 1.78, 95% CI: 1.03–3.08).[66] Overall, there is some evidence that insufficient or impaired sleep is associated with cardiovascular disease and hypertension, but more rigorous studies are required to fully understand this association.

Limitations

The majority of the observational studies described above had consistent findings, but we must still consider the methodological limitations of these studies. First, the vast majority of these studies relied on a self-reported measure of sleep duration, which may not be very accurate. Recent analysis comparing sleep durations estimated from wrist actigraphy to self-reported sleep in a sample of over 600 middle-aged adults indicated only moderate agreement between these measures ($r = 0.47$).[67] In

addition, there may be important confounders that are not taken into account in these analyses, including race, socioeconomic status, physical activity, alcohol and caffeine consumption, and psychological disorders.[67,68] Future studies need to incorporate objective measures of sleep and include detailed measures of potential confounding variables.

Potential mechanisms

The mechanisms underlying the association between cardiometabolic disease risk and sleep duration or quality are not fully understood. However, laboratory studies have provided some clues about potential pathways leading from insufficient or disturbed sleep to diabetes and obesity. The figure below presents potential pathways linking disturbed or insufficient sleep to the development of obesity, type 2 diabetes and cardiovascular disease (CVD) or hypertension (HTN). It is unlikely that any single pathway is responsible, but rather a combination of mechanisms leads to increased cardiometabolic risk. Furthermore, there are probably other pathways that remain to be identified, including effects of sleep disturbances on physical activity and energy expenditure (Fig. 1).

One pathway from short sleep to cardiometabolic disease involves an increase in appetite. The subjective increase in hunger after sleep restriction may be a result of decreased inhibition of hypothalamic activity in appetite centers and a loss of inhibition of the activity of orexigenic neurons in the hypothalamus, leading to increased hunger.[69,70] If increased hunger led to increased food intake without compensatory increases in physical activity, weight gain would result and could eventually lead to obesity. The second pathway indicates that sleep loss results in a decrease in brain glucose utilization, which would promote reduced glucose tolerance. Studies of total sleep deprivation that

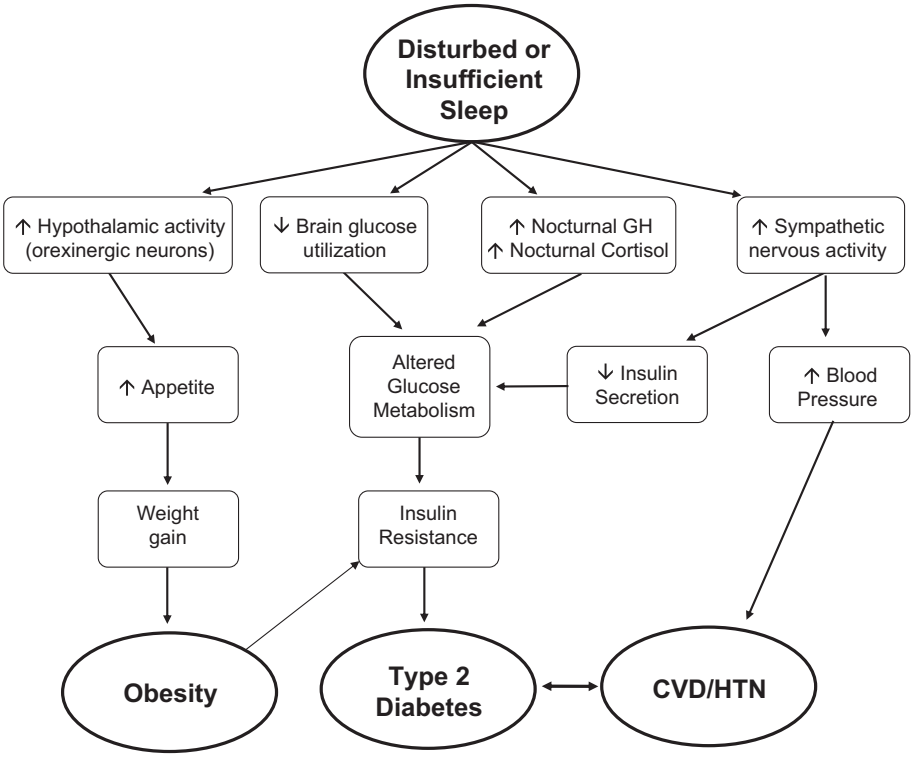

Fig. 1. Schematic representation of possible mechanistic pathways linking disturbed or insufficient sleep to obesity, diabetes, cardiovascular disease (CVD) and hypertension (HTN).

used positron emission tomography (PET) did in fact observe decreased brain glucose utilization after sleep deprivation.[70] The third pathway involves increases in daytime release of growth hormone (GH) and ghrelin, as well as evening release of cortisol. A laboratory study of six days of sleep restriction observed an extended duration of elevated nighttime GH concentrations [71] and an increase in evening cortisol levels.[72] Elevated evening cortisol concentrations are likely to result in reduced insulin sensitivity on the following morning, an alteration that can further impair glucose tolerance following sleep restriction.[73] Increased levels of GH can lead to an induction of transient insulin resistance in muscle cells, resulting in decreased glucose uptake, elevated blood glucose levels and subsequent increased in insulin resistance in other tissues. Thus, both the second and third pathways can have a deleterious impact on glucose metabolism. The fourth pathway in the figure proposes that disturbed and insufficient sleep is associated with an increase in sympathetic nervous activity. Laboratory studies observed that sleep restriction was associated with elevated cardiac sympatho-vagal balance estimated from heart rate variability, which likely reflects an increased influence of sympathetic tone.[35,72] Increased sympathetic nervous activity at the level of the pancreas could result in a reduction of insulin secretion from pancreatic beta-cells, but sympatho-vagal balance at the level of the pancreas has not yet been assessed in any sleep restriction study. Deleterious alterations in glucose metabolism could lead to the development of insulin resistance, which is a risk factor for the development of type 2 diabetes. In addition, increased sympathetic nervous activity would also be associated with increased blood pressure, which could predispose individuals to the development of hypertension and cardiovascular disease. Finally, obesity is a risk factor for insulin resistance and diabetes and diabetes and CVD are closely linked conditions.

As described above, numerous observational studies have also documented an association between long sleep duration and obesity, diabetes or hypertension. To date, no biological mechanisms have been identified to explain this association. Several explanations have been postulated, however. An analysis of the Nurses' Health study indicated that the presence of depression and low socioeconomic status were the most likely explanations for the association between long sleep and mortality.[74] It is important to note that in all of the studies that observed a U-shaped association, sleep duration was based on self-report. Therefore, it is not clear if long sleepers are actually obtaining more physiologic sleep or if they are just spending more time in bed. A study that recruited individuals whose self-reported sleep duration was $\geq$9 h per night provides some evidence for the latter explanation. In this study, the self-reported long sleepers only obtained an average of 7–7.5 h of sleep per night based on wrist actigraphy monitoring despite reporting sleeping more than 9 h per night.[75] The large discrepancy between self-reported and objectively-measured sleep duration is not explained, but could represent either a sleep disorder or other pathological condition(s). Given the large number of studies that have found an association between long sleep duration and morbidity risk, it is important that more research into possible mechanisms or explanations be conducted.

Summary

The accumulated evidence from numerous observational studies suggests that insufficient or disturbed sleep may play a role in the development of cardiometabolic disease risk. Potential pathways through which sleep could lead to the development of obesity, diabetes, cardiovascular disease and hypertension have been discussed. In particular, these pathways involve impairments in glucose metabolism, appetite regulation, and sympatho-vagal balance. However, more research is required to better understand how sleep impacts cardiometabolic risk (see Research Agenda). In particular, whether gender or age modifies the association between sleep and cardiometabolic diseases needs to be investigated further. Obesity, diabetes and cardiovascular disease have enormous negative impacts on quality of life, life expectancy and financial burden. Therefore, a better understanding of the factors that can influence the development or prognosis of these conditions could help improve the lives of millions of people. Evidence reviewed here suggests that sleep duration or quality may be a novel risk factor that is potentially modifiable. Future research should test whether a sleep intervention could ameliorate the cardiometabolic consequences of impaired or insufficient sleep.

Practice points

- Short sleep duration is associated with increased prevalence of obesity in adults and children.
- Associations between sleep and body mass index/obesity appear stronger at younger ages.
- Short sleep duration is associated with increased risk of diabetes and hypertension in adults.
- Long sleep duration has also been associated with increased obesity, diabetes and hypertension in some studies.
- Possible mechanisms for these observations include alterations in hypothalamic activity that relate to appetite regulation, alterations in hormonal profiles, such as GH and cortisol, and increased sympathetic nervous activity.

Research agenda

- The potential impact of sleep disturbances on energy expenditure warrants further examination.
- More research is required to assess the relationship between habitual sleep duration and quality and food intake.
- Intervention studies to examine the effect of improving or extending sleep on cardiometabolic risk factors are important for establishing a causal link.
- Future observational studies should be prospective and include objective measures of habitual sleep.
- More research is needed to understand the association between long sleep and morbidity risk.
- Future studies should investigate whether the associations between sleep duration and morbidity vary by gender or age.

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