Review

Sleep and Obesity

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Rising global prevalence and incidence of obesity lead to increased cardiovascular-renal complications and cancers. Epidemiological studies reported a worldwide trend towards suboptimal sleep duration and poor sleep quality in parallel with this obesity epidemic. From rodents and human models, it is highly plausible that abnormalities in sleep, both quantity and quality, impact negatively on energy metabolism. While excess dietary intake and physical inactivity are the known drivers of the obesity epidemic, promotion of healthy sleep habits has emerged as a new target to combat obesity. In this light, present review focuses on the existing literature examining the relationship between sleep physiology and energy homeostasis. Notably, sleep dysregulation perturbs the metabolic milieu via alterations in hormones such as leptin and ghrelin, eating behavior, neuroendocrine and autonomic nervous systems. In addition, shift work and trans-meridian air travel may exert a negative influence on the hypothalamic-pituitary-adrenal axis and trigger circadian misalignment, leading to impaired glucose tolerance and increased fat accumulation. Amassing evidence has also suggested that uncoupling of the circadian clock can increase the risk of adverse metabolic health. Given the importance of sleep in maintaining energy homeostasis and that it is potentially modifiable, promoting good sleep hygiene may create new avenues for obesity prevention and treatment.

Key words: Sleep, Energy metabolism, Leptin, Ghrelin, Pituitary-adrenal system, Circadian rhythm

INTRODUCTION

The global prevalence of obesity has doubled since 1980, affecting 107.7 million children and 603.7 million adults in 2015, with more than two-thirds of the United States population being either overweight or obese.[1] This rapid surge in obesity is driven mainly by lifestyle factors such as physical inactivity, unhealthy dietary choices and patterns.[2] Emerging evidence suggests that sleep disturbances (e.g., suboptimal sleep duration, poor sleep quality, circadian misalignment and insomnia), may contribute to obesity and type 2 diabetes mellitus (T2DM).[2] Physiologically, sleep duration declines during transition from infancy, puberty to late adulthood.[3] Optimal sleep duration has been a matter of controversy but recent consensus of the American Academy of Sleep Medicine defines short sleep duration as <8−10 hours and <7 hours per day in adolescents and adults aged 18−60 years respectively, considering the potential risks in association with the development of cardiometabolic disease and death.[4-6] Due to increasing demand from school, work and leisure activities[2], along with the prevalent usage of Internet and electronic devices, there is a global phenomenon for a shift in both adolescents and adults to have shorter sleep duration compared to a few decades ago. Based on the 2014 U.S. Behavioral Risk Factor Surveillance System, more than one-third of adults were short sleepers, particularly prevalent in those who were young, obese (body mass index [BMI] ≥30 kg/m^2) or with low socioeconomic and education status.[7] In China, a meta-analysis of 17 cross-sectional population-based studies reported that every one in six adults had insomnia, which was again more commonly seen in

young individuals.[8] Paradoxically, long sleep duration (> 9 hours per day) was also observed in 23%–37% of the general population in developed countries[9], and a meta-analysis of 137 prospective cohort studies reported a dose-response relationship with incident cardiovascular disease and death, attesting a U-shaped relationship between sleep duration and health outcomes across all age groups.[10,11] Alarmingly, poor sleep quality (defined as global Pittsburgh Sleep Quality Index score > 5) was also independently associated with an increase in BMI and worse glycemic control.[6] Given that obesity is closely linked to multiple chronic diseases, notably diabetes and cancer which are the leading causes of morbidities and mortality in many parts of the world[12], the perplexing relationship between sleep and energy metabolism call for more research and clinical attention, as sleep is an essential part of life and a potentially modifiable behavioral risk factor for metabolic health. Here, we review some of the important findings in this field, and discuss the mechanisms linking sleep, energy metabolism and obesity.

SLEEP AND NEUROHORMONAL DYSREGULATION

Sleep and satiety

The appetite center, located at the ventromedial and arcuate nuclei of the hypothalamus, is regulated by hormones including leptin and ghrelin. Leptin is an adipocyte-derived hormone which suppresses appetite, whilst ghrelin is mainly a stomach-derived hunger-promoting peptide.[13,14] High total energy and fat intake, night-time snacking and binge eating tendencies have been reported to be associated with sleep curtailment.[15,16] The potential mechanisms mediating the effects of sleep debt on obesity are complex, which include alterations in eating behavior (e.g., skipping meals, snacking, and irregular meal times), increased ghrelin to leptin ratio and activation of hedonic pathways.[15,17,18] Several small scale experimental studies involving the healthy population (number of subjects, 11 to 26 in each study) examined the effect of sleep restriction on dietary intake and patterns under the controlled environment, which included objective sleep measurements and planned meals in both phases of short and habitual sleep.[19,20] Sleep restriction was reported to be associated with an increase in total energy, total fat and saturated fatty acids intake[19], as well as high consumption of carbohy-

drate-rich night-time snacks.[20] These were accompanied by a lack of compensatory increase or even with a reduction in 24-hour energy expenditure, leading to positive energy balance.[19,20] In keeping with these findings, an inverse relationship between sleep duration and total energy and macronutrient intake was evident in epidemiological cohorts.[15,17,21,22] In a meta-analysis of 14,906 Europeans from the Cohorts for the Heart and Aging Research in Genomic Epidemiology Consortium, younger people (aged 20–64 years) with short sleep duration were independently associated with higher relative saturated fatty acids intake, whereas older women (aged 65–80 years) with similar exposure demonstrated higher relative carbohydrate, lower relative total fat and polyunsaturated fatty acids consumption.[22] In the 2005–2010 U.S. National Health and Nutrition Examination Survey involving 15,199 community-dwelling adults, short sleepers reported frequent snacking and increased total glucose intake.[17] Similarly, amongst 2,828 Chinese adults, those with less than 7-hour sleep had excess fat intake than the group with 7- to 9-hour sleep.[21]

Accumulating evidence suggests that sleep disruption may interfere with the feeding and satiety signals at the hypothalamic feeding circuits.[23] A shift towards increased hunger in short sleepers was driven by decreased leptin level with or without a concomitant change in the diurnal rhythm amplitude of leptin, increased ghrelin level or both.[24,25] In healthy young adults with stable caloric intake and activity levels, 6 days of sleep restriction (4 hours in bed per night) was independently associated with a 26% reduction in leptin than sleep extension (12 hours in bed per night), on top of a flattened diurnal profile of leptin secretion.[25] In the prospective Wisconsin Sleep Cohort Study involving 1,024 healthy adults, compared with those with 8-hour of sleep, short sleepers (5-hour of sleep per day) had a 16% decrease in leptin and 15% increase in ghrelin level.[24] Interestingly, diminished activity of the appetitive desire and food stimulus evaluation regions within the frontal, insular and cingulate cortices, along with enhanced activity of amygdala are other plausible pathways linking sleep curtailment to obesity.[26-28] The disrupted neural circuits led to hedonic hunger and preferences for highly palatable and rewarding energy-dense food[26-28], albeit with inter-individual variation in the magnitude of change in eating behavior proportional to the severity of sleep curtailment.[26] On the other hand, short sleepers have prolonged wakefulness that

promotes obesogenic eating behavior e.g., meal-skipping, frequent snacking and increase intake of low-quality diet.[17,29,30] Late-time eating, which was defined as caloric intake after 8:00 PM, also significantly predicted an increase in BMI, suggesting that eating late at night may lead to obesity.[29] Moreover, decreased nocturnal ghrelin levels were found in men with insomnia compared with their age- and body weight-matched healthy control (n = 25), while no difference of leptin levels was found between groups.[31]

Sleep and growth hormone-insulin like growth factor-1 axis

The growth hormone (GH)-insulin like growth factor-1 (IGF-1) axis also plays a role in the regulation of adiposity and glucose homeostasis. Under a normal sleep/wake cycle, there is a spontaneous nocturnal GH pulse during the restorative slow wave sleep (SWS) that occurs within the first 3 hours of sleep, with both demonstrating a dose-dependent relationship.[32] Increasing evidence suggests that there are biological interactions of GH/IGF-1 axis with sleep dysregulation. Sleep curtailment and late chronotype are associated with suppressed GH and IGF-1 pulsatility, followed by a compensatory increase in IGF-binding protein 3 (IGFBP-3) level via the negative feedback loop.[33] In a 4-year prospective cohort study of normoglycemic adults, low circulating IGF-1 level had a 50% excess risk of developing either impaired glucose tolerance or T2DM, consequent to decreased peripheral insulin sensitivity and hyperinsulinemia.[34] In the Danish-Monitoring Trends in Cardiovascular Diseases study, after a mean follow-up of 15 years, either a low IGF-1 or high IGFBP-3 level was independently associated with a relative risk (RR) of 1.94−2.22 of incident coronary heart disease, after adjustment for other cardiovascular risk factors.[35] Several mechanisms were postulated to explain the pleiotropic effects of GH/IGF-1 axis on the retardation of atherosclerosis e.g., reduced systemic and vascular oxidative stress (low interleukin-6 and tumor necrosis factor-alpha levels), decreased aortic stiffness and control of de novo hepatic lipid metabolism.[35,36]

In contrast to the aforementioned findings, another experimental sleep restriction (4 hours in bed per night for six consecutive nights) study involving 11 healthy young men revealed a biphasic pattern of nocturnal GH release, with the first pulse occurred at 3-hour prior to the sleep onset and the second peak corresponded to the usual circadian rhythm as seen during the sleep extension period (12 hours in bed per night for a week).[32] This prolonged exposure to elevated GH level may interact with the hunger-promoting ghrelin centrally or stimulate peripheral glucose and lipid catabolism, resulting in insulin resistance and positive energy balance.[37] These findings were supported by some but not all observational studies, which reported a U-shaped relationship between IGF-1 to IGFBP-3 ratio, anthropometric traits (e.g., BMI and waist circumference) or risk of metabolic syndrome.[38,39] To this end, a better understanding of the cellular-microenvironment interactions and their downstream signaling cascades integrating sleep, GH/IGF-1 axis and metabolic functions is warranted.

Sleep and hypothalamic-pituitary-adrenal axis

Sleep disturbances, including short sleep, sleep debt, and circadian misalignment, may also disrupt glucose homeostasis and cause metabolic perturbations via other hormonal and cellular signaling cascades.[23,24,40] In a pilot study conducted in 11 healthy young men, decreased glucose tolerance, increased evening cortisol level and sympathetic over-activity were observed after sleep restriction (4 hours in bed per night for six consecutive nights) compared with the measurements taken after a sleep-restorative period (12 hours in bed per night for seven consecutive nights), indicating that sleep debt had a detrimental effect on glucose metabolism and endocrine function.[40]

The bidirectional relationships between sleep and the activity of hypothalamic-pituitary-adrenal (HPA) axis may exert negative metabolic consequences. Dysregulation of the HPA axis and its circadian rhythm can mediate the impact of sleep disturbances on cardiometabolic risk, mainly via the actions of two counter-regulatory hormones, namely the glucocorticoids and catecholamines. Physiologically, cortisol level peaks after 30−45 minutes of awakening (defined as cortisol awakening response [CAR]), followed by a sharp decline over the next 3 hours, more gradual decline over the rest of the day, and reaching nadir during the first half of sleep cycle.[41] Existing studies examining the associations between sleep and circadian variability of cortisol secretion is inconclusive, due to differences in the sleep measurements (actigraphy/polysomnography vs. self-reported sleep parameters), definitions used for sleep duration and quality, and the number of real-time sampling points for

modelling of 24-hour cortisol profile. Several reports indicated that short sleepers have flattened diurnal cortisol slope and raised evening cortisol followed by an aggravated CAR, yielding an increase in total daily cortisol secretion which ends up in a state of hyper-cortisolism and catabolism.[42-44] In school-age children, high CAR and subsequent diurnal cortisol level were inversely associated with short sleep duration, low sleep efficiency and low frequency of SWS.[45,46] Conversely, two other studies found no association between objective sleep duration and salivary awakening cortisol[44] or 24-hour urinary cortisol level.[47] Poor sleep quality has been reported to be an independent stressor for excess cortisol and catecholamines secretion, particularly with greater magnitude in adolescents at late puberty.[42,44] Increased HPA axis activation has also been reported in subjects with insomnia.[48,49] Furthermore, it has been suggested that a gender difference on this stress reaction related to sleep disturbances which may be modulated by the type of sleep disorders involved, calling for more studies to investigate the impact of sex hormones on sleep and energy balance.[44,50]

Sympathetic over-activity may also contribute to the neurohormonal dysregulation linking sleep curtailment to energy imbalance. In addition to a 1.5-hour delay in the nocturnal nadir of cortisol level, experimental sleep restriction with 4 hours in bed per night for six consecutive nights in healthy volunteers had shown a concomitant 24-hour lowering of heart rate variability (measured by the autocorrelation coefficient of consecutive interbeat intervals) especially during awakening, which reflected an increase in cardiac sympathetic activity and/or diminished vagal tone, compared with sleep extension phase (12 hours in bed per night for seven consecutive nights).[25] Physiologically, sleep onset is associated with decreased catecholamines release, reaching a nocturnal nadir an hour into a restful sleep.[51] Amongst short sleepers, the secretion of norepinephrine was pathologically elevated during early awakening in early morning, between 3:00 AM and 6:00 AM, with epinephrine showing a similar trend.[44,51] Furthermore, patients with mild to moderate hypertension with acute sleep restriction reported an early morning elevation in blood pressure (systolic blood pressure of 7 mmHg and diastolic blood pressure of 4 mmHg) and heart rate (5.5 beats per minute) with potential risk of silent cardiovascular event, as sequelae of their blunted nocturnal dipping related to a surge in norepinephrine release.[52]
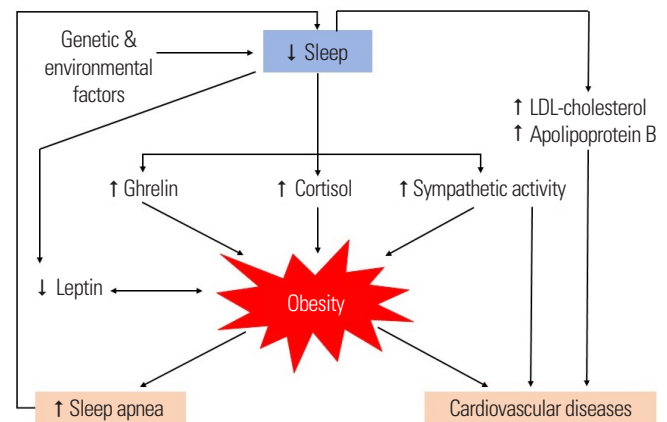
Figure 1. Association between sleep, obesity, cardiovascular risks and possible underlying neurohormonal dysregulation. LDL, low-density lipoprotein.

SLEEP, OBESITY AND DIABETES

Multiple studies have consistently demonstrated significant associations between sleep curtailment with decreased resting and postprandial energy expenditure (~5% and 20%, respectively), increased appetite and insulin resistance in general population.[2,11] In addition, a randomized cross-over study demonstrated a 30% decrease in the intracellular insulin sensitivity within adipocytes from the subcutaneous fat samples of seven healthy adults collected after sleep restriction compared with after normal sleep.[53] It has also been demonstrated that short sleep duration is associated with atherogenic dyslipidemia.[54,55] Once obesity sets in, there may be a vicious cycle as obesity associated comorbidities such as obstructive sleep apnea may further compromise sleep quality in affected individuals (Fig. 1). Taken together, evidence to date suggests that sleep curtailment affects the resiliency of neurohormonal stress response and predisposes to metabolic disturbances with possible long-term cardiovascular risk. Besides sleep curtailment, there have been a wealth of clinical evidence supporting the association of sleep disturbances, both quantity and quality, with obesity and diabetes (Tables 1 and 2).[11,56-103] However, the associations of insomnia with obesity and glucose metabolism is under debate.

Insomnia is a common sleep problem worldwide and affects 15% of the Chinese population.[8] It is defined as difficulty in initiating sleep (DIS), difficulty in maintaining sleep (DMS) and/or early morning awakening (EMA) at least three times per week with associated impairment of daytime functioning.[104] Nonrestorative

Table 1. Clinical studies examining the association between sleep duration with obesity and diabetes

Author (year)	Type of study/country or region	Study population (sample size)	Definition of sleep disturbances	Method of sleep assessment	Age (yr) and male (%)	Outcome
Sleep duration and overweight/obesity						
Ayas et al. (2003)[11]	Prospective (mean follow-up: 10 yr)/the United States	Female married registered nurses from the Nurses' Health Study (n=70,026)	Short sleep: ≤5 hr/day Long sleep: ≥9 hr/day Reference: 8 hr/day	Self-reported sleep duration	40–65, 0%	New-onset obesity Short sleep: RR, 1.18; 95% CI, 0.96–1.44 Long sleep: RR, 1.29; 95% CI, 1.05–1.59
Patel et al. (2006)[56]	Prospective study (follow-up: 16 yr)/the United States	Female nurses from the Nurses' Health Study (n=68,183)	Sleep duration was categorized as: ≤5, 6, 7, 8, and ≥9 hr/day Reference: 7 hr/day	Self-reported	39–65, 0%	New-onset obesity Sleep duration ≤5 hr/day: HR, 1.15; 95% CI, 1.04–1.27 Sleep duration 6 hr/day: HR, 1.06; 95% CI, 1.01–1.12 Sleep duration ≥9 hr/day: HR, 1.03; 95% CI, 0.93–1.14 ≥15 kg weight gain Sleep duration ≤5 hr/day: HR, 1.28; 95% CI, 1.15–1.42 Sleep duration 6 hr/day: HR, 1.10; 95% CI, 1.04–1.17 Sleep duration ≥9 hr/day: HR, 1.04; 95% CI, 0.92–1.16
Chaput et al. (2008)[57]	Prospective study (follow-up: 6±0.9 yr)/Canada	General population form the Quebec Family Study (n=276; nonobese: n=224)	Short sleep: 5–6 hr/day Long sleep: 9–10 hr/day Reference: 7–8 hr/day	Self-reported	21–64, 42.4%	Weight gain Short-duration sleepers gained 1.84 kg; 95% CI, 1.08–2.61 Long-duration sleepers gained 1.49 kg; 95% CI, 0.92–2.48 New-onset obesity Short-duration sleepers: OR, 1.27; 95% CI, NS Long-duration sleepers: OR, 1.21; 95% CI, NS
López-García et al. (2008)[58]	Prospective study (follow-up: 2 yr)/Spain	Elderly population (n=3,235)	Sleep duration was categorized as: ≤5, 6, 7, 8, 9, and ≥10 hr/day Reference: 7 hr/day	Interview	Male, 71.6±8.0; female, 72.1±7.6, 43.6%	ORs of obesity Sleep ≤5 hr: OR, 1.33; 95% CI, 1.00–1.77 Sleep 8 hr: OR, 1.39; 95% CI, 1.11–1.75 ORs of severe obesity Sleep ≤5 hr: OR, 2.08; 95% CI, 1.31–3.32 Sleep 8 hr: OR, 1.82; 95% CI, 1.21–2.73 Sleep 9 hr: OR, 1.57; 95% CI, 1.00–2.47 Weight gain ≥5 kg In women sleeping ≤5 hr: OR, 3.41; 95% CI, 1.34–8.69 In women sleeping 8 hr: OR, 3.03; 95% CI, 1.29–7.12 In women sleeping 9 hr: OR, 3.77; 95% CI, 1.55–9.17 In total or men: no significant findings
Stranges et al. (2008)[59]	Prospective study (follow-up: 1997–1999 to 2003–2004)/the United Kingdom	White-collar British civil servants from the Whitehall II Study (n=10,308)	Short sleep: ≤5 hr/day Normal sleep: 7 hr/day	Self-reported	35–55, 72.1%	Changes in BMI Short sleep: β, −0.06; 95% CI, −0.26–0.14 Changes in WC Short sleep: β, 0.44; 95% CI, −0.23–1.12 New-onset obesity Short sleep: OR, 1.05; 95% CI, 0.60–1.82
Nishiura et al. (2010)[60]	Prospective study (follow-up: 4 yr)/Japan	Nonobese Japanese male workers (n=2,632)	Short sleep: <6 hr/day Normal sleep: 7–7.9 hr/day	Self-reported	40–59, 100%	New-onset obesity Short sleep: OR, 2.46; 95% CI, 1.41–4.31

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Table 1. Continued

Author (year)	Type of study/ country or region	Study population (sample size)	Definition of sleep disturbances	Method of sleep assessment	Age (yr) and male (%)	Outcome
Watanabe et al. (2010)[61]	Prospective study (follow-up: 1 yr)/ Japan	Employees for an electric power company (n=23,212)	Sleep duration was categorized as: <5, 5–<6, 6–<7, 7–<8, 8–<9, and ≥9 hr/day Reference: 7–<8 hr/day	Self-reported	39.8±9.6, 86.3%	Weight gain Male with sleep <5 hr/day: β, 0.016; 95% CI, 0.024–0.146; P<0.01 Male with sleep <5 hr/day: β, 0.0013; 95% CI, 0.001–0.061; P=0.04 Male with sleep ≥9 hr/day: β, 0.018; 95% CI, 0.079–0.340; P<0.01 New-onset obesity Male with sleep <5 hr/day: OR, 1.91; 95% CI, 1.36–2.67 Male with sleep 5–6 hr/day: OR, 1.50; 95% CI, 1.24–1.80 No significant association between sleep duration and weight gain or obesity was found for women.
Itani et al. (2011)[62]	Prospective study (follow-up: 7 yr)/ Japan	Workers in a local government organization (n=22,743)	Short sleep: <5 hr/day Normal sleep: 5–7 hr/day	Self-reported	NS, 95.4%	New-onset obesity Male subjects with short sleep: RR, 1.20; 95% CI, 1.09–1.32 Female subjects with short sleep: RR, 1.71; 95% CI, 1.11–2.87
Lyytikäinen et al. (2011)[63]	Prospective study (follow-up: 5–7 yr)/ Finland	Middle-aged municipal employees from the Helsinki Health Study (n=7,027)	Short sleep: ≤5 hr/day Long sleep: ≥9 hr/day Reference: 7 hr/day	Self-reported	40–60, 18.5%	Weight gain ≥5 kg Female with short sleep: OR, 1.42; 95% CI, 1.01–2.01 Female with long sleep: OR, 1.30; 95% CI, 0.97–1.76 Male with short sleep: OR, 0.88; 95% CI, 0.44–1.74 Male with long sleep: OR, 1.06; 95% CI, 0.48–2.32
Kobayashi et al. (2012)[64]	Prospective study (follow-up: 3 yr)/ Japan	Healthy population (n=11,136)	Sleep duration was categorized as: ≤5, 6, 7, and ≥8 hr/day Reference: 7 hr/day	Self-reported	≥20, 44.0%	Weight gain Sleep ≤5: β coefficient, 0.03; 95% CI, 0.03–1.1; P=0.02 Sleep ≥8: β coefficient, 0.01; 95% CI, −0.03–0.1; P=0.34 New-onset obesity Sleep ≤5: OR, 1.5; 95% CI, 1.1–2.0 Sleep ≥8: OR, 1.3; 95% CI, 0.9–1.8
Yiengprugsawan et al. (2012)[65]	Prospective study (follow-up: 4 yr)/ Thailand	Distance learners at Sukhothai Thammathirat Open University (n=60,569)	Sleep duration was categorized as <6, 6, 7, 8 and ≥9 hr/day, Short sleep: <6 hr/day Long sleep: ≥9 hr/day Reference: 7 hr/day	Self-reported	35.6 (20–49), 45.2%	Overweight Female with short sleep: OR, 1.33; 95% CI, 1.18–1.51 Female with long sleep: OR, 1.22; 95% CI, 1.07–1.39 Male with short sleep: OR, 1.13; 95% CI, 1.00–1.28 Male with long sleep: OR, 1.03; 95% CI, 0.91–1.16 New-onset obesity Female with short sleep: OR, 1.49; 95% CI, 1.32–1.68 Female with long sleep: OR, 1.36; 95% CI, 1.20–1.53 Male with short sleep: OR, 1.36; 95% CI, 1.21–1.52 Male with long sleep: OR, 1.16; 95% CI, 1.03–1.30
Nagai et al. (2013)[66]	Prospective study (follow-up: 11 yr)/ Japan	General population (n=9,658)	Short sleep: ≤5 hr/day Long sleep: ≥9 hr/day Reference: 7 hr/day	Self-reported	40–79, NS	Weight gain ≥5 kg Total subjects with short sleep: OR, 0.93; 95% CI, 0.73–1.20 Total subjects with long sleep: OR, 1.05; 95% CI, 0.91–1.20 BMI ≥25 kg/m² with short sleep: RR, 0.86; 95% CI, 0.58–1.29 BMI ≥25 kg/m² with long sleep: OR, 1.36; 95% CI, 1.09–1.70 New-onset obesity Short sleep: OR, 1.08; 95% CI, 0.77–1.51 Long sleep: OR, 1.06; 95% CI, 0.86–1.29

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Table 1. Continued

Author (year)	Type of study/ country or region	Study population (sample size)	Definition of sleep disturbances	Method of sleep assessment	Age (yr) and male (%)	Outcome
Ohkuma et al. (2013)[67]	Cross-sectional study/Japan	Japanese patients with T2DM (n=4,870)	Sleep duration was categorized as: <4.5, 4.5–5.4, 5.5–6.4, 6.5–7.4, 7.5–8.4, and ≥8.5 hr/day; Reference: 6.5–7.4 hr/day	Self-reported	≥20, 57%	ORs (95% CIs) for obesity Sleep <4.5 hr/day: OR, 1.78; 95% CI, 1.26–2.52 Sleep ≥8.5 hr/day: OR, 1.24; 95% CI, 0.97–1.58 *P* for quadratic trend: <0.001
Sayón-Orea et al. (2013)[68]	Prospective study (median follow-up: 6.5 yr)/Spain	General population from the SUN Mediterranean Cohort (n=10,532)	Sleep duration was categorized as <5, 5–<7, 7–<8, ≥8 hr/night; Reference: 7–<8 hr/day	Self-reported	39±12, NS	New-onset obesity Total with sleep <5 hr/night: HR, 1.94; 95% CI, 1.19–3.18 Male with sleep <5 hr/night: HR, 2.09; 95% CI, 1.18–3.69 Female with sleep <5 hr/night: HR, 1.26; 95% CI, 0.44–3.57 Total with sleep ≥8 hr/night: HR, 1.13; 95% CI, 0.89–1.43 Male with sleep ≥8 hr/night: HR, 0.88; 95% CI, 0.64–1.21 Female with sleep ≥8 hr/night: HR, 1.43; 95% CI, 0.97–2.10
Xiao et al. (2013)[69]	Prospective study (follow-up: 7.5 yr)/the United States	General population from the National Institutes of Health-AARP Diet and Health Study (n=83,377)	Sleep duration was categorized as <5, 5–6, 7–8, ≥9 hr/day; Reference: 7–8 hr/day	Self-reported	51–72, 51.8%	Weight gain ≥5 kg Male with sleep <5 hr/day: OR, 1.27; 95% CI, 1.07–1.52 Female with sleep <5 hr/day: OR, 1.30; 95% CI, 1.12–1.51 Male with sleep ≥9 hr/day: OR, 1.16; 95% CI, 0.99–1.36 Female with sleep ≥9 hr/day: OR, 1.02; 95% CI, 0.88–1.17 New-onset obesity Male with sleep <5 hr/day: OR, 1.45; 95% CI, 1.06–1.99 Female with sleep <5 hr/day: OR, 1.37; 95% CI, 1.04–1.79 Sleep duration ≥9 hr/day Male with sleep ≥9 hr/day: OR, 1.12; 95% CI, 0.84–1.49 Female with sleep ≥9 hr/day: OR, 0.91; 95% CI, NS
Vgontzas et al. (2014)[70]	Prospective study (total follow-up: 7.5 yr; women: 4.5 yr; men: 10.5 yr)/the United States	General population from the Penn State Cohort (n=815)	Sleep duration was categorized as ≤5, 5–6, 6–7, ≥7 hr/night; Reference: ≥7 hr/night	Self-reported (subjective) and PSG (objective)	48.9±13.4, 50.5%	New-onset obesity Subjective sleep duration ≤5hr/night: OR, 1.08; 95% CI, 0.48–2.41 Objective sleep duration ≤5hr/night OR, 0.51; 95% CI, 0.22–1.18
Gutiérrez-Repiso et al. (2014)[71]	Prospective study (follow-up: 11 yr)/Spain	General population from the Pizarra cohort study (n=1,145)	Short sleep: ≤7 hr/night; Normal sleep: ≥8 hr/night	Self-reported	18–65, 38.8%	ORs of becoming obese in subjects with short sleep At the 6-yr follow-up: OR, 1.99; 95% CI, 1.12–3.55 At the 11-yr follow-up: OR, 2.73; 95% CI, 1.47–5.04
Kim et al (2015)[72]	Prospective study (follow-up: 2.6 yr)/Korea	General population from the ARIRANG Study (n=3,862)	Short sleep: <6 hr/day; Long sleep: ≥10 hr/day; Reference: 6–7.9 hr/day	Self-reported	40–70, 41.1%	New-onset metabolic syndrome Short sleep: OR, 1.41; 95% CI, 1.06–1.88 Long sleep: OR, 0.68; 95% CI, 0.39–1.17 High WC Short sleep: OR, 1.30; 95% CI, 0.98–169 Long sleep: OR, 0.97; 95% CI, 0.62–1.50

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Table 1. Continued

Author (year)	Type of study/country or region	Study population (sample size)	Definition of sleep disturbances	Method of sleep assessment	Age (yr) and male (%)	Outcome
Zhang et al. (2015)[73]	Cross-sectional study/China	School-aged children (n=3,086)	Sleep duration was categorized as: ≤8.00, 8.01–9.00, 9.01–10.00, and >10 hr/night; Reference: >10 hr/night; Sleep compensated group: (weekend [or holiday] sleep duration−weekday sleep duration)/weekday sleep duration×100% ≥10% Reference: noncompensated group	Self-reported	7–14, 52.1%	Risk of being overweight/obese Weekdays sleep ≤8.00 hr/night: OR, 1.995; 95% CI, 0.917–4.219 Weekends sleep ≤8.00 hr/night: OR, 2.691; 95% CI, 1.513–4.785 Long holidays sleep ≤8.00 hr/night: OR, 2.921; 95% CI, 1.630–5.323 Sleep compensation during weekends: OR, 1.197; 95% CI, 1.004–1.493 Sleep compensation during holidays: OR, 1.309; 95% CI, 1.052–1.630
Sleep duration and risk of diabetes						
Ayas et al. (2003)[11]	Prospective (mean follow-up: 10 yr)/the United States	Female married registered nurses from the Nurses' Health Study (n=70,026)	Short sleep: ≤5 hr/day Long sleep: ≥9 hr/day Reference: 8 hr/day	Self-reported	40–65, 0%	New-onset symptomatic diabetes Short sleep: RR, 1.34; 95% CI, 1.04–1.72 Long sleep: RR, 1.35; 95% CI, 1.04–1.75
Mallon et al. (2005)[74]	Prospective (mean follow-up: 12 yr)/Sweden	General population (n=1,170)	Short sleep: ≤5 hr/night Long sleep: ≥9 hr/night Reference: 5–8 hr/night	Self-reported	45–65, 47.0%	New-onset diabetes Male with short sleep: RR, 2.8; 95% CI, 1.1–7.3 Female with short sleep: RR, 1.8; 95% CI, 0.5–6.8 Male with long sleep: NS Female with long sleep: RR, 2.9; 95% CI, 0.6–15.0
Yaggi et al. (2006)[75]	Prospective study (follow-up: 15–17 yr)/the United States	Men from the Massachusetts Male Aging Study without diabetes (n=1,139)	Average sleep duration was divided into: ≤5, 6, 7, 8, and >8 hr/night; Reference: 7 hr/night	Self-reported	40–70, 100%	New-onset diabetes Sleep ≤5 hr/night: RR, 1.95; 95% CI, 0.95–4.01 Sleep >8 hr/night RR, 3.12; 95% CI, 1.53–6.37 Further adjusted for testosterone Sleep ≤5 hr/night: RR, 1.51; 95% CI, 0.71–3.19 Sleep >8 hr/night RR, 2.81; 95% CI, 1.34–5.90
Gangwisch et al. (2007)[76]	Prospective study (follow-up: 8-10 yr)/the United States	General population from the First National Health and Nutrition Examination Survey I (n=8,992)	Short sleep: ≤5 hr/night Long sleep: ≥9 hr/night Reference: 7 hr/night	Self-reported	32–86, 37%	New-onset diabetes Short sleep: OR, 1.47; 95% CI, 1.03–2.09 Long sleep: OR, 1.52; 95% CI, 1.06–2.18
Hayashino et al. (2007)[77]	Prospective study (median follow-up: 4.2 yr)/Japan	Asian workers from High-risk and Population Strategy for Occupational Health Promotion Study (n=6,509)	Short sleep: sleep duration <6 hr/day Long sleep: ≥9 hr/day Reference: 6–7 hr/day	Self-reported	38.2 (19–69), 73.9%	New-onset diabetes Short sleep: HR, 1.15; 95% CI, 0.76–1.74 Long sleep: HR, 1.03; 95% CI, 0.62–1.70
Beihl et al. (2009)[78]	Prospective study (follow-up: 5 yr)/the United States	General population from the Insulin Resistance Atherosclerosis Study (n=900)	Short sleep: ≤7 hr/night Long sleep: ≥9 hr/night Reference: 8 hr/night	Self-reported	40–69, 43.3%	New-onset diabetes Non-Hispanic whites and Hispanics with short sleep: OR, 2.36; 95% CI, 1.11–5.00 Non-Hispanic whites and Hispanics with long sleep: OR, 2.15, 95% CI, 0.50–9.30 African American with short sleep: OR, 0.63; 95% CI, 0.14–2.90 African American with long sleep: OR, 0.39; 95% CI, 0.02–7.19

(Continued to the next page)

Table 1. Continued

Author (year)	Type of study/country or region	Study population (sample size)	Definition of sleep disturbances	Method of sleep assessment	Age (yr) and male (%)	Outcome
Chaput et al. (2009)[79]	Longitudinal study (mean follow-up: 6.0±0.9 yr)/Canada	General population from the Quebec Family Study (n=276)	Short sleep: ≤6 hr/night Long sleep: ≥9 hr/night Reference: 7–8 hr/night	Self-reported	21–64, 42.4%	New-onset T2DM or IGT Short sleep: OR, 2.42; 95% CI, 1.49–3.33 Long sleep: OR, 2.31; 95% CI, 1.41–3.15
Xu et al. (2010)[80]	Prospective study (follow-up: 6 yr)/the United States	General population from the National Institutes of Health-American Association of Retired Persons Diet and Health cohort (n=164,399)	Average sleep duration was divided into: <5, 5–6, 7–8, and ≥9 hr/night; Reference: 7–8 hr/night Day napping was categorized as: none, <1 hr, and ≥1 hr/day; Reference: none	Self-reported	50–71, 56.8%	New-onset diabetes Sleep <5 hr/night: OR, 1.34; 95% CI, 1.20–1.50 Sleep 5–6 hr/night: OR, 1.06; 95% CI, 1.01–1.11 Sleep ≥9 hr/night: OR, 1.09; 95% CI, 0.97–1.22 Day napping <1 hr/day: OR, 1.23; 95% CI, 1.18–1.29 Day napping ≥1 hr/day: OR, 1.55; 95% CI, 1.45–1.66 Hours of day napping×night sleep on diabetes: $P<0.0001$; among participants with no napping, only short night sleeping was associated with higher occurrence of diabetes (OR, 1.32), whereas among those with ≥1 hr of napping, both long (OR, 1.55) and short (OR, 1.78) sleeping was associated with higher risk.
Kita et al. (2012)[81]	Prospective, occupational-based study (follow-up: 4 yr)/Japan	Local government employees (n=3,570)	Short sleep: ≤5 hr/day Reference: >7 hr/day	Self-reported	35–55, 79.0%	New-onset diabetes Short sleep: OR, 5.37; 95% CI, 1.38–20.91
von Ruesten et al. (2012)[82]	Prospective study (mean follow-up: 7.8 yr)/Germany	General population from the European Prospective Investigation into Cancer and Nutrition-Potsdam Study (n=23,620)	Short sleep: <6 hr/day Long sleep: ≥9 hr/day Reference: 7–<8 hr/day	Self-reported	35–65, 38.6%	New-onset diabetes Short sleep: HR, 1.06; 95% CI, 0.80–1.40 Long sleep: HR, 1.05; 95% CI, 0.82–1.33
Holliday et al. (2013)[83]	Prospective study (mean follow-up: 2.3 yr)/Australia	General population from the 45 and Up Study (n=212,388)	Average sleep duration was categorized as: <6, 6–<7, 7–<8, 8–<9, 9–<10, and ≥10 hr/day; Reference: 7–<8 hr/day	Self-reported	≥45, 47.3%	New-onset diabetes Sleep <6 hr: HR, 1.29; 95% CI, 1.08–1.53 Sleep ≥10 hr: HR, 1.03; 95% CI, 0.88–1.19
Gutiérrez-Repiso et al. (2014)[71]	Prospective study (follow-up: 11 yr)/Spain	General population from the Pizarra cohort study (n=1,145)	Short sleep: ≤7 hr/night Reference: ≥8 hr/night	Self-reported	18–65, 38.8%	New-onset diabetes At the 6-yr follow-up, short sleep: OR, 1.96; 95% CI, 1.10–3.50 At the 11-yr follow-up, short sleep: OR, 1.28; 95% CI, 0.60–2.69
Heianza et al. (2014)[84]	Prospective study (follow-up: 8 yr)/Japan	Workers (n=38,987)	Average sleep duration was categorized as: <5.5, 5.5–<6.5, 6.5–<7.0, 7.0–7.5, >7.5–8.0, or >8.0 hr/day; Short sleep: <5.5 or 5.5–<6.5 hr/day; Reference: 7.0–7.5 hr/day	Self-reported	18–83, 64.2%	New-onset diabetes Sleep <5.5 hr: OR, 1.53; 95% CI, 1.19–1.97 Sleep 5.5–<6.5 hr: OR, 1.25; 95% CI, 1.10–1.42 Sleep >8 hr/day: OR, 1.03; 95% CI, 0.81–1.30 In age <45 yr, sleep <5.5 hr: OR, 1.61; 95% CI, 1.08–2.42 In age 46–59 yr, sleep <5.5 hr: OR, 1.56; 95% CI, 1.10–2.22 In age ≥60 yr, sleep <5.5 hr: OR, 1.72; 95% CI, 0.75–3.92
Lou et al. (2015)[85]	Prospective study (median follow-up: 5 yr)/China	General population (n=11,842)	Short sleep: ≤6 hr/night Long sleep: ≥8 hr/night Reference: 6–8 hr/night	Self-reported	44.8±14.7, 45.4%	New-onset T2DM Short sleep: RR, 1.67; 95% CI, 1.34–2.16 Long sleep: RR, 1.45; 95% CI, 1.02–1.77

Table 1. Continued

Author (year)	Type of study/country or region	Study population (sample size)	Definition of sleep disturbances	Method of sleep assessment	Age (yr) and male (%)	Outcome
Kim et al. (2015)[72]	Prospective study (follow-up: 2.6 yr)/Korea	General population (n=3,862)	Short sleep: <6 hr/day Long sleep: ≥10 hr/day Reference: 6–7.9 hr/day	Self-reported	40–70, 41.1%	High blood glucose Short sleep: OR, 1.31: 95% CI, 0.96–1.79 Long sleep: OR, 0.56; 95 CI, 0.29–1.04
Han et al. (2016)[86]	Prospective Study (follow-up: 3–4.75 yr)/China	Retired employees from the Dongfeng-Tongji cohort (n=16,399)	Sleep duration was categorized as: <7, 7–<8 (reference), 8–<9, 9–<10, and ≥10 hr/night; afternoon napping was divided into: no napping (0 min, reference), 1–30, 31–60, 61–90, and >90 min	Self-reported	62.5, 43.2%	New-onset diabetes Sleep <7 hr/night: HR, 0.93; 95% CI, 0.72–1.19 Sleep ≥10 hr/night: HR, 1.42; 95% CI, 1.08–1.87 Napping >90 min: HR, 1.28; 95% CI, 1.03–1.59 Sleep duration ≥10 hr/night and napping >60 min: HR, 1.72; 95% CI, 1.03–2.85

Sleep duration and glycemic control

Author (year)	Type of study/country or region	Study population (sample size)	Definition of sleep disturbances	Method of sleep assessment	Age (yr) and male (%)	Outcome
Knutson et al. (2006)[87]	Cross-sectional study/the United States	African-American women and men with diabetes (n=161)	Perceived sleep debt: the difference between weekday sleep duration and preferred sleep duration	Self-reported	57±12, 26.1%	Glycemic control (lnHbA1c) Sleep debt in patients without diabetic complications: β, 0.51; P=0.04 Sleep debt in patients with 1 or more diabetic complications: β, −0.005; P=0.85
Kim et al. (2013)[88]	Cross-sectional study/Korea	Korean patients with diabetes (n=2,134)	Sleep duration was categorized as: <6, 6, 7, 8, and ≥9 hr/day; Reference: 7 hr/day	Self-reported	61.7±12.3, 49.9%	OR of high HbA1c (≥7.0%) Total with sleep <6 hr/day: OR, 1.15; 95% CI, 0.85–1.60 Total with sleep ≥9 hr/day: OR, 1.38; 95% CI, 0.93–2.03 Female with sleep <6 hr/day: OR, 1.46; 95% CI, 0.96–2.21 Female with sleep ≥9 hr/day: OR, 1.31; 95% CI, 0.75–2.27 Age <65 yr with sleep <6 hr/day: OR, 1.34; 95% CI, 0.86–2.09 Age <65 yr with sleep ≥9 hr/day: OR, 1.33; 95% CI, 0.84–2.41
Ohkuma et al. (2013)[67]	Cross-sectional study/Japan	Japanese patients with T2DM (n=4,870)	Sleep duration was categorized as: <4.5, 4.5–5.4, 5.5–6.4, 6.5–7.4, 7.5–8.4, and ≥8.5 hr/day	Self-reported	≥20, 57%	Adjusted geometric means (95% CIs) of HbA1c Sleep <4.5 hr/day: 7.52(7.38–7.67) Sleep 6.5–7.4 hr/day: 7.32(7.28–7.37) Sleep ≥8.5 hr/day: 7.43(7.34–7.52) P for quadratic trend: 0.004
Wang et al. (2015)[89]	Cross-sectional study/China	Patients with diabetes from the baseline survey of the REACTION Study (n=56,032)	Sleep duration was categorized as: <6, 6–7.9, 8–8.9, and ≥9 hr/night; Reference: 6–7.9 hr/night	Self-reported	Sleep <6 hr/night: 61.2±8.8, 37%; Sleep ≥9 hr/night: 61.4±9.7, 38%; Reference: 60.5±8.8, 39%	Poor glycemic control (HbA1c ≥7.0%) Sleep <6 hr/night OR, 1.09; 95% CI, 0.99–1.21 Sleep ≥9 hr/night: OR, 1.11; 95% CI, 1.05–1.18
Kong et al. (2017)[90]	Cross-sectional study/Hong Kong	Hong Kong Chinese patients with T2DM (n=3,508)	Sleep duration: the period between bedtime and wake-up time on weekdays and weekends	Self-reported	53.9±8.7, 59%	Sleep duration difference between weekdays and weekends is curvilinearly associated with both HbA1c and FPG. One hour more sleep during weekends than weekdays was associated with a decrease in HbA1c (−0.13%; 95% CI, −0.24 to −0.02).

Values are presented as range, mean±standard deviation, or mean (range).
RR, relative risk; CI, confidence interval; HR, hazard ratio; OR, odds ratio; NS, not specified; BMI, body mass index; WC, waist circumference; T2DM, type 2 diabetes mellitus; PSG, polysomnography; IGT, impaired glucose tolerance; FPG, fasting plasma glucose.

Table 2. Clinical studies examining the association between sleep quality with obesity and diabetes

Author (year)	Type of study/ country or region	Study population (sample size)	Definition of sleep disturbances	Method of sleep assessment	Age (yr) and male (%)	Outcome
Sleep quality and weight gain/obesity						
Lytikäine et al. (2011)[91]	Prospective study (follow-up: 5–7 yr)/Finland	Middle-aged municipal employees from the Helsinki Health Study (n=7,022)	Trouble falling asleep, waking up several times per night, trouble staying asleep, or waking up early feeling tired; the corresponding sleep problems ≥15 nights in the past 4 weeks	Self-reported (the Jenkins Sleep Questionnaire)	40–60, 18.5%	Weight gain of ≥5 kg Female with trouble falling asleep: OR, 1.49; 95% CI, 1.09–2.03 Female with waking up several times per night: OR, 1.34; 95% CI, 1.09–1.65 Female with trouble staying asleep: OR, 1.29; 95% CI, 1.02–1.62 Female with waking up tired: OR, 1.04; 95% CI, 0.83–1.30 Male: NS
Huang et al. (2013)[92]	Cross-sectional study/China	Patients with insomnia (n=141)	Slow wave sleep time and rapid eye movement sleep time	PSG	Insomnia: 42.2±9.8, 44% Healthy: 38.9±12.4, 51%	BMI Slow wave sleep time (min): β, −0.013; 95% CI, −0.026 to −0.001; P=0.043 Rapid eye movement sleep time (min): β, 0.007; 95% CI, −0.008 to 0.023; P=0.352
Piccolo et al. (2013)[93]	Prospective study (follow-up: 4.8±0.6 yr)/the United States	General population from the Boston Area Community Health Survey (n=4,145)	Restless sleep: experiencing restless sleep much of the time during the past week	Self-reported	30–79, NS	New-onset obesity Experiencing restless sleep: OR, 1.66; 95% CI, 1.10–2.49
Sivertsen et al. (2014)[94]	Prospective study (follow-up: 11 yr)/Norway	General population from the Nord-Trøndelag Health Studies (n=24,715)	Insomnia: "often" or "almost every night" had difficulties in initiating or maintaining sleep in the preceding month, in addition to reporting impaired work performance caused by insomnia during the preceding year	Self-reported	32–66, 43.1%	New-onset obesity Insomnia: OR, 1.13; 95% CI, 0.96–1.33
Vgontzas et al. (2014)[70]	Prospective study (total follow-up: 7.5 yr; women: 4.5 yr; men: 10.5 yr)/the United States	General population (n=815)	Insomnia: a complaint of insomnia with a duration of ≥1 yr Poor sleep: a moderate-to-severe complaint of difficulty falling asleep, difficulty staying asleep, early morning awakening, or non-restorative sleep. Normal sleep: absence of either of these two categories.	Self-reported	48.9±13.4, 50.5%	New-onset obesity Insomnia with adjustment for subjective sleep duration: OR, 0.48; 95% CI, 0.15–1.53 Poor sleep with adjustment for subjective sleep duration: OR, 1.78; 95% CI, 1.02–3.13 Insomnia with adjustment for objective sleep duration: OR, 0.59; 95% CI, 0.20–1.77 Poor sleep with adjustment for objective sleep duration: OR, 1.76; 95% CI, 1.03–3.00
Tan et al. (2015)[95]	Cross-sectional study/Finland	Overweight middle-aged men (n=211)	OSA: an AHI of 5 or greater with EDS or an AHI of 15 or greater, regardless of associated symptoms Insomnia: DIS and/or DMS and/or NRS, and lasted for at least 1 month during the last 3 months Reference: overweight participants free from any sleep disorders	Specialist physician diagnosis (through Vitalmed sleep questionnaire and PSG)	30–65, 100%	BMI Reference, 15.8±4.3; OSA, 19.7±6.0 (P<0.05); insomnia, 18.5±5.9; OSA+insomnia, 19.7±7.1 (P<0.05) Waist circumference (cm) Reference, 98.0±7.6; OSA, 110.4±9.0 (P<0.05); insomnia, 106.5±10.2 (P<0.05); OSA+insomnia, 111.4±14.7 (P<0.05) Fat mass trunk (kg) Reference, 15.8±4.3; OSA, 19.7±6.0 (P<0.05); insomnia, 18.5±5.9 (P<0.05); OSA+insomnia, 19.7±7.1 (P<0.05) Fat mass android region (kg) Reference, 2.9±0.9; OSA, 3.7±1.1 (P<0.05); insomnia, 3.5±1.2 (P<0.05); OSA+insomnia, 3.8±1.4 (P<0.05)

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Table 2. Continued

Author (year)	Type of study/ country or region	Study population (sample size)	Definition of sleep disturbances	Method of sleep assessment	Age (yr) and male (%)	Outcome
Sleep quality and risk of diabetes						
Nilsson et al. (2004)[96]	Prospective study (mean follow-up: 14.8±2.4 yr)/ Sweden	Healthy men from the Malmo Preventive Project (n=6,599)	Sleep disturbances: had either or both positive reply to difficulty in falling asleep or generally use sleeping pills more than 3 times a week	Self-reported questionnaire	35–51, 100%	New-onset diabetes Sleep disturbances: OR, 1.52; 95% CI, 1.05–2.20
Björkelund et al. (2005)[97]	Prospective study (follow-up: 32 yr)/Sweden	Swedish women from the Population Study of Women in Gothenburg (n=661)	Sleep complaints: sleep problems (without specified time frame) and/ or having consulted a doctor for sleep problems and/or hospital admission for this reason	Self-reported	70–92, 0%	New-onset diabetes Sleep complaints: RR, 1.04; 95% CI, 0.91–1.18
Mallon et al. (2005)[74]	Prospective study (mean follow-up: 12 yr)/Sweden	General population (n=1,170)	DIS: had severe difficulties (scores 4 and 5) in initiating sleep DMS: had severe difficulties (scores 4 and 5) in maintaining sleep	Self-reported (the Uppsala Sleep Inventory)	45–65, 47.0%	New-onset diabetes Male with DIS: RR, 2.4; 95% CI, 0.7–8.6 Male with DMS: RR, 4.8; 95% CI, 1.9–12.5 Female with DIS: NS Female with DMS: RR, 1.8; 95% CI, 0.5–6.0
Meisinger et al. (2005)[98]	Prospective study (mean follow-up: 7.5 yr)/Germany	General population (n=8,269)	DIS: often had trouble falling asleep DMS: often woke up during the night	Self-reported	25–74, 49.9%	New-onset diabetes Male with DIS: HR, 1.10; 95% CI, 0.59–2.03 Female with DIS: HR, 1.42; 95% CI, 0.81–2.50 Male with DMS: HR, 1.60; 95% CI, 1.05–2.45 Female with DMS: HR, 1.60; 95% CI, 1.05–2.45
Hayashino et al. (2007)[77]	Prospective study (median follow-up: 4.2 yr)/Japan	Asian healthy workers from High-risk and Population Strategy for Occupational Health Promotion Study (n=6,509)	DIS: sometimes or often had difficulties initiating sleeping DMS: sometimes or often had difficulties maintaining sleeping	Self-reported	38.2 (19–69), 73.9%	New-onset diabetes Sometimes DIS: HR, 1.42; 95% CI, 1.05–1.91 Often DIS: HR,1.61; 95% CI, 1.00–2.58 Sometimes DMS: HR, 1.31; 95% CI, 0.97–1.76 Often DMS: 1.37; 95% CI, 0.87–2.16
Kita et al. (2012)[81]	Prospective, occupational-based study (follow-up: 4 yr)/Japan	Local government employees (n=3,570)	Any sleep difficulties participants may have experienced ≥3 times a week during the previous month in sleep induction, awakening during the night, early morning awakening, self-perceived insufficient sleep duration, and overall quality of sleep	Self-reported questionnaire	35–55, 79.0%	New-onset diabetes Awakening during the night: OR, 5.03; 95% CI, 1.43–17.64 Self-perceived insufficient sleep duration: OR, 6.76; 95% CI, 2.09–21.87 Unsatisfactory overall quality of sleep: OR, 3.71; 95% CI, 1.37–10.07
Piccolo et al. (2013)[93]	Prospective study (mean follow-up: 4.8±0.6 yr)/ the United States	General population from the Boston Area Community Health Survey (n=4,145)	Restless sleep: experiencing restless sleep much of the time during the past week	Self-reported	30–79, NS	New-onset T2DM Restless sleep: OR, 1.05; 95% CI, 0.67–1.64
Sivertsen et al. (2014)[94]	Prospective study (follow-up: 11 yr)/Norway	General population from the Nord-Trøndelag Health Studies (n=24,715)	Insomnia: "often" or "almost every night" had difficulties in initiating or maintaining sleep in the preceding month, in addition to reporting impaired work performance caused by insomnia during the preceding year	Self-reported	32–66, 43.1%	New-onset T2DM Insomnia: OR, 1.07; 95% CI, 0.82–1.41

Table 2. Continued

Author (year)	Type of study/ country or region	Study population (sample size)	Definition of sleep disturbances	Method of sleep assessment	Age (yr) and male (%)	Outcome
Lou et al. (2015)[85]	Prospective study (follow-up: 5 yr)/China	General population (n=11,842)	Poor sleep: had difficulties with initiating and maintaining sleep ≥8 days per month on average during the previous year	Self-reported	44.8±14.7, 45.4%	New-onset T2DM; Poor sleep quality: RR, 1.91; 95% CI, 1.31–2.74; Poor sleep quality with short sleep duration (≤6 hr/night): RR, 6.21; 95% CI, 2.78–11.81
Lee et al. (2016)[99]	Prospective study (median follow-up period: 2.5 yr)/Korea	General population from the family cohort study in primary care (the FACTS) (n=563)	Poor sleep quality: the score of the PSQI ≥5	Self-reported	10–75, 45.6%	New-onset T2DM; RR, 2.64; 95% CI, 1.03–6.78
Sleep quality and glycemic control						
Knutson et al. (2006)[87]	Cross-sectional study/ the United States	African-American women and men with diabetes (n=161)	Modified PSQI score: PSQI score after removing the sleep duration component to assess sleep quality independently from sleep quantity	Self-reported questionnaire	57±12, 26.1%	Glycemic control (lnHbA1c); Modified PSQI score in patients without diabetic complications: β, –0.014; P=0.16; Modified PSQI score in patients with at least 1 diabetic complications: β, 0.043; P=0.002
Wan Mahmood et al. (2013)[100]	Cross-sectional study/Ireland	Caucasian patients with T2DM (n=114)	Poor sleep quality: the score of PSQI >5	Self-reported questionnaire	NS, 54.4%	Log HbA1c; Poor sleep quality: β, 0.038; P=0.826
Cho et al. (2014)[101]	Cross-sectional study/Korea	Patients with T2DM (n=614)	Sleep apnea: SDQ-SA ≥36 for males and ≥32 for females; Poor sleep: PSQI score ≥5; Insomnia: any difficulty in falling asleep, maintaining sleep, early morning waking, and non-restorative sleep occurring at least three times per week over the preceding month	Self-reported questionnaires	59.7±11.1, 62.1%	Postprandial glucose; Sleep apnea score (SDQ-SA): r=0.100, P=0.032; HbA1c; No significant association between HbA1c values and poor sleep, insomnia
Nefs et al. (2015)[102]	Cross-sectional study/the Netherlands	Dutch adults with T1DM (n=267) or T2DM (n=361), (total n=628)	Poor sleep quality: PSQI score >5	Self-reported questionnaire	T1DM: 47±16, 41% T2DM: 62±9, 54%	Most recent HbA1c, % (mmol/mol); In T1DM, good sleep quality vs. poor sleep quality: 7.5±0.9 (58±10) vs. 7.5±1.1 (59±12), P=0.68; In T2DM, good sleep quality vs. poor sleep quality: 7.1±1.3 (54±14) vs. 7.3±1.3 (57±14), P=0.09
Osonoi et al. (2015)[103]	Cross-sectional study/Japan	Patients with T2DM (n=724)	Poor sleep quality: PSQI score ≥9; Average sleep quality: PSQI score 6–8; Good sleep quality: PSQI score ≤5	Self-reported questionnaire	57.8±8.6, 62.9%	Fasting blood glucose (mg/dL); Good sleep: 132±31; average sleep: 136±31; poor sleep: 141±32 (P>0.05); HbA1c (%); Good sleep: 6.9±1.0; average sleep: 7.1±1.1; poor sleep: 7.1±0.8; (P>0.05)

Values are presented as range or mean± standard deviation.
OR, odds ratio; CI, confidence interval; NS, not specified; PSG, polysomnography; BMI, body mass index; OSA, obstructive sleep apnea; AHI, apnea hypopnea index; EDS, excessive daytime sleepiness; DIS, difficulty in initiating sleep; DMS, difficulty in maintaining sleep; NRS, nonrestorative sleep; RR, relative risk; HR, hazard ratio; T2DM, type 2 diabetes mellitus; PSQI: the Pittsburgh Sleep Quality Index; SDQ-SA, the Sleep Disorders Questionnaire Sleep Apnea subscale; T1DM, type 1 diabetes mellitus.

sleep (NRS) is also suggested by the International Classification of Sleep Disorders as a subtype of insomnia.[104]

Although the pathophysiology of insomnia is still not understood, it has long been considered to be a disorder of hyperarousal during both daytime and nighttime, which is associated with increased activation of whole-body and brain metabolism, hyperactivity of HPA axis and hormonal dysregulation.[49] A study involving 1,042 monozygotic and 828 dizygotic twin pairs demonstrated a 10% phenotypic correlation between insomnia and obesity, suggesting a shared genetic mechanism that underlies these conditions.[105] However, the findings about this association were inconsistent in other clinical studies, which mostly reported either no association or an inverse relationship between insomnia and BMI. In a cross-sectional study conducted in 211 Finnish men aged 30−65 years, among the overweight or obese participants (n = 163), those with insomnia (n = 40) had higher fat mass in the trunk and android regions than the group without sleep disorder (n = 76, $P < 0.05$), but no between-group differences in BMI or total fat mass.[95] There was also no difference in BMI when comparing 141 Chinese patients with primary insomnia with 55 healthy volunteers (22.54 ± 2.76 kg/m² vs. 22.84 ± 3.28 kg/m², $P = 0.526$).[92] However, this study found that among patients with insomnia, there was a significant negative correlation between the amount of SWS and BMI after controlling for potential confounders (β, −0.013; 95% confidence interval [CI], −0.026 to −0.001; $P = 0.043$), suggesting that impaired sleep quality in subjects with insomnia may be the culprit linking insomnia with obesity. By contrast, some researchers had reported positive relationships between insomnia and obesity indices. The prospective Helsinki Health Study which included 7,022 middle-aged respondents demonstrated that DIS (odds ratio [OR], 1.65; 95% CI, 1.22−2.22) and DMS (OR, 1.41; 95% CI, 1.13−1.75) were associated with a weight gain of 5 kg or more after 5 to 7 years of follow-up, being more evident in women than in men.[91] In the prospective Penn State Cohort involving 815 nonobese adults with a follow-up duration of 7.5 years, a moderate to severe complaint of any DIS, DMS, EMA, or NRS was associated with an increased incidence of obesity (OR, 1.76−1.78), while insomnia tended towards significance after adjusted for sleep duration, emotional stress, and other potential confounders.[70] Another prospective study conducted in Norwegian population (n = 24,715)

reported that insomnia was associated with an 18% increased risk (95% CI, 1.06−1.33) of incident obesity after 11 years of follow up, which was independent of baseline demographics, anxiety and depression. However, this association was negated when further adjusted for other comorbidities, such as angina, T2DM and hypertension (OR, 1.09; 95% CI, 0.97−1.24).[94] Taken together, these inconclusive results may be related to the adoption of different definitions of insomnia and obesity.

Although conflicting results have been reported for obesity, it appears that most studies support an association between insomnia and diabetes risk. In a meta-analysis of 107,756 participants from 13 independent cohorts, those with insomnia had stronger association with incident diabetes (DIS: RR, 1.57; 95% CI, 1.25−1.97; DMS: RR, 1.84; 95% CI, 1.39−2.43), compared with participants with short sleep duration of ≤ 5−6 hours per night (RR, 1.28; 95% CI, 1.03−1.60).[106] In another larger meta-analysis of nearly 1.1 million participants from 36 studies, insomnia (RR, 1.38; 95% CI, 1.18−1.62) and its subtypes (DIS: RR, 1.55; 95% CI, 1.23−1.95; DMS: RR, 1.72; 95% CI, 1.45−2.05) also demonstrated an independent association with excess risk of developing diabetes.[107]

Short sleep duration with coexistent insomnia may further aggravate the risk of future diabetes. In the Penn State Cohort of 1,741 participants, participants with insomnia and sleep curtailment (< 5-hour per day) had an OR of 2.95 (95% CI, 1.24−7.03) for diabetes after adjustment for age, race, sex, BMI, smoking, alcohol use, depression and sleep-disordered breathing, compared with those who had > 6-hour sleep per day and without insomnia.[108] Conversely, in the retrospective Freiburg Insomnia Cohort involving 328 patients with primary insomnia (203 women and 125 men; mean age, 44.3 ± 12.2 years), those with concomitant short sleep duration did not have increased risk of T2DM (OR, 1.39; 95% CI, 0.34−5.67 for first night of short sleep and OR, 2.30; 95% CI, 0.48−10.96 for second night of short sleep), perhaps due to a small number of patients with T2DM (n = 9).[109] Indeed, there are possible pathogenetic mechanisms underpinning the link between insomnia and risk of diabetes, including reduction of glucose tolerance[40], alteration of HPA axis and sympathetic nervous system[110], and elevated markers of chronic inflammation.[111] Hence, well-designed studies with sufficient sample size are required to unravel the relationship between insomnia and diabetes.

SLEEP AND GENES REGULATING THE CIRCADIAN CLOCK

Clock genes may play a key role in linking sleep and the effect of circadian disruptions on metabolic functions.[23] A central clock which is located within the suprachiasmatic nuclei of the hypothalamus orchestrates the environmental light/dark cycles with human physiology and behavior. Genetic or environmental perturbations of this synchronized molecular mechanism can lead to metabolic disturbances. In the core clock mechanism, the brain and muscle Arnt like protein-1 (BMAL1)/circadian locomotor output cycles kaput (CLOCK) heterodimer binds to the E-box elements in the promoter regions of *Per* and *Cry* genes, thus activating their transcription proteins with feedback inhibition on the BMAL1/CLOCK.[112] Six hours of sleep curtailment was sufficient to reduce BMAL1 binding to the E-box elements of *Per* gene.[23] Other important regulators that integrate the effects of circadian clock on metabolic pathways include the clock-controlled genes and certain transcription factors e.g., REV-ERBα, retinoid-related orphan receptor α, and peroxisome proliferator-activated receptor α.[2,113] These genes can also be categorized by type of regulations e.g., circadian cycle only (BMAL1), sleep-wake cycle only (Homer1a) or both (*Per*). Hence, the effects of sleep on gene expression, subsequent epigenetic modifications and metabolic perturbations require further translational research to improve our understanding about the genes involved and the details of the regulation.[23]

Coordination of the sleep/wake cycle as well as the metabolic and fasting/feeding cycle are all essential to maintain a normal circadian oscillatory system for healthy bodily functions. Glucose homeostasis is regulated by both the central clock that synchronizes sleep and feeding, and peripheral tissue clocks that coordinate one's behavior with glucose synthesis and utilization.[114] When BMAL1/CLOCK heterodimer colocalizes with the pancreatic transcription factor pancreatic and duodenal homeobox 1 on the regulatory sites of beta-cell cycling genes, pancreatic beta-cell maturation is enhanced with possible pulsatile insulin secretion according to the circadian rhythmicity.[114] Similarly, BMAL1-ablation in mice reduces insulin exocytosis from pancreatic beta-cell, resulting in hyperglycemia.[23] Based on the genome-wide association studies, individuals with T2DM and melatonin receptor 1B (*MTNR1B*) risk allele may have high melatonin level that interacts with dietary intake, with subsequent impairment in glucose metabolism and increased risk of T2DM.[23]

Conditions that are often associated with circadian misalignment are shift work and trans-meridian air travel (jet lag). Shift work can desynchronize the central and peripheral circadian clocks, which further perturbs the glucose metabolism by decreasing insulin sensitivity, independent of sleep curtailment.[23,115] In healthy adults, 3-week sleep curtailment with concomitant circadian misalignment is demonstrated to reduce the resting metabolic rate and impair pancreatic beta-cell secretion.[116] In mice model, chronic jet lag disrupts the circadian cycle by uncoupling the central and peripheral clocks in the adipose tissue, and triggers leptin resistance leading to development of obesity, an effect independent of other risk factors.[117] In the large prospective Nurses' Health Study 2, early chronotype combined with increasing years of rotating night shift work aggravated diabetes risk, even after adjustment for patients' attributes, family history of diabetes, diet, physical activity and self-reported sleep duration.[118] Interestingly, late chronotype alone predicted a 51% (hazard ratio, 1.51; 95% CI, 1.13–2.03) excess risk of developing T2DM, which was attenuated by longer night shift exposure, presumably due to less interference to the "usual" circadian rhythm.[118] These findings support the notion that chronotype-adapted work schedules can possibly reduce the circadian misalignment and prevent future cardiometabolic risk.

The circadian clock has been demonstrated to regulate the diurnal fluctuations of certain human metabolites such as the fatty acids and amino acids, independent of the fasting/feeding cycle.[119] In the first human metabolomics study conducted during a 48-hour sleep/wake cycle, 27 of the 171 measured metabolites (e.g., fatty acids, tryptophan, taurine, and serotonin) were significantly elevated with sleep curtailment.[120] This creates novel opportunities for potential therapeutic intervention targeting the key clock-regulated metabolic pathways and application of these noninvasive biomarkers for disease prediction and monitoring.

CONCLUSION

Good sleep hygiene is crucial to maintain optimal functions of the neuroendocrine and appetite regulation systems. To date, there

is clear evidence in support of a causal relationship between sleep, circadian misalignment and cardiometabolic risk. Thus, health promotion campaigns should look beyond conventional strategies by emphasizing the pivotal role of improving sleep environment to curb the obesity epidemic. Nonetheless, there is a pressing need for future research to delineate the molecular intersections between sleep, circadian clock and metabolic pathways, as well as to explore potential preventive and therapeutic approaches to optimize sleep and circadian rhythm in predisposed individuals.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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