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Connecting insufficient sleep and insomnia with metabolic dysfunction

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Abstract

The global epidemic of obesity and type 2 diabetes parallels the rampant state of sleep deprivation in our society. Epidemiological studies consistently show an association between insufficient sleep and metabolic dysfunction. Mechanistically, sleep and circadian rhythm exert considerable influences on hormones involved in appetite regulation and energy metabolism. As such, data from experimental sleep deprivation in humans demonstrate that insufficient sleep induces a positive energy balance with resultant weight gain, due to increased energy intake that far exceeds the additional energy expenditure of nocturnal wakefulness, and adversely impacts glucose metabolism. Conversely, animal models have found that sleep loss–induced energy expenditure exceeds caloric intake resulting in net weight loss. However, animal models have significant limitations, which may diminish the clinical relevance of their metabolic findings. Clinically, insomnia disorder and insomnia symptoms are associated with adverse glucose outcomes, though it remains challenging to isolate the effects of insomnia on metabolic outcomes independent of comorbidities and insufficient sleep durations. Furthermore, both pharmacological and behavioral interventions for insomnia may have direct metabolic effects. The goal of this review is to establish an updated framework for the causal links between insufficient sleep and insomnia and risks for type 2 diabetes and obesity.

Graphical Abstract

The global epidemic of obesity and type 2 diabetes parallels the rampant state of sleep deprivation in our society. Epidemiological studies consistently show an association between insufficient sleep and metabolic dysfunction. The goal of this review is to establish an updated framework for the causal links between insufficient sleep and insomnia and risks for type 2 diabetes and obesity.

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D.D., L.J.K., J.C.J., and V.Y.P. contributed to the conception and design of the manuscript. D.D. and L.J.K. drafted the manuscript. D.D., L.J.K., J.C.J., and V.Y.P. revised the intellectual contents and approved the final version of the submitted manuscript.

Competing interests

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Keywords

insomnia; insufficient sleep; obesity; diabetes; metabolism

INTRODUCTION

Sleep and metabolism are present in all living organisms and serve life-sustaining functions. Given the homeostatic nature of both processes, the relationship between sleep and metabolism is complex and bidirectional. Sleep insufficiency and disorders have metabolic consequences, while metabolic dysfunction can similarly adversely affect sleep. Furthermore, the global epidemic of obesity and type 2 diabetes parallels the rampant state of sleep deprivation in our society. As sleep is increasingly recognized as a potentially modifiable behavior, understanding how sleep influences metabolic outcomes is a crucial first step in investigating common pathogenesis and therapeutic implications.

In this review, we will focus on the effects of volitional (i.e., insufficient sleep duration) and involuntary (i.e., insomnia) sleep loss on energy homeostasis and glucose metabolism and, consequently, the risks for the development of type 2 diabetes and obesity. We recognize that insufficient sleep and insomnia are not the same physiological states and each has distinct mechanisms and metabolic consequences. The relationships between metabolic diseases and sleep disorders such as obstructive sleep apnea and circadian rhythm disorders are widely discussed in the literature and are beyond the scope of this review. Our goal is to establish a framework for the causal links between sleep loss and risks for type 2 diabetes and obesity. We will first review metabolic and hormonal processes that occur during normal sleep. Next, we will delve into metabolic dysfunction as a result of insufficient sleep and insomnia from both epidemiological and mechanistic perspectives. Lastly, we will discuss the metabolic effects of sleep interventions, both pharmacological and behavioral.

METABOLIC AND HORMONAL PROCESSES DURING NORMAL SLEEP

Normal sleep architecture

Normal sleep is categorized into two states: rapid eye movement (REM) and non-rapid eye movement (NREM) sleep. The first part of normal sleep is typically NREM sleep, and REM sleep begins ~80 minutes or longer into sleep. Thereafter, 90-minute sleep cycles occur throughout the night, with alternating stages of NREM and REM sleep within each sleep cycle. REM sleep accounts for an increasing proportion of sleep time as the night progresses. REM sleep is characterized by electroencephalography (EEG) activation, low muscle tone, and rapid eye movements. REM sleep is associated with dreaming and is particularly sensitive to circadian timing and extremes of temperature. NREM sleep is further subdivided into three stages: N1 (stage 1), N2 (stage 2), and N3 (stage 3). Stage 1 sleep typically occurs at the sleep onset and has a low arousal threshold. Stage 2 sleep, characterized by sleep spindles or K-complexes on EEG, requires a more intense stimulus to produce arousal. Stage 3 sleep, also known as slow-wave sleep (SWS), delta sleep, or deep sleep, is characterized by high-voltage, slow-wave activity on EEG. In addition to its importance in memory consolidation, SWS also plays an important role in metabolic and

hormonal changes during sleep, such as glucose metabolism and growth hormone (GH) secretion. In fact, selective suppression of SWS without changing total sleep time has been shown to impair glucose tolerance.[1]

Two-process model of sleep regulation

The two-process model is a classic conceptual model that describes the relationship between the sleep-wake homeostat (Process S) and the circadian pacemaker (Process C) in sleep regulation.[2] Process S represents the propensity to sleep as a result of the length of time spent awake (i.e., sleep debt). Hence, Process S increases during wakefulness and declines during sleep and is time-of-day independent. In contrast, Process C represents the rhythmic variation in sleep propensity driven by the circadian system. The central circadian clock is located in the suprachiasmatic nucleus (SCN) of the hypothalamus and generates an endogenous ~24-hour rhythm. In humans, entrainment of the endogenous circadian rhythm to the light/dark cycle optimizes the overall physiology to be active during the daytime and restful at night. Although the two processes have traditionally been considered to function independently, recent literature have explored the potential influence of the sleep-wake homeostat on the circadian system and vice versa.[3,4] Notably, the discovery of peripheral circadian clocks located outside of the SCN has expanded the conventional view of Process C.[5] While peripheral clocks are under the control of the central clock, they can also generate their own oscillations and entrain to behavioral zeitgebers such as food intake and physical activity. Thus, behavioral rhythms such as feeding/fasting cycles can directly influence peripheral circadian clocks and create desynchrony between central and peripheral circadian systems,[6] inducing metabolic dysfunction. The growing body of literature on metabolic consequences of circadian misalignment, particularly pertaining to night shift work, has been expertly reviewed elsewhere and is beyond the scope of this review.[7,8]

Sleep and circadian influences on glucose, insulin, cortisol, and growth hormone

Hormones and other metabolic variables exhibit 24-hour rhythmicity, due to a combination of circadian and sleep homeostatic effects. In a landmark study done by Van Cauter et al.,[9] 8 young healthy men underwent 8 hours of nocturnal sleep, then 28 hours of recumbent continuous wakefulness, and followed by 8 hours of daytime recovery sleep, all during continuous glucose infusion without other caloric intake. This study design isolated circadian (time-of-day dependent) effects from sleep (time-of-day independent) effects and demonstrated that glucose metabolism and insulin secretion are under the influence of both circadian and sleep effects. As such, nocturnal elevations in glucose levels and insulin secretion rates persist even in the absence of sleep, indicating a circadian effect. Recovery sleep during the circadian day time after nocturnal sleep deprivation similarly increases glucose levels and insulin secretion rates, suggesting that sleep has an independent effect on glucose regulation.

This study also showed that cortisol, which exhibits a morning awakening peak and a nocturnal nadir, is largely under circadian influence: this diurnal rhythm persisted despite manipulations of the sleep-wake cycle. In contrast, pulsatile GH secretion is mainly under the influence of sleep, as sleep onset consistently elicits an abrupt pulse in GH secretion, which is independent of the time of day. GH release is stimulated by GH-releasing hormone

(GHRH) produced by hypothalamic neurons. GHRH stimulates both GH secretion and NREM sleep via separate pathways. GHRH released from neuronal terminals in the median eminence travel via the portal venous system to the anterior pituitary, stimulating GH secretion. Simultaneously, GHRH activates GABAergic neurons in the preoptic area of the anterior hypothalamus to promote sleep. In addition, a nocturnal rise in ghrelin levels contributes to GH secretion during sleep, as the acylated or active form of ghrelin, a gut peptide, is a known GH secretagogue.[10] There is a well-established, positive relationship between GH release and SWS. Holl et al. demonstrated that maximal GH release occurs at the onset of SWS.[11] Furthermore, stimulation of SWS enhances GH secretion.[12,13] Taken together, cortisol is strongly controlled by the circadian system while GH is mainly under the influence of sleep. Insulin and glucose metabolism are under the control of both sleep and circadian factors.

Sleep and circadian influences on appetite regulation

Ghrelin, a gut hormone that promotes hunger, exhibits 24-hour rhythmicity that is modulated by sleep. During the daytime, ghrelin levels rise in anticipation of a meal and decline after food intake. At night, ghrelin levels rise in the beginning of sleep, then gradually decline as the night advances, and then rise again in the morning in anticipation of the first meal.[14] Dynamic changes in night-time ghrelin levels are likely due to the interaction of distinct mechanisms at different points throughout the night. In the beginning of the night, the increase in ghrelin may be partly attributed to sleep.[15,16] Ghrelin secretion during the first hours of sleep is positively correlated with peak GH concentrations, suggesting that ghrelin enhances GH secretion and thus contributes to the promotion of SWS.[16] During total sleep deprivation, the nocturnal rise in ghrelin at the beginning of sleep was blunted, further supporting a ghrelin-promoting effect of sleep that is independent of food intake. As the night progresses, ghrelin levels decline despite continued fasting, suggesting an inhibitory effect of sleep on ghrelin.[15] In contrast, total sleep deprivation resulted in sustained ghrelin levels in the latter half of the night, further supporting a ghrelin-inhibiting effect of sleep in the second half of the night.[16]

Leptin, an adipocyte-derived satiety hormone that regulates energy balance, has a diurnal rhythm that peaks before midsleep and declines until midmorning. During the daytime, leptin levels increase in response to food intake.[17] Simon et al. showed that during continuous enteral nutrition, which eliminated the effect of food intake, there was a ~10% maximal increase in leptin levels above the 24-hour mean during nocturnal sleep and a nadir in the late afternoon. During one night of sleep deprivation, leptin levels rose by ~5% of the 24-hour mean, suggesting an endogenous circadian rhythm. Nocturnal rise of leptin is postulated to suppress hunger during sleep. Daytime recovery sleep demonstrated an ~8% increase in leptin levels relative to the 24-hour mean, suggesting an intrinsic effect of sleep on leptin levels.[18] Furthermore, three nights of total sleep deprivation demonstrated the persistence of leptin’s diurnal rhythm but with a lower amplitude than during normal sleep.[19]

Orexins or hypocretins are hypothalamic excitatory neuropeptides that promote both wakefulness and food intake. Orexins were initially recognized as regulators of feeding

behavior but have since been found to play diverse roles in sleep regulation, emotion, and energy homeostasis, with correspondingly diverse brainstem neuron distributions. Normally, orexin neurons promote food-seeking behaviors and are activated by fasting-related metabolic cues such as increased ghrelin and decreased glucose levels. Increased leptin and glucose levels inhibit orexin neurons.[20–22] Additionally, orexigenic neurons promote arousal and the loss of orexin A neurons in the lateral hypothalamus causes narcolepsy type 1, a sleep disorder characterized by excessive sleepiness, cataplexy, sleep paralysis, sleep fragmentation, and hallucinations at sleep onset and morning awakening. Despite the loss in orexin neurons, an increased prevalence of overweight and obesity in patients with narcolepsy has been widely reported.[23] Proposed mechanisms for this counter-intuitive phenomenon include increased binge-eating behaviors through abnormal melanocortin-4-receptor signaling in the hypothalamus[24] and reduction in basal metabolic rate.[25] Lastly, obesity in orexin-deficient mice is associated with impaired brown adipose tissue (BAT) thermogenesis.[26] However, a study in patients with type 1 narcolepsy showed no difference in BAT activity after cold exposure compared to healthy controls.[27]

Taken together, peripheral cues for appetite regulation including ghrelin and leptin are modulated by both sleep and circadian effects while the orexin system serves as an integrator of sleep and energy homeostasis.

Sleep and circadian influences on energy metabolism

Metabolic rate falls during sleep by ~15% and reaches a minimum early in the morning.[28,29] This decline in metabolic rate is the result of both sleep and circadian influences. Total sleep deprivation with continued wakefulness for 24 hours minimally increased total energy expenditure (TEE) in whole-room calorimetry studies. The minimally increased TEE occurs exclusively during nocturnal wakefulness,[30,31] indicating that the fall in metabolic rate is in part mediated by sleep. Other studies have demonstrated that energy expenditure exhibits an endogenous circadian rhythm, independent of sleep-wake status. Zitting et al. found that in healthy adults who underwent a forced desynchrony protocol where sleep and food intake were evenly distributed across a 28-hour circadian cycle, resting energy expenditure was lowest at the nadir of the circadian phase, corresponding to endogenous core body temperature nadir (late biological night), and was highest ~12 hours later, corresponding to biological afternoon and evening.[32] Additionally, 26-hour constant routine protocols (where environmental and behavioral factors were held constant) showed that, in healthy adults, fat oxidation was highest in the biological evening while carbohydrate oxidation was highest in the biological morning.[32,33] In summary, sleep and circadian rhythm together mediate a nocturnal decline in metabolic rate, while circadian rhythm *per se* controls whole-body substrate preference, with fat oxidation upregulated at night in anticipation of an overnight fast.

INSUFFICIENT SLEEP AND METABOLIC DYSFUNCTION

The American Academy of Sleep Medicine and Sleep Research Society recommend 7 hours or more of sleep per night for optimal health and well-being for adults.[34] As such, short sleep duration is defined as <7 hours of sleep per 24-hour period. Over the past several

decades, there has been a slow decline in the average sleep duration among US adults.[35] According to the latest CDC data, 35.2% of adults report insufficient sleep, with the highest prevalence among those aged 45–54 years (39%) and lowest prevalence among older adults ≥ 65 years (26.3%).[36] The prevalence is similar between men (35.5%) and women (34.8%). Sleep loss at the epidemiological level is thought to reflect the modernization of society with the advent of the internet, electronics, longer working hours, and prolonged artificial lighting, but may also be attributed to the complex interactions between individual and health-related factors such as socioeconomic status, behavioral and lifestyle habits, stress, and comorbidities.[37]

There are dramatic racial disparities in the prevalence of insufficient sleep. Notably, age-adjusted prevalence of short sleep duration is significantly higher among non-Hispanic African Americans (45.8%), compared to Whites (33.4%).[36] A recent study reported that from 2004 to 2018, the annual estimated prevalence of short sleep duration was persistently the highest among Black adults.[38] Additionally, African Americans are more likely to hold multiple jobs and perform shift work,[39] placing them at higher risk for insufficient sleep. Similarly, obesity and related metabolic comorbidities are especially common in underrepresented minority populations,[40] which account for disproportionately high morbidity and mortality.[41] While the causes of these health disparities have been partly attributed to socioeconomic factors,[42] the role of insufficient sleep in the disproportionately high cardiometabolic morbidity and mortality in under-represented minorities remains under-explored.

Epidemiological trends

Epidemiology studies have consistently found a U-shaped relationship between sleep duration and the development of obesity and metabolic dysfunction.[43–46] In a meta-analysis of 12 prospective cohort studies, the relative risk for obesity was 1.09 for each 1-hour decrement in those who slept <7–8 hours/day and 1.02 for each 1-hour increment in those who slept >7–8 hours/day.[43] Additionally, in a longitudinal study that investigated the relationship between sleep duration and visceral adiposity changes over 6 years, participants with baseline short (≤6 hours/day) and long (≥9 hours/day) sleep duration gained more visceral adipose tissue than those who slept 7–8 hours/day.[47]

Similarly, a U-shaped dose-response relationship between sleep duration and risk of type 2 diabetes has been reported in a meta-analysis of 10 studies totaling over 480,000 participants with follow-up periods ranging 2.5 to 16 years, with the lowest risk observed for the 7–8 hours/day category.[44] Relative risk for type 2 diabetes was 1.09 for each 1-hour decrement in sleep duration for those who slept <7 hours/day and 1.14 for each 1-hour increment in sleep duration. Similarly, a recent meta-analysis of 33 cross-sectional and 9 longitudinal studies found a U-shaped relationship between habitual self-reported sleep duration and metabolic syndrome and an association between short sleep duration but not long sleep duration with incident metabolic syndrome in longitudinal studies.[45] Notably, long sleep duration has been associated with all-cause mortality, incident diabetes mellitus, cardiovascular disease, stroke, coronary heart disease, and obesity.[48] The relationship

between long sleep duration and adverse health outcomes is not well-understood and may be related to comorbidities such as obstructive sleep apnea and depression.

Limitations of these studies include self-reported sleep duration instead of objective measures, cross-sectional assessment of the exposure (i.e., sleep duration), and lack of data on other sleep dimensions such as sleep quality and continuity. While longitudinal studies can point to a causal relationship between short sleep duration and metabolic dysfunction, findings may be confounded by unmeasured covariates such as dietary intake and physical activity levels.

Genetic variants of short sleep

Genetic variants have been identified in families of natural short sleepers, who appear to be resistant to the cognitive effects of sleep deprivation. However, the metabolic consequences of these genetic variants remain unexplored. Mutations in a transcriptional repressor called DEC2 and a rare mutation in the β1-adrenergic receptor gene have both been identified to be associated with human short sleep phenotypes.[49–51] Natural short sleepers only need 4 to 6 hours of sleep and feel well-rested. Hirano et al. then demonstrated that DEC2 regulates sleep/wake duration at least in part by modulating orexin expression.[52] While metabolic consequences of these mutations have not been fully explored, Pellegrino et al. reported that the carrier of the DEC2 variant for short sleep duration had nearly identical BMI as the noncarrier dizygotic twin, with both BMIs in the normal range.[49] Overall, the effects of the identified mutations associated with natural short sleepers warrant further investigation and can potentially provide novel insights in the underlying mechanisms linking sleep and metabolism.

Potential mechanisms

Evidence from experimental sleep restriction in humans—Interventional studies in healthy adults have explored the effects of total or partial sleep restriction on the following metabolic domains: (1) energy expenditure; (2) energy intake; (3) dysregulated eating behaviors such as hedonic and reward-driven eating behaviors and alterations in appetite hormone levels; and (4) glucose homeostasis. Figure 1 shows an overview of the mechanisms by which insufficient sleep leads to dysregulation in energy balance and highlights the differences seen in animal models compared to human observations. Figure 2 summarizes the potential mechanisms linking insufficient sleep and insulin resistance in humans. Findings from randomized controlled studies are summarized in Tables 1 and 2. Total sleep deprivation (TSD) describes continuous wakefulness for 24 hours and has been implemented in healthy individuals only, and usually lasts only one 24-hour period. Partial sleep deprivation (PSD) typically involves restricting sleep to 3.5–5 hours though the timing of restricted sleep often varies. Both TSD and PSD are commonly implemented in a cross-over study design with a relatively small sample size.

Energy expenditure: Overall, both TSD and PSD studies demonstrate either no changes[53–55] or minimal increases in total energy expenditure (TEE).[30,31] Whole-room calorimetry studies have found that 24-hour TEE increased by 7% (~134 kcal) following 40-hour TSD[30] and by 5% (~111 kcal) following 5-hour PSD (compared to 9 hours of

sleep).[31] Additionally, the increase in TEE occurred exclusively during the nocturnal sleep deprivation period, indicating the energy cost of additional wakefulness. Another whole-room calorimetry study found no differences in 24-hour TEE or substrate utilization after 3.5-hour PSD (compared to 7 hours of sleep), but there was a 55 kcal increase in night-time TEE during PSD.[53] In contrast, studies that used the doubly labeled water method found no difference in TEE with PSD.[54,55] Notably, the doubly labeled water method quantifies TEE over a period of days to weeks and may not capture dynamic changes in TEE within a 24-hour period.

TEE is composed of resting energy expenditure (or resting metabolic rate), thermic effect of food, and expenditure from physical activity. Studies on the effect of PSD on individual components of TEE show mixed results. Resting metabolic rate has been reported to be unchanged with PSD.[54–57] Other studies showed a mild reduction of resting metabolic rate following 24-hour TSD by 5%[58] or following PSD by 2.6%.[59] Thermic effect of food after high-fat breakfast was found to be unchanged after 4-hour PSD (compared to 8 hours of sleep) in 10 healthy women (measured by whole-room calorimeter)[57] while thermic effect of food following a breakfast liquid meal was reduced by ~20% in the morning after 24-hour TSD (measured by metabolic cart).[58] Lastly, some studies report no or minimal increase in physical activity[53,60,61] while other studies report less time spent in high intensity physical activity with PSD.[55,62] One study found that moderate intensity physical activity increased when PSD was achieved via delayed bedtime while vigorous intensity physical activity increased when PSD was achieved via advanced wake-time.[63] It would be interesting to examine the time of day that physical activity changes occur during PSD.

Overall, insufficient sleep induces a modest increase in total energy expenditure due to the energy cost of nocturnal wakefulness. The effects of sleep restriction on thermic effect of food and physical activity are mixed, which is likely due to methodological differences in study protocol and outcome assessment.

Energy intake: Overall, sleep restriction in healthy adults increases energy intake, with one meta-analysis reporting an increase of 252.8 kcal/day.[64] As such, the increase in energy intake exceeds the minimal increase or no changes in TEE. This positive energy balance can lead to weight gain (Figure 1).

Studies that measure ad libitum intake *during* TSD or PSD have consistently found increased caloric intake with sleep restriction,[31,54,55,59,61,65,66] which occur primarily during nocturnal wakefulness.[31,54,65,66] Notably, Fang et al. found that participants consumed nearly 1000 kcal overnight during TSD.[65] Despite this additional intake at night, participants consumed the same total intake the day after TSD as compared to the day after normal sleep. Similar findings are seen during PSD, with studies reporting an increased intake ranging 200–500 kcal/day,[31,54,55,66] which primarily occurred during nocturnal wakefulness and from snacks. Furthermore, studies have reported that during sleep deprivation, participants ingested an increased proportion of energy intake from fats[55,59,66] or carbohydrates.[31,54]

When increased energy intake occurs in the context of sleep deprivation, weight gain ensues.[31,59,61,66] Studies have reported weight gain ranging from a mean of 0.4 kg to

1.31 kg. One study reported no significant weight changes following PSD despite increased energy intake but noted considerable inter-individual variability in weight changes.[54] On the other hand, in studies where caloric intake was controlled during the sleep restriction period, no changes in weight were observed.[56,58,63,67–69] Overall, weight gain following sleep restriction occurred in the context of increased energy intake.

Other studies of the effect of sleep deprivation on energy intake control caloric intake during the sleep deprivation period and then measure ad libitum intake *after* the night of sleep deprivation. Following PSD, increased energy intake has been widely reported,[55,60,67,68] with intake primarily from snacks instead of meals.[67,68] Furthermore, following sleep deprivation, studies have reported an increase in the proportion of energy intake from fats,[55,59,60,62,65,68,70] carbohydrates,[63,67] or proteins.[68,70] One TSD study found no difference in food intake the day after, which may have been confounded by a relatively high calorie intake during the TSD period.[58] In addition, a few studies found no differences in total energy intake following PSD but both studies still found an increased proportion of energy intake from fats compared to control sleep.[62,70]

In summary, insufficient sleep results in increased energy intake and adverse eating behaviors, such as late-night eating and snacking either during or immediately after sleep deprivation.

Dysregulated eating: roles of appetite hormones and hedonic drive for food: Increased energy intake as a result of insufficient sleep is driven by dysregulated eating. Increased subjective hunger, alterations in appetite hormone levels, and increased activity in brain regions related to hedonic and reward-driven behaviors all contribute to dysregulated eating. Many studies have demonstrated increased subjective hunger and appetite ratings and decreased fullness sensation with TSD[58,71–74] and PSD.[53,60,68,69,75] Additionally, fMRI studies following TSD showed that sleep deprivation enhanced the activity in brain regions responsible for hedonic drive for food consumption and reward pathways,[71,76] impaired cognitive control in response to food stimuli,[72] and reduced activity in cortical regions involved in appetite regulation, which correlated with an increased desire for high-calorie foods.[77]

The neuroendocrine mediators of increased appetite and hunger are still being investigated. Ghrelin is a hunger-promoting gut peptide that increases in some studies of sleep restriction. As previously discussed, ghrelin normally increases in the beginning of the night due to sleep promoting ghrelin release. But in the latter half of the night, ghrelin tends to decrease as sleep inhibits ghrelin and suppresses overnight hunger. During TSD, ghrelin decreased in the beginning of the night and increased in the latter half of the night compared to normal sleep[16,58] culminating in elevated ghrelin the following morning.[73,74,78] This pattern suggests that nocturnal wakefulness increases ghrelin in the latter half of the night, augmenting hunger and promoting food intake. Similarly, PSD increased 24-hour mean ghrelin,[67] 12-hour mean daytime ghrelin,[69] and fasting ghrelin.[74] On the other hand, other PSD studies reported no changes in fasting ghrelin[61,62,70] or 24-hour mean ghrelin.[54,68] St-Onge et al. reported increased fasting total ghrelin only in men but not in women during PSD.[79]

Leptin is an adipocyte-derived satiety hormone that signals adequate energy stores. In some studies, sleep deprivation reduces leptin, theoretically contributing to increased energy intake. Following TSD or PSD, the diurnal amplitude of leptin was reduced[19,68,80] and 12-hour mean leptin was also found to decrease significantly following PSD.[69] However, other studies have reported no changes in fasting leptin[53,61,62,70,79] or 24-hour mean leptin.[31,54,68] Some studies even found an increase in fasting leptin.[81,82] The anorexigenic gut hormones PYY and GLP-1, which also serve as satiety signals, were decreased after PSD.[53,79] However, some studies found no changes in fasting PYY[79] or 24-hour PYY.[31] The discrepancy in findings regarding appetite and satiety hormones may be related to the differences in the duration and chronicity of sleep restriction, sampling frequency, study population, and energy intake.

The endogenous endocannabinoid system is a neuromodulatory system implicated in the control of feeding and appetite, particularly with the hedonic drive for food. 2-Arachidonoylglycerol (2-AG), an endogenous agonist of endocannabinoid CB1 and CB2 receptors, was found to oscillate over 24 hours, with a nadir in the middle of the sleep/overnight fast period, followed by continuous increase and a peak in the early afternoon. Hanlon et al. found that the 2-AG peak was higher and prolonged with PSD, suggesting that the early afternoon drive for hedonic eating may be stronger and last longer after PSD.[68]

Experimental sleep restriction induces an increase in subjective hunger, alterations in appetite and satiety hormone profiles, and an increase in the hedonic drive for food intake due to enhanced activity in neural reward regions and activation of the endogenous endocannabinoid system. These changes contribute to dysregulated eating that leads to excess energy intake.

Glucose homeostasis: Studies that examined glucose and insulin dynamics reveal that sleep restriction reduces insulin sensitivity. TSD decreased insulin sensitivity (measured via insulin suppression test with octreotide) in 14 healthy individuals.[83] A hyperinsulinemic clamp study by Donga et al found that one night of 4-hour PSD versus 8.5-hour control in 9 healthy individuals increased endogenous glucose production and decreased glucose disposal rate, indicating increased hepatic insulin resistance and decreased peripheral insulin sensitivity, respectively.[84] Similarly, Rao et al. found that 5 nights of 5-hour PSD versus 8-hour control in 14 healthy adults decreased whole-body insulin sensitivity by 25% and peripheral insulin sensitivity by 29%. In contrast, hepatic insulin sensitivity (as indicated by endogenous glucose production) did not change significantly in this study.[56] Another study showed that one night of 4-hour PSD increased peripheral insulin resistance as determined by hyperinsulinemic-euglycemic clamp and increased plasma levels of acylcarnitines (an essential intermediate in mitochondrial fatty acid oxidation) using targeted plasma metabolomics in both healthy individuals ($n = 9$) and patients with type 1 diabetes ($n = 7$), suggesting sleep loss could induce insulin resistance via dysfunction in mitochondrial fatty acid oxidation.[85] Buxton et al. found that one week of 5-hour PSD in 20 healthy men reduced insulin sensitivity as measured by euglycemic-hyperinsulinemic clamp and IV glucose tolerance test (IVGTT).[86] Other studies that employed IV or oral GTTs following PSD similarly found reduced insulin sensitivity.[82,87–91] Speculative mechanisms for reduced insulin sensitivity following insufficient sleep include (Figure 2): increased

nocturnal lipolysis as evidenced by elevated free fatty acid levels,[56,87] impaired insulin signaling in human adipocytes that paralleled a reduction in total body insulin sensitivity measured by frequently sampled IVGTT,[92] prolonged nocturnal GH secretion,[87] increased cortisol levels,[56] and increased activation of the sympathetic nervous system as evidenced of increased levels of norepinephrine levels.[56,87,89,93]

Summary of findings from experimental sleep restriction in humans: Experimental sleep restriction studies in humans demonstrate a very modest increase in TEE, which indicates the energy cost of additional wakefulness. A substantial increase in energy intake accompanies sleep restriction, which exceeds the small TEE boost, resulting in a net positive energy balance. This increased energy intake might be facilitated by increased hunger mediated by increased ghrelin, and/or a decreased leptin, PYY, and GLP-1. Augmented activity in brain reward regions related to food promotes hedonic drive for eating. These combined changes could lead to the development of obesity. Lastly, independent of dysregulations in energy homeostasis and weight changes, sleep restriction consistently reduces insulin sensitivity. Notably, extant data are all from short-term interventions occurring in controlled laboratory conditions, while long-term outcomes in free-living environments remain unknown. Additionally, almost all studies were conducted in healthy, normal-weight adults without existing metabolic dysfunction and thus may have limited generalizability to those with obesity and/or diabetes.

Evidence from animal models—Different animal models have been used to study the effects of sleep deprivation on metabolism. Most of these studies have been conducted in rodents and applied methods of total or state-dependent sleep deprivation. These methods include the disk-over-water protocol, gentle handling, single or multiple platform technique, rotating drum, and lesions of brain sleep-promoting areas[94–98]. In general, protocols of sleep deprivation are extremely stressful, causing an overactivation of hypothalamic-pituitary-adrenal axis and elevation of corticosterone levels.[99–101] Most protocols involve forced locomotion, extenuating physical exercise, or exposure to cold water in order to keep the animals awake, which could account for changes in metabolism.[102] Thus, the clinical relevance of findings from animal models of sleep deprivation has been ambiguous.

Regardless of the type of protocol, chronic sleep deprivation induces a combination of hyperphagia and increased energy expenditure in rodents, similar to that of humans. Unlike humans, sleep loss-induced energy expenditure exceeds caloric intake resulting in net weight loss (Figure 1). Across several studies, sleep deprivation in rodents led to ~15% body weight reduction[94,99,100,103–105] and the degree of weight loss appears to be dose-dependent[106] or method-dependent. This effect of sleep deprivation on body weight occurs despite robust increases in food intake. Sleep deprivation-induced hyperphagia is characterized by increased consumption of fat, but not protein.[94,99,100,102–104,107,108] At the neuroendocrine level, sleep suppresses leptin[95,100,105,108] and activates orexinergic pathways, stimulating neuropeptide Y expression in the arcuate nucleus of the hypothalamus.[96,109]

Sleep deprivation progressively increases metabolic rate and energy expenditure in rodents.[97,99,100,105,107] The cause of this hypermetabolism is not fully understood, but increased locomotor activity and imbalance of neuropeptides in the brain may play a role.

Sleep loss increases the levels of orexin in the brain[110] and stimulates the activity of orexin neurons.[111] Orexin induces arousals, spontaneous physical activity, and weight loss in rats by promoting increases in energy expenditure during rest and sleep.[112] Hypermetabolism induced by sleep deprivation is also associated with a compromised thermoregulation. In rodents, the main thermoregulatory mechanism is mediated by BAT-induced thermogenesis. Sleep-deprived rats exhibit a hypermetabolic state related to an upregulation of uncoupling protein 1 (UCP-1) mRNA in BAT.[103,113] Paradoxically, sleep loss increases heat dissipation and induces progressive hypothermia.[114] The mechanisms by which sleep loss enhances BAT activity are unknown. The upregulation of UCP-1 in BAT of sleep-deprived mice elicits increases in sleep rebound. In UCP-1–deficient mice, sleep rebound is attenuated by 35–45%. In this sense, the intact thermogenic activity of BAT appears to contribute as a downstream signaling to increase sleep after sleep deprivation.[113]

Different metabolic consequences of sleep deprivation between rodents and humans may suggest distinct physiological responses to sleep loss between species. As previously discussed by our group, rodents have a proportionately increased metabolic rate associated with a greater sleep necessity compared to larger mammals.[115] Rats exhibit an augmented rise in energy expenditure during acute sleep deprivation compared to humans, indicating that rodents manifest a wider difference in metabolism across sleep-wake states.[30,115] Thus, rodents and humans exhibit different energetic costs of wakefulness (Figure 1).

Sleep deprivation in rodents induces hyperglycemia, glucose intolerance, and insulin resistance.[108,116–119] Sleep-deprived rodents exhibit increased hepatic expression of lipogenic genes, such as the elongation of very long chain fatty acids-like 3.[116] Sleep deprivation also induces changes in the enzymes involved in glucose metabolism. In rats, REM-specific sleep deprivation was associated with reduced activity of glucose-6-phosphatase and hexokinase in the brain.[120] Although the underlying mechanisms of sleep loss-induced glucose impairments are still not entirely clear, it is conceivable that a disturbed control of the autonomic nervous system plays a role. Catecholamines increase glycolysis, hepatic glucose output from glycogenolysis and gluconeogenesis, and inhibit insulin-mediated glycogenesis.[121] Sleep deprivation in rodents induces sympathetic activation and catecholamine release, which in turn may stimulate gluconeogenesis and insulin resistance.[117] Centrally, several pathways could be involved in abnormal sympathovagal balance induced by sleep deprivation. In addition to sleep-wake regulation, the orexinergic system also appears to participate in the control of glucose metabolism. Intracerebroventricular administration of orexin-A has detrimental effects on glucose metabolism, inducing hyperglycemia and preventing the daytime reduction of endogenous glucose production in rats.[122] The effects of orexin-A on glucose levels are abolished by the hepatic sympathetic denervation. Orexin receptors type 1 and 2 are abundantly expressed in serotoninergic neurons of the raphe nucleus. The specific inactivation of orexin receptor 1 in these serotoninergic neurons decreases insulin sensitivity in obesity by reducing glucose utilization. On the other hand, deficiency of orexin receptor 2 activity in serotoninergic neurons improves glucose tolerance and insulin sensitivity by decreasing hepatic gluconeogenesis.[123] Thus, orexin signaling in serotoninergic neurons of raphe nucleus appears to be a pivotal mechanism of regulation of glucose metabolism, and

the exacerbation of this axis could explain the metabolic dysfunction induced by sleep deprivation.

Overall, all protocols of sleep deprivation have several limitations, which may impact the clinical relevance of metabolic findings and raise questions regarding the feasibility of appropriate rodent models of sleep loss. However, rodents exhibit qualitatively similar changes in hyperphagia, increased energy expenditure, and glucose metabolism, albeit to different degrees than humans, which can provide insights into the mechanisms leading to metabolic consequences of sleep loss.

INSOMNIA AND METABOLIC DYSFUNCTION

Insomnia is defined as dissatisfaction with sleep quantity or quality associated with one or more insomnia symptoms, which include difficulty initiating sleep, difficulty maintaining sleep, and early morning awakening with inability to return to sleep. The sleep disturbance associated with insomnia disorder causes clinically significant impairment in social, occupational, educational, behavioral, and other areas of functioning. Insomnia is the most common sleep disorder and is likely present in 5–15% of the US population, with ~30% reporting significant symptoms at any given time.[124] Insomnia is one of the most prevalent complaints in primary care,[125] increases with age, and are twice as prevalent in women compared to men.[124] Additionally, insomnia commonly coexists with other psychiatric or medical disorders, other sleep disorders, or the use of medications or substances. As such, it remains challenging to isolate effects of insomnia on metabolic outcomes independent of comorbidities and insufficient sleep durations.

Epidemiological trends

Epidemiological studies demonstrate an association between insomnia and adverse glucose outcomes. A recent meta-analysis of 12 studies found that individuals with insomnia had 1.29 times risk of having hyperglycemia compared to those without insomnia.[126] Similarly, a meta-analysis of 5 studies demonstrated an association between insomnia symptoms such as difficulty initiating sleep and the development of diabetes mellitus (RR = 1.57) and difficulty maintaining sleep and incident diabetes mellitus (RR = 1.84).[127] It has been suggested that insomnia with short sleep duration, but not insomnia without short sleep duration, is the phenotype associated with adverse glycemic outcomes. Vgontzas et al. previously reported that chronic insomnia with short sleep duration (≤5 hours) was associated with the highest risk of diabetes (OR = 2.95).[128] It has not yet known whether adverse glucose outcomes related to insomnia are independent of short sleep duration.

Among people with type 2 diabetes, there is a high prevalence of insomnia and insomnia symptoms, which have been associated with worse glycemic control. A meta-analysis of 78 studies found that the prevalence of insomnia and insomnia symptoms among individuals with type 2 diabetes was 39%, with an even higher prevalence of 44% amongst those 60 years and older.[129] This prevalence is nearly 4 times as high that reported in the general population.[130] Additionally, insomnia and insomnia symptoms were associated with an increased risk of having a higher hemoglobin A1c (HbA1c), a higher fasting glucose, and a higher BMI.[129] Notably, this large meta-analysis reported a high degree of heterogeneity

of insomnia and insomnia symptoms prevalence estimates and inadequate control of confounders such as diabetes medications and other sleep problems such as obstructive sleep apnea. Ding et al. similarly found that patients with insomnia and type 2 diabetes (compared to those with type 2 diabetes but without insomnia), had higher fasting glucose and HbA1c even after adjusting for diabetes and sleep-related confounders.[131] Furthermore, in the Multi-Ethnic Study of Atherosclerosis (MESA) cohort, among individuals with diabetes (20% of the population), those who slept <5 hours per night had greater HbA1c than those who slept 7–8 hours per night with no attenuation of the associations after adjusting for obstructive sleep apnea/hypoxemia.[132]

Impaired sleep efficiency, defined as a low percentage of time spent asleep out of total time spent in bed, is another sleep parameter seen in insomnia that is associated with adverse glucose outcomes. In the subgroup of women with diabetes in MESA, those in the lowest quartile of actigraphy-derived sleep maintenance efficiency had greater HbA1c than those in the highest quartile of sleep maintenance efficiency.[132] Similarly, insomnia (defined as self-reported difficulty falling asleep or waking up in the night ≥3 times per week and average sleep efficiency of <80% based on actigraphy) was associated with a 23% higher fasting glucose level and 48% higher fasting insulin levels in subjects with diabetes in the Coronary Artery Risk Development in Young Adults Study.[133]

Insomnia has also been associated with diabetes complications and other comorbidities. Higher insomnia risk, assessed by the Insomnia Severity Index, has been associated with the presence of diabetic retinopathy in a cross-sectional study.[134] Additionally, poor sleep quality as assessed by the Pittsburgh Sleep Quality Index (PSQI) has been associated with higher self-care burden, depressive and anxiety symptoms, and diabetes-specific distress in a cross-sectional study of Dutch adults with diabetes.[135]

The association between insomnia and obesity are mixed. A meta-analysis found that those with insomnia had 1.31 times the risk of having obesity.[126] However, a meta-analysis with 67 studies showed that the odds of having obesity among those who had insomnia disorder was not greater than those who did not have insomnia disorder.[136] Longitudinal data on the relationship between insomnia symptoms and future incidence of obesity are sparse and inconclusive,[137,138] likely due to methodological differences in the definition of insomnia disorder and/or symptoms and challenges in adequately controlling for confounders. Sleep duration again appears to be a major factor underlying the association between insomnia symptoms and obesity. Cai et al. found that in over 18,000 adults in the Swedish EpiHealth cohort study, there were significant associations between the combination of both short (OR = 1.48) and long (OR = 1.77) sleep duration with insomnia symptoms and obesity. However, there was no significant association between insomnia symptoms and obesity in participants with normal sleep duration.[139]

Potential mechanisms

Chronic hyperarousal—One model for insomnia posits that insomnia is a chronic state of physiological hyperarousal.[140] In turn, chronic physiological stress is associated with adverse metabolic outcomes such as obesity.[141] Studies in patients with insomnia have shown evidence of physiological stress, including enhanced sympathetic activation

with increased heart rate and low/high-frequency spectral power during both sleep and wakefulness,[142] elevated nocturnal norepinephrine levels,[143] increased activation of the hypothalamic-pituitary-adrenal (HPA) axis during the entire 24-hour period,[144] and a modest increase in 24-hour metabolic rate (by 6–9%).[145,146] While increased sympathetic activation and metabolic rate could theoretically lead to weight loss, the augmented HPA axis promotes food cravings and overeating, which leads to increased food intake with consequent weight gain.[147] In fact, one study found that food cravings partially mediate the positive relationship between chronic stress and BMI.[148] Thus, the mechanisms linking chronic hyperarousal and weight gain in insomnia are similar to those seen in the experimental sleep deprivation studies discussed previously.

Evidence from animal models—Several animal models of insomnia have been described. In rodents, exposure to psychological stressors induces sleep disturbances and reproduces features of sleep observed in insomnia patients. Stress-induced insomnia in rodents is manifested by increased sleep latency, decreased total sleep time, sleep fragmentation, and augmented high-frequency activity in the EEG during NREM sleep.[149] Animals also exhibit activation of wake-promoting brain regions, indicated by increased expression of cFos in cerebral cortex, limbic system, and tuberomammillary nucleus.[149] Different stressors have been used to induce insomnia in rodents, including protocols of cage exchange, food deprivation, and restraint stress. Overall, chronic exposure to environmental stress activates orexin neurons in the lateral hypothalamus,[150,151] which could link the pathophysiology of insomnia to metabolic dysfunctions. Mice exposed to chronic stress-induced insomnia develop hyperphagia with reduced leptin/ghrelin ratio.[36] Under high-fat diet, circulating levels of glucose and free fatty acids are increased in mice exposed to chronic stress, whereas insulin levels remain similar to that of mice under chow diet. Chronic stress-induced insomnia also augments glucose intolerance, but does not significantly change body weight.[152] Similar metabolic dysfunctions are observed in other animal models of insomnia. *Insomnia-like* (*ins-l*) flies are a line of *Drosophila* that are obtained by successive breeding of flies expressing insomnia traits. After 60 generations, *ins-l* flies show increased sleep latency, reduced total sleep duration, and difficulty maintaining sleep. Sleep disturbances in *ins-l* flies are associated with augmented concentration of dopamine and increased levels of triglycerides, cholesterol, and free fatty acids.[153]

Overall, different animal models manifest some features of human insomnia and reproduce metabolic impairments related to sleep insufficiency. However, as with any animal model, these protocols have several limitations and questionable clinical relevance, especially regarding human primary insomnia. Perceptual components of insomnia cannot be reproduced, and it remains unclear whether these models accurately mimic conditions of difficulty to initiate and maintain sleep, rather than just sleep loss. Unifying mechanisms between insomnia and metabolic dysfunctions are also still speculative in these models and can be confounded by the exposure to intense stress or successive genetic selection. Thus, metabolic outcomes in animal models of insomnia should be carefully interpreted.

METABOLIC EFFECTS OF INSOMNIA AND INSUFFICIENT SLEEP TREATMENTS

Given the high prevalence of insomnia in metabolic disorders such as type 2 diabetes and obesity, it is worth exploring whether treatment of insomnia and insufficient sleep could ameliorate or worsen metabolic diseases.

Pharmacotherapy

According to the latest CDC data from 2017–2018, 8.2% of adults took medication to help fall or stay asleep ≥4 times in the past week (6.6% for men and 9.7% for women).[154] Benzodiazepine receptor agonists (BzRAs or "Z" drugs) were the most commonly prescribed insomnia medication, followed by trazodone, benzodiazepines (BZDs), quetiapine, and doxepin, according to NHANES data from 1999–2010.[155] Despite the prevalence of sleep aid use and frequent co-occurrence of insomnia and metabolic diseases, there are limited studies examining the metabolic impacts of insomnia medications, with most reporting only glucose outcomes. Studies on BzRAs and BZDs suggest adverse glucose metabolism. Suvorexant, an orexin receptor agonist and a newer agent for insomnia, has demonstrated promising results in beneficial glucose outcomes in early studies. Lastly, approximately 1.3% of the US population (3.1 million) report regular melatonin use as an over-the-counter sleep aid,[156] despite melatonin being not recommended to be used as a treatment for sleep onset or sleep maintenance insomnia in adults by the American Academy of Sleep Medicine.[157] Studies on the effects of melatonin on glucose outcomes report mixed findings.

Benzodiazepine receptor agonists ("Z" drugs) and benzodiazepines—

Benzodiazepine receptor agonists (i.e., zolpidem, eszopiclone, zaleplon) and benzodiazepines both activate the $GABA_A$ receptor. These classes of medications are frequently prescribed for treatment of insomnia and may adversely affect glucose metabolism. A population-based retrospective cohort study with 45,000 adults from Taiwan followed from 1997–2011 found that patients using zolpidem had a higher risk for developing type 2 diabetes compared to patients not using zolpidem (HR = 1.41; 95% CI: 1.35–1.48).[158] This association was more pronounced in patients using both zolpidem and BZDs (HR = 1.77, 95% CI: 1.64–1.91). Among patients with type 2 diabetes, the prevalence of hypnotic use is high. A Dutch study reported that 10.1% of >7000 patients with type 2 diabetes were prescribed hypnotics or anxiolytics or both.[159]

Despite the high rate of BZD prescriptions in patients with type 2 diabetes, studies on the glycemic impact of BZDs or BzRAs are sparse and limited to healthy populations. To date, only one study has been conducted in patients with type 2 diabetes and insomnia. In this study, Wu et al. randomized patients to dexzopiclone (BzRA) versus estazolam (BZD) for 14 days and found that while the sleep dysfunction rating scale significantly decreased in both treatment arms, fasting blood glucose decreased only in the dexzopiclone group,[160,161] suggesting a potentially beneficial effect of dexzopiclone on glycemia in patients with type 2 diabetes and insomnia. A randomized, double-blind, placebo-controlled clinical trial found that eszopiclone (BzRA) for 2 months in 20 adults with primary insomnia

without diabetes did not significantly change any sleep measures, insulin sensitivity, or glucose tolerance assessed by IVGTT, compared to placebo.[162] However, this study was likely underpowered. Gramaglia et al. evaluated glucose and insulin responses to an oral GTT following 2-week therapy of brotizolam (BZD) and zolpidem (BzRA) in 12 healthy volunteers.[163] Glucose responses to the OGTT increased by 122% after brotizolam and 86% after zolpidem without significant changes in insulin levels. Mechanistically, BZDs are known to reduce SWS and increase stage 2 sleep,[164] which could contribute to adverse glucose metabolism given that disruption in SWS increases type 2 diabetes risk.[1] On the other hand, BzRAs such as zolpidem have not been consistently found to alter sleep architecture.[165] Furthermore, a single intravenous dose of clonazepam, another BZD, reduced the acute insulin response during a frequently sampled IVGTT in a concentration-dependent manner.[166] Taken together, BZDs and possibly BzRAs appear to impair glucose tolerance in healthy volunteers. However, studies of BZDs or BzRAs in patients with type 2 diabetes and insomnia are lacking and are clinically relevant given the adverse effects of insomnia on glycemic outcomes and complications in patients with type 2 diabetes.

Suvorexant—Suvorexant is a dual orexin receptor antagonist that is approved for insomnia treatment. Suvorexant promotes sleep by blocking the binding of wake-promoting neuropeptides orexin A and orexin B to receptors OX1R and OX2R and is efficacious in reducing wake after sleep onset, improving subjective measures of sleep onset and maintenance.[167] In a study with type 2 diabetic *db*/*db* mice, daily administration of suvorexant at the beginning of the resting phase for 2–4 weeks increased NREM sleep time, reduced awake time, and improved glucose tolerance without changes in weight gain, food intake, or systemic insulin sensitivity.[168] Notably, only suvorexant administration during the rest phase, but not during the awake phase, improved glucose tolerance. This suggests that the beneficial glucose outcome may be mediated by improvement in sleep parameters. Nakamura et al. found that in 37 patients without diabetes who were hospitalized in an inpatient psychiatry unit treated with suvorexant for 8 weeks, fasting glucose significantly decreased at 4 and 8 weeks from baseline without changes in weight and BMI.[169] Suvorexant was subsequently studied in an inpatient, 7-day, open-label, single-arm trial with 18 patients with type 2 diabetes and insomnia and was found to increase total sleep time and sleep efficiency, with a significant decrease in 24-hour mean glucose, particularly in the early glucose surge after the midnight nadir.[170] Most recently, suvorexant was studied in 13 Japanese patients with type 2 diabetes and primary insomnia for 14 weeks and it improved sleep diary–derived sleep efficiency and subjective sleep duration, reduced abdominal circumference, and reduced daily sucrose intake. However, there were no changes in HbA1c, glucose parameters, and body weight, which may be related to the limited sample size and length of intervention.[171] Taken together, suvorexant has demonstrated promising results in preclinical and small clinical studies to potentially induce beneficial effects on glucose metabolism in patients with type 2 diabetes and insomnia. Moreover, given that the orexin neuropeptides increases wakefulness and food intake, orexin antagonism theoretically could inhibit feeding.[172] Overall, suvorexant's potential impacts on glucose tolerance and energy homeostasis warrant further investigation.

Melatonin and melatonin receptor agonist—Melatonin is a popular sleep aid. Melatonin is a hormone secreted by the pineal gland and is under tight regulation of the central circadian clock in the SCN. Endogenous melatonin levels are highest at night and lowest during the day. While melatonin has been directly implicated in the pathogenesis of type 2 diabetes, extant literature on melatonin and glucose metabolism are inconclusive. Epidemiological studies have reported that low nocturnal melatonin levels were prospectively associated with increased risk for type 2 diabetes.[173,174] Melatonin administration in patients with insomnia and either type 2 diabetes or metabolic syndrome have reported a reduction in HbA1c.[175] However, other studies have demonstrated that exogenous melatonin can acutely decrease glucose tolerance in healthy subjects without diabetes or sleep issues.[176–179]

The differential response to exogenous melatonin may be related to a genetic variant in *MTNR1B*, a gene that encodes melatonin M2 receptor (G protein–coupled receptor). This risk allele, present in ~30% of the population, was discovered in genome-wide association studies and associated with the development of type 2 diabetes,[180–182] higher fasting glucose,[181,182] faster deterioration of insulin secretion over time, and impairment of early insulin response to glucose, even in non-diabetic subjects.[180] The most widely proposed mechanism underlying this association is the “gain-of-function” hypothesis, which posits that melatonin binds to MT2 receptor in pancreatic beta-cells, inhibits adenylate cyclase activity via Gi and thus reduces the formation of cAMP.[183] This results in inhibition of glucose-stimulated insulin secretion. Several human studies have demonstrated a genotype-specific difference in glucose tolerance to both exogenous melatonin administration or endogenous melatonin elevation (i.e., night-time), with more marked glucose intolerance in *MTNR1B* risk allele carriers.[178,179,184] Taken together, the widespread prevalence of melatonin use is alarming given the potentially deleterious and patient-specific consequences of melatonin on glucose metabolism.

Ramelteon is a highly selective melatonin receptor agonist prescribed for sleep-onset insomnia. Compared to melatonin, ramelteon has more potent affinity for melatonin 1 and melatonin 2 receptors, with weak affinity for melatonin 3 receptors.[185] In a prospective randomized controlled trial in patients with type 2 diabetes and insomnia, ramelteon was administered for 3 months followed by a second period of randomized continuation or discontinuation for 3 additional months.[186] While global PSQI score improved with ramelteon, HbA1c level did not change at 3 months. However, during the 3 additional follow-up months, the discontinuation group had a mild rebound of HbA1c (from 6.7% to 6.9%) while the continuation group did not. Piromelatine is a novel melatonin agonist, which has been developed for the treatment of insomnia. Animal studies have suggested possible efficacy of piromelatine in sleep maintenance, anxiety, and depression. In addition, piromelatine has been shown to inhibit weight gain and improve insulin sensitivity in high-fat/high-sucrose-fed rats. Under piromelatine or melatonin treatment, the levels of plasma glucose, triglyceride, total cholesterol decreased and HDL-C, glucose tolerance, and antioxidative potency increased when compared with the vehicle-treated group.[42]

Other medications—Metabolic outcomes of other FDA-approved and off-label medications used for insomnia have been reported in limited observational studies.

All hypnotic agents discussed in this section (doxepin, trazodone, mirtazapine, diphenhydramine) have sedative effects mediated by histamine H_1 receptor antagonism. H_1 antihistamine use is associated with increased risk of obesity in US adults and higher fasting insulin levels.[187] Furthermore, histamine H_1 receptor affinity has been shown to predict weight gain.[188]

Doxepin is a tricyclic antidepressant medication that is approved for treatment of sleep-maintenance insomnia in adults at low doses (3–6 mg per night). At low doses, doxepin mainly acts as an antagonist of the histamine H_1 receptor and thus produces sedative effects without causing additional side effects seen at the higher doses of doxepin used for depression.[189] Given the association of H_1 antistamine and obesity,[187] doxepin can potentially cause weight gain. However, at low doses, doxepin has been reported as a weight neutral agent.[190,191] While studies on tricyclic antidepressants have shown an increased risk of developing diabetes,[192] this effect is seen largely with prolonged use and in moderate to high doses, which one study defined as >30 mg for doxepin.[192]

Interestingly, a study in mice found that 4 weeks of doxepin in diet-induced obese mice and in *db/db* diabetic mice improved hyperglycemia, hepatic steatosis, and obesity, likely through activation of a mitochondrial protein (FAM3A) that suppresses hepatic gluconeogenesis and lipogenesis.[193] Conversely, another study found that 8 weeks of doxepin in diet-induced obese mice caused more weight gain, food intake, severe fatty liver disease, insulin resistance, and renal impairment compared to obese mice that received saline.[194] Notably, the investigators found that mice fed a standard diet did not exhibit any difference in weight gain when administered doxepin versus saline, suggesting that doxepin may induce metabolic dysfunction only when combined with pre-existing obesity or an obesogenic lifestyle. Conflicting preclinical findings regarding doxepin's effects on glucose metabolism and weight regulation are likely due to different dosages and lengths of treatment along with the presence of comorbid conditions. Observational clinical data suggest that low-dose doxepin used for insomnia likely will not cause significant weight gain or increased diabetes risk.

Commonly prescribed off-label medications for insomnia include trazodone and mirtazapine. Trazodone, an antidepressant that acts as an antagonist of serotonin 5-HT_{2A}, central α_1-adrenergic, and histamine H_1 receptors, is the second most prescribed medication for insomnia.[155] Trazodone has been reported as weight neutral.[195] Mirtazapine is a tetracyclic antidepressant that acts as an antagonist of central α_2-adrenergic, serotonin 5-HT_2 and 5-HT_3 receptors, peripheral α_1-adrenergic and muscarinic receptors, and histamine H_1 receptors.[196] Mirtazapine stimulates appetite and causes significant weight gain,[197,198] likely via its antagonistic effects on histaminergic and serotonin 5-HT_2 receptors. Some studies report improved glucose tolerance after mirtazapine treatment in nondiabetic patients with depression.[199,200] But in an inpatient study in 10 healthy men without metabolic or depressive disorders, where caloric intake, physical activity, and sleep were controlled, 7 days of mirtazapine resulted in increased insulin secretion without changes in glucose levels in response to a standardized meal, despite mild weight loss.[201] Overall, weight gain is a potential side effect of these off-label hyponotic agents as a result of histamine H_1 receptor antagonism. Alterations in glucose homeostasis are understudied and may be confounded by

the presence of comorbid conditions such as depression and obesity. Given the widespread use of these hynotics, more clinical investigations are needed.

Behavioral interventions

Sleep extension—Several studies have examined the effects of sleep extension in habitual short sleepers on metabolic parameters. In general, sleep extension strategies include single or multiple personalized sleep consultation sessions, sleep hygiene recommendations, time-in-bed extension with or without bedtime recommendations. The duration of the intervention ranges from 3 days to 6 weeks, with 2 weeks being the most common. In healthy adults with overweight or normal weight, effective sleep extension by ≥1 hour per night with resultant total sleep duration >6 hours improved insulin sensitivity,[202–204] and decreased leptin and PYY,[203] appetite,[205] desire for sweet and salty foods,[205] and intake of free sugar.[206] Most recently, Tasali et al. demonstrated that in 80 adults with overweight and habitual sleep duration <6.5 hours per night, a 2-week sleep extension where sleep duration was increased by 1.2 hours per night reduced daily energy intake by 270 kcal/day, with a resultant 0.48 kg weight loss.[207] Notably, energy intake was calculated based on TEE from doubly labeled water and changes in energy stores (determined from changes in body composition). Although this method ensures an objective assessment of energy intake, it does not allow for exploration of the timing and distribution of energy intake. Additionally, the study provided limited or no data on changes in subjective appetite ratings or hormone levels. Overall, sleep extension in short sleepers appears beneficial for metabolic outcomes.

Cognitive behavioral therapy for insomnia—Metabolic outcomes after cognitive behavioral therapy for insomnia (CBT-I) have only been investigated in a few clinical studies. Carroll et al. found that in 109 older adults with chronic and primary insomnia who were randomized to CBT-I for 4 months improved their PSQI scores and their composite multi-system cardiometabolic risk score, which comprised HDL, LDL, triglycerides, HbA1c, glucose, insulin, C-reactive protein, and fibrinogen levels, at 4 months and 16 months.[208] More recently, Alsheri et al. examined the effects of CBT-I on glycemic control in patients with type 2 diabetes and insomnia. In this randomized controlled trial, patients were randomized to CBT-I or health education for 6 weekly one-hour sessions.[209] The CBT-I group showed significantly greater improvement in HbA1c, diabetes self-care behavior, and fatigue. Overall, these two studies demonstrate that effective CBT-I that improves insomnia symptoms can potentially produce benefits on glycemic control. Given the potentially adverse metabolic effects of insomnia pharmacotherapy, CBT-I is certainly the safer option for patients with type 2 diabetes if adequate access can be provided.

CONCLUSIONS

Sleep and circadian rhythm exert considerable influences on hormones involved in appetite regulation and energy metabolism. As such, insufficient sleep induces dysregulation in energy balance and glucose homeostasis, increasing the risks of developing obesity and type 2 diabetes. Current research gaps related to insufficient sleep and metabolic outcomes include (1) the role of insufficient sleep in the disproportionately high cardiometabolic morbidity and mortality in under-represented minorities; (2) potentially compensatory or

adaptive metabolic mechanisms to chronic exposure of insufficient sleep; (3) metabolic consequences of the identified mutations associated with natural short sleepers; and (4) differences in metabolic outcomes between healthy, normal-weight individuals and those with obesity and/or diabetes. Clinically, insomnia disorder and symptoms are strongly associated with adverse glucose outcomes, including in those with type 2 diabetes. Animal models of sleep deprivation and insomnia provide some mechanistic insights into pathways of hyperphagia, increased energy expenditure, and impaired glucose homeostasis, although the net effect of sleep loss in rodents is weight loss rather than weight gain. Insomnia treatments, including both pharmacological and behavioral interventions, can have metabolic impacts that may or may not be dependent on objective sleep improvements. There are several knowledge gaps pertaining to insomnia and metabolic dysfunction. Given the high prevalence of comorbid insomnia and metabolic diseases, the potential dual effects of treatment on both sleep and metabolic outcomes remain relatively under-explored. In particular, behavioral interventions that target improvement in sleep hold promise in their potential for optimizing overall metabolic health. Lastly, while insomnia is twice more prevalent in women, potential sex differences in the risk of metabolic diseases in patients with insomnia are scarcely reported.

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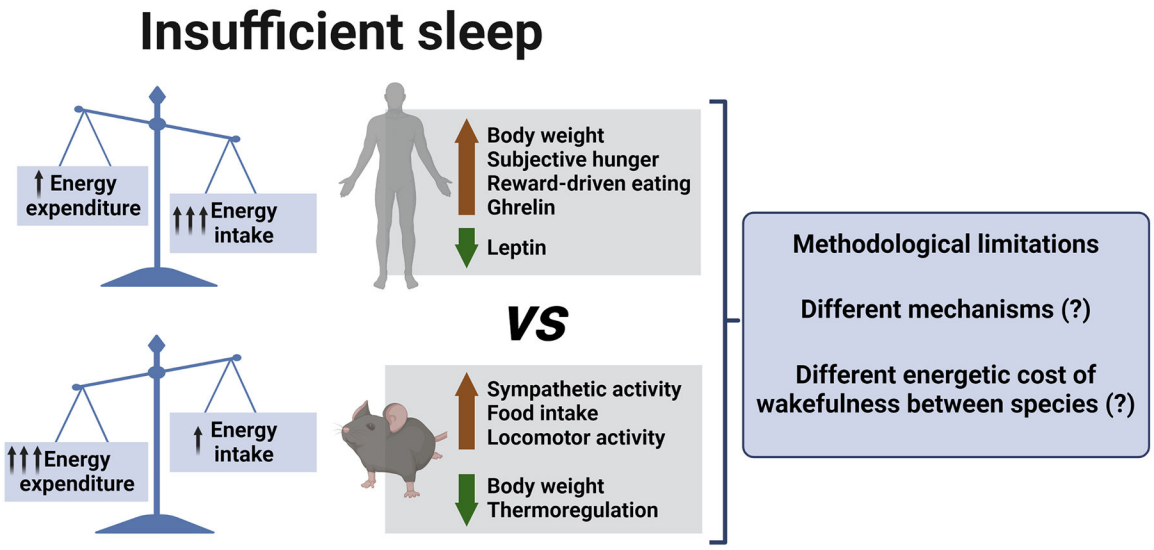

Figure 1.
Effects of insufficient sleep on energy balance in animal versus human studies.

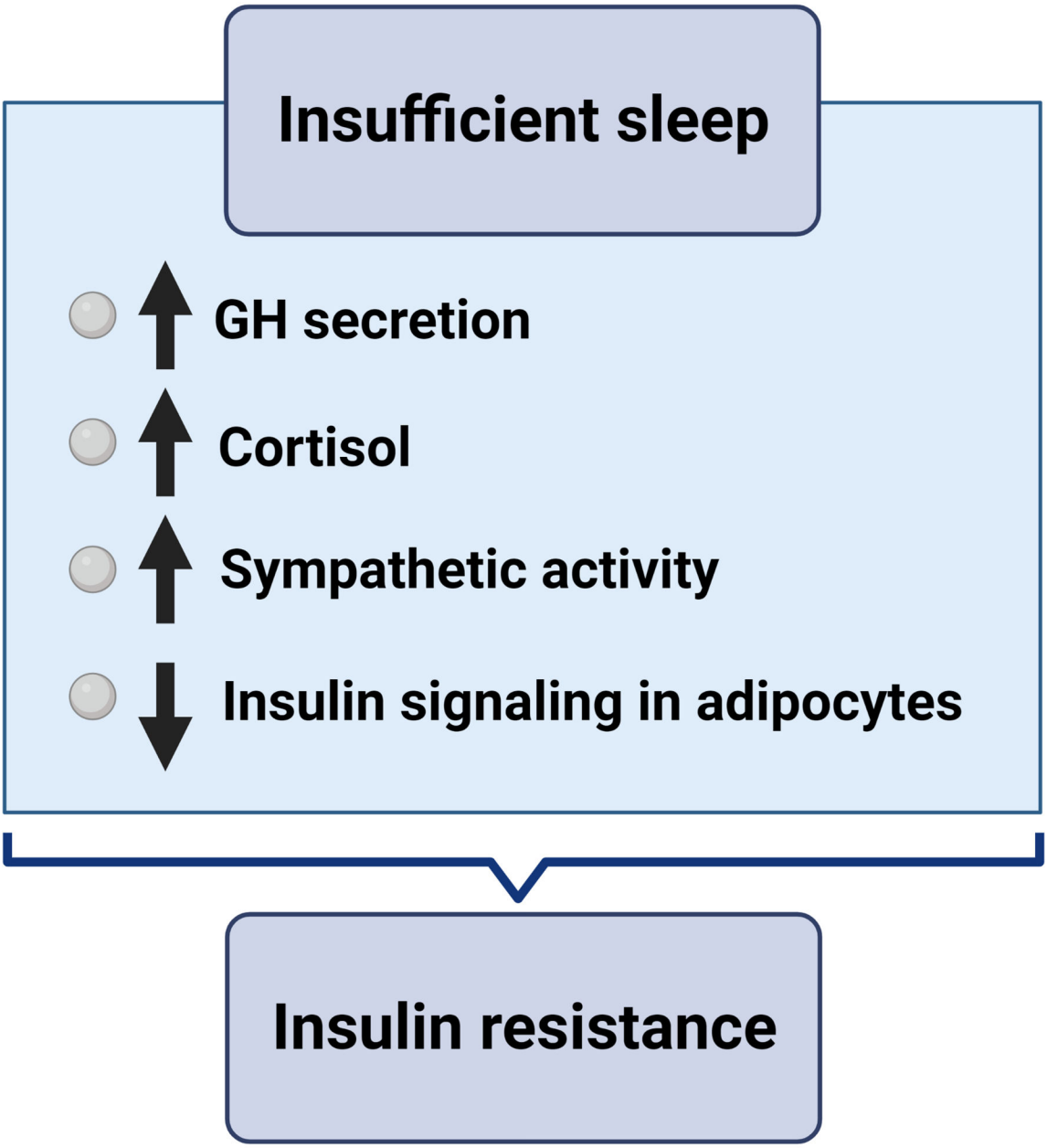

Figure 2.
Mechanisms linking insufficient sleep and insulin resistance in humans.

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Table 1.

Randomized controlled studies of total sleep deprivation on metabolic outcomes

Study	Participants	Study design & intervention	Caloric intake	Subjective hunger	Appetite hormones	Energy expenditure	Glucose/insulin	Weight
Benedict, Am J Clin Nutr 2011[58]	14 normal-weight men	8 h nocturnal sleep versus 24 h continuous wakefulness Duration: 1 night Crossover with ≥4-week washout	Design: Controlled during the intervention Findings: Post-intervention food intake during buffet were not different	↑ hunger morning after TSD	During TSD, early nocturnal ghrelin ↓ by ~10%; nocturnal ghrelin in the second half of sleep ↑ by ~11% No difference in leptin across 24h	REE ↓ by 5% the morning after Postprandial EE ↓ by 20% the morning after	↓ night-time glucose without changes in insulin levels with TSD ↑ Morning-after post-breakfast glucose, without changes in postprandial insulin after TSD	No difference
Benedict, JCEM 2012[71]	12 normal-weight men	7 h nocturnal sleep versus 24 h continuous wakefulness Duration: 1 night Crossover with ≥2-week washout	Design: Controlled; no food provided during TSD	↑ hunger morning after TSD	NR	NR	No difference in morning fasting glucose	NR
Cedernaes, Obesity 2014[72]	14 normal-weight men	8.5 h nocturnal sleep versus TSD Duration: 1 night Crossover with >4-week washout	Design: Controlled; no food provided during TSD	↑ Self-reported hunger	NR	NR	No difference in morning fasting glucose	NR
Chapman, Obesity 2013[78]	14 normal-weight men	8 h nocturnal sleep versus TSD Duration: 1 night Crossover with >4-week washout	Design: Controlled; no food provided during TSD	NR	↑ Fasting morning total ghrelin following TSD	NR	NR	NR
Dzaja, Am J Physiol Endocrinol Metab 2004[16]	10 non-obese men	8 h nocturnal sleep versus TSD Duration: 1 night Crossover with ≥2-week washout	Design: Controlled; no food provided during TSD	NR	Blunting of nocturnal rise in total ghrelin during normal sleep period during TSD	NR	NR	NR
Fang, Sci Rep 2015[65]	46 non-obese adults *n* = 34 TSD *n* = 12 control	8 h nocturnal sleep versus TSD Duration: 1 night Parallel arm	Design: AL intake during 3 daytime meals and 1 overnight period during TSD Findings: Consumed ~1000 kcal during overnight wakefulness; no difference in total	NR	NR	NR	NR	NR

Study	Participants	Study design & intervention	Caloric intake	Subjective hunger	Appetite hormones	Energy expenditure	Glucose/insulin	Weight
			caloric intake the day after TSD but ↑ % calories from fat, ↓ % of calories from carbohydrates					
Greer, Nat Comm 2013[77]	23 non-obese adults (13 women, 10 men)	8.2 h nocturnal sleep versus TSD Duration: 1 night Crossover with ≥7-day washout	Design: Controlled intake; had a controlled snack at 02:30 during TSD	No difference in hunger on VAS morning after standardized breakfast but ↑ desirability for high-calorie foods during food-desire task.	NR	NR	NR	NR
Hogenkamp, Psychoneuroendocr 2013[73]	16 normal-weight men	8 h nocturnal sleep versus TSD Duration: 1 night Crossover with ≥28-day washout	Design: Controlled; no food provided during TSD	↑ fasting self-reported hunger after TSD Portion size task: After TSD, larger portions were chosen irrespective of the type of food when fasting; following breakfast, TSD subjects still chose larger portions of snacks	↑ Fasting morning total ghrelin following TSD	NR	NR	NR

Abbreviations: AL, ad libitum; EE, energy expenditure; NR, not reported; REE, resting energy expenditure; TSD, total sleep deprivation; VAS, visual analog scale.

Table 2.

Randomized controlled studies of partial sleep deprivation on metabolic outcomes

Study	Participants	Study design & intervention	Caloric intake	Subjective hunger	Appetite hormones	Energy expenditure	Glucose/ insulin	Weight
Brondel, Am J Clin Nutr 2010[60]	12 normal-weight men	8 h versus 4 h nocturnal sleep Duration: 2 nights Crossover with >5-day washout	Design: Standardized dinner before intervention night; no food provided during intervention; for the day after intervention, standardized breakfast to be eaten AL, lunch buffet, rest of meals eaten AL in free-living environment. Findings: 22% ↑ (559 kcal) total energy intake the day after PSD; longer duration of intake during breakfast the day after PSD; ↑ fat intake at dinner the day after PSD	↑ preprandial hunger before breakfast and dinner after PSD	NR	During PSD night, ↑ PA due to less sleep. ↑ PA (48 kcal) after during afternoon and evening the day after	NR	NR
Broussard, Obesity 2016[67]	19 normal-weight men	8.5 h versus 4.5 h nocturnal sleep Duration: 4 nights Crossover with >4-week washout	Design: Controlled during intervention until AL lunch and dinner buffets on the day following the 4th night of PSD Findings: ↑ total caloric intake from snacks (328 kcal), primarily from carbohydrates, during AL period; no difference in caloric or macronutrient intake from lunch or dinner buffets.	NR	↑ 24-h mean, nocturnal, and postprandial ghrelin with PSD 24-h mean, nocturnal, and diurnal pattern in leptin was not different	Similar activity counts by accelerometry	NR	No changes
Calvin, Chest 2013[61]	17 normal-weight adults *n* = 8 sleep restriction *n* = 9 control	Usual sleep versus sleep restriction of 2/3 of normal sleep time Duration: 8 days/ nights Parallel arm	Design: AL food and drink during the study Findings: ↑ Caloric intake by 559 kcal/d in sleep restriction, ↓ in control by −118 kcal/d, net change +677 kcal/d	NR	No change in morning leptin or total ghrelin on last day of study period	No change in PA (accelerometer)	NR	+PSD significantly increased by 0.9 kg but not in control
Hanlon, Sleep 2016[68]	14 normal-weight adults 11 men, 3 women	8.5 h versus 4.5 h nocturnal sleep Duration: 4 nights Crossover with >4-week washout	Design: Controlled during intervention until AL lunch and dinner buffets on the day following the 4th night Findings: No difference in AL intake for the first meal; trend	During PSD, ↑ hunger and overall appetite scores, concomitant with afternoon elevation of 2-AG	24-h mean ghrelin was not different; trend toward higher nocturnal ghrelin during PSD; nocturnal ghrelin peak occurred earlier in PSD	NR	NR	No difference in weight changes

Study	Participants	Study design & intervention	Caloric intake	Subjective hunger	Appetite hormones	Energy expenditure	Glucose/ insulin	Weight
			for ↑ in caloric intake (381 kcal) for snack period, with consumptions of twice as much fat and protein without affecting carbohydrate intake		24-h mean leptin was not different; amplitude of 24-h leptin variation was blunted following PSD 24-h mean eCB was similar; amplitude of 24-h 2-AG profile was ↑ with PSD due to an elevation and prolongation of peak levels			
Hart, Behav Sleep Med 2015[70]	12 women with overweight/ obesity	5 h versus 9 h nocturnal sleep Duration: 2 nights Crossover with >7-day washout	Design: Controlled during intervention; AL buffet on the day following the 2nd night Findings: No difference in total energy intake but considerable individual variability; ↑ % calories from protein and trend towards ↑ % calories from fat following PSD	No difference in hunger VAS throughout the day	No difference in fasting morning leptin and ghrelin	NR	No difference in fasting morning glucose and HOMA-IR	NR
Hibi, Sci Rep 2017[53]	9 normal-weight men	3.5 h versus 7 h nocturnal sleep Duration: 3 nights (followed by 1 night of recovery 7 h sleep for both sleep conditions) Crossover with >2-week washout	Design: Controlled during intervention	↑ Subjective hunger ↓ Fullness	↓ Fasting PYY and GLP-1 (anorexigenic gut hormones) No difference in fasting leptin	No difference in 24-h TEE (includes PSD) and 48-h TEE (whole-room indirect calorimetry) 55kcal ↑ in night-time EE during PSD ↑ 24-h activity during PSD	No difference in fasting glucose, fasting insulin, or 24-h urinary C-peptide profiles	NR
Markwald, PNAS 2013[31]	16 normal-weight adults 8 men, 8 women	3 days of BL 9 h sleep followed by intervention period: 5 h versus 9 h nocturnal sleep Duration: 5 nights Crossover without washout, in 2 separate groups based on visit order: *n* = 8 in Order A (9 h followed by 5 h sleep); *n* = 8 in Order B (5 h followed by 9 h sleep) *Unclear if assignment of	Design: AL feeding during scheduled meals with snacks freely available during scheduled wakefulness Findings: 6% (~180 kcal/d) ↑ energy intake during PSD; consumed and used ↑ carbohydrates; consumed smaller breakfast but 42% ↑ calories as after-dinner snacks during sleep loss; ↑ calories consumed at night after dinner than calories consumed for any individual meal	No difference in subjective hunger between 5 h versus 9 h during intervention period	No difference between 5 h versus 9 h sleep in 24-h mean leptin, ghrelin, or PYY during intervention period Compared to BL period of 9 h sleep, both 5 h and 9 h sleep in intervention period had ↑ 24-h mean leptin, ↓ 24-h mean ghrelin, and ↑ 24-h PYY	5% (111 kcal/d) ↑ TEE during PSD (whole-room indirect calorimetry) ↑ Hourly EE during night-time wakefulness versus scheduled sleep	NR	+0.82kg weight gain in 5h PSD compared to 9h sleep −0.03kg weight loss when transitioning from 5h to 9h sleep

Study	Participants	Study design & intervention	Caloric intake	Subjective hunger	Appetite hormones	Energy expenditure	Glucose/ insulin	Weight
		order groups were randomized						
McNeil, Physiol & Behav 2016[63] McNeil, Appetite 2017[75]	18 non-obese adults 12 men, 6 women	Control sleep versus 50% PSD with delayed bedtime versus 50% PSD with advanced wake-time Duration: 1 night Crossover with >7-day washout	Design: No food during PSD night; next-morning standardized breakfast, in-lab AL lunch, at home AL food the rest of the day Findings: ↑ Carbohydrate intake, trend for ↑ energy intake during delayed bedtime versus control	↑ Fasting and post-meal appetite ratings following advanced wake-time compared to the other 2 conditions. ↑ Explicit liking and wanting high fat foods following advanced wake-time compared to control.	NR	Trend for ↑ EE during delayed bedtime versus control (accelerometry) ↑ moderate intensity PA time with delayed bedtime versus the other 2 conditions ↑ vigorous intensity PA time with advanced wake-time versus delayed bedtime	NR	No differences in weight
Nedeltcheva, Am J Clin Nutr 2009[89]	11 normal-weight adults 6 men, 5 women	5.5 h versus 8.5 h nocturnal sleep Duration: 14 nights Crossover with >3-month washout	Design: AL intake for 3 scheduled meals; unrestricted access to AL snacks Findings: ↑ Total intake (297 kcal) with PSD; no difference in intake or macronutrients of meals; ↑ intake (221 kcal) from snacks with ↑ carbohydrates, especially overnight	NR	No difference in 24-h mean leptin and ghrelin	No difference in TEE (doubly labeled water) or RMR (metabolic cart) No difference in PA levels (TEE/RMR calculation)	NR	No difference in 14-day changes in weight or body fat but with individual variability
Rao, JCEM 2015[56]	14 normal-weight adults 8 men, 6 women	4 h versus 8 h nocturnal sleep Duration: 5 nights Crossover with >4-week washout	Design: Controlled	NR	NR	No difference in REE (metabolic cart) RQ ↓ during PSD Trend towards ↑ beta-hydroxybutyrate with PSD	No difference in fasting glucose/ insulin ↑ Insulin AUC from OGTT with PSD HIEC: ↓ whole-body and peripheral insulin sensitivity with PSD; EGP during HEIC ↓ ↑ circulating NEFAs during PSD	No weight changes

Study	Participants	Study design & intervention	Caloric intake	Subjective hunger	Appetite hormones	Energy expenditure	Glucose/ insulin	Weight
Schmid, J Sleep Res 2008[74]	9 normal-weight men	4.5 h versus 7 h versus TSD Duration: 1 night Crossover with >2-week washout	Design: Arrived at research unit at 21:00, no food intake during the night	↑ hunger after TSD compared to 4.5 h or 7 h No difference in hunger between 4.5 h versus. 7 h	↑ fasting ghrelin with TSD than 7 h; trend for ↑ fasting ghrelin with 4.5 h compared to 7 h No difference in leptin amongst the 3 conditions	NR	NR	NR
Schmid, Am J Clin Nutr 2009[62]	15 normal-weight men	4 h versus 8 h nocturnal sleep Duration: 2 nights Crossover with >6-week washout	Design: No food during 2 nights of the sleep period; 1st day after sleep period, standard breakfast then usual eating habits in free-living condition; 2nd day after sleep period, standardized breakfast AL, snack AL buffet available the whole day Findings: No difference in total energy intake on day 2; ↑ fat intake with PSD	No difference in rating scores of appetite, hunger, and satiety	No difference in 16-h profiles of leptin and ghrelin during the 2nd day after intervention	↓ time spent in high-intensity PA and ↑ time spent in low-intensity PA following PSD (accelerometry)	NR	NR
Shechter, Int J Obesity 2014[57]	10 non-obese women	4 h versus 8 h nocturnal sleep Duration: 3 nights Crossover with 4-week washout	Design: Controlled weight-maintenance diet	NR	NR	No difference in mean RMR morning after intervention period No difference in postprandial EE and RQ and mean TEF after high-fat breakfast after intervention period ↓ Fasting RQ after PSD	NR	NR
Spaeth, Sleep 2013[66]	225 non-obese adults *n* = 198 in PSD *n* = 27 control	4 h versus 10 h nocturnal sleep Duration: 5 nights Parallel arm	Design: AL intake from 3 scheduled meals and 1 additional night meal during PSD; can also consume food at any other times Findings: 130% of daily caloric requirement consumed for PSD versus 100.6% for control; ↑ meals and consumption of 552.9 additional calories between 10pm–4am; ↑ % of calories from fat during late-night hours in PSD	NR	NR	NR	NR	↑ weight gain in PSD than control (0.97 versus 0.11 kg)

Study	Participants	Study design & intervention	Caloric intake	Subjective hunger	Appetite hormones	Energy expenditure	Glucose/ insulin	Weight
Spaeth, Obesity 2015[59]	47 non-obese adults *n* = 36 PSD *n* = 11 control	4 h versus 10 h nocturnal sleep Duration: 5 nights Parallel arm	Design: AL intake from 3 scheduled meals and 1 additional night meal during PSD; can also consume food at any other times PSD consumed ↑ calories, ↑% calories from fat, ↓% of calories from protein	NR	NR	↓ RMR after PSD (2.6%) and returned to baseline after recovery sleep (ventilated hood)	NR	PSD gained 1.31 kg versus +0.62 kg in control (p = 0.097 for between-group difference)
Spiegel, Ann Internal Med 2004[69]	12 normal-weight men	4 h versus 10 h nocturnal sleep Duration: 2 nights Crossover with >6-week washout	Design: Standardized dinner before and standardized breakfast after 1st night, then usual eating habits in free-living conditions (not monitored); standardized dinner before 2nd night then continuous glucose infusion for 24 hours	↑ hunger and appetite ratings, especially for calorie-dense foods with high carbohydrate content	↓ 12-h mean leptin and ↑ 12-h mean ghrelin with PSD	NR	NR	No difference in weight
St-Onge, Am J Clin Nutr 2011[55] St-Onge, Sleep 2012[79]	15 normal-weight men, 15 normal-weight women	4 h versus 9 h nocturnal sleep Duration: 5 nights/6 days Crossover with >3-week washout	Design: Controlled for the first 4 days; AL for the last 2 days Findings: ↑ eating occasions during PSD ↑ caloric intake by ~300 kcal/d; ↑ fat consumption	No difference in feelings of hunger, satiety, or fullness	PSD ↑ fasting morning total ghrelin in men but not in women No difference in fasting active ghrelin PSD ↓ afternoon GLP1 in women but not men No difference in fasting leptin or PYY	No difference in RMR (ventilated hood) and TEE (doubly labeled water) No difference in total PA; PSD ↓ % time spent in sedentary activity, ↑ % time spent in light activity, ↓ % time spent in heavy PA	No difference in fasting glucose/ insulin or HOMA-IR In women, fasting insulin ↓ following PSD	Both sleep conditions lost weight (2.2 lb for 9 h and 1.7 lb for 4 h)
Van Leeuwen, Int J Endocr 2010[82]	23 normal-weight men *n* = 15 PSD *n* = 8 control	4 h versus 8 h nocturnal sleep Duration: 5 nights Parallel-arm	Design: Controlled	No difference in feelings of satiety	Fasting leptin ↑ increased after PSD, remained elevated after recovery	NR	Fasting glucose ↓, fasting insulin ↑ with PSD	NR

Abbreviations: eCB, endocannabinoid; EGP, endogenous glucose production; HIEC, hyperinsulinemia-euglycemic clamp; HOMA-IR, homeostasis model assessment-estimated insulin resistance; NR, not reported; PA, physical activity; PSD, partial sleep deprivation; RMR, resting metabolic rate; RQ, respiratory quotient; TEF, thermic effect of food; VAS, visual analog scale; 2-AG, 2-arachidonoylglycerol.