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REVIEW ARTICLE

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Crosstalk between sleep disorders and adipokine secretory profiles: novel mechanisms for metabolic disease risk

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ABSTRACT

Background: Sleep disorders—including sleep deprivation, obstructive sleep apnea (OSA), and circadian rhythm disruption—and metabolic diseases such as obesity and type 2 diabetes represent major, interconnected public health challenges. This review aims to synthesize current evidence on the bidirectional crosstalk between these conditions, with a focus on the mediating role of dysregulated adipokine secretion.

Discussion: We elaborate a mechanistic framework wherein specific sleep disturbances disrupt circadian rhythms and alter the secretory profiles of key adipokines, including leptin, adiponectin, interleukin-6 (IL-6), and angiopoietin-like protein 4 (ANGPTL4). Sleep deprivation and fragmentation promote a state of leptin dysregulation and reduce adiponectin levels, while OSA-driven intermittent hypoxia potently upregulates IL-6 and ANGPTL4. These alterations collectively contribute to insulin resistance, dyslipidemia, and chronic low-grade inflammation, thereby elevating metabolic disease risk. Conversely, obesity and diabetes exacerbate sleep disorders through pathways involving visceral adiposity, neuroendocrine dysfunction (e.g. HPA-axis activation), and diabetes-related symptoms (e.g. nocturia, neuropathic pain), forming a vicious cycle. Clinical and preclinical evidence underscores that the synchronization of sleep-circadian biology is fundamental to maintaining adipokine homeostasis and metabolic health.

Conclusion: The evidence positions sleep and circadian health as critical, modifiable determinants of metabolic risk. Integrating sleep assessment and evidence-based interventions (e.g. CPAP for OSA, sleep extension, circadian realignment) into standard preventive and clinical frameworks for metabolic diseases is a promising strategy. Public health initiatives should elevate 'quality sleep' as a pillar of health alongside nutrition and physical activity to mitigate the intertwined epidemics of metabolic and sleep disorders.

KEY MESSAGES

1. Sleep disorders and metabolic diseases engage in a vicious cycle mediated by the dysregulation of key adipokines (leptin, adiponectin, IL-6, and ANGPTL4), which disrupts circadian rhythms and promotes insulin resistance, inflammation, and dyslipidemia.
2. Adipokine profiling offers a novel mechanistic framework for understanding metabolic risk and serves as a potential early biomarker for individuals with sleep disturbances such as insomnia and obstructive sleep apnea.
3. Integrating sleep assessment and targeted interventions into routine metabolic care represents a promising and cost-effective public health strategy to break this cycle and reduce the global burden of obesity and type 2 diabetes.

STATEMENT OF SIGNIFICANCE

This review reveals a critical bidirectional relationship between sleep disorders and metabolic diseases mediated by dysregulated adipokine secretion. It proposes an innovative mechanistic framework elucidating how sleep disturbances lead to insulin resistance, dyslipidemia, and obesity—conditions that further impair sleep quality,

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creating a vicious cycle. A critical knowledge gap currently exists regarding therapeutic interventions targeting circadian rhythm-adipokine interactions. This study underscores the importance of integrating sleep health into public health strategies and highlights adipokines as early biomarkers of metabolic risk. Translational research should prioritize sleep interventions to reduce the burden of cardiovascular and metabolic diseases.

1. Sleep disorders

1.1. Overview of sleep disorders

Sleep is a physiological process that can relieve fatigue and improve body function. It plays an important role in the normal operation of various physiological processes of the human body, and therefore is the basis for ensuring overall health [1]. According to the statistics of the National Sleep Foundation, the recommended sleep time for adults is 7 to 9 h. However, in recent decades, the incidence of sleep disorders has increased and become more common due to social and lifestyle pressures. This is likely to become a global challenge, hence causes a significant burden on individuals, families, and society.

Sleep disorders can interfere with the body's normal circadian rhythm. In addition, long-term sleep disorders will have a negative impact on physical health. For example, they can lead to neurological and behavioral diseases [2], cardiovascular and metabolic diseases, obesity, diabetes [3], and Alzheimer's disease [4].

In clinical practice and research, sleep disorders cover a range of diseases with different pathophysiological mechanisms. For the purpose of this review, we focus on metabolic interactions and highlight several common forms most often associated with adverse metabolic outcomes. Insomnia disorder is characterized by continuous difficulty in falling asleep or maintaining sleep. Even if there is sufficient sleep opportunities, it often leads to short chronic sleep time or inability to recover energy during sleep. Obstructive sleep apnea (OSA) is a major form of sleep-related respiratory disorders, which is defined as repeated attacks of partial or complete obstruction of the upper airway during sleep, leading to intermittent hypoxia, sleep fragmentation and autonomic nerve fluctuations. Another important category associated with metabolic disorders is circadian rhythmic sleep-awake disorders, such as disorders caused by shift work or social jet lag, in which the mismatch between the internal biological clock and the external environment/behavioral cycle can destroy the time and continuity of sleep. In addition, specific diseases such as paroxysmal sleeping sickness, whose core characteristics include excessive daytime lethargy, sudden fall and abnormal regulation of rapid eye movement sleep, have also been found to be related to metabolic changes. It is important to note that these conditions often co-exist and share common pathways influencing systemic metabolism [5]. Circadian disruption can be quantified in clinical settings using several metrics, including: shift work exposure (duration and intensity of night work), social jetlag (the difference in sleep timing between workdays and free days), chronotype (morningness-eveningness preference), light at night exposure (duration and intensity of artificial light) and meal timing variability. These factors are potentially modifiable targets for circadian-based interventions aimed at preventing metabolic disease.

Sleep disorders arise from a complex interplay of environmental, behavioural, and physiological factors. Societal environmental factors, such as shift work schedules, are critical as they induce chronic circadian rhythm disruption by forcing alterations to sleep-wake patterns. Personal behavioral habits, like excessive evening exposure to artificial light from electronic devices, delay sleep onset and suppress endogenous melatonin secretion, further disrupting circadian rhythms. Furthermore, increased psychosocial stress and the use of certain psychoactive substances such as caffeine and nicotine, significantly impair sleep architecture and continuity [6].

1.2. Bidirectional pathological relationship between sleep disorders and obesity

Obesity is a major global public health issue. Current efforts to mitigate obesity and its related metabolic diseases (such as type 2 diabetes and metabolic associated steatotic liver disease) consider mainly the

traditional risk factors, like excessive energy intake and inadequate physical activity. However, such traditional risk factors alone cannot fully explain the continuous increase of global obesity rates over the past few decades conclusively [7]. For the past two decades, sleep disorders and circadian misalignment have been increasingly recognized by the scientific community as important, yet interrelated, risk factors contributing to the development and progression of obesity and related metabolic diseases [8].

Sleep disorders can lead to circadian rhythm disorders, thus interfering with the normal secretion of hormones that control energy metabolism and appetite [9]. Circadian rhythm disorder is a state of desynchronisation between the body's internal biological rhythms and external environmental factors like light exposure or feeding cycle. This is normally, characterised by abnormal energy intake, activity, and wakefulness at night when one should be asleep. On one hand, circadian rhythm disruption can cause neuroendocrine disorders, resulting in increased ghrelin levels and decreased leptin levels thus enhancing hunger and driving an energy surplus [10]; On the other hand, it can trigger disturbances in the substrate metabolic rhythms. Physiologically, lipid oxidation predominates at night, while carbohydrate oxidation is most pronounced during the day. Diurnal rhythm disorders, such as shift work or irregular sleep-awake patterns, can disrupt the normal metabolic processes associated with day and night. Typically, carbohydrate oxidation is predominant during active periods, while lipid oxidation rises during rest. Both animal and human studies indicate that misalignment of biorhythms can diminish peak carbohydrate oxidation during the day, leading to a shift in fuel utilization towards lipids. This shift is evidenced by lower respiratory quotients [11]. This metabolic inflexibility may promote the development of insulin resistance and favor fat storage over time [12]. However, we should acknowledge that these metabolic changes are influenced by concurrent alterations in food intake timing and composition driven by the disrupted circadian system. Research has demonstrated that when the human body is in a state of sleep disturbance, energy expenditure increases. Similarly, ad libitum food intake increased significantly, leading to a positive energy balance, particularly postprandial carbohydrate intake, causing positive energy balance and subsequent weight gain. A strictly controlled hospitalised trial ($n = 12$) revealed that while sleep disorders increase daily energy expenditure slightly, excessive food intake compensates for this. As a result, there is a positive energy balance, significant weight gain, increased visceral fat [13].

Obesity impacts sleep in various ways, for instance, visceral fat accumulation and increased neck circumference exacerbate the risk of OSAS [14] and abnormal secretion of adipokines by visceral fat can disrupt sleep homeostasis. This is likely to form a vicious cycle of obesity and sleep disorders.

The interconnected pathways linking sleep disturbances to obesity—encompassing neuroendocrine dysregulation, disruption of substrate metabolic rhythms, and mechanical factors such as visceral fat accumulation—are summarized in Figure 1.

1.3. Bidirectional pathological relationship between sleep disorders and diabetes

The association between sleep disorders, particularly OSA and sleep deprivation, and impaired glucose tolerance or type 2 diabetes is well established, and this relationship is bidirectional. Sleep disorders increase insulin resistance and diabetes risk independently, while pre-existing diabetes can exacerbate sleep issues through multiple pathways (such as nocturia and neuropathic pain, creating a self-reinforcing vicious cycle.

Analyzing the relationship between sleep disorders and impaired glucose metabolism requires careful consideration of confounding factors, especially the co-occurrence of obesity and obstructive sleep apnea (OSA). Evidence can be stratified based on population characteristics.

In healthy, non-obese individuals, experimental sleep deprivation studies offer the most direct evidence of causality. For instance, a rigorously controlled trial in healthy, lean subjects demonstrated that short-term sleep deprivation alone impairs insulin signaling pathways in subcutaneous adipocytes, as evidenced by significantly reduced Akt phosphorylation levels. By eliminating the confounding effects of obesity and OSA, these studies unequivocally demonstrate that sleep deprivation itself is sufficient to impair peripheral insulin sensitivity [15].

In obese individuals without OSA, the effects of sleep disturbances are often intertwined with adipose tissue dysfunction. Research in these populations aims to differentiate the independent contributions of sleep disruption and obesity to adipokine levels, such as leptin and adiponectin. Although direct

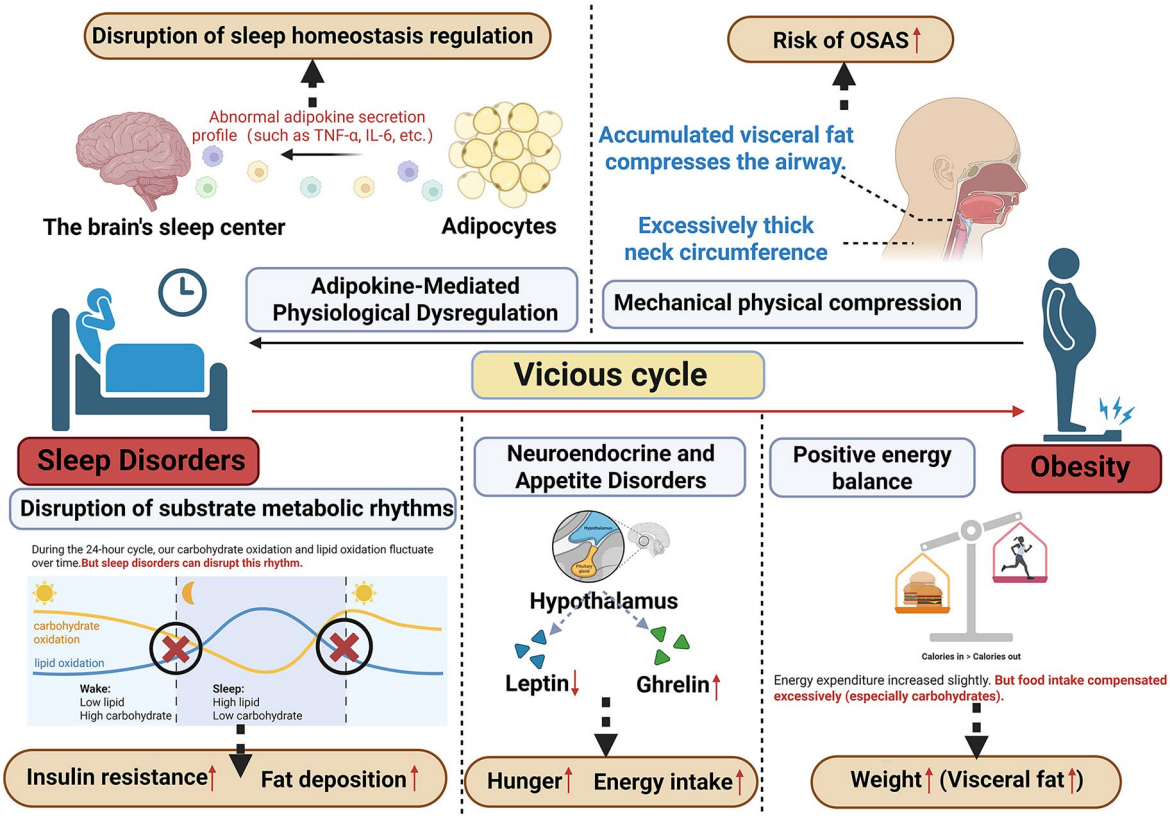

Figure 1. The vicious cycle between sleep disturbance and obesity.

evidence in obese patients with insomnia remains scarce, studies on circadian regulation suggest that sleep disturbances can disrupt leptin rhythmicity independently of adiposity [16]. Emerging evidence indicates that disrupting the molecular clock within leptin-sensitive cells affects leptin sensitivity in a time-dependent manner, potentially contributing to metabolic dysregulation even when absolute leptin levels are confounded by obesity [17]. These findings support the idea that sleep fragmentation and circadian misalignment may have direct metabolic effects beyond those attributable to excess adiposity alone.

In patients with OSA, regardless of obesity status, chronic intermittent hypoxia (CIH) is a primary pathophysiological mechanism. Numerous observational studies have confirmed that OSA is an independent risk factor for insulin resistance and type 2 diabetes. Within this group, alterations in adipokines, such as the significant upregulation of IL-6 and ANGPTL4, correlate directly with the severity of hypoxia, forming a distinct 'hypoxia-adipokine-metabolic dysfunction' axis [18,19].

Individuals with normal weight who experience insomnia are particularly important for understanding the metabolic effects of 'pure' sleep disorders. Although direct studies on this group are limited, experimental sleep deprivation research in healthy, non-obese individuals provides indirect evidence that sleep deprivation can impair peripheral insulin signaling even without obesity [15]. A meta-analysis of 21 sleep restriction studies, most of which included healthy, non-obese individuals, consistently showed that sleep restriction significantly reduces insulin sensitivity [20]. This strongly suggests that fragmented sleep and circadian rhythm disruption pose direct metabolic risks independent of traditional risk factors.

The mechanisms by which sleep disturbances disrupt glucose homeostasis are multifaceted and interconnected. One core pathway involves neuroendocrine dysregulation. Sleep deprivation elevates ghrelin levels and reduces leptin levels, promoting high-calorie food intake, and it also impairs insulin signaling in peripheral tissues. A study involving healthy thin participants ($n=7$) demonstrated that insulin treatment of the participants' subcutaneous fat cells resulted in a 30% reduction in Akt phosphorylation levels after four consecutive nights of sleep deprivation, indicating impaired signal transmission of the insulin receptor substrate [15]. In addition to leptin, sleep deprivation significantly alters ghrelin, a key hormone that promotes appetite, typically leading to elevated levels. This pattern of dysregulation—decreased leptin and

increased ghrelin—provides a neuroendocrine basis for increased appetite and cravings for high-calorie foods following insufficient sleep [10]. From an energy expenditure perspective, indirect calorimetry studies reveal that while sleep restriction may slightly increase resting metabolic rate, the resulting increase in food intake far surpasses this expenditure, ultimately leading to a net positive energy balance and weight gain [13]. Mechanistically, hyperinsulinemic-euglycemic clamp studies of sleep-deprived individuals provide strong evidence, directly quantifying the degree of impaired insulin sensitivity in the liver and peripheral tissues, which supports the conclusion that sleep disorders impair glucose homeostasis [21]. A 2022 systematic review corroborated previous findings that sleep restriction reduces clamp-measured, whole-body insulin sensitivity, suggesting that sleep duration is a modifiable risk factor for insulin resistance [20].

Secondly, systemic low-grade inflammation caused by lack of sleep is also very important. As mentioned earlier, sleep disorders – especially chronic intermittent hypoxia caused by obstructive sleep apnea (OSA) – can lead to elevated levels of inflammatory mediators such as IL-6, which in turn promote insulin resistance by destroying the insulin signaling pathway. In addition, the disorder of the biological clock system also plays a key role in this process. Core circadian clock genes regulate the diurnal rhythm of glucose metabolism, and behavioral circadian dysregulation caused by shift work, irregular sleep-wake schedules, or nighttime eating directly impairs glucose tolerance. Melatonin, as a key circadian output signal, exhibits functional genetic variants in its receptor MTNR1B (e.g. rs10830963) that correlate with elevated fasting blood glucose and increased risk of type 2 diabetes [22]. A large-scale study indicates that individuals with the highest endogenous melatonin secretion have a 42% reduced risk of diabetes compared to those with the lowest melatonin levels. This finding underscores the significance of a complete circadian rhythm for metabolic protection [23]. In addition, chronic intermittent hypoxia (CIH) – a pathophysiological stimulus unique to OSA – is an independent risk factor for beta cell dysfunction and decreased insulin sensitivity. Animal models confirm that CIH exposure can quickly cause impaired glucose tolerance, and some of these metabolic defects are reversible after stopping hypoxia, suggesting that early intervention may have potential value [24]. In the end, even in the absence of obvious hypoxia, intermittent sleep itself will cause stress in the hypothalamic endoplasmic reticum and upregulate the protein tyrosine phosphatase 1B (PTP1B), resulting in loss of leptin dysregulation and satiety. This, in turn, promotes weight gain and worsens glucose metabolism [25]. It is worth noting that intervention studies aimed at improving sleep (such as prolonged sleep time) provide counter-esubstantiation of this causal relationship. Meta-analysis of a number of randomized controlled trials shows that prolonged sleep significantly improves insulin sensitivity, further consolidating the evidence basis for sleep duration as an adjustable metabolic risk factor [26].

The opposite effect is equally significant. Patients with diabetes often experience interrupted sleep due to various disease-related factors. Hyperglycemia can lead to osmotic diuresis, resulting in frequent nighttime urination. Additionally, diabetic peripheral neuropathy may cause nocturnal pain or abnormal sensations, and treatments aimed at strictly controlling blood sugar can increase the risk of nocturnal hypoglycemia, which may lead to awakenings. Collectively, these factors undermine both the continuity and quality of sleep.

In summary, sleep disorders and diabetes are closely interconnected through several mechanisms, including neuroendocrine factors, inflammation, circadian rhythm disruptions, and oxidative stress. This creates a vicious cycle that is challenging to break. Future research should not only delve deeper into these molecular mechanisms but also prioritize the significant epidemiological effects of circadian rhythm disorders influenced by social behavioral factors, such as shift work. Furthermore, intervention research should focus on developing comprehensive sleep and circadian rhythm management strategies tailored to these specific populations.

The bidirectional vicious cycle between sleep disorders and diabetes, involving melatonin-mediated circadian disruption, impaired insulin signaling, and diabetes-related symptoms that further fragment sleep, is illustrated in Figure 2.

2. Overview of adipokines

In the following discussion, we will integrate evidence from multiple levels to understand the role of adipokines in the sleep-metabolism axis. This evidence includes: population-based observational

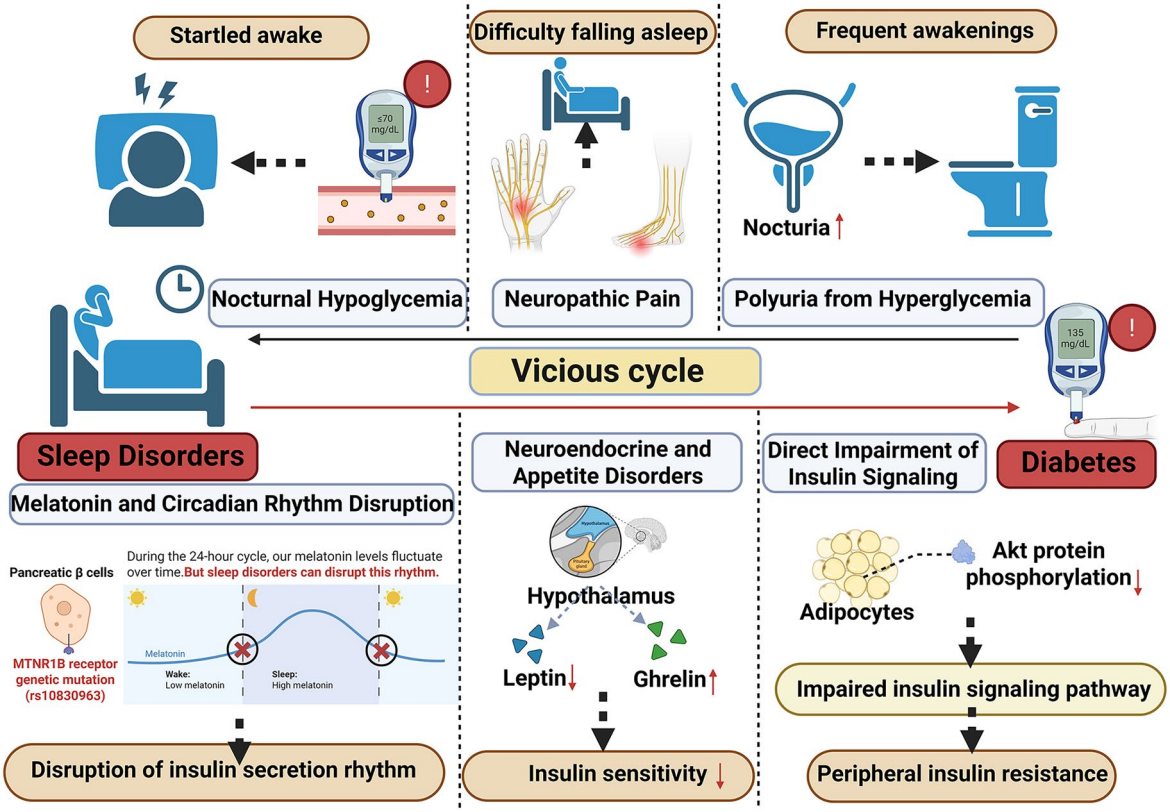

Figure 2. The molecular mechanisms in the sleep disturbance-diabetes vicious cycle.

studies that reveal associations; clinical intervention trials, such as those involving CPAP therapy and sleep extension, which provide causal indications; and preclinical research using animal and cellular models that elucidates molecular mechanisms. Distinguishing between these levels of evidence is critical for accurately interpreting the translational potential of adipokines as biomarkers or therapeutic targets.

Adipose tissue is a dynamic organ with a variety of physiological functions: (1) energy metabolism center; as the largest energy reserve of the human body, it maintains energy homeosis through the storage and mobilization of triglycerides; (2) active endocrine organs; secrete more than 20 fatty factors, such as leptin, adipolin and ANGPTL4, regulating systemic metabolism through endocrine and parasecretory pathways, (3) regulator of the tumor microenvironment; fat cells interact with cancer cells to reshape local immunity and vascularize the microenvironment [27]. The adipokines secreted by adipose tissue help to regulate systemic metabolic processes.

The secretion of fat factors is regulated by the three-level cascading mechanism: (1) Multiple stimuli: including factors of tumor origin such as TGF-β and HIF-1α), metabolic stress such as hyperglycemia), mechanical stress, and exocrine miRNA, such as miR-27a downregulation of PPARγ [28]; (2) Adipocyte differentiation status: Long-term lipoiogenic differentiation (LTAD) is a key factor in regulating the secretion of a variety of fat factors by fat cells [29]; (3) Rhythm regulation: The core biological clock gene *BMAL1/CLOCK* directly regulates the transcription of adipocyte hormones through the E-box element. In the Bmal1 iKO mouse study, the nocturnal secretion peak of serum leptin decreased by 45%, and the circadian rhythm disappeared, confirming that BMAL1 regulated the secretion rhythm of leptin through the E-box element [30].

Under normal physiological conditions, fat factors help to maintain the homeostasis in the body. This article reviews how sleep disorders can destroy the above regulatory networks, leading to dysregulation of fat factor secretion, and thus promoting the progression of metabolic diseases.

A comprehensive summary of the alterations, underlying mechanisms, and clinical significance of these adipokines in the context of sleep disorders is provided in Table 1.

Table 1. Summary of adipokine alterations, underlying mechanisms, and clinical significance in sleep disorders.

Adipokine & source	Primary functions & regulation	Response to sleep disturbance	Underlying mechanisms	Clinical significance
Interleukin-6 (IL-6) Immune cells, Adipose tissue (30%)	**Pro-inflammatory cytokine.** • Regulates inflammation *via* classic & trans-signaling (STAT3). • Correlates with obesity and IR. • Circadian rhythm: Peaks at 19:00 & 05:00.	↑ **Levels** (e.g. >12.7 pg/mL). • Loss of nocturnal peak. • Shift to diurnal secretion pattern. • CPAP therapy reduces levels.	1. **HPA axis activation:** GCs → NF-κB → synthesis↑. 2. **Intermittent hypoxia (CIH):** HIF-1α → binds IL -6 HRE → promoter demethylation.	Independent risk factor for metabolic inflammation and IR. Dynamic assessment is challenging due to circadian peaks.
Leptin Adipocytes (SC > VAT)	**Satiety hormone.** • Inhibits appetite (POMC/CART neurons). • Promotes thermogenesis (BAT). • Improves insulin sensitivity. • Circadian rhythm: Nocturnal peak (↑30–50%).	**Contradictory findings:** • ↓ (Most common, e.g. ↓>30%) • → (No change) • ↑ (Acute stress/compensation)	1. **HPA/SNS activation** disrupts rhythm. 2. **Leptin dysregulation:** BBB transport↓, Ob-Rb internalization, SOCS3↑ (JAK2-STAT3 inhibition).	Bidirectional link with sleep. Loss of rhythm promotes weight gain and IR. Confounded by BMI, race, and resistance.
Adiponectin Adipocytes (SC > VAT)	**Insulin-sensitizing hormone.** • Activates AMPK/PPARα. • Enhances glucose uptake, FA oxidation. • Anti-atherosclerotic & anti-tumor. • Levels ↓ before obesity onset.	↓ **Levels** (e.g. ↓26.7% in severe SD). • Race/Gender-specific: - ↑ in African American women with insomnia. - ↓ in White women.	1. **HPA/SNS activation** suppresses transcription. 2. **Race-specific:** Higher androgen/estrogen ratio in African Americans → PPARγ/AMPK activation.	Early biomarker for metabolic risk. Changes are race- and gender-dependent. Indirect circadian regulation.
ANGPTL4 Adipocytes, Liver	**LPL inhibitor.** • Fasting: ↑ (200–300%). • High-fat diet: ↓ (40–60%). • Inhibits LPL → ↑TG, ↓HDL-C.	↑ **Levels** in OSA (e.g. ↑65%). • mRNA and protein levels correlate with ODI severity.	**Intermittent hypoxia (CIH):** HIF-1α → binds ANGPTL4 HRE → transcriptional activation.	Key mediator of OSA-related dyslipidemia (hypertriglyceridemia, low HDL-C). Potential therapeutic target.

AMPK: AMP-activated protein kinase; BAT: brown adipose tissue; BBB: blood-brain barrier; CPAP: continuous positive airway pressure; CIH: chronic intermittent hypoxia; GCs: glucocorticoids; HPA: hypothalamic-pituitary-adrenal; HRE: hypoxia response element; IR: insulin resistance; LPL: lipoprotein lipase; ODI: oxygen desaturation index; OSA: obstructive sleep apnea; PPARα: peroxisome proliferator-activated receptor alpha; SC: subcutaneous adipose tissue; SNS: sympathetic nervous system; STAT3: signal transducer and activator of transcription 3; VAT: visceral adipose tissue.

2.1. Sleep disorders exacerbate metabolic disease via interleukin-6 (IL-6) dysregulation

IL-6 is a glycosylated secretory protein weighing 22–27 kDa. Approximately 30% of IL-6 originates from the adipose tissue. Its main functions are: (1) Inflammation regulation; IL-6 activates the STAT3 pathway through classical signalling (membrane-bound IL-6R) and trans-signalling (soluble IL-6R) and (2) Metabolic association; Serum IL-6 levels are positively correlated with obesity severity and insulin resistance, and weight loss can reduce them by 40–60% [31]. Overactivation of the JAK-STAT signalling pathway by IL-6 prevents tyrosine phosphorylation of insulin receptor substrate (IRS), thereby interfering with glucose transporter (GLUT4) membrane translocation, hence leading to insulin resistance.

IL-6 secretion exhibits a circadian rhythm, peaking at 19:00 pm and 5:00 am. The rhythm is regulated by the circadian clock genes *BMAL1/CLOCK* that controlled by the suprachiasmatic nucleus (SCN). They influence the phase of IL-6 secretion in peripheral tissues through the STAT3 signalling pathway. Besides, night-time sleep facilitates an increase in the IL-6 concentration at night [32].

A study regarding the relationship between sleep disorders and serum IL-6 levels ($n = 148$) demonstrated that the baseline serum IL-6 levels in the sleep disorder group were significantly higher than those in the good sleep group (>12.7 pg/mL) ($p < 0.05$). This meant that sleep disorders are an independent risk factor for high IL-6 levels [33]. Another study ($n = 14$) showed that sleep loss due to simulated night shifts led impaired the nocturnal IL-6 secretion peak ($p < 0.01$), delayed nocturnal rise in IL-6 levels, and shifted the IL-6 secretion pattern from nocturnal to diurnal secretion. As a result, there was a sustained 30% rise in diurnal IL-6 secretion ($p < 0.001$) [18]. A meta-analysis on OSA, including 12 IL-6 studies and involving 1,126 OSA patients, revealed that IL-6 levels decreased significantly after CPAP treatment ($p < 0.05$). Besides, subgroup analysis showed that the reduction in IL-6 levels correlated positively with the nocturnal hypoxia index (ODI) ($p = 0.03$) [34].

Sleep disorders facilitate IL-6 dysregulation based on dual pathways: (1) HPA axis activation; sleep disorders promote elevated glucocorticoid levels, which enhance NF-κB transcriptional activity and subsequently increase IL-6 production [18]. Similar inflammatory activation has been observed in chronic insomnia, where sustained hyperarousal and HPA axis overactivity drive IL-6 elevation independent of sleep apnea [35]. Likewise, simulated night shift protocols in healthy volunteers recapitulate the shift of IL-6 secretion from nocturnal to diurnal pattern, demonstrating that circadian misalignment alone can perturb inflammatory cytokine rhythms [18]. (2) Hypoxia induction: Intermittent hypoxia related to OSA causes HIF-1α to bind to the HRE element of the IL-6 gene, resulting in demethylation of the promoter, ultimately causing a rise in IL-6 gene expression.

Overall, the available evidence demonstrates that sleep disorders contribute to IL-6 dysregulation *via* dual pathways involving the hypoxia-inflammation axis and the circadian-metabolic axis. They facilitate the pathological processes of metabolic inflammation and insulin resistance, thus exacerbating the risk of metabolic diseases. However, the dual-peak secretion of IL-6 requires multiple blood samples per day; at least at 19:00 and 05:00. Additionally, home-based detection technologies like microneedle sensors, are not readily accessible, making it difficult to conclusively assess individual rhythms. As a result, challenges still exist in clinical translation.

2.2. Leptin dysregulation: a bidirectional link between sleep disorders and metabolic disease

Leptin is a 167-amino acid polypeptide hormone encoded by the ob (obesity) gene. It controls appetite and energy balance through hypothalamic arcuate nucleus (ARC) neurons. It works together with ghrelin to maintain metabolic homeostasis [36]. Its core physiological functions include: (1) Inhibiting food intake by activating POMC/CART neurons to create satiety signals, (2) Promoting thermogenesis by enhancing brown adipose tissue (BAT) thermogenesis and skeletal muscle fatty acid oxidation through sympathetic nervous system activation mediated by the brain-derived neurotrophic factor (BDNF) pathway [37], (3) Enhancing glucose and lipid metabolism as well as skeletal muscle fatty acid oxidation while inhibiting hepatic gluconeogenesis to optimize insulin sensitivity [38].

Leptin levels are jointly regulated by fat tissue distribution, nutritional status, and circadian rhythms [34,39,40]. Its secretion reveals typical circadian dynamics: peaking at night (30 to 50% higher than daytime levels) and decreases gradually during the latter part of sleep. The rhythm is controlled by the circadian clock genes *BMAL1/CLOCK* [40].

Studies have demonstrated a bidirectional relationship between sleep duration and leptin levels. Leptin not only regulates appetite but is also associated with the central nervous system-specific effects [41]. Leptin antagonises orexin neuron activity in the lateral hypothalamic area (LHA), prolonging slow-wave sleep (SWS) duration and contributes to maintenance of deep sleep [42]. Research has pointed out that activation of leptin receptor (LepR) neurons in the ventral nucleus of the preoptic area (PMv) by emotional stimuli can prolong sleep latency and increase wakefulness time [43]. A study on leptin signalling deficiency models (ob/ob and db/db) in mice, revealed that the ob/ob mouse group (leptin-deficient) had a 35% reduction in stage R sleep and impaired sleep continuity [44]. The findings suggest that interfered leptin signalling can impact sleep duration regulation adversely and is therefore crucial in metabolic coordination.

The relationship between sleep disorders and circulating leptin levels is complex, with findings varying significantly due to differences in study design, population characteristics (such as BMI and sex), the type and duration of sleep disturbance, and the presence of leptin dysregulation. This heterogeneity likely arises from a combination of factors. Acute sleep deprivation may temporarily decrease leptin levels through sympathetic activation. In contrast, chronic sleep restriction may trigger compensatory increases in leptin or the development of central leptin dysregulation. Additionally, reported race-specific differences could stem from genetic variations in leptin pathway genes or variations in adipose tissue distribution [45,46]. Some studies have indicated that acute sleep deprivation (e.g. 1–2 nights) can lead to decreased leptin levels [47], potentially due to increased energy expenditure and neuroendocrine stress responses. Conversely, other studies, particularly those focusing on chronic sleep restriction or poor sleep quality, has reported no significant change [45] or even an increase in leptin levels [46]. For instance, a six-month observational study of individuals with moderate to severe insomnia found that

leptin levels were significantly reduced compared to a control group [47]. Conversely, a study involving patients with chronic spontaneous urticaria, a condition often associated with sleep issues, found elevated leptin levels [46]. This discrepancy may suggest that acute stressors can cause a compensatory increase in leptin due to activation of the hypothalamic-pituitary-adrenal axis, while chronic conditions may lead to long-term down-regulation or leptin dysregulation. Nonetheless, a consistent finding across many studies is the disruption of the leptin circadian rhythm; even if the 24-hour average leptin level remains unchanged, the nocturnal peak may diminish or vanish [48]. This loss of rhythmicity could negatively impact metabolism, regardless of whether leptin concentrations remain stable.

In shift workers, chronic misalignment between behavioral cycles and endogenous circadian rhythms leads to blunted nocturnal leptin peaks and increased daytime hunger, providing a molecular link between occupational sleep schedules and metabolic risk [49]. For insomnia patients without short sleep duration, leptin levels may not significantly differ from controls, but the circadian amplitude of leptin secretion is often attenuated, suggesting that rhythm disruption rather than absolute level change is a key feature.

Understanding leptin dysregulation is essential for grasping the link between chronic sleep disorders and metabolic diseases. Leptin dysregulation is characterized by a diminished biological response to leptin, typically indicated by elevated blood levels of leptin that fail to effectively suppress appetite or prevent weight gain. Sleep disturbances may contribute to leptin dysregulation through several mechanisms: (1) Reduced blood-brain barrier (BBB) transport, where chronic hyperleptinemia may saturate the transport systems for leptin into the hypothalamus [50]; (2) Downstream signaling inhibition, where inflammatory pathways activated by sleep disorders (e.g. through SOCS3 upregulation) can impede leptin receptor (Ob-Rb) signaling *via* the JAK2-STAT3 pathway [51]; and (3) Interaction with insulin signaling, as sleep disruption-induced insulin resistance can further hinder communication between insulin and leptin signaling pathways in both the brain and peripheral tissues, creating a vicious cycle [38]. Consequently, regardless of whether sleep disorders lead to acute increases or decreases in leptin, the long-term outcome typically results in a state of functional leptin deficiency in the brain, which promotes hyperphagia and subsequent weight gain.

Complementing the mechanistic insights derived from experimental models, emerging human clinical evidence across various disease contexts corroborates the critical role of leptin in sleep regulation. In patients with congenital leptin deficiency—a rare autosomal recessive disorder caused by LEP gene mutations—the absence of leptin signaling is associated not only with hyperphagia and severe early-onset obesity but also with profound disturbances in sleep architecture and ventilatory control [44]. Mechanistically, leptin deficiency in humans has been linked to attenuated central respiratory drive, diminished hypercapnic ventilatory responses, and impaired sleep maintenance [44]. Notably, recent single-case reports in patients with anorexia nervosa—characterized by acquired relative hypoleptinemia—have shown significantly improved sleep within days of initiating off-label metreleptin (recombinant human leptin) treatment [44]. This rapid improvement suggests that leptin's effects on sleep are not solely mediated by long-term changes in body weight but may also involve direct neuroendocrine pathways. In adults, the connection between leptin and sleep extends beyond OSA to central sleep-disordered breathing. A clinical study in patients with heart failure reported that low circulating leptin concentrations are independently associated with the presence of central sleep apnea, indicating that leptin deficiency may serve as a screening biomarker for this condition [52]. Moreover, meta-analyses of short sleep duration in general populations have confirmed that insufficient sleep is associated with significant alterations in leptin levels, though the direction of change varies depending on study design (acute vs. chronic sleep restriction) [53]. Collectively, these human observations complement the preclinical and mechanistic data discussed above, strengthening the argument that hypoleptinemia—whether absolute (as in congenital deficiency or starvation) or relative (as in anorexia nervosa or heart failure)—contributes to sleep disturbances in various clinical settings.

Based on in-depth exploration of multiple experimental studies, it has been realised that sleep disorders affect leptin metabolism, hence promote weight gain through increased hunger and subsequent food intake [10]. This lowers insulin sensitivity and accelerates the progression of type 2 diabetes. As a result, the progression of diabetes, exacerbates the deterioration in sleep quality, leading to a vicious

cycle. The current research however, focuses on the differences in the direction of leptin concentration changes after sleep disorders among various populations. Based on the current gaps in literature, future studies should be carried out using BMI stratification to exclude the effect of leptin dysregulation in individuals with obesity. In addition, it should include more people from different ethnic groups to determine the contribution of ethnic differences to the direction of leptin changes.

The complex interplay between sleep disorders and leptin signaling—including circadian regulation, central and peripheral leptin actions, and the progression to leptin dysregulation—is depicted in Figure 3.

2.3. Adiponectin: a key mediator linking sleep disorders to metabolic dysregulation

Adiponectin is a fat cell-specific secreted protein encoded by the ADIPOQ gene. It is the most abundant adipokine in the human body, with plasma concentrations ranging from 5 to 30 μg/mL. Its expression exhibits tissue-specific heterogeneity: in white adipose tissue (WAT), subcutaneous fat secretion is significantly higher than visceral fat (approximately 2.5 times higher), accounting for over 90% of the total circulating amount. Despite this, its expression level in brown adipose tissue (BAT) is only between 10 to 15% of that in WAT [54]. Research has shown that adiponectin has multiple metabolic protective effects,

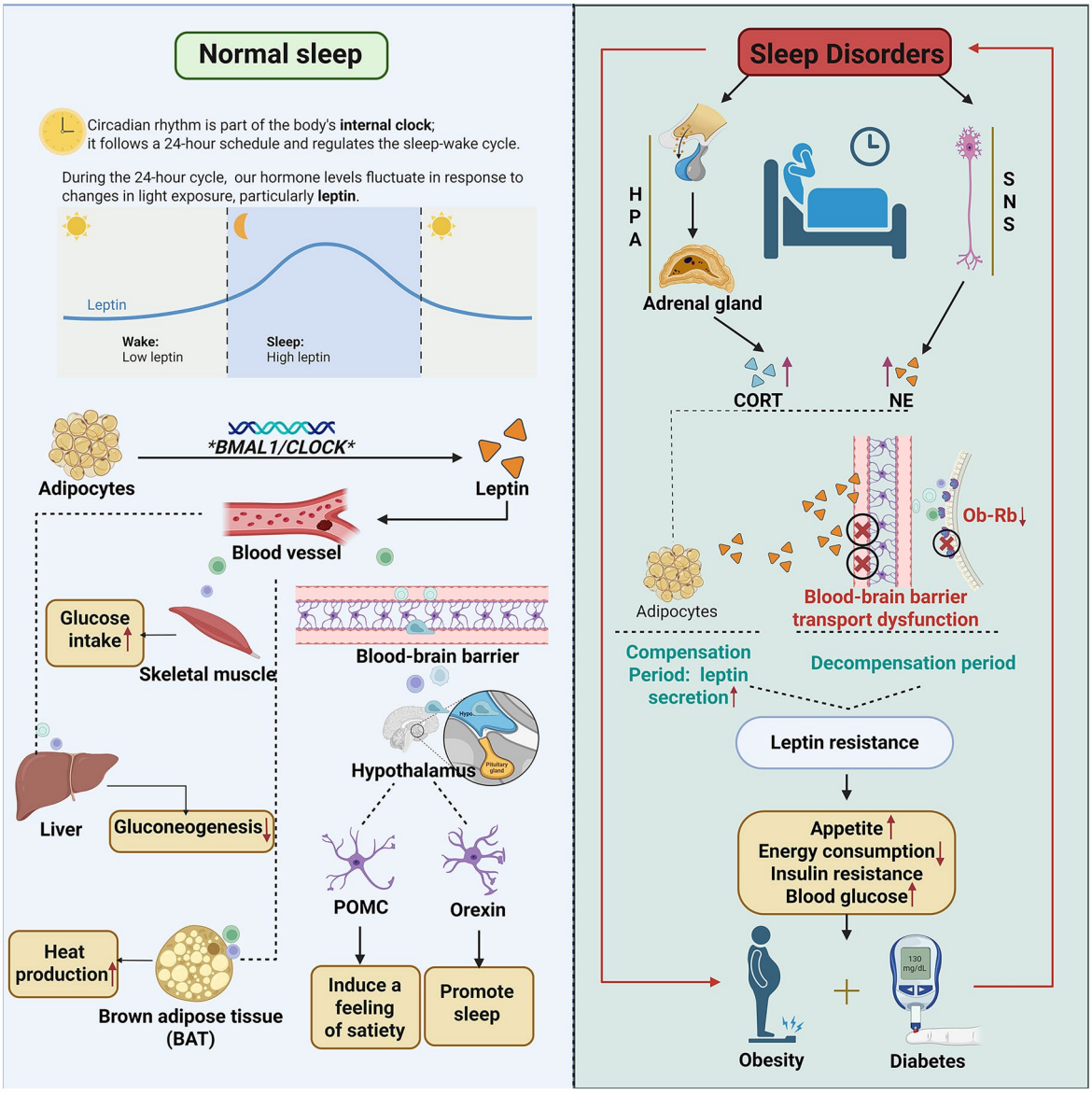

Figure 3. The bidirectional interplay between sleep disturbance and leptin signaling: underlying mechanisms and implications for metabolic dysregulation.

through the activation of the adenosine monophosphate-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor α (PPARα) pathways: It promotes glucose uptake in the skeletal muscle and inhibits hepatic gluconeogenesis, hence exert anti-diabetic physiological effects; by lowering the expression of vascular endothelial cell adhesion molecules (VCAM-1/ICAM-1), it exerts anti-atherosclerotic effects; and by causing tumour cell apoptosis (activation of the caspase-3 pathway), it exerts anti-tumour effects [55]. It is vital to understand that, adiponectin levels decrease significantly before the onset of obesity (35 to 50% lower than in individuals with normal BMI), meaning that, it can help to signal metabolic disorders early [56].

Sleep disorders affect ADIPOQ transcription by activating HPA axis and sympathetic nervous system excitation, resulting in alterations in adiponectin levels. A case-control study of patients suffering from endocrine metabolic diseases ($n = 332$) demonstrated that sleep deprivation was significantly negatively correlated with adiponectin levels, whereby the total adiponectin levels in the severe sleep disorder was 26.7% lower than in the normal group ($p = 0.003$). Besides, for every 1-hour reduction in sleep duration, the adiponectin levels decreased by 0.78 µg/mL (*r* = −0.72, $p < 0.001$). The inhibitory effect of sleep disorders on adiponectin was stronger in female than in the male patients (34% decrease in females vs. 19% decrease in males, $p = 0.01$) [57]. Another study ($n = 400$) showed that in the OSAS group, adiponectin levels decreased by 40% in white women and 12% in African American women, while in the psychogenic insomnia group, adiponectin levels decreased by 18% in white women and increased by 18% in African American women [58]. The outcomes reveal that changes in adiponectin levels caused by sleep disorders are strongly associated with race and gender.

Putting into perspective the metabolic protective effects of adiponectin and the impact of sleep disorders on adiponectin levels, it means that, it can serve as an early biomarker for metabolic risks related to sleep disorders. Current evidence supports the idea that *BMAL1/CLOCK* regulates adiponectin through indirect pathways like PPARγ, though the direct E-box binding mechanism has not yet been confirmed. Future studies should consider fat tissue-specific clock gene editing models to establish if ADIPOQ is a direct transcriptional target of the circadian clock.

2.4. Angiopoietin-like protein 4 (ANGPTL4): a hypoxia-sensitive mediator of metabolic dysfunction in OSA

ANGPTL4 is a nutrient-sensitive adipokine whose circulation levels increase significantly (↑200–300%) under fasting conditions. Its expression is normally suppressed by a high-fat diet (decrease of 40–60%) [59]. Its main metabolic function is regulation of lipid metabolism *via* allosteric inhibition of lipoprotein lipase (LPL) activity: ANGPTL4 binds to the catalytic domain of LPL, hence inhibiting LPL dimerisation and inactivating LPL enzyme activity. This leads to increased plasma triglycerides (TG) and decreased high-density lipoprotein cholesterol (HDL-C) [60]. This regulatory mechanism positions ANGPTL4 as a vital mediator against atherosclerosis and type 2 diabetes.

A cohort study of OSA patients ($n = 125$) reported that in the visceral adipose tissue of OSA patients, the severity of CIH (assessed by the oxygen deficit index ODI) was significantly positively correlated with ANGPTL4 mRNA expression (*r* = 0.78, $p < 0.001$), serum ANGPTL4 protein levels rose by 65% in the severe OSA group ($p = 0.003$), and were positively correlated with triglycerides ($r = 0.63$), indicating transcriptional-translational consistency [19]. Another case-control study (OSA group $n = 52$ vs. healthy control group $n = 22$) showed that ANGPTL4 concentrations in the OSA group (179.26 ± 12.89 ng/mL) were significantly higher than those in the control group (142.63 ± 7.99 ng/mL). The ANGPTL4 concentrations had a statistically significant difference ($p = 0.018$) [61]. The aforementioned human studies indicate that ANGPTL4 is elevated in patients with obstructive sleep apnea (OSA). This finding aligns with preclinical research, which demonstrates that CIH upregulates ANGPTL4 transcription and expression *via* HIF-1α activation [62]. Importantly, this pathway has direct physiological consequences: in both OSA patients and animal models, ANGPTL4 upregulation correlates with delayed clearance of postprandial triglyceride-rich lipoproteins, establishing a mechanistic link between sleep apnea and atherogenic dyslipidemia [63]. Recent studies further confirm that ANGPTL4-mediated lipoprotein lipase inhibition plays a central role in obstructive sleep apnea (OSA)-associated dyslipidemia, independent of body mass index [64].

ANGPTL4 upregulation is associated with metabolic disorders in OSA patients: ANGPTL4 upregulation inhibits LPL, resulting in delayed clearance of chylomicrons after meals. This in turn leads to hypertriglyceridemia, lowers the level of high-density lipoprotein cholesterol (HDL-C), and weakens the ability to reverse transport cholesterol, thus forming a vicious circle. The study also shows that ANGPTL4 interferes with insulin-mediated glucose uptake through the EGFR/ERK1/2 pathway and aggravates insulin resistance [65]. Therefore, monitoring the ANGPTL4 level of OSA patients may help to identify high-risk lipid metabolic disorders at an early stage, and have higher diagnostic value than traditional lipid indicators.

3. Conclusions and outlook

Translating these mechanistic insights into clinical practice requires acknowledging the current evidence landscape. While the molecular pathways linking sleep disruption to adipokine dysregulation are well characterized in animal models, human studies—particularly interventional trials targeting specific sleep disorders—remain less abundant. Nevertheless, emerging clinical evidence, including CPAP trials in obstructive sleep apnea and sleep extension studies in habitually short sleepers, supports the concept that improving sleep health can ameliorate metabolic parameters, albeit with variable effect sizes. Therefore, the public health recommendations offered below are grounded in a combination of robust mechanistic understanding and preliminary clinical evidence, recognizing that further large-scale randomized controlled trials are needed to establish causality and quantify the magnitude of benefit.

Given the evidence presented, sleep health should be incorporated into the standard framework for preventing and managing metabolic diseases. This aligns with the position statements of major health organizations. For example, the nursing standards of the American Diabetes Association now recognize sleep health as a crucial controllable factor in diabetes management [66]. Similarly, the American Heart Association has included sleep duration among the cardiovascular health indicators in its 'Eight Elements of Life' [67].

Several challenges impede the clinical implementation of adipokine-based risk assessment. For example, IL-6 exhibits circadian variation, with dual peaks at 19:00 and 05:00, meaning accurate rhythm assessment requires multiple daily samples—a logistical obstacle in routine clinical practice. Furthermore, single-timepoint measurements of leptin and adiponectin are complicated by within-person variability influenced by factors such as recent meal timing and sleep quality. While future development of home-based monitoring technologies such as microneedle sensors for continuous adipokine tracking, may mitigate these limitations, rigorous standardization of sampling conditions remains essential.

We propose several directions for translational and public health initiatives: (1) Integrate validated sleep questionnaires, such as the Pittsburgh Sleep Quality Index, and screen for OSA risk into routine care for patients with obesity or diabetes. (2) Develop and enforce 'sleep-friendly' workplace policies, especially for shift workers, and incorporate 'circadian hygiene' into urban planning to mitigate light pollution at night. (3) Future studies should prioritize randomized controlled trials that test whether interventions aimed at improving sleep (e.g. CBT-I, CPAP) or aligning circadian rhythms (e.g. timed light/food) can normalize adipokine profiles and reduce significant metabolic endpoints. Addressing sleep and circadian health offers a novel and cost-effective approach to combat the intertwined epidemics of metabolic and sleep disorders.

4. Future directions: key unanswered questions and testable predictions

Despite the accumulation of evidence, several key questions remain unresolved, pointing the way for future research:

1. Mechanism specificity: What are the specific adipokine fingerprints induced by different sleep disorders (e.g. insomnia, OSA, shift work)? How do they contribute to metabolic risk?
2. Causal Relationship Validation: Do interventions designed to improve sleep—such as CBT-I for insomnia and CPAP for OSA—consistently normalize disrupted adipokine profiles? Furthermore, does this normalization mediate the metabolic improvements associated with these interventions (e.g. reduced triglycerides, improved insulin sensitivity)?

3. Clinical Application Pathway: To establish adipokines (e.g. IL-6) as stable and reproducible clinical biomarkers, how can we mitigate the impact of circadian fluctuations on their secretion? Furthermore, would integrating sleep assessment with adipokine testing into current metabolic disease risk prediction models improve their predictive power?
4. Individual Variability: How do genetic background (e.g. core clock gene variants), age, and sex influence an individual's metabolic susceptibility to sleep disorders and adipokine responses?
5. Testable predictions: Within the current mechanistic framework, we can propose several testable hypotheses. For example, CPAP therapy for OSA should reduce serum ANGPTL4 levels, with the magnitude of the reduction correlating with improvements in triglyceride levels. This effect should also be independent of weight changes. As another example, if cognitive behavioral therapy for insomnia restores the circadian rhythm of leptin, we should observe improvements in appetite and weight control.

Author contributions

CRediT: **Penghui Shi**: Conceptualization, Formal analysis, Resources, Visualization, Writing – original draft, Writing – review & editing; **Xinyan Liu**: Conceptualization; **Danyang Li**: Conceptualization; **Xinyu Zhou**: Conceptualization; **Xiaocen Chang**: Conceptualization; **Zihui Xu**: Conceptualization; **Yuyan Zhao**: Supervision, Validation.

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References

[1] Zhao MX, Tuo HZ, Wang SH, et al. The effects of dietary nutrition on sleep and sleep disorders. Mediators Inflamm. 2020;2020:3142874–3142877. doi: 10.1155/2020/3142874.
[2] Zamore Z, Veasey SC. Neural consequences of chronic sleep disruption. Trends Neurosci. 2022;45(9):678–691. doi: 10.1016/j.tins.2022.05.007.
[3] Zhuang P, Wu YQ, Yao JX, et al. Marine n-3 polyunsaturated fatty acids slow sleep impairment progression by regulating central circadian rhythms in type 2 diabetes. Cell Rep Med. 2025;6(5):102128. doi: 10.1016/j.xcrm.2025.102128.
[4] Parhizkar S, Gent G, Chen Y, et al. Sleep deprivation exacerbates microglial reactivity and Aβ deposition in a TREM2-dependent manner in mice. Sci Transl Med. 2023;15(693):eade6285. doi: 10.1126/scitranslmed.ade6285.
[5] American Academy of Sleep Medicine. International classification of sleep disorders. 3rd ed. Darien, IL: American Academy of Sleep Medicine; 2014.
[6] Chaput JP, McHill AW, Cox RC, et al. The role of insufficient sleep and circadian misalignment in obesity. Nat Rev Endocrinol. 2023;19(2):82–97. doi: 10.1038/s41574-022-00747-7.

[7] Zhu BQ, Shi CG, Park CG, et al. Effects of sleep restriction on metabolism-related parameters in healthy adults: a comprehensive review and meta-analysis of randomized controlled trials. Sleep Med Rev. 2019;45:18–30. doi: 10.1016/j.smrv.2019.02.002.
[8] McHill AW, Wright KP.Jr. Role of sleep and circadian disruption on energy expenditure and in metabolic predisposition to human obesity and metabolic disease. Obes Rev. 2017;18 (S1):15–24. doi: 10.1111/obr.12503.
[9] Boege HL, Bhatti MZ, St-Onge MP. Circadian rhythms and meal timing: impact on energy balance and body weight. Curr Opin Biotechnol. 2021;70:1–6. doi: 10.1016/j.copbio.2020.08.009.
[10] Kulkarni SS, Singh O, Zigman JM. The intersection between ghrelin, metabolism and circadian rhythms. Nat Rev Endocrinol. 2024;20(4):228–238. doi: 10.1038/s41574-023-00927-z.
[11] Chellappa SL, Qian J, Vujovic N, et al. Daytime eating prevents internal circadian misalignment and glucose intolerance in night work. Sci Adv. 2021;7(49):eabg9910. doi: 10.1126/sciadv.abg9910.
[12] Shen YC, Roh HC, Kumari M, et al. Adipocyte glucocorticoid receptor is important in lipolysis and insulin resistance due to exogenous steroids, but not insulin resistance caused by high fat feeding. Mol Metab. 2017;6(10):1150–1160. doi: 10.1016/j.molmet.2017.06.013.
[13] Covassin N, Singh P, McCrady-Spitzer SK, et al. Effects of experimental sleep restriction on energy intake, energy expenditure, and visceral obesity. J Am Coll Cardiol. 2022;79(13):1254–1265. doi: 10.1016/j.jacc.2022.01.038.
[14] Meurling IJ, Shea DO', Garvey JF. Obesity and sleep: a growing concern. Curr Opin Pulm Med. 2019;25(6):602–608. doi: 10.1097/MCP.0000000000000627.
[15] Broussard JL, Ehrmann DA, Van Cauter E, et al. Impaired insulin signaling in human adipocytes after experimental sleep restriction: a randomized, crossover study. Ann Intern Med. 2012;157(8):549–557. doi: 10.7326/0003-4819-157-8-201210160-00005.
[16] Szewczyk-Golec K, WoźNiak A, Reiter RJ. Inter-relationships of the chronobiotic, melatonin, with leptin and adiponectin: implications for obesity. J Pineal Res. 2015;59(3):277–291. doi: 10.1111/jpi.12257.
[17] Marino G, Arble DM. Peripheral clock disruption and metabolic disease: moving beyond the anatomy to a functional approach. Front Endocrinol. 2023;14:1182506. doi: 10.3389/fendo.2023.1182506.
[18] Liu PY, Irwin MR, Krueger JM, et al. Night shift schedule alters endogenous regulation of circulating cytokines. Neurobiol Sleep Circadian Rhythms. 2021;10:100063. doi: 10.1016/j.nbscr.2021.100063.
[19] Li XY, Li CY, Xue WJ, et al. T266M variants of ANGPTL4 improve lipid metabolism by modifying their binding affinity to acetyl-CoA carboxylase in obstructive sleep apnea. Ann Med. 2024;56(1):2337740. doi: 10.1080/07853890.2024.2337740.
[20] Sondrup N, Termannsen AD, Eriksen JN, et al. Effects of sleep manipulation on markers of insulin sensitivity: a systematic review and meta-analysis of randomized controlled trials. Sleep Med Rev. 2022;62:101594. doi: 10.1016/j.smrv.2022.101594.
[21] Beals JW, Smith GI, Farabi SS, et al. Sleep extension improves sleep health but not insulin sensitivity in people with overweight/obesity who maintain habitual short sleep schedules. Diabetes Care. 2026;49(5):740–745. doi: 10.2337/dc25-2083.
[22] Vejrazkova D, Vankova M, Vcelak J, et al. The rs10830963 polymorphism of the MTNR1B gene: association with abnormal glucose, insulin and C-peptide kinetics. Front Endocrinol. 2022;13:868364. doi: 10.3389/fendo.2022.868364.
[23] Huang XR, Qiu Y, Gao YF, et al. Gut microbiota mediate melatonin signalling in association with type 2 diabetes. Diabetologia. 2022;65(10):1627–1641. doi: 10.1007/s00125-022-05747-w.
[24] Polak J, Shimoda LA, Drager LF, et al. Intermittent hypoxia impairs glucose homeostasis in C57BL6/J mice: partial improvement with cessation of the exposure. Sleep. 2013;36(10):1483–1490. doi: 10.5665/sleep.3040.
[25] Guo YF, Wang J, Zhang DM, et al. Diabetes-associated sleep fragmentation impairs liver and heart function via SIRT1-dependent epigenetic modulation of NADPH oxidase 4. Acta Pharm Sin B. 2025;15(3):1480–1496. doi: 10.1016/j.apsb.2024.12.031.
[26] Zuraikat FM, Laferrère B, Cheng B, et al. Chronic insufficient sleep in women impairs insulin sensitivity independent of adiposity changes: results of a randomized trial. Diabetes Care. 2024;47(1):117–125. doi: 10.2337/dc23-1156.
[27] Weng YS, Tseng HY, Chen YA, et al. MCT-1/miR-34a/IL-6/IL-6R signaling axis promotes EMT progression, cancer stemness and M2 macrophage polarization in triple-negative breast cancer. Mol Cancer. 2019;18(1):42. doi: 10.1186/s12943-019-0988-0.
[28] Feng YJ, Wang YJ, Deng YF, et al. Crosstalk between perivascular adipose tissue and adipocyte-derived peptide in the pathogenesis of diabetic cardiomyopathy. Cardiovasc Diabetol. 2025;24(1):332. doi: 10.1186/s12933-025-02863-w.
[29] Tada A, Kober AH, Islam MA, et al. Evaluation of fat accumulation and adipokine production during the long-term adipogenic differentiation of porcine intramuscular preadipocytes and study of the influence of immunobiotics. Cells. 2020;9(7):1715. doi: 10.3390/cells9071715.
[30] Chen M, Lin YK, Dang YK, et al. Reprogramming of rhythmic liver metabolism by intestinal clock. J Hepatol. 2023;79(3):741–757. doi: 10.1016/j.jhep.2023.04.040.

[31] Bulmer C, Avenell A. The effect of dietary weight-loss interventions on the inflammatory markers interleukin-6 and TNF-alpha in adults with obesity: a systematic review and meta-analysis of randomized controlled clinical trials. Obes Rev. 2025;26(7):e13910. doi: 10.1111/obr.13910.
[32] Fang JL, Wang SW, Liu LJ, et al. Gut microbiota: a potential influencer of insomnia occurring after COVID-19 infection. Front Psychiatry. 2024;15:1423715. doi: 10.3389/fpsyt.2024.1423715.
[33] Zhao L, Sun T, Tong P, et al. A cross-sectional study investigating the underlying inflammatory mechanisms of post-stroke insomnia. Cytokine. 2025;192:156975. doi: 10.1016/j.cyto.2025.156975.
[34] Zhu QH, Luo QY, Wang ZC, et al. Effects of continuous positive airway pressure therapy on inflammatory markers in patients with obstructive sleep apnea: a meta-analysis of randomized controlled trials. Sleep Breath. 2025;29(2):182. doi: 10.1007/s11325-025-03348-6.
[35] Vgontzas AN, Zoumakis M, Papanicolaou DA, et al. Chronic insomnia is associated with a shift of interleukin-6 and tumor necrosis factor secretion from nighttime to daytime. Metabolism. 2002;51(7):887–892. doi: 10.1053/meta.2002.33357.
[36] Tan HL, Yin LP, Tan YQ, et al. Leptin-activated hypothalamic BNC2 neurons acutely suppress food intake. Nature. 2024;636(8041):198–205. doi: 10.1038/s41586-024-08108-2.
[37] Wang P, Loh KH, Wu M, et al. A leptin-BDNF pathway regulating sympathetic innervation of adipose tissue. Nature. 2020;583(7818):839–844. doi: 10.1038/s41586-020-2527-y.
[38] Yoon H, Spinelli JB, Zaganjor E, et al. PHD3 loss promotes exercise capacity and fat oxidation in skeletal muscle. Cell Metab. 2020;32(2):215–228.e7. doi: 10.1016/j.cmet.2020.06.017.
[39] Solheim MH, Stroganov S, Chen WY, et al. Hypothalamic PNOC/NPY neurons constitute mediators of leptin-controlled energy homeostasis. Cell. 2025;188(13):3550–3566.e22. doi: 10.1016/j.cell.2025.04.001.
[40] Villanueva-Carmona T, Cedó L, Madeira A, et al. SUCNR1 signaling in adipocytes controls energy metabolism by modulating circadian clock and leptin expression. Cell Metab. 2023;35(4):601–619.e10. doi: 10.1016/j.cmet.2023.03.004.
[41] Mosavat M, Mirsanjari M, Arabiat D, et al. The role of sleep curtailment on leptin levels in obesity and diabetes mellitus. Obes Facts. 2021;14(2):214–221. doi: 10.1159/000514095.
[42] Hirota T, Morioka T, Yoda K, et al. Positive association of plasma leptin with sleep quality in obese type 2 diabetes patients. J Diabetes Investig. 2018;9(5):1100–1105. doi: 10.1111/jdi.12826.
[43] Yuan XS, Xiang Z, Jiang JB, et al. Leptin receptor neurons in the ventral premammillary nucleus modulate emotion-induced insomnia. Cell Discov. 2024;10(1):59. doi: 10.1038/s41421-024-00676-x.
[44] Hebebrand J, Denecke S, Antel J. The role of leptin in rodent and human sleep: a transdiagnostic approach with a particular focus on anorexia nervosa. Neurosci Biobehav Rev. 2023;149:105164. doi: 10.1016/j.neubiorev.2023.105164.
[45] Mosini AC, Adami LNG, da Silva Vallim JR, et al. Leptin moderates the relationship between sleep quality and memory function: a population-based study. Sleep Med. 2024;117:146–151. doi: 10.1016/j.sleep.2024.03.021.
[46] Gultuna S, Akdogan BB, Gonul M, et al. Sleep quality in patients with chronic spontaneous urticaria and relation with Orexin-A, leptin, and ghrelin. Allergy Asthma Proc. 2024;45(4):e38–e45. doi: 10.2500/aap.2024.45.240023.
[47] Li A, Li X, Zhou T, et al. Sleep disturbance and changes in energy intake and body composition during weight loss in the POUNDS lost trial. Diabetes. 2022;71(5):934–944. doi: 10.2337/db21-0699.
[48] Reynolds AC, Dorrian J, Liu PY, et al. Impact of five nights of sleep restriction on glucose metabolism, leptin and testosterone in young adult men. PLoS One. 2012;7(7):e41218. doi: 10.1371/journal.pone.0041218.
[49] McHill AW, Melanson EL, Higgins J, et al. Impact of circadian misalignment on energy metabolism during simulated nightshift work. Proc Natl Acad Sci USA. 2014;111(48):17302–17307. doi: 10.1073/pnas.1412021111.
[50] Asimakidou E, Saipuljumri EN, Lo CH, et al. Role of metabolic dysfunction and inflammation along the liver-brain axis in animal models with obesity-induced neurodegeneration. Neural Regen Res. 2025;20(4):1069–1076. doi: 10.4103/NRR.NRR-D-23-01770.
[51] De la Cruz-Color L, Dominguez-Rosales JA, Maldonado-González M, et al. Evidence that peripheral leptin resistance in omental adipose tissue and liver correlates with MASLD in humans. Int J Mol Sci. 2024;25(12):6420–6411. doi: 10.3390/ijms25126420.
[52] Kuo CH, Wang SH, Juan HC, et al. Angiopoietin-like protein 4 induces growth hormone variant secretion and aggravates insulin resistance during pregnancy, linking obesity to gestational diabetes mellitus. Biofactors. 2024;50(6):1176–1191. doi: 10.1002/biof.2076.
[53] Lin J, Jiang Y, Wang G, et al. Associations of short sleep duration with appetite-regulating hormones and adipokines: a systematic review and meta-analysis. Obes Rev. 2020;21(11):e13051. doi: 10.1111/obr.13051.
[54] Blandin A, Amosse J, Froger J, et al. Extracellular vesicles are carriers of adiponectin with insulin-sensitizing and anti-inflammatory properties. Cell Rep. 2023;42(8):112866. doi: 10.1016/j.celrep.2023.112866.
[55] El-Araby RE, Tu QS, Xie Y, et al. Adiponectin mRNA conjugated with lipid nanoparticles specifically targets the pathogenesis of type 2 diabetes. Aging Dis. 2024;16(2):1059–1079. doi: 10.14336/AD.2024.0162.
[56] He LJ, Xuan WT, Liu DX, et al. The role of adiponectin in the association between abdominal obesity and type 2 diabetes: a mediation analysis among 232,438 Chinese participants. Front Endocrinol. 2024;15:1327716. doi: 10.3389/fendo.2024.1327716.

[57] de Oliveira RF, da Costa Daniele TM, Façanha CFS, et al. Adiponectin levels and sleep deprivation in patients with endocrine metabolic disorders. Rev Assoc Med Bras. 2018;64(12):1122–1128. doi: 10.1590/1806-9282.64.12.1122.
[58] McNeil J, Clark KG, Adams WM, et al. Sleep, Health Outcomes and Body Weight (SHOW) study: a measurement burst design study on sleep and risk factors for obesity in black emerging adults in North Carolina, USA. BMJ Open. 2024;14(7):e087950. doi: 10.1136/bmjopen-2024-087950.
[59] Martynowicz H, Kornafel-Flak O, Urbanik D, et al. Coexistence of obstructive sleep apnea and telomerase activity, concentration of selected adipose tissue hormones and vascular endothelial function in patients with arterial hypertension. Respir Med. 2019;153:20–25. doi: 10.1016/j.rmed.2019.05.009.
[60] Aryal B, Price NL, Suarez Y, et al. ANGPTL4 in metabolic and cardiovascular disease. Trends Mol Med. 2019;25(8):723–734. doi: 10.1016/j.molmed.2019.05.010.
[61] Li J, Yang YY, Jiao XL, et al. The clinical role of angiopoietin-like protein 3 in evaluating coronary artery disease in patients with obstructive sleep apnea. Cardiovasc Drugs Ther. 2020;34(6):773–780. doi: 10.1007/s10557-020-06991-1.
[62] Drager LF, Yao Q, Hernandez KL, et al. Chronic intermittent hypoxia induces atherosclerosis via activation of adipose angiopoietin-like 4. Am J Respir Crit Care Med. 2013;188(2):240–248. doi: 10.1164/rccm.201209-1688OC.
[63] Drager LF, Li J, Shin M-K, et al. Intermittent hypoxia inhibits clearance of triglyceride-rich lipoproteins and inactivates adipose lipoprotein lipase in a mouse model of sleep apnoea. Eur Heart J. 2012;33(6):783–790. doi: 10.1093/eurheartj/ehr097.
[64] Janmohammadi P, Raeisi T, Zarei M, et al. Adipocytokines in obstructive sleep apnea: a systematic review and meta-analysis. Respir Med. 2023;208:107122. doi: 10.1016/j.rmed.2023.107122.
[65] Cundrle I, Somers VK, Singh P, Jr, et al. Leptin deficiency promotes central sleep apnea in patients with heart failure. Chest. 2014;145(1):72–78. doi: 10.1378/chest.12-2914.
[66] American Diabetes Association Professional Practice Committee. Facilitating positive health behaviors and well-being to improve health outcomes: standards of care in diabetes – 2025. Diabetes Care. 2025;48(Suppl 1):S80–S113. doi: 10.2337/dc25-S005.
[67] Lloyd-Jones DM, Allen NB, Anderson CAM, et al. Life's essential 8: updating and enhancing the American Heart Association's Construct of Cardiovascular Health: a presidential advisory from the American Heart Association. Circulation. 2022;146(5):e18–e43. doi: 10.1161/CIR.0000000000001078.