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REVIEW ARTICLE

# The effects of sleep disruption on metabolism, hunger, and satiety, and the influence of psychosocial stress and exercise: A narrative review

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## Abstract

Sleep deficiency is a ubiquitous phenomenon among Americans. In fact, in the United States, ~78% of teens and 35% of adults currently get less sleep than recommended for their age-group, and the quality of sleep appears to be getting worse for many. The consequences of sleep disruption manifest in a myriad of ways, including insulin resistance and disrupted nutrient metabolism, dysregulation of hunger and satiety, and potentially increased body weight and adiposity. Consequently, inadequate sleep is related to an increased risk of various cardiometabolic diseases, including obesity, diabetes, and heart disease. Exercise has the potential to be an effective therapeutic to counteract the deleterious effects of sleep disruption listed above, whereas chronic psychosocial stress may causally promote sleep disruption and cardiometabolic risk. Here, we provide a narrative review of the current evidence on the consequences of short sleep duration and poor sleep quality on substrate metabolism, circulating appetite hormones, hunger and satiety, and weight gain. Secondly, we provide a brief overview of chronic psychosocial stress and its impact on sleep and metabolic health. Finally, we summarise the current evidence regarding the ability of exercise to counteract the adverse metabolic health effects of sleep disruption. Throughout the review, we highlight areas where additional interrogation and future exploration are necessary.

KEYWORDS
adverse childhood experiences, cardiometabolic health, leptin, sleep duration, sleep quality

## 1 | INTRODUCTION

The United States (U.S.) National Sleep Foundation (NSF) recommends that adults get between 7 and 9 h sleep per night.[1] Greater incidence of obesity, heart disease, stroke, diabetes, chronic kidney disease, and depression are observed among those who sleep less than 7 h per night.[2,3] Alarmingly, Americans sleep an average of 6 h and 31 min during the work week and over 35% of Americans report sleeping fewer than 7 h per night.[1,4] Both habitual short sleep duration and experimentally induced reductions in sleep duration have been associated with lower whole body insulin sensitivity, impaired nutrient metabolism, increased subjective hunger, increased

caloric intake, and weight gain.[3,5] Based on this robust emerging evidence, sleep is becoming recognised as a key behavioural determinant of cardiometabolic health. Accordingly, the American Heart Association has recently added sleep health to its list of essential, modifiable factors for improving and maintaining cardiovascular health (i.e., Life's Essential 8),[1] and the American Diabetes Association has recognised sleep as an important behaviour for the management of hyperglycemia in individuals with Type 2 Diabetes (T2D).[2]

Given the ease with which it is measured and experimentally manipulated, **sleep duration** is the most well-studied sleep dimension and is therefore the dimension for which the strongest body of evidence exists. However, sleep is multi-dimensional, and both sleep quality and consistency are likely unique contributors to cardiometabolic health. Notably, there has been a worldwide decline in sleep quality over the last several decades.[3] The NSF defines **sleep quality** as a combination of sleep continuity and sleep architecture and suggests that the ideal sleep architecture consists of spending ≤5% of time in stage 1 sleep, <81% in stage 2 sleep, 16%–20% in slow wave sleep (SWS), and 21%–30% in rapid eye movement (REM) sleep.[4] Reductions in sleep quality (i.e., reduced SWS) may also negatively impact whole body insulin sensitivity and impair substrate metabolism.[5,6] Similarly, disruption to natural sleep patterns or increased **sleep variability** can cause chronobiological misalignment, promoting cardiometabolic risk.[6] For example, shift work, which is characterised by variable day and night shifts and constantly changing circadian alignments, has been shown to be an independent risk factor for the development of T2D,[7] and shift workers have a 40% increased risk of T2D compared with non-shift workers.[7] Furthermore, a small but emerging body of evidence indicates that less extreme variability in sleep patterns, such as variability in bedtimes or bedtime delays, may promote cardiometabolic disruption as evidenced by insulin resistance[8] and increased adiposity.[9] However, given the emerging nature of this evidence, we chose not to conduct an in-depth review of the effect of sleep variability on metabolic health herein, which has very recently been reviewed elsewhere.[10]

The purpose of this review is to evaluate the existing epidemiological and experimental evidence linking short sleep duration and poor sleep quality with altered substrate metabolism, hunger and satiety, and body weight regulation, while highlighting current gaps and limitations with recommendations for future studies. We also briefly highlight the potential roles of psychosocial stress and physical exercise in the association of sleep with cardiometabolic health.

## 2 | INSULIN AND GLUCOSE METABOLISM

### 2.1 | Epidemiologic evidence on sleep disruption

Data from both small and large cohort studies suggest that short sleep duration is associated with impaired insulin sensitivity and glucose metabolism (Table 1). For example, Rafalson et al. reported that those who sleep fewer than 6 h per night are 3 times more likely to have impaired fasting glucose compared with those who sleep 6–8 h per night.[11] Among 276 adults, Chaput et al.[12] reported that individuals who sleep ≤6 h per night had a 2.8-fold greater probability (relative risk = 2.78 [1.61–4.12]) and those who slept ≥9 h per night had 2.54-times greater probability of developing type 2 diabetes or impaired glucose tolerance over ~6 years compared with those who slept 7–8 h per night. The inclusion of waist circumference, BMI, or relative body fat attenuated the relative risk ratios, suggesting that adiposity may partially mediate the association of sleep disruption with impaired insulin sensitivity and glucose metabolism. Importantly, however, the data from these studies were derived from primarily White, non-Hispanic cohorts and sleep durations were obtained from retrospective, self-report. Wong et al. reported that the association of self-reported short sleep duration with lower insulin sensitivity was only significant in White individuals and additional sex stratification indicated that this relationship persisted only for white men and not white women.[13] However, this study was also conducted in primarily (89%) White, non-Hispanic adults. Thus, it is highly plausible that null findings among non-White individuals were due to small sample size and limited by retrospective, self-reported assessments of sleep duration. Accordingly, these findings should be interpreted with caution, especially in light of well-documented racial disparities in sleep health.[15,21]

Among a more diverse samples (43% non-White) of adolescents, actigraphy-measured short sleep duration was associated with insulin resistance even after adjustment for age, sex, race, and activity levels.[14] This association was attenuated but still significant following adjustment for adiposity. Similarly, among 426 individuals from the Midlife in the United States Cohort Study, actigraphy-measured sleep time explained 41% of the difference in composite cardiometabolic risk (which included insulin resistance and glucose control [e.g., HbA1c]) between White and Black adults.[15] In a cross-sectional cohort study of Chinese twins, self-reported short sleep duration was associated with greater insulin resistance in women but not in men, an effect that was partially mediated by visceral adiposity.[16] Finally, in the large ($n$ = 70,026), prospective Nurse's Health Study, self-reported sleep durations ≤5 h per day were associated with a 1.57-fold increase in risk of diabetes diagnosis among women, an effect that was mediated by body mass index (BMI).[17]

Taken together, there is strong evidence that short sleep duration is associated with greater insulin resistance and disrupted glucose metabolism. Further, whereas it has been suggested that the effects of short sleep duration on insulin and glucose metabolism are strongest in White men,[22] such findings are limited and likely influenced by a lack of representation of understudied minoritised racial/ethnic groups and small sample sizes. Studies with greater representation of minoritised racial/ethnic groups instead suggest that short sleep duration may partially explain racial differences in metabolic health,[15] while findings from large cohorts composed only of women indicate that short sleep duration also negatively impacts

**TABLE 1** Epidemiological/cohort evidence linking disrupted sleep with impaired glucose and insulin metabolism.

| Reference | Study sample | Study design | Sleep assessment | Dependent variable | Primary findings |
|---|---|---|---|---|---|
| Rafalson et al.[11] | 1455 men and women (age range = 35–79 years) free of known cardiometabolic disease at baseline | Nested case-control; Baseline (1996–2001) with follow-up (2003–2004) clinical assessment | Self-reported sleep duration during last 5 weekday nights, categorised as: short sleep (<6 h), reference (6–8 h), long sleep (>8 h) | Cases of impaired fasting glucose, defined as fasting glucose <100 mg/dL at baseline but fasting glucose of 100–125 mg/dL at follow-up. | Short sleep duration associated with 3-fold (OR = 3.0 [95% CI: 1.05–8.59]) increased risk for impaired fasting glucose |
| Chaput et al.[12] | 276 Caucasian men and women (age range = 21–64) | Longitudinal Cohort, Retrospective | Self-reported sleep duration, categorised as: short sleepers (≤6 h), reference (7–8 h), long sleepers (≥9 h) | Type 2 diabetes (T2D) and impaired glucose tolerance (IGT) incidence. T2D defined as: use of insulin or hypoglycemic agent, fasting plasma glucose ≥126 mg/dL, or 2 h post-OGTT glucose ≥200 mg/dL; IGT defined as 2 h post-OGTT glucose ≥140 mg/dL and not meeting T2D criteria | Increased risk (Relative Risk (RR) = 2.78 [95% CI: 1.61–4.12]) for T2D/IGT in short sleepers compared to reference. Increased risk (RR = 2.54 [1.42–3.53]) for T2D/IGT in long sleepers compared to reference. Adiposity partially mediated associations. |
| Wong et al.[13] | 244 men and women (age range = 30–54 years) free of atherosclerotic cardiovascular or kidney disease | Cross-sectional | Self-reported sleep duration over last 7 days averaged and weighted across weekday nights and weekend nights, modelled continuously | Insulin sensitivity (Si) and acute insulin secretion (AIRg) assessed during an intravenous glucose tolerance test | Shorter sleep duration associated with lower Si in full sample ($\beta = 0.13$, $p = 0.04$) and in men only ($\beta = 0.29$, $p = 0.003$).<br>Short sleep duration associated with greater AIRg in White men only ($\beta = -0.29$, $p = 0.004$). |
| Javaheri et al.[14] | 387 adolescents (age range = 13–19 years; 51% female; 43% racial minority) | Cross-sectional | Sleep duration assessed by wrist actigraphy across ≥3 weekday nights and 1 or 2 weekend nights | HOMA Insulin Resistance (HOMA-IR) index | Both short sleep (≤5 h) and long sleep (≥10.5 h) durations associated with ~25% greater HOMA-IR |
| Curtis et al.[15] | 426 men and women (mean age = 57 years; 61% female; 33% African American) | Cross-sectional | Sleep duration and sleep efficiency measured by wrist actigraphy across ≥3 nights (96% of sample had ≥6 nights), modelled continuously | Total cardiometabolic risk score (CRS) indexed using clinical or risk cutpoints for: HOMA-IR, $HbA_{1c}$, waist circumference, blood pressure, CRP, triglycerides, and HDL | Shorter sleep duration ($B = -0.07$) and lower sleep efficiency ($B = -0.007$) associated with greater CRS.<br>Both short sleep duration and low sleep efficiency mediated racial differences in CRS, explaining 41% and 58% of the CRS difference between African American versus European American adults.<br>Sex moderated the association between sleep and CRS, with this link stronger in females than males. |

(Continues)

TABLE 1 (Continued)

| Reference | Study sample | Study design | Sleep assessment | Dependent variable | Primary findings |
|---|---|---|---|---|---|
| Liu et al.[16] | 1494 Chinese men and women twin pairs (age range = 20–70 years) | Cross-sectional | Self-reported sleep duration assessed via PSQI and modelled continuously and categorically (e.g., short sleep = ≤ 7 h/night) | HOMA-IR | Short sleep duration associated with greater HOMA-IR in women, but not men. Adjustment for BMI and trunk fat tempered but did not fully explain this association. |
| Ayas et al.[17] | 70,026 women without prior diabetes diagnosis (age range at sleep assessment = 40–65 years) | Longitudinal Cohort | Self-reported sleep duration at baseline, categorised as ≤5 h, 6 h, 7 h, 8 h (reference), or ≥9 h of sleep/night | Incidence rate of diabetes diagnosis during 10 years of follow-up | Short sleep (≤5 h/night) associated with 1.57 [95% CI: 1.3–1.9] relative risk for diabetes. Relative risk (1.18 [0.96–1.4]) was reduced and no longer significant upon adjustment for BMI. |
| Kim et al.[18] | 374 (63% women) | Cross-sectional | Sleep duration, sleep onset latency (SOL), and wakefulness after sleep onset (WASO) measured by wrist actigraphy across all valid nights from a 7-day sleep study | HOMA-IR | Greater SOL associated with greater HOMA-IR in univariate analysis among full sample. Sex-stratified analyses indicated that the association was present among women ($B = 0.43$, $p = 0.005$) but not men ($B = -0.03$, $p = 0.86$). Both CRP and IL-6 partially mediated the association of SOL with HOMA-IR in women, but SOL remained a significant predictor. |
| Kline et al.[19] | 347 women (mean age = 58 ± 7 years) with overweight/obesity | Cross-sectional | Sleep quality assessed using the six-item Medical Outcomes Study Sleep Scale, composite sleep quality values categorised into quartiles | HOMA-IR | Women in the lowest quartile for sleep quality had the greatest HOMA-IR. Analysis of HOMA-IR by specific sleep symptoms indicated that sleep onset >30 min, frequent restless sleep, and frequent daytime drowsiness were each also associated with greater HOMA-IR. |
| Rawat et al.[20] | 203 adolescent/young adults (mean age = 18.5 years, 65% male) characterised into three groups as (1) evening chronotype, (2) intermediate chronotype, or (3) morning chronotype | Cross-sectional | Sleep quality and duration assessed using the PSQI | Fasting and 2-h post-prandial (OGTT) blood glucose, HOMA-IR | Poor sleep quality associated with higher fasting blood glucose and HOMA-IR across all participants. Among chronotypes, poor sleep quality associated with HOMA-IR in evening ($r = 0.51$) and intermediate ($r = 0.30$) chronotypes, but not in morning chronotypes ($r = 0.22$). |

Abbreviations: BMI, body mass index; CI, confidence interval; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; OGTT, oral glucose tolerance test; OR, odds ratio; PSQI, Pittsburgh Sleep Quality Index.

women's cardiometabolic health.[17] Furthermore, it appears that the effect of short sleep duration on impaired insulin and glucose metabolism may be mediated by increased central adiposity. The directionality of this association is not clear at present, but as we discuss below, experimental sleep disruption causes insulin resistance and negatively impacts hunger, satiety, and body weight regulation. Finally, these epidemiologic and cohort studies are limited in so much that they primarily rely on fasting assessments of insulin sensitivity and glucose metabolism, such as fasting insulin and fasting glucose, or the homoeostatic model assessment of insulin resistance (HOMA-IR) method and mostly self-reported sleep duration. However, as discussed below, these findings are bolstered by studies examining the effect of experimental sleep restriction on insulin sensitivity and glucose metabolism and also by robust evidence indicating that individuals with short sleep durations (≤6–7 h/night) are at 30% greater risk for developing T2D.[23,24]

Although the data are less robust, epidemiologic evidence also shows that poor sleep quality promotes impairments in insulin and glucose metabolism. For example, cross-sectional evidence in a sample subset from the Midlife Development in the United States II study indicated that actigraphy-measured sleep onset latency was linked with greater insulin resistance among men and women in univariate analyses.[18] When this relationship was explored in men and women separately, the association persisted for women but not men and was robust to inclusion of additional covariates such as inflammatory markers, BMI, and depression.[18] Among postmenopausal women both with and without metabolic syndrome, greater self-reported sleep onset latencies and more restless sleep have been associated with greater insulin resistance by HOMA-IR.[19] Similarly, among individuals with obesity or who are overweight, sleep quality and sleep onset latency—assessed using the Pittsburgh Sleep Quality Index—were associated with 1.33- and 1.23-fold increased risk of insulin resistance defined as a HOMA-IR ≥3.4.[19]

Interestingly, evidence also exists to suggest that the strength of the association between poor sleep quality and insulin resistance is dependent on chronotype, such that individuals with an evening chronotype may be at greatest risk.[20] Importantly, the evening chronotype has been linked to greater risk of depression and anxiety,[25] greater dietary energy density,[26] as well as reduced physical activity and lower cardiorespiratory fitness,[27] which all may act to amplify cardiometabolic risk. Finally, in the aforementioned study examining the contributions of habitual sleep to racial differences in cardiometabolic health, Curtis et al. reported that low sleep efficiency (sleep duration relative to the time spent in bed), explained an astonishing 58% of the difference in composite cardiometabolic risk between Black and White American adults.[15] As we discuss below in Section 6, it is plausible that heightened psychosocial stress exposure due to factors subsequent of structural racism may explain racial disparities in sleep health, which may causally promote racial disparities in cardiometabolic health. These hypotheses warrant further investigation with studies on effective interventions and policies ultimately needed.

## 2.2 | Experimental sleep manipulation

Several randomised controlled trials have been conducted to establish whether short sleep duration and poor sleep quality are causally associated with cardiometabolic health impairments as evidenced by the growing body of epidemiological evidence. Experimental manipulation of sleep duration is relatively straightforward and is most often accomplished by restricting the amount of time in bed (TIB) available to sleep, mimicking short sleep duration and referred to herein as ***sleep restriction***. Complementing the epidemiological data, Spiegel et al. reported that 6 nights of 4-h TIB increased postprandial glucose concentrations following breakfast consumption without effecting postprandial insulin responses in young men, suggesting reduced insulin sensitivity.[28] In another study examining the metabolic effects of a mild 1.5-h reduction in habitual sleep duration, Robertson et al. reported that 3 weeks of sleep restriction decreased insulin sensitivity in young, healthy men assessed using a hyperinsulinemic-euglycemic clamp.[29] It has also been shown that 14 days of ~2 h of sleep reduction reduces glucose tolerance and reduces insulin sensitivity when overlaid on a Western lifestyle (high sedentarism and ad libitum food intake).[30] In the first study examining the effect of sleep restriction on insulin sensitivity in post-menopausal women, Singh et al.[31] observed that 4-day of sleep restriction (40% reduction in habitual sleep duration; ~5-h TIB) caused reduced whole-body insulin sensitivity as indicated by an increase in glucose infusion rate during a hyperinsulinemic-euglycemic clamp. Broussard et al.[32] examined the effects of 4 days of 4.5-h versus 8.5-h TIB on insulin sensitivity of adipocytes collected from subcutaneous fat biopsies in healthy young adult men and women. To do so, adipocytes were exposed to increasing concentrations of insulin, and phosphorylation of Akt—a critical early step in the insulin signalling cascade—was measured during in vitro experiments. The findings indicated that adipocyte insulin sensitivity was markedly reduced (~30%) by experimental sleep restriction. As we discuss below in Section 5.2, there is also evidence that sleep restriction impairs insulin sensitivity in other tissues such as skeletal muscle,[33] together indicating that sleep has effects specific to peripheral tissues that may contribute to or exacerbate metabolic disorders.[32] Finally, while all of the aforementioned studies have used multiple days (e.g., ≥4 days) of sleep restriction, the deleterious effects of short sleep on insulin sensitivity have been shown to begin after just 1 night of sleep restriction (4-h TIB) in healthy subjects.[34,35]

Experimental manipulation of sleep quality is not as straight forward as employing sleep restriction to modify sleep duration. Studies that have manipulated sleep quality typically do so by suppressing stage 3 non-REM sleep, also known as SWS. SWS is associated with neural, hormonal, and metabolic changes that influence glucose homoeostasis, such as growth hormone release, decreased corticotropic activity, decreased sympathetic nervous system activity, and increased vagal tone.[6] In an elegantly designed study, Tasali et al.[6] demonstrated that 3 nights of SWS suppression, by careful

delivery of varying acoustic stimuli, elicited a 25% decrease in insulin sensitivity that reached levels associated with heightened T2D risk. This decrease in insulin sensitivity was strongly correlated ($r = 0.89$) with the magnitude of SWS suppression. Notably, whereas a decrease in insulin sensitivity should be compensated by increased insulin release from beta cells, this did not occur, and mirrors the decrease in beta-cell function observed before T2D onset.[36] Similarly, Herzog et al. showed that reducing SWS, but not REM sleep, for one night via acoustic tone delivery promoted a 15% decrease in insulin sensitivity compared to normal sleep, and the degree of sleep fragmentation during SWS was correlated with insulin sensitivity in the SWS-suppression condition.[5] Thus, these experimental findings indicate that reduced SWS has a particularly potent and unique adverse effect on glucose metabolism, while the disruption of REM sleep may be less noxious. Given the strong effect of SWS suppression, future studies may seek to understand if the effects of sleep restriction on glucose metabolism are driven by, or are independent of, an overall decrease in SWS, although this may be a difficult question to address experimentally.

Together, these experimental sleep restriction studies support the robust body of epidemiological evidence suggesting that short sleep durations promote insulin resistance. Furthermore, experimental manipulation of sleep quality by SWS suppression has robust effects on insulin sensitivity, supporting the evidence linking poor quality with insulin resistance in various cohorts.

## 3 | LIPID METABOLISM

### 3.1 | Epidemiologic evidence on sleep disruption

Impairments or alterations in both fasting and postprandial lipids and lipoproteins predict cardiometabolic risk.[37–39] However, in comparison to glucose metabolism, data on the associations between sleep and lipid metabolism are scarce. Aho et al. sought to address this gap by analysing blood transcriptome and serum metabolome data in two independent epidemiological cohorts (DILGOM and Young Finns Study [YFS]; total $n = 2739$) in whom self-reported sleep insufficiency was also quantified.[40] Participants who had shorter self-reported sleep durations had fewer large HDL-C particles in circulation in both cohorts, and this effect was independent of age and gender. In addition, gene expression data from the DILGOM study indicated that sleep restriction was associated with reduced cholesterol and sterol transporter expression (e.g., ABCG1) independent of BMI, which was replicated in the YFS cohort.[40] Together, these findings show that short sleep duration suppresses cholesterol transport, particularly from peripheral macrophages to HDL particles. A 2017 systematic review and meta-analysis of prospective studies indicated that the available evidence does not support a significant association of short sleep with dyslipidemia,[41] although there may be meaningful associations between short sleep and low HDL-C and elevated total cholesterol to HDL-C ratio. However, these conclusions were drawn based on a small available body of evidence that, as described by the authors, is insufficient to inform public health policy.[41] Further, given the apparent importance of particle-size and the particle-size specific effects of short sleep,[40] it may not be sufficient (or sufficiently sensitive) to simply measure traditional lipid and lipoprotein profiles to understand the effects of short sleep duration on lipid metabolism.

Apolipoproteins, including apolipoprotein B (ApoB), are core structural proteins of cholesterol particles and subendothelial trapping of ApoB is a primary mechanism for the development of atherosclerosis.[42] Notably, circulating ApoB concentrations reflect on 1:1 based on the total number of atherogenic particles in circulation[42] and thus examination of ApoB concentrations may be a more sensitive approach to understand the relationship between sleep duration and atherogenic risk. Among 3918 Chinese women, those who self-reported short sleep duration (≤6 h/night) were 2.6-times more likely (Odds Ratio [OR] = 2.64 [1.74–4.02]) to have elevated ApoB (≥1.18 g/L) than those who self-reported sleeping 7–8 h each night, and this association was robust to adjustment for potential confounders (OR = 1.75 [1.12–2.72]).[43] Among 3403 Chinese men in this same study,[43] short sleep was also associated with increased odds (OR = ~1.34 [1.1–1.56]) of elevated ApoB (≥1.17 g/L), but it is not clear if it was robust to adjustment because this was not reported. Similarly, among 4149 Chinese adults with overweight/obesity, ApoB concentrations were elevated among those who self-reported sleeping ≤6 h each night, and this association was strongest among individuals with a 'metabolically unhealthy' phenotype (e.g., presence of ≥2 metabolic syndrome components) and among adults <45 years.[44] In contrast, among a sample of 644 children and 992 adults, actigraphy-measured sleep duration was not significantly associated with ApoB levels ($\beta = -0.50$ in children, $\beta = -0.05$ in adults) where sleep duration was modelled continuously.[45] Clearly, additional work is needed with careful consideration of lipoprotein sizes, such as can be provided by metabolomic analyses or by specific interrogation of ApoB to understand the influence of short sleep duration on lipid metabolism and atherogenic risk.

Very few data are available quantifying the effects of sleep quality on lipid metabolism. However, poor sleep quality has also been identified as a risk factor for cardiometabolic disease.[46] A secondary analysis of the FIT-AGEING study indicated that neither actigraphy-measured sleep efficiency nor wake after sleep onset was associated with resting whole-body fat oxidation rate among 70 middle-aged sedentary adults, although PSQI global score was ($R^2 = 0.225$–0.391). In 812 middle-aged and older adults from the community-based Heart Strategies Concentrating on Risk Evaluation study, loud snoring was associated with an increased risk of low HDL-C, perhaps by snoring related sleep fragmentation or via a sleep disordered breathing-related mechanism.[47] Among ~6500 40 to 60-year-old Finnish adults, frequent insomnia symptoms, such as difficulty in initiating and maintaining sleep and having non-restorative sleep, were associated with a 59% increase in the likelihood that dyslipidemia medication would be prescribed during 5 years of follow-up, suggesting a link between poor sleep quality and dyslipidemia. Overall,

the size and quality of the current body of evidence make it difficult to draw concrete conclusions regarding the association of poor sleep quality with altered lipid metabolism/dyslipidemia.

### 3.2 | Experimental sleep manipulation

In our search, we found only one study that directly examined the effects of experimental sleep restriction on postprandial lipaemic responses to a high-fat meal,[48] while one other reported the effects of experimental sleep restriction on fasting serum lipids and lipoprotein profiles as well as the activity of lipid transfer proteins.[40] In the former study, Ness et al. examined postprandial lipaemic responses following 4 consecutive nights of sleep restriction versus control (5-h vs. 10-h TIB) in 15 young healthy men. While an increase in postprandial lipaemia may have been expected, sleep restriction instead suppressed the postprandial triglyceride (TG) area-under-the-curve and non-esterified fatty acid (NEFA) levels compared with control. However, while the provided meal was high in fat (49 g), it was also high in carbohydrate (111 g) and elicited a robust postprandial insulin response. Importantly, the insulin response to the meal was greater following sleep restriction.[48] Therefore, it is reasonable to speculate that this augmented insulin response resulted in enhanced TG clearance by insulin-stimulated lipoprotein lipase translocation; however, this should be investigated in future studies. Aho et al. reported that 5 consecutive nights of sleep restriction (4-h vs. 8-h TIB) promoted a decrease in the number of small, medium, and large LDL-C particles, as well as VLDL-C in circulation without impacting HDL-C levels, again a seemingly counterintuitive finding that does not entirely agree with the aforementioned epidemiological evidence. However, sleep restriction also promoted the down-regulation of genes involved in intracellular lipid, cholesterol, and sterol transport and homoeostasis.[40] In contrast to the findings of Aho et al., O'Keeffe et al. reported that 5 consecutive nights of sleep restriction (4-h vs. 9-h TIB) had no effect on 24-h TG profiles or on LDL-C or HDL-C.[49] However, it is plausible that O'Keeffe et al. did not observe the effect of sleep restriction on lipoprotein levels because the traditional spectrophotometric-based quantification of lipoprotein levels used in this study cannot provide an indication of particle size. As previously described, it will be necessary for future studies to consider lipoprotein particle size to fully understand the effects of sleep disruption on lipid metabolism.

Insulin resistance affects both peripheral tissues such as skeletal muscle and the liver, where it manifests as decreased insulin-stimulated glucose disposal and elevated endogenous glucose production, respectively. Notably, insulin resistance is also associated with a decreased ability to suppress lipolysis in adipose tissue and altered fatty acid oxidation.[50,51] Thus, a few studies have also determined the effects of experimental sleep restriction on indicators of postprandial lipid metabolism in response to either glucose tolerance tests or hyperinsulinemic-euglycemic clamps.[33] Rao et al. reported that a 4-h versus 8-h TIB induced a modest increase in cortisol and catecholamines, a 62% increase in fasting NEFA levels, and a decrease in the respiratory quotient indicating an increase in whole body fat oxidation that was coincident with a 24% decrease in fasting TG levels, but no effect on total or LDL-cholesterol. Importantly, these effects were observed alongside a 25% decrease in whole-body insulin sensitivity and a 29% decrease in peripheral insulin sensitivity.[33] However, there was no effect on hepatic insulin sensitivity as evidenced by a lack of change in endogenous glucose production (due to a modest increase gluconeogenesis and a decrease in glycogenolysis).[33] These findings led the authors to speculate that sleep restriction impacts lipid metabolism by (1) causing stress-hormone induced lipolysis, which elevates circulating NEFA levels that promote peripheral insulin resistance by decreasing skeletal muscle glucose uptake and (2) by decreasing de novo lipogenic flux.[33] These findings demonstrate that it may be difficult to separate the effects of sleep restriction on glucose versus lipid metabolism, which are instead intricately linked. Interestingly, however, Ness et al. reported that, whereas 5 nights of 5-h TIB reduced insulin sensitivity and suppressed the rebound in NEFAs observed following glucose clearance from plasma during an intravenous glucose tolerance test, two nights of subsequent sleep recovery restored NEFA kinetics to baseline but did not recover insulin sensitivity.[52] These findings suggest a dissociation between the recovery of NEFA and glucose metabolism during sleep recovery (i.e., extending sleep duration to sufficient durations following restriction) that seems to be counter to the linked effects of sleep restriction on NEFA and glucose metabolism. Additional mechanistic studies utilising tracers are necessary to better understand these inter-relationships to determine tissue-specific (e.g., peripheral vs. hepatic) metabolic changes in response to acute and chronic sleep restriction as well as in response to sleep recovery. Finally, to our knowledge, little or no work has been done to understand sex- or age-specific effects, with many of the aforementioned studies completed primarily or only in young healthy men.

Overall, it appears that the effects of acute (e.g., experimental) sleep restriction on lipid metabolism are opposite to what may be expected in light of the extant epidemiological evidence. It has been hypothesised that this may be subsequent to the acute phase inflammatory response that is induced by sleep restriction.[53] Sleep restriction may also impair adipocyte function while increasing sympathetic tone and stress hormone production, thus augmenting intracellular lipolysis and altering NEFA metabolism.[32,33,52,54] Importantly, it appears that elevated circulating NEFAs are at least partially responsible for decreased peripheral insulin sensitivity caused by experimental sleep restriction.[55] Experimental studies will be necessary to understand how and if sleep fragmentation or SWS suppression impair lipid metabolism.

## 4 | HUNGER AND SATIETY HORMONES

Two of the primary hormones that have major regulatory roles in energy balance are leptin and ghrelin. Leptin is satiety promoting hormone produced and secreted primarily by adipose tissue that helps to regulate energy balance by reducing food intake and

increasing energy expenditure via activation of hypothalamic circuits.[56,57] Circulating leptin changes rapidly in response to acute caloric intake or restriction, assisting in the control of short-term feeding via mechanisms such as augmentation of the anorectic effects of cholecystokinin,[57–59] and is thought to be an important mediator of long-term energy balance regulation.[57] Ghrelin is commonly referred to as the hunger hormone and is produced primarily in the oxyntic glands of the gastric fundus and stomach. Ghrelin has potent orexigenic (or appetite stimulating) and gastric emptying effects and acts on hypothalamic receptors.[60] Typically, ghrelin rapidly decreases postprandially and then returns to baseline levels in the late postprandial and inter-digestive periods in a pattern that is reciprocal of insulin.[61] Both leptin and ghrelin release also display diurnal rhythms that are in phase with each other, falling throughout the night until reaching a nadir between 0800 and 1000.[61] Data also exist suggesting that the release of these hormones may be influenced by the autonomic nervous system, with cholinergic (vagal) activity suppressing ghrelin secretion and sympathetic activity decreasing leptin production.[62,63] Thus, sleep disruption has the potential to disrupt leptin and ghrelin metabolism via circadian disruption or altered vagal and sympathetic activity.

## 4.1 | Epidemiologic evidence on sleep disruption

In a study of 1024 participants enroled in the Wisconsin Sleep Cohort Study, Taheri et al.[64] measured total sleep time from nocturnal polysomnography and average sleep duration from a 6-day sleep diary, and quantified fasting leptin and ghrelin levels from a serum sample obtained soon after awakening. Ghrelin concentrations were strongly and inversely associated with total sleep time ($\beta = -0.69$, $p = 0.008$), and leptin concentrations were positively associated with average sleep duration ($\beta = 0.11$, $p = 0.01$). In addition, wakefulness after sleep onset, an indicator of sleep quality, was positively associated with ghrelin ($\beta = 0.81$, $p = 0.05$) but not with leptin concentrations ($\beta = -0.04$, $p = 0.40$). Similarly, in a cohort of 769 postmenopausal women, Stern et al.[65] reported that fasting and morning leptin concentrations were positively associated with self-reported sleep duration, such that women reporting ≤6 h of sleep had lower leptin concentrations than those reporting ≥8 h of sleep. Among children, it has been reported that short sleep is associated with lower leptin concentrations at age 7 in girls and during adolescence in boys, suggesting potential sex-specific associations that should be explored more carefully.[66] Notably, a recent meta-analysis also demonstrated that short sleep duration is associated with increased ghrelin levels among cross-sectional studies.[67] Among men with primary insomnia who have reduced stage 2 and REM sleep, lower sleep efficiency, and greater stage 1 sleep, nocturnal ghrelin levels were reduced compared to control participants; however, no differences were observed in leptin concentration.[68] Finally, among 95 adults with obesity, it was reported that self-reported sleep efficiency was associated with lower postprandial cholecystokinin, and lower subjective sleep quality was linked with increased basal and postprandial active ghrelin in men only.[69]

These data provide initial epidemiological evidence that short sleep duration is associated with altered circulating concentrations of ghrelin and leptin that may promote increased appetite. Both measured (i.e., WASO) and self-reported indicators of sleep quality appear to indicate that poor sleep quality may be associated with increased circulating ghrelin; however, the overall body of evidence is currently weak and future studies should be powered to examine potential sex-differences. Although there is preclinical[70] and cross-sectional evidence[64] suggesting that low sleep quality (i.e., high sleep fragmentation) may be associated with impaired leptin metabolism, it appears that these associations may be weaker than for sleep duration. However, additional work is needed to replicate and better understand these links before firm conclusions can be made.

## 4.2 | Experimental sleep manipulation

In 11 healthy men, Speigel et al. assessed 24-h leptin levels at the end of three different conditions with varying sleep durations performed across a consecutive 16-night period: 3 nights of 8-h TIB, 6 nights of 4-h TIB, and 7 nights with 12-h TIB. Leptin levels decreased in a stepwise fashion across the 4-h, 8-h, and 12-h TIB conditions. Accordingly, mean, maximal, and rhythm amplitude leptin levels were 19%, 26%, and 20% lower, respectively, during the 4-h TIB condition compared to the 12-h TIB condition.[71] Similarly, another study by Speigel et al. examined the effect of 4-h versus 10-h TIB on leptin and ghrelin levels as well as on subjective hunger and appetite across a 12-h period from 0900 to 2100 during which a constant intravenous infusion of glucose (5 g/kg) was provided.[72] Notably, sleep restriction promoted 18% lower leptin and 28% greater ghrelin across the day. These hormonal differences were accompanied by a 24% increase in hunger and a 23% increase in appetite ratings for all food categories, which tended to be greatest for sweet, salty, and starchy foods (33%–45%). St. Onge et al. observed that 4-h TIB sleep restriction promoted an increase in fasting ghrelin concentrations among men but not women when compared to 9-h TIB habitual sleep. Interestingly, there was no effect of sleep restriction on fasting leptin in this study, although 24-h leptin concentrations were also lower in men but not women.[73]

Subsequent studies have found mixed results regarding leptin, with some showing elevations as opposed to decreases in leptin levels following sleep restriction[74–77] and others showing no changes.[77,78] This discrepancy may be partially explained by the caloric intake of the participants during the study period. If participants were allowed to overeat or if they gained weight, an increase in leptin levels would be expected. Indeed, Markwald et al. reported increased 24-h leptin levels following sleep restriction that were accompanied by both greater caloric intake and significant weight gain.[75] In a study that controlled for diet and maintained body weight, Hanlon et al. observed a significant decrease in diurnal leptin

variation amplitude.[79] Similarly, in a study performed by Reynolds et al. in 2012, leptin levels were significantly reduced following 5 nights of 4-h TIB compared with 2 nights of 10-h TIB.[80] In the only study to our knowledge that has experimentally examined the effect of sleep fragmentation on 24-h leptin and ghrelin concentrations, Gonnissen et al. reported that sleep fragmentation did not influence leptin or ghrelin, although they did note lower glucagon-like peptide 1 and self-reported fullness.[81] Notably, the fragmentation protocol used in this study—alarms at varying frequencies and intensities every 90 min during sleep—reduced REM sleep but had no influence on SWS. It is possible that selective SWS suppression may have more substantial effects, but this hypothesis remains to be tested.

Collectively, these findings suggest that sleep restriction may affect leptin's ability to accurately signal energy balance and promote an increase in ghrelin, ultimately promoting increases in hunger. It is plausible that these effects may be important in the short term to compensate for an increased caloric need caused by increased wakefulness,[81] but chronically these effects may have a significant impact on the ability to regulate bodyweight. Additional studies utilising experimental manipulation of sleep quality, and in particular SWS suppression, are needed to better understand how sleep quality impacts appetite hormone regulation.

## 5 | BODYWEIGHT REGULATION

### 5.1 | Epidemiologic evidence on sleep disruption

In light of the previously described effects of sleep disruption on leptin and ghrelin, it would follow that sleep disruption would also promote body weight gain and increased risk of obesity. Indeed, a 2008 meta-analysis of epidemiological studies on the association of self-reported sleep duration and obesity risk by Cappuccio et al. reported that, across 604,509 adults, a 1-h increase in sleep duration was associated with a 0.35 kg/m$^2$ reduction in BMI.[82] This same meta-analysis also reported that children (1.89 [CI = 1.46–2.43]) and adults (1.55 [1.43–1.68]) were more likely to be obese (BMI > 30 kg/m$^2$) if they were short sleepers. Several high-quality narrative reviews of the existing epidemiological evidence have similarly concluded that short sleep duration is undoubtedly associated with, and perhaps causally linked with, increased susceptibility to obesity.[83–85] However, given the cross-sectional nature of much of this epidemiologic evidence, it is hard to determine the directionality of these associations.

Among those studies that longitudinally observed weight change in individuals with short versus optimal sleep durations, weight gain may be greater among those with short sleep duration (see Table 2 for study summaries). However, among adults, this association is inconsistent. Furthermore, in studies where the association is present, the size of this effect is rather modest, with ~2 kg greater weight gain noted across a 6-year period in Canadian adults[86] and 0.7–1.14 kg greater weight gain across a 16-year period noted in those with short sleep (≤5–6 h/night) in the Nurses' Health Study.[92] In a 5-year study of African Americans and Hispanic Americans adults, individuals 40 years and younger who self-reported sleeping ≤5-h per night had a 1.8 kg/m$^2$ greater change in BMI than those reporting 6–7 h of sleep per night.[87] In contrast, using data from the NHANES I studies, Gangwisch et al.[88] reported that while individuals between 32–49 years of age who self-reported sleeping less than 7 h per night had greater BMIs than individuals who slept 7 h or more each night in cross-sectional analysis at baseline and follow-up examinations, sleep duration was not significantly associated with 8–10 years longitudinal change in BMI ($\beta = -0.053$, $p = 0.27$). Similarly, Lauderdale et al.[89] reported that whereas actigraphy-measured sleep duration was inversely associated with BMI ($B = -1.61$, $p < 0.001$) in cross-sectional analysis, there was no association of sleep duration with 5-year changes in BMI ($B = -0.02$, $p = 0.86$) among adults (mean age ~ 45 years) in the Coronary Artery Risk Development in Young Adults Sleep Study. Thus, overall, whereas there appears to be a consistent cross-sectional association of sleep duration with body weight and/or body mass index in adults, longitudinal associations are much weaker, making it difficult to infer causality. However, one hypothesis put forward is that weight gain is not linear among those with short sleep.[106] That is, short sleep may cause initial, relatively dramatic weight gain, but this effect is tempered as weight increases.

It is also possible that the effect of short sleep on weight gain is attenuated over time with advancing age or development. Notably, among children, the longitudinal association between short sleep and weight gain appears to be stronger and more consistent[107] (Table 2), suggesting strong developmental origins. Future longitudinal prospective cohort studies beginning in early life and continuing into adulthood will be necessary to more clearly understand the causal links between short sleep duration and body weight gain across the lifespan. It is also important to point out that while body weight is a commonly used end point, it may not accurately reflect adiposity. As such, the measurement of body composition and particularly of visceral adiposity, will continue to be important in future studies such as these. We also note that the association of sleep duration with bodyweight appears to be best described by a U-shape, where long sleep durations may also be associated with increased bodyweight.[108] Finally, it has been cautioned that the longitudinal association of sleep duration with changes in BMI may be upwardly biased by unobserved and/or unmeasured time-invariant confounders, and also that confounding, mediating, or moderating factors such as psychosocial or mental health-related factors may influence the sleep and BMI association but have not always been well characterised in prior studies.[109]

### 5.2 | Experimental sleep manipulation

In support of these epidemiological data, Markwald et al. reported that 5 days of insufficient sleep led to a significant 0.82 kg increase in body weight in a clinical, experimental study.[75] It is unclear whether this increase in weight was due to body fat gain or to some other cause. For

**TABLE 2** Epidemiological/cohort evidence linking disrupted sleep with altered hunger, Satiety, and bodyweight regulation.

| Reference | Study sample | Study design | Sleep assessment | Dependent variable | Primary findings |
|---|---|---|---|---|---|
| Taheri et al.[64] | 1024 adults (mean age = 52.7 years [range 30–60 years], 46.2% female) | Cross-sectional analyses of a longitudinal cohort (Wisconsin Sleep Cohort Study) | Overnight PSG for total sleep time, wakefulness after sleep onset (WASO), and sleep efficiency (SE); self-reported usual sleep duration; average nightly sleep (with/without naps) from sleep diaries; self-reported usual sleep duration | Leptin, Ghrelin, and BMI | Average nightly sleep with ($B = 0.12$, $p = 0.006$) and without naps ($B = 0.11$, $p = 0.01$), and usual sleep ($B = 0.089$, $p = 0.006$) linearly associated with Leptin concentrations. Total sleep time ($B = -0.69$, $p = 0.008$), SE ($B = -5.1$, $p = 0.05$), WASO ($B = 0.81$, $p = 0.05$), and average nightly sleep with naps ($B = -0.66$, $p = 0.05$) linearly associated with Ghrelin concentrations. U-shaped curvilinear association of sleep duration with BMI, where short (<7.7 h/night) and long (>7.7 h/night) were associated with increased BMI |
| Stern et al.[65] | 769 postmenopausal women (median age = 63 years [IQR = 57–69 years]) | Cross-sectional analyses of prospective longitudinal cohort (Women's Health Initiative) | Self-reported usual sleep duration, categorised as ≤6 h, 7 h, or ≥8 h; Self-reported sleep quality, categorised as Very sound or restful/Sound or restful, average, or very restless/restless | Leptin, energy intake and dietary quality | Short sleepers (≤6 h/night) had lower Leptin concentrations than those sleep ≥8 h/night. Short sleepers also had a 1% increase in dietary energy intake and lower dietary quality relative to those sleeping 7 h/night. Long sleepers (≥8 h/night) also had lower sleep quality than those sleeping 7 h/night. Poor sleep quality had lower diet quality than those reporting very sound sleep, primarily due to an increase in relative energy intake from fat. |
| Boeke et al.[66] | 655 children (47% female); 502 adolescents (mean age = 17.7 years; 49.6% female) | Longitudinal analyses of children from infancy to age 7 (Project Viva Study (PVS) and cross-sectional analyses of adolescent children (Cleveland Children's Sleep & Health Study [CCSHS]) | PVS: Average sleep duration reported by mothers; CCSHS: Self-reported sleep duration, PSG-based sleep efficiency, arousal index, and slow wave sleep | Leptin | PVS: Sleep duration was not cross-sectionally associated with leptin in infancy, or at age 3 or 7 years in males or females. However, lower cumulative childhood sleep duration score was associated with lower leptin at age 7 years in females. The association of cumulative sleep duration score with leptin was |

TABLE 2 (Continued)

| Reference | Study sample | Study design | Sleep assessment | Dependent variable | Primary findings |
|---|---|---|---|---|---|
| | | | | | strongest among girls with overweight or obesity. CCSHS: Each 1 h decrease in weekday and weekend sleep duration was associated with a 0.053 and 0.056 decrease in log leptin among adolescent males, respectively. |
| Motivala et al.[68] | 14 men diagnosed with primary insomnia (mean age = 45 years) versus 24 age- and weight-matched men without insomnia (mean age = 49 years) | Cross-sectional, between group comparison | Two nights of laboratory based PSG assessment of sleep architecture | Overnight leptin and ghrelin concentrations (measured at 2300 h, 0200 h, and 0600 h) | Insomnia patients had lower total sleep, poorer sleep efficiency, greater WASO, greater stage 1, and lower stage 2 and REM sleep. Insomnia patients also had lower ghrelin levels across the night than healthy controls. No differences in leptin concentrations were observed. Stage 1 sleep correlated negatively with ghrelin at 2300 h ($\rho = -0.28$, $p = 0.07$), at 200 h ($\rho = -0.30$, $p = 0.05$), and at 600 h ($\rho = -0.41$, $p = 0.007$) in the full sample. |
| Nymo et al.[69] | 95 healthy adults with obesity | Cross-sectional | Sleep duration and quality assessed using Pittsburgh Sleep Quality Index | Subjective feelings of appetite, and fasting and postprandial plasma active ghrelin, total peptide YY, active glucagon-like peptide 1, cholecystokinin, and insulin | No associations of sleep duration or overall quality with appetite. Lower sleep efficiency was associated with lower postprandial cholecystokinin ($\beta = -60.1$, $p = 0.028$), shorter habitual sleep was associated with lower postprandial desire to eat ($\beta = 1.67$, $p = 0.029$). In males only, shorter sleep duration and lower subjective sleep quality were associated with increased basal ($\beta = -0.29$, $p = 0.016$ and $\beta = 0.58$, $p = 0.008$, respectively) and postprandial ($\beta = -0.30$, $p = 0.002$ and $\beta = 0.42$, $p = 0.028$, respectively) active ghrelin. |

(Continues)

TABLE 2 (Continued)

| Reference | Study sample | Study design | Sleep assessment | Dependent variable | Primary findings |
|---|---|---|---|---|---|
| Chaput et al.[86] | 276 adults (mean age = 38.8 years; 53% female) | Secondary analyses of longitudinal cohort (Quebec Family) study; baseline assessment (1989–1994) with follow up ~6 years later (1995–2001) | Short sleep (5–6 h/night), reference (7–8 h/night), and long sleep (9–10 h/night) determined from self-reported usual sleep duration | BMI, waist circumference, relative body fat via underwater weighing | Short sleepers had greater BMI, body fat%, and waist circumference at baseline than reference. Short sleepers gained 1.98 kg more and long sleepers gained 1.58 kg more weight than reference over 6 years of follow-up. Similar patterns were observed for body fat% and waist circumference. Accordingly, short sleepers (27%, $p < 0.05$) and long sleepers (21%, $p < 0.05$) were at increased risk of developing obesity relative to the reference group. |
| Hairston et al.[87] | 1107 adults (mean age = 41.7 years; 30% Black/70% Hispanic; 62% female) | Extension of longitudinal Insulin Resistance Atherosclerosis Study, with baseline (1999–2002) and ~5-year follow-up examinations | Short sleep (≤5 h/night), reference (6–7 h/night), or long sleep (≥8 h/night) determined from self-reported usual sleep duration | BMI and abdominal fat mass (VAT) by CT scan | Among adults <40 years old, short sleep associated with a 1.79 kg/m$^2$ ($p < 0.001$) increase and long sleep associated with 0.9 kg/m$^2$ ($p < 0.001$) increase in BMI over 5 years relative to reference. Among adults <40 years old, short sleep associated with 13 cm$^2$ increase ($p < 0.01$) and long sleep associated with 7 cm$^2$ increase ($p < 0.05$) in VAT relative to reference. No significant association of sleep duration and BMI/adiposity was observed among adults ≥40 years of age. |
| Gangwisch et al.[88] | 9588 and 8073 adults (age range = 25–74 years) were including in the cross-sectional and longitudinal analyses, respectively | Longitudinal Epidemiologic Study (NHANES 1), survey years 1982–1984, 1987, and 1992 | Self-reported usual sleep duration | BMI | Inverse association of sleep duration with BMI, particularly among 32–49 years old ($X^2 = 55.3$, $p < 0.001$), but not older, adults in cross sectional analyses. However, no significant association between sleep duration and longitudinal change in BMI was observed ($\beta = -0.053$, $p = 0.27$) |

TABLE 2 (Continued)

| Reference | Study sample | Study design | Sleep assessment | Dependent variable | Primary findings |
|---|---|---|---|---|---|
| Lauderdale et al.[89] | 612 adults (mean age = 45 ± 4 years; 57.5% female; 56.5% White) | 5-year ancillary study nested in CARDIA Study with Baseline (CARDIA Year 15) and Follow-up (CARDIA Year 20) Examinations | Sleep duration assessed using wrist actigraphy worn for 6 nights; all available nights were used for measurement | BMI | Inverse association of sleep duration with BMI in cross-sectional analyses ($B = -1.61$, $p < 0.001$). However, no association of sleep duration with longitudinal change in BMI ($B = -0.02$, $p = 0.86$) |
| Stranges et al.[90] | 5021 and 4378 White adults (47–67 years at baseline; 28% female) were included in cross-sectional and longitudinal analyses, respectively | Prospective cohort study of white-collar British civil servants (Whitehall II Study) with baseline (Phase 5: 1997–1999) and follow-up (Phase 7: 2003–2004) assessments | Self-reported usual sleep duration | BMI and waist circumference | Significant inverse association of sleep duration with BMI ($\beta = -0.36$ [−0.49 to −0.24]) and waist circumference ($\beta = -0.96$ [−1.32 to −0.60]) in cross-sectional analyses. Relative to sleeping 7 h/night, short sleep duration (≤5 h/night) was not associated with significant longitudinal changes in BMI ($\beta = -0.06$ [−0.26 to 0.14]) or waist circumference ($\beta = 0.44$ [−0.23 to 1.12]). Similarly, no significant associations of sleep duration with longitudinal changes in BMI or waist circumference were observed when sleep duration was modelled continuously. |
| Lopez-Garcia et al.[91] | 3576 and 2335 older adults (aged ≥60 years) were included in cross-sectional and longitudinal analyses, respectively | Prospective, longitudinal (2-year), population-based cohort | Self-reported usual sleep duration | BMI and waist circumference | In cross-sectional analyses, adults sleeping ≤5 h/night had higher frequency of obesity (OR = 1.45 [1.09–1.92]) and severe obesity (OR = 2.36 [1.50–3.74]) than those sleeping 7 h/night. Adults sleeping 9 h/night also had greater frequency of severe obesity (OR = 1.68 [1.08–2.61]). During 2-year follow-up, women sleeping ≤5 h/night (OR = 3.61 [1.45–9.01]) and ≥8 h/night (OR = 3.02 [1.30–7.02]) were more likely to gain ≥5 kg than women sleeping 7 h/night. There was no association of sleep duration with longitudinal weight gain in men. |

(Continues)

TABLE 2 (Continued)

| Reference | Study sample | Study design | Sleep assessment | Dependent variable | Primary findings |
|---|---|---|---|---|---|
| Patel et al.[92] | 68,183 women (mean age = 52.4 years at baseline) | Longitudinal cohort (Nurses' Health Study) study across 16 years | Self-reported total sleep duration | Self-reported body weight; two discrete outcomes also determined for analyses: BMI >30 kg/m$^2$ and weight gain of ≥15 kg | Those with ≤5 h sleep gained 1.14 kg [0.49–1.79] more while those with 6 h of sleep gained 0.71 [0.41–1.00] more than those sleeping 7 h of sleep per night. Those sleeping 7–8 h/night had the lowest risk for major (≥15 kg) weight gain, while those sleeping 6 h and ≤5 h were 12% and 32% more likely to gain ≥15 kg over the 16-year follow-up period. Associations persisted with adjustment for other lifestyle behaviours. |
| Nishiura et al.[93] | 3803 Japanese male (mean age = 47.8 years) white-collar workers | Longitudinal cohort study with a baseline (1994–1995) and 4-year follow-up (1998–1999) assessment | Self-reported average sleep duration, categorised into: ≤5 h/night, 6 h/night, 7 h/night (reference), ≥8 h/night | BMI | Those sleeping ≤5 h ($B$ = 0.34 [0.03–0.65]) and 6 h ($B$ = 0.27 [0.08–0.45]) had greater BMI at baseline relative to those sleeping 7 h/night. Those sleeping ≤5 h/night ($B$ = 0.15 [0.03–0.27]) had greater longitudinal change in BMI than those sleeping 7 h/night. |
| Brooks Holliday et al.[94] | 1115 predominantly Black (95.2%) adults (mean age = 56 ± 16 years; 77% female) with median annual income of $12,500 | Secondary analysis from Pittsburgh Research on Neighbourhood Change and Health employing a Quasi-experimental design with Longitudinal Assessment (2013, 2016, 2018) | Total sleep time, as well as sleep quality (sleep efficiency and WASO) determined objectively by wrist actigraphy (≥4 nights); sleep quality also assessed subjectively on a scale of 1 (very poorly) to 5 (very well) | BMI | No association of total sleep time ($B$ = 0.02 [95% CI: −0.36–0.40), sleep efficiency ($B$ = 0.04 [95% CI: −0.38–0.47], or WASO ($B$ = −0.01 [95% CI: −0.54–0.52]) in unadjusted or adjusted analyses, nor in adjusted analyses |

TABLE 2 (Continued)

| Reference | Study sample | Study design | Sleep assessment | Dependent variable | Primary findings |
|---|---|---|---|---|---|
| Hasler et al.[95] | 496 young adults (~50% female) aged 27 years at baseline | Longitudinal cohort study (Zurich Cohort Study); secondary analyses of data from 3rd–6th interviews (1986, 1988, 1993, and 1999) corresponding to ages 27, 29, 34, and 40 years respectively. | Self-reported sleep duration assessed from questions assessing bedtime, wake time, and sleep onset latency | BMI and BMI-defined obesity (≥30 kg/m$^2$) | Significant cross-sectional association between sleep duration and BMI and obesity at ages 27, 29, and 34 years, but not at age 40 years. At ages 27 (OR = 8.2 [1.9–36.3]), 29 (OR = 4.6 [1.3–16.5]), and 34 years (OR = 3.5 [1.0–12.2]), short sleep duration was also associated with risk for later obesity with risk decreasing as participants aged. The average rate of change in BMI and average rate of change in sleep duration tended to be, but were not significantly associated ($\beta$ = −0.082, $p$ = 0.08). |
| Huang et al.[96] | 599 Chinese children | Prospective longitudinal cohort (Understand Children's Activity and Nutrition) with annual assessments over 2 years | Usual sleep duration from parental report | Odds of obesity (defined by BMI based on International Obesity TaskForce reference for children) | Higher usual sleep duration was associated with lower odds of obesity (OR = 0.84 [0.71–0.999]). |
| Araujo et al.[97] | 1171 European urban adolescents aged 13 years at baseline and 17 years at follow-up | Prospective longitudinal cohort (EPITeen cohort) with baseline assessment in 2003–2004 and follow-up in 2007–2008 | Usual sleep duration from self-reported usual bedtimes and waketimes | BMI z-scores in accordance with CDC growth charts and relative body fat (%) by bioelectrical impedance analysis | At age 13, sleep duration was inversely associated with BMI z-score in males ($\beta$ = −0.16 [−0.27–−0.04]). At age 17, sleep duration was positively associated with BF% in females ($\beta$ = 0.51 [0.07–0.96]). Sleep duration at age 13 was inversely associated with adiposity at age 17 in males (BMI z score: $\beta$ = −0.12, [−0.233–−0.012]; BF %: $\beta$ = −0.73, [−1.38–−0.08), but positively associated with change in BMI z-score from 13 to 17 years in females ($\beta$ = 0.05, [0.002–0.097]). These associations were no longer significant with adjustment for baseline adiposity. Finally, cross-lagged analyses did not indicate significant associations of sleep at 13 years to BMI at 17 years in either males or females. |

(Continues)

TABLE 2 (Continued)

| Reference | Study sample | Study design | Sleep assessment | Dependent variable | Primary findings |
|---|---|---|---|---|---|
| Touchette et al.[98] | 1138 children (95.6% Caucasian) aged 29 months at baseline and 74 months at final follow-up | Prospective longitudinal cohort (Quebec Longitudinal Study of Child Development) from Mar–Dec 1998 to Dec 2004 | Usual sleep duration from parental report; used to define sleep trajectories (short increasing, short persistent, 10 h persistent, 11 h persistent) across first 74 months of life | Overweight/obesity at 2.5 and 6 years define by BMI using international standards | Short persistent sleepers (OR = 3.9 [1.7–8.8]) and short increasing sleepers (OR = 3.2 [1.4–7.6]) were more likely to be overweight/obese at 6 years old than 11 h persistent sleepers. After controlling for potential confounders, the risk of overweight/obesity among persistently short sleepers increased (OR = 4.2 [1.6–11.1]) and 10 h sleepers were also at increased risk (OR = 1.8 [1.1–2.9]) relative to persistent 11 h sleepers. In addition, at 2.5 years of age, there was a greater percentage of overweight/obese children among those who slept <9 h/night compared to those who slept ≥9 h/night (31.3% vs. 24.7%, $p = 0.05$). |
| Reilly et al.[99] | 8234 European children aged 7 years at final assessment | Prospective longitudinal cohort (Avon Longitudinal Study of Parents and Children) | Sleep duration at age 30 months by parental report | Obesity at age 7 years defined as a BMI ≥95 percentile relative to reference for the UK population in 1990 | Sleep duration in children aged 30 months was independently associated obesity prevalence at age 7 years. Specifically, children sleeping <10.5 h/night had 1.45 [1.1–1.9] greater and those sleeping 10.5–10.9 h/night had 1.35 [1.0–1.8] greater odds for obesity than children sleeping >12 h/night. |
| Snell et al.[100] | 2281 children (50% female, 63% White) mean age 8.1 y at baseline and 13.7 years at follow-up | Longitudinal epidemiologic cohort (Child Development Supplement of Panel Survey of Income Dynamics) with baseline assessment in 1997 (wave 1) and follow-up in 2002–2003 (wave 2) | Sleep duration derived from parental and/or parental-assisted time diaries that included detailed accounting of all activities in a 24 h period on a week and weekend day | BMI standardised by child age and sex, as well as dichotomously defined overweight status | For each additional hour of sleep at baseline, BMI at follow-up decreased by 0.12 standard deviations ((SD); $\beta = -0.115$, $p < 0.01$). This association was strongest among younger children ($\beta = -0.153$, $p < 0.01$) who were 3–7.9 years at baseline. Moreover, children sleeping 10–10.9 h had 0.16 SD lower BMI ($\beta = -0.164$, $p < 0.10$) and those sleeping ≥11 h had |

TABLE 2 (Continued)

| Reference | Study sample | Study design | Sleep assessment | Dependent variable | Primary findings |
|---|---|---|---|---|---|
| | | | | | 0.26 SD lower BMI ($\beta = -0.257$, $p < 0.05$) than children sleeping 9–9.9 h. Again, these effects tended to be strongest among younger children. Later bedtime at baseline was also associated with greater BMI at follow-up ($\beta = 0.116$, $p < 0.01$). Finally, greater sleep duration at baseline was also shown to be associated with a lower probability of being overweight at follow-up ($\beta = -0.053$, $p < 0.01$). |
| Lumeng et al.[101] | 785 children (50% female, 81% White) mean age 9 years at baseline and 11.6 years at follow-up | Secondary analyses of prospective longitudinal cohort (NICHD Study of Early Child Care and Youth Development) | Sleep duration and sleep problems derived from maternal report on Children's Sleep Habits Questionnaire (CSHQ) | Overweight defined dichotomously as a BMI $\geq 95^{th}$ percentile for age and sex based on National Centre for Health Statistics normative data. | Greater sleep duration was associated with lower likelihood of being overweight at 11.6 years of age in cross-sectional analysis (OR = 0.8 [0.65–0.98], $p < 0.05$). Greater sleep duration at 9 years of age was also associated with reduced likelihood of being overweight at 11.6 years of age (OR = 0.6 [0.36–0.99], $p < 0.05$). Further, children with the greatest decline in sleep duration were more likely to be overweight at 11.6 years of age than children who's sleep durations were stable from 9 to 11.6 years of age (OR = 3.5 [1.1–11.1], $p = 0.04$). |
| Agras et al.[102] | 150 newborn infants followed to 9.5 years of age | Prospective longitudinal cohort study | Sleep duration by parental report at ages 2–5 years | Overweight defined dichotomously as a BMI above the $85^{th}$ percentile for age and sex | Sleep duration from 3–5 years of age was negatively associated (–0.21) with overweight at 9.5 years of age. Children who were overweight slept about 30 min less than non-overweight children. |

(Continues)

TABLE 2 (Continued)

| Reference | Study sample | Study design | Sleep assessment | Dependent variable | Primary findings |
|---|---|---|---|---|---|
| Maume et al.[103] | 974 adolescents (50% female) aged 12 years at baseline and 15 years at follow-up | Secondary analyses of prospective longitudinal cohort (NICHD Study of Early Child Care and Youth Development) with baseline assessment at age 12 years and follow-up at age 15 years | Sleep duration derived from self-reported bedtimes and wake times | BMI standardised by age and sex to percentile scores | Sleep duration declined from age 12–15 years. Sleep duration was among strongest predictors of youth health and predicted BMI at age 15 ($\beta = -0.21$, $p < 0.05$). Notably, there was no evidence that BMI, depression, or substance use had an effect on sleep duration, suggesting the association of sleep duration on BMI is uni-directional. |
| Michels et al.[104] | 193 children (48% female) ages 6–12 years | Secondary analyses of longitudinal cohort (Belgian Longitudinal ChiBS) with baseline assessment in 2010 and follow-up assessment in 2012 | Sleep duration derived from time in bed and time out of bed from sleep diaries (4–7 nights); Sleep onset latency, WASO, actual sleep duration, and sleep efficiency assessed using 4–7 nights of actigraphy | Age- and sex-specific BMI z-scores, relative body fat (BF%) measured by air-displacement plethysmography, and waist circumference | Reported sleep duration was inversely associated with longitudinal change in BMI ($B = -0.38$, $p = 0.03$), BF% ($B = -2.35$, $p = 0.002$), and waist circumference ($B = -1.67$, $p = 0.016$). Actual sleep duration also inversely associated with longitudinal change in BMI ($B = -0.23$, $p = 0.09$), BF% ($B = -1.08$, $p = 0.067$), and waist circumference ($B = -1.08$, $p = 0.014$). |
| Landhuis et al.[105] | 1037 participants (48% female) aged 5 years at baseline and 32 years at final assessment | Prospective longitudinal cohort (Dunedin Multidisciplinary Health and Development Study) with baseline assessment at 5 years of age in 1977–1978 and final assessment (at 32 years of age in 2004–2005. | Sleep duration derived from parent reported usual bedtimes and wake-up times at ages 5, 7, 9, and 11 years | BMI at 32 years of age | Sleep duration at 5 (−0.08, $p < 0.05$), 7 (−0.07, $p < 0.05$), 11 (−0.10, $p < 0.01$), and averaged across 5–11 (−0.11, $p < 0.01$) years of age were associated with BMI at age 32 years. In fully adjusted linear regression analyses, average sleep duration across 5–11 years of age predicted both BMI ($B = -0.93$ [−1.54 to −0.31], $\beta = -0.09$, $p = 0.003$) and risk of obesity (OR = 0.65 [0.43–0.97], $p = 0.034$). |

*Note*: Studies on sleep duration and body weight included are primarily those examining longitudinal associations of sleep duration with weight gain in general adult populations or children/adolescents.
Abbreviations: BF%, relative body fat; BMI, body mass index; CI, confidence interval; OR, odds ratio; VAT, visceral adipose tissue; WASO, wakefulness after sleep onset.

example, it is plausible that increased fluid retention or compartmental shifts could explain this weight gain via alterations in autonomic and renin-angiotensin system activity. Indeed, plasma renin activity and aldosterone oscillate rhythmically during sleep coincident with non-REM and REM periods and changes in vagal tone,[110] and disruption could plausibly promote changes in hydromineral balance. However, current evidence suggests that acute sleep deprivation decreases activated renin, aldosterone, and angiotensin II, which is accompanied by increased natriuresis and osmotic diuresis.[111,112] Alternatively, there is evidence that body fat regulation may be disrupted by periods of sleep restriction. While not examining the influence of sleep restriction on body weight gain, Wang et al. observed lower fat mass loss in a group of individuals undergoing 8-week of hypocaloric weight loss with just 1 h of sleep restriction on 5 nights per week.[113] Covassin et al.[114] reported that 21-day of experimental sleep restriction using a 4-h sleep opportunity promoted the consumption of an additional ~310 kcals per day and an 11% increase in abdominal visceral adiposity and a 0.5 kg increase in body weight when compared to the control 9-h sleep opportunity condition in healthy young adults. Accordingly, it has also been reported that a single night of 4 versus 8 h of sleep resulted in increased pre-prandial hunger and resulted in 22% greater (+559 kcals) ad libitum food intake in men.[115] Similarly, Ness et al. reported reduced satiety in response to a standardised high-fat mixed-meal after a 4-day sleep restriction period compared with a normal sleep control period.[48] Therefore, not only does sleep restriction alter hunger hormone concentrations, but these effects appear to also be born out in actual changes in hunger and satiety levels that decrease the ability to regulate bodyweight. Together, this evidence suggests that sleep restriction may represent an important causal risk factor contributing to body weight dysregulation and increased risk of obesity, particularly by promoting central adiposity. However, additional work is necessary to bolster the strength of this evidence.

## 6 | THE ROLE OF PSYCHOSOCIAL STRESS IN THE ASSOCIATION OF POOR SLEEP WITH CARDIOMETABOLIC DYSFUNCTION

Psychosocial stress is increasingly being recognised as an important determinant of cardiometabolic health. Psychosocial stressors are characterised by both a psychological and social component. Examples include interpersonal stress, harassment, abuse or neglect, lack of access to resources or social support, community-level adversity, and discrimination and systemic racism.[116–120] Acutely, the neural response to psychosocial stress includes activation of the limbic system (e.g., the hippocampus, amygdala, and hypothalamus) and subsequently the hypothalamic-pituitary-adrenal (HPA) and sympathetic-adrenal-medullary (SAM) axes.[121] The acute downstream effects of HPA and SAM axis activation include increased peripheral resistance, parasympathetic withdrawal, increased sympathetic nervous system activity (SNA), increased release of stress hormones such as norepinephrine and cortisol, and immune system activation.[122] These effects act to increase peripheral resistance, cardiac output, heart rate, blood pressure, circulating inflammatory cytokines, and thrombotic factors, as well as to increase the availability of metabolic substrates, including glucose and free fatty acids, by enhancing lipolysis and gluconeogenesis and decreasing insulin sensitivity.[123] Furthermore, acute psychosocial stress exposure appears to alter circulating levels of centrally acting appetite-regulating hormones, including leptin[124,125] and ghrelin.[126–128] While these responses are typically adaptive and transient, they may instead synergistically act to promote cardiometabolic disease when psychosocial stressors are frequent and recurrent.[127,129,130] This hypothesis is supported by several bodies of literature illustrating that chronic psychosocial stress exposure, including exposure to adverse childhood experiences (ACEs) or social or socioeconomic stress, promotes increased lifetime risk of cardiometabolic diseases such as T2D,[131–133] obesity,[134,135] and cardiovascular disease.[119,131,136]

The effects of chronic psychosocial stress exposure on metabolism likely also explain cardiometabolic health disparities, such as racial differences in T2D prevalence. In a recent analysis of biomarker data from 1170 adults (20% Black, 56% women) enrolled in the Midlife in the United States Study, Fuller-Rowell et al. examined whether ACEs and adult psychosocial stress—including discriminatory and socioeconomic stressors—mediated race differences in insulin resistance.[137] Notably, ACEs and adult stress together mediated 65% of the difference in HOMA-IR between Black and White adults in the United States.[137] In a prospective, longitudinal study of 342 Black individuals (59% women) from the southeastern US, Barton et al.[138] assessed childhood socioeconomic status (years living in poverty) using the income-to-needs ratio based on family size at ages 11–18 years and quantified insulin resistance in young adulthood at ages 25, 27, and 29 years using the updated HOMA-IR method. Childhood socioeconomic status predicted insulin resistance in young adulthood, such that every additional year living in poverty in childhood was associated with a 1.04-unit increase in HOMA-IR.[138] Perceived life chances partially mediated this association, suggesting that a more hopeful outlook may provide resilience to the adverse effect of psychosocial stress on glucose metabolism.[138] Together, these data support that a life course psychosocial perspective should be taken to understand and reduce the risk of cardiometabolic disease development.

Notably, via the disruption of stress regulatory systems that also play an important role in the homoeostatic regulation of sleep, psychosocial stress is associated with sleep disturbance. For example, stress promotes activation of the HPA and SAM axes, which may promote heightened arousal and impair sleep (Figure 1). ACEs have recently been linked with reduced medial prefrontal cortex activation, which is an area of the brain important to normal sleep physiology and thought to play a role in initiating slow wave (stage N3) sleep.[139,140] Two recent population studies indicate that there is a dose-response relationship between the degree of exposure to ACEs and sleep disturbance.[141,142] Using self-report sleep duration data from the 2011 Behavioural Risk Factor Surveillance System (BRFSS), Sullivan et al.[141] reported that each ACE exposure is independently

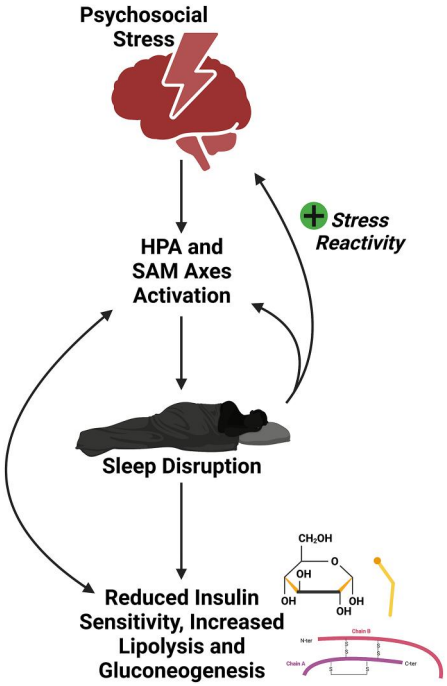


**FIGURE 1** Plausible pathways link psychosocial stress exposure with sleep disruption and altered metabolism. Note that these pathways are likely bidirectional and co-reinforcing. HPA, hypothalamic-pituitary-adrenal; SAM, sympathetic-adrenal medullary. Created using BioRender.com.

associated with a 22% increased risk of short sleep duration in adults (mean age 47 years), and exposure to 5 or more ACEs is associated with a 3.5-fold increase in odds of short sleep duration when compared to individuals with no ACEs.[141] Similarly, a graded-association has been observed between ACE exposure and poor sleep quality among adults aged 20–54 years, such that individuals with 3 or more ACEs have 3.6-fold increased likelihood of reporting poor sleep quality compared to individuals with no ACEs.[142] Notably, this risk persisted with adjustment for employment status, smoking and alcohol use, and recent stressful life events. The relationship also persisted after adjustment for the use of psychotropic drugs such as anti-depressants, anti-anxiety drugs, and sleep aids, although it was attenuated (OR = 2.6 [2.3–3.0]).[142] In support of these findings, Jenkins et al. recently reported that young adult women with a history of moderate-to-severe (4+) exposure to ACEs self-report poorer sleep and display reduced circadian variability in salivary cortisol.[143] However, it should be noted that all of these findings rely on self-reported sleep measures that may be vulnerable to bias, and studies are needed to confirm and better understand the sleep disturbances experienced by individuals with ACE exposure. Using a unique, within person prospective study design, Fuller-Rowell et al.[144] recently reported that on days when African American college students experienced greater discrimination, they also had poorer sleep quality. Moreover, internalised racism, or the degree to which African American students internalised negative racial stereotypes, moderated this relationship such that those with greater internalisation experienced greater sleep disruption.[144] These findings show that psychosocial stressors such as childhood adversities and racism play a causal role in adult sleep disturbance.

Together, this body of evidence suggests that disrupted sleep is a downstream effect of chronic psychosocial stress that could plausibly mediate or moderate the association of psychosocial stress with cardiometabolic risk. However, both prospective cohort and experimental studies will be necessary to carefully untangle the role of sleep in this association. Given the bidirectional relationships between sleep and stress[145,146] and because peripheral metabolic signals may also influence biological stress responses,[147,148] it is also possible that intervening to improve sleep could reduce the physiological stress response to psychosocial stress[147,149,150] and thus reduce cardiometabolic risk. Again, longer-term experimental studies will be necessary to test this hypothesis. Finally, it is evident that chronic psychosocial stress does not influence health outcomes equally across individuals. High levels of social and emotional support, access to social resources, greater psychological coping (e.g., control, self-efficacy, resilience, hope) and lower negative effect have all been suggested to provide a measure of resilience to the effects of psychosocial stress.[120,151] Work will also be needed to understand how these factors moderate the association of psychosocial stress with disrupted sleep and cardiometabolic health.

## 7 | THE ROLE OF PHYSICAL EXERCISE IN THE ASSOCIATION OF POOR SLEEP WITH CARDIOMETABOLIC DYSFUNCTION

Exercise is a primary zeitgeber, or an external stimulus that regulates circadian rhythms by regulating molecular clocks.[152,153] Because circadian disruption is one potential consequence of disrupted sleep, the implementation of exercise may theoretically ameliorate the negative impacts of sleep disruption. Although research in this area is still in relative infancy, the current evidence is promising. Saner et al. conducted a study in 2021 showing that the incorporation of 3 high intensity interval training (HIIT) sessions during a 5-day period of sleep restriction (4-h TIB) mitigate the negative effects that sleep loss has on circadian rhythmicity, glucose tolerance, skeletal muscle mitochondrial function, and sarcoplasmic protein synthesis in young healthy men aged 18–40 years.[154] Similarly, de Souza et al. reported that 6 HIIT sessions during the 2 weeks prior to a 24-h sleep restriction period was an effective strategy to reduce the basal and postprandial glycaemic and insulinemic responses, and basal free fatty acid levels induced by 24 h of sleep deprivation in healthy young adult men.[155] Similarly, Sweeney et al. showed that exercise mitigated the late-phase insulin response during OGTT following 4-h TIB sleep restriction when compared to sleep restriction alone in healthy men.[156] Porter et al. assessed the effects of 5 nights of sleep restriction (6-h vs. 8-h TIB) with and without daily exercise (45 min at 65% $VO_2$max) in individuals with obesity (7 men, 6 women).[157] Sleep restriction increased the peak glucose response but not 3-h glucose AUC during a meal tolerance test, elevated fasting NEFA, and increased fat oxidation and perceived stress. However, exercise did

not normalise any of these outcomes. Thus, Porter et al. concluded that exercise is not an optimal strategy for ameliorating the negative effects of sleep restriction in individuals with obesity.[157] Of note, this was the first sleep restriction and exercise study completed in individuals with obesity, it appears to be the only one to date to also include women. Premenopausal women have previously been shown to be protected against other insulin resistance-inducing behaviours, namely consuming sugar sweetened beverages and reducing the daily physical activity over 10 days, compared to men.[158] Thus, future studies should specifically explore whether there are sex differences in the metabolic responses to sleep restriction and sleep restriction with exercise. It is also plausible that an un-measured attribute strongly related to obesity such as low cardiorespiratory fitness may explain the inability of exercise to rescue the cardiometabolic impairments caused by sleep restriction in individuals with obesity. In partial support of this hypothesis, there is evidence that habitual moderate intensity physical activity has a strong effect on the relationship between sleep quality and insulin concentrations, whereas light intensity activity does not.[159] Similarly, a very recent study indicates that performing a high volume of physical activity attenuates associations of short sleep duration with all causes and CVD mortality compared with performing low volumes of physical activity.[160] It can be hypothesised that these individuals, that is, those performing higher-intensity physical activity, would have greater cardiorespiratory fitness. Thus, it is plausible that cardiorespiratory fitness may moderate the adverse cardiometabolic effects of impaired sleep, but to our knowledge, there is no direct evidence that this is the case. Thus, future experimental studies will be needed to understand if and how fitness may interact with sleep to promote cardiometabolic health.

Lin et al. posited that skeletal muscle transcriptomic alterations may contribute to improvements in insulin sensitivity commonly observed in response to exercise.[161–164] Sleep deprivation alters the skeletal muscle transcriptome, increasing mRNA expression of inflammatory pathways, decreasing expression of oxidative phosphorylation and muscle protein synthesis pathways, and altering transcription of circadian clock genes.[165] As exercise alters these same pathways in opposite directions, Lin et al. hypothesised that exercise may be able to mitigate the adverse alterations in these transcriptional pathways caused by sleep restriction. To test their hypothesis, 20 young men completed one of three separate 5-night conditions: control (8-h TIB, $n = 6$), sleep restriction (4-h TIB $n = 7$), or sleep restriction + exercise (4-h TIB with 3 HIIT sessions, $n = 7$). In partial accordance with their hypothesis, gene set enrichment analyses revealed increased enrichment of immune response and inflammatory pathways, and decreased the enrichment of gene pathways associated with mitochondrial function following sleep restriction, but exercise counteracted this pattern of gene set enrichment.[166] It should be noted that the degree of enrichment was much smaller than in prior studies that used total sleep deprivation, suggesting that moderate sleep restriction is not as detrimental as total sleep deprivation. It should also be noted that these findings were observed alongside reduced skeletal muscle mitochondrial function and impaired glucose tolerance following sleep restriction that were also counteracted by exercise.[154] A very recent study using accelerometer data from the UK Biobank provides additional evidence supporting the protective effect of physical activity for counteracting the negative effects of disturbed sleep.[160] Liang et al.[160] demonstrated that, among ~92,000 middle-aged and older adults (mean age 62 ± 8 years), meeting the recommended weekly dose of moderate-to-vigorous physical activity (MVPA) reduced the incidence of all-cause and CVD-related mortality by 2.3–2.5-fold among those with short sleep duration (<6 h/day) compared to those who did not meet MVPA guidelines. Thus, these findings support that exercise (or physical activity) may be able to offset the metabolic impairments induced by short-term sleep restriction, but additional work is necessary to understand if these effects extend to populations other than young healthy men.

## 8 | CONCLUSIONS

Overall, sleep should be considered an important modifiable risk factor whenever seeking to improve metabolic health in all populations, with both sleep duration and sleep quality considered. Collectively, the body of evidence demonstrates that short sleep duration and poor sleep quality are associated with, and causally promote, decreased peripheral insulin sensitivity. Evidence regarding the impact of sleep disruption on lipid metabolism is not as strong but also suggests that short sleep durations may causally promote impairments in lipid metabolism, although more work is needed to understand the effects of sleep quality (i.e., SWS suppression). Finally, there is evidence to suggest that sleep disruption alters leptin and ghrelin metabolism, hunger and satiety, and thus impairs the ability to regulate bodyweight. Notably, most studies examining the association of sleep disruption with bodyweight have done so using self-reported sleep with BMI as the primary endpoint. However, evidence exists to suggest that sleep disruption could alter body composition and perhaps where body fat is deposited (i.e., viscerally). Future studies should consider this and use a more specific endpoint (i.e., waist circumference) to better define the cardiometabolic impacts of long-term sleep disruption. Additional work is needed to better understand if there are sex-specific metabolic effects of sleep disruption, especially in experimental restriction studies, given that the vast majority of evidence currently exists using male-only subject populations. As we have shown, psychosocial stress represents an important and overlooked risk factor for cardiometabolic risk and poor sleep that can also explain extant racial disparities in cardiometabolic and sleep health. However, additional work is needed to carefully untangle the interplay between psychosocial stress, sleep disruption, and cardiometabolic risk. Finally, the assumption of reverse causality represents a major current weakness in the sleep and cardiometabolic health literature. That is, experimental evidence shows that disrupting sleep causes impairments to cardiometabolic health. However, very few data exist to show that improving sleep (duration or quality) in individuals with disrupted sleep causes

improvements in cardiometabolic health; existing studies are limited by small sample sizes and inconsistent outcome assessments.[167] Therefore, larger, sufficiently powered randomised controlled trials will be necessary to advance our understanding of the benefits of sleep intervention(s) on cardiometabolic health.

## AUTHOR CONTRIBUTIONS

Emily M. Rogers and Nathaniel D. M. Jenkins completed the original draft and all authors (Emily M. Rogers, Nile F. Banks, Nathaniel D. M. Jenkins) contributed to reviewing and editing. All authors have read and approved the final submitted manuscript. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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## CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

## DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

## ETHICS STATEMENT

None.

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## PEER REVIEW

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