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CLINICAL REVIEW

Effects of sleep restriction on metabolism-related parameters in healthy adults: A comprehensive review and meta-analysis of randomized controlled trials

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SUMMARY

This review aimed to provide a comprehensive examination of the effect of sleep restriction on metabolism-related parameters by synthesizing the emerging, best evidence. A systematic search was conducted in six electronic databases from inception to January 2018. We identified 41 randomized controlled trials using sleep restriction intervention. The outcomes included: subjective hunger, appetite-regulating hormones, changes in brain activity, energy intake and expenditure, weight change, insulin sensitivity or resistance. Sleep restriction resulted in a significant increase in subjective hunger on a 100 mm scale (mean difference = 13.4, $p < 0.001$). Participants consumed 252.8 more kcal/d ($p = 0.011$) under sleep restriction than under normal sleep. Partial sleep restriction resulted in a 0.34 kg weight gain ($p = 0.003$). Sleep restriction also decreased insulin sensitivity (standardized mean difference = -0.70 , $p < 0.01$). Significant changes in brain activity in response to food stimuli were observed under sleep restriction, particularly regions related to cognitive control and reward. Overall, we did not find strong evidence supporting the significant impact of sleep restriction on mean leptin or ghrelin levels or energy expenditure. Findings from this review enhanced our knowledge about the detrimental effects of sleep restriction on metabolism and provided novel directions in preventing metabolic diseases including obesity and diabetes.

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Introduction

Adequate sleep is essential for the physiological, psychological, and cognitive wellbeing of an individual [1]. Adults are recommended to have at least 7h sleep [2]. Nevertheless, sleep restriction is becoming a prevalent public health issue. Modern Americans are

sleep deprived of about 1.5h sleep per night [3]. Large cohort studies conducted in the 1990s and 2010s suggested that 41.1% [4] and 64.3% [5] of adults reported less than 7h nocturnal sleep, respectively. Over the same period, metabolic diseases are also becoming more prevalent. More than one-third of U.S. adults have obesity [6], and 9.4% of adults have diabetes [7]. An increasing body of literature has suggested that sleep restriction may be a risk factor for these metabolic diseases [8]. A recent meta-analysis of prospective cohort studies found that short sleep was associated with an increased risk for obesity [relative risk = 1.38; 95% Confidence Interval (CI), 1.25–1.53] and diabetes (relative risk = 1.37; 95% CI, 1.22–1.53) [9].

Sleep restriction may increase the risk of metabolic diseases through multiple behavioral and physiological pathways [10]. Behaviorally, sleep restriction has been associated with increased

Abbreviations: CI, confidence interval; MD, mean difference; PRISMA, preferred reporting items for systematic reviews and meta-analysis; PSR, partial sleep restriction; RCT, randomized controlled trial; SD, standard deviation; SMD, standardized mean difference; TSD, total sleep deprivation.

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feelings of hunger [11] and food intake [12]. Sleep restriction could promote reward-driven eating behavior that can lead to overeating [13]. Sleep restriction may also lead to impaired executive functions, increased reward sensitivity, emotional stress, and impulsivity. Those changes could contribute to increased food intake [14,15]. Physiologically, sleep restriction has resulted in changes in appetite-regulating hormones (e.g., leptin, ghrelin, and endocannabinoids) [16,17] and glucose metabolism [18].

An increasing number of experimental studies has examined the impact of sleep restriction on various metabolism-related parameters. Al Khatib and colleagues [19] meta-analyzed seven randomized controlled trials (RCTs) and found that sleep restriction resulted in a 364 kcal increase in energy intake but no significant impact on energy expenditure. Similarly, Capers et al. [12] meta-analyzed four RCTs and find an insignificant effect on energy expenditure. Capers and colleagues also examined the impact of sleep restriction on other parameters including appetite-regulating hormones and weight but found insignificant effects. These negative findings may be due to the limited number of studies. Additionally, the impact of sleep restriction on glucose metabolism remains to be examined. Since the publication of the previous reviews, more clinical trials have been conducted [17,18,20–30]. There is a need to review the emerging, best evidence and provide an up-to-date, comprehensive examination of the impact of sleep restriction on metabolism-related factors. An updated review could provide stronger evidence. Therefore, the aim of this study was to review RCTs examining the effect of sleep restriction on various metabolism-related parameters. Findings from this review will provide insights and new directions in preventing metabolic diseases, such as obesity and diabetes.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol [31] was developed and registered in the international prospective register of systematic reviews (registration# 42018087646). This review was reported in accordance with the PRISMA guideline [32].

Search strategy

A systematic search was conducted in PubMed, Embase, Web of Science, CINAHL, PsycInfo, and Cochrane from inception to January 2018. No language restriction was applied during the searching process. Combinations of the following search terms were used: 1) sleep; 2) eating, energy, food, appetite, leptin, ghrelin, endocannabinoid, calori*, insulin, glucose, brain, and weight. The bibliographies of relevant studies were reviewed to identify additional studies. ClinicalTrial.gov was searched for potential completed trials. In this review, we did not search for grey literature as it has been reported representing a very small percentage of included studies and rarely impacting the results [33].

The **inclusion criteria** were: 1) RCTs with experimental sleep restriction; 2) Conducted in healthy adults (aged 18 years or over); and 3) At least one of the outcomes must be measured: hunger, appetite-relating hormones (e.g., leptin, ghrelin or endocannabinoid), caloric intake, energy expenditure, weight, or changes in brain activity in response to food stimuli, insulin sensitivity or resistance. The **exclusion criteria** were 1) Studies conducted in people with a diagnosis of chronic disease (e.g., diabetes, metabolic syndrome, or cardiovascular disease); psychiatric disorder (e.g., depression or anxiety); sleep disorder (e.g., insomnia, sleep apnea, or narcolepsy); eating disorder; 2) Sleep intervention not appropriate (e.g., combined interventions where the effects of sleep restriction cannot be separated from other components or sleep

intervention was not sleep restriction); 3) Studies conducted at home where compliance with study protocol cannot be closely monitored; 4) Variables of interest not measured or relationships of interest not reported; 5) Duplicated report; 6) Other types of paper (e.g., review, abstract, secondary analysis, or non-English paper).

The PRISMA flowchart [32] was used to guide the study selection. Initial screening was conducted by one reviewer (BZ) based on the title/abstract. Full-text of potential studies was independently reviewed by two reviewers (BZ and CS) based on the inclusion and exclusion criteria to determine the final inclusion. If more than one paper was developed from the same trial, only the one with the most detailed information was included in the final analysis. However, if the papers provided different information, both were included. Disagreements were solved by a third reviewer (SR).

Data extraction

A data extraction matrix was developed to tabulate the main information from each study. Extracted data included study characteristics (e.g., design and sample) and participant characteristics (e.g., age and gender). Data were independently extracted by two reviewers (BZ and CS). Discrepancies were resolved by a third reviewer (XZ).

Variabilities in the timing and frequencies of outcome measures were anticipated among different studies. For clarity and consistency, we focused on study outcomes that were collected closest to the end of the intervention. Data were extracted from the graphs if not presented in the text using WebPlotDigitizer (V4.1) [34]. If data cannot be extracted from the paper or calculated from available information, we contacted the authors via email.

Outcome measures

The outcomes included various metabolism-related parameters. Specifically, subjective hunger, appetite-regulating hormones (e.g., leptin, ghrelin, or endocannabinoids), energy intake and expenditure, weight changes, insulin sensitivity or resistance, and changes in brain activity in response to food stimuli were included.

Risk of bias assessment

Following the Cochrane risk of bias tool [35], we assessed each study for five areas: selection, performance, detection, attrition, and reporting bias. We also evaluated additional five areas related to crossover design following the Cochrane Handbook [36]. Risk of bias was assessed by two reviewers (BZ and CS). Discrepancies were resolved by a third reviewer (XZ).

Data analysis

Stata 13.0 (StataCorp LP, College Station, Texas) was used for statistical analyses. Mean and SD (standard deviation) or standard error of the mean was extracted. SD was calculated from available information if not reported. For crossover RCTs, when the data required to include a paired analysis were not reported, the sum score was analyzed as if the trial used a parallel-group design. This approach was conservative, in that studies were under-weighted rather than over-weighted [36]. For outcomes reported in two or more studies, the pooled mean difference (MD) with the 95% CI was calculated for each outcome, using the inverse variance method. Forest plot was used to present the results of individual studies and the pooled MD. MD was calculated when the outcome was measured using the same scale or unit. Otherwise, the standardized mean difference (SMD) was calculated by the method of Hedge's *g*, which can adjust for the overestimation of SMD in studies with

small samples [37]. In terms of the interpretation of SMD, 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 a large effect [38]. Heterogeneity among studies was examined by I^2 value ($I^2 > 50\%$ considered significant) [39]. A fixed-effect model was used if no significant heterogeneity was detected and a random-effect model was used otherwise [40]. Statistical significance was set at $p < 0.05$. We used qualitative, narrative review if the data could not be pooled.

Subgroup analysis

Subgroup analyses were conducted based on the type of intervention: total sleep deprivation (TSD) where participants were completely deprived of any sleep or partial sleep restriction (PSR) where participants' sleep was reduced relative to a basal amount. Additional subgroup analysis was conducted based on sex and the methods of assessment (wherever applicable).

Sensitivity analysis and publication bias

Sensitivity analysis was performed using the leave-one-out approach to test the robustness of the pooled estimates. The funnel plot was used to examine publication bias. The degree of funnel plot asymmetry was visually inspected, and asymmetry of the plot suggests publication bias. Publication bias was also evaluated using Egger's test [41].

Results

The results of the literature search are shown in Fig. 1. The initial search resulted in 3449 records and 41 were included in this review.

Participant and study characteristics

Participant and study characteristics are presented in Table 1. Individual sample size ranged from 9 [42] to 225 [43]. Mean age was between 20.5 (SD 1.8) [44] and 44.6 (14.7) [42] years. Most of the studies screened for sleep apnea using polysomnography, except in four studies [16,45–47] where the absence of sleep disturbance was confirmed by sleep diary or actigraphy. Seven

studies used a [26,28,43,45,48–50] parallel-group design, among which two [43,50] were cluster RCT. The remaining studies used a crossover design. Duration of the intervention ranged from one to 14 days. Most of the studies used PSR ($n = 31$) where the time in bed was restricted to between 3.5h and 5.5h. In the control condition, the prescribed time in bed was between 7h and 10h.

Only one study [46] presented separate mean \pm SD for both groups (those receiving PSR first and those receiving normal sleep first) under different conditions (PSR or normal sleep). However, no p values or CI were available for the use of paired analysis. Therefore, data from all studies were analyzed as if the trial used a parallel-group design. Table S2 shows the effect size for each outcome.

Effect of sleep restriction on subjective hunger

Subjective hunger was measured in 18 studies, 13 of which used the visual analog (0–100 mm) (Table 1). Findings from each study are presented in Table S1. Fifteen studies were included in the meta-analysis. Overall, sleep restriction resulted in a significant increase in hunger level (mm): MD = 13.4; 95%CI, 7.3–19.6; $p < 0.001$ (Table S2). Both TSD and PSR had a significant effect on subjective hunger (Fig. 2). The MD for TSD and PSR were 22.8 (95% CI, 9.7–35.9; $p = 0.001$) and 7.5 (95%CI, 0.9–14.1; $p = 0.027$), respectively.

Effect of sleep restriction on appetite-regulating hormones

Leptin and ghrelin

Table 1 shows the measurement of appetite-regulating hormones. Most of the studies collected one fasting sample and only a few obtained hourly samples. The fasting value or mean levels (typically 24h mean) were meta-analyzed. Findings from each study are presented in Table S1. A total of 13 and 11 studies were included in the meta-analysis for leptin and ghrelin, respectively. Neither fasting nor mean level of leptin differed between conditions (Fig. S1a). Subgroup analyses were conducted for ghrelin based on the type of sleep intervention (PSR vs. TSD) and the measurements of ghrelin (fasting vs. mean) (Fig. S1b and Fig. S1c). No significant difference was observed. There was no sex difference in the impact of sleep restriction on leptin (Fig. S1d) or ghrelin (Fig. S1e). The pooled MD for leptin was 0.13 ng/ml (95% CI, -0.45–0.71; $p = 0.663$); the pooled MD for ghrelin was 20.5 pg/ml (95%CI, -24.9–65.8; $p = 0.376$) (Table S2).

Nine studies conducted profile analyses of ghrelin using hourly samples. Findings from these studies were mixed and thus were summarized. In three studies, the peak of ghrelin typically occurred around midnight and then the concentration gradually decreased until the next early morning under both sleep conditions [23,25,51]. However, in Dzaja et al. study [52], ghrelin only showed this pattern during normal sleep. In comparison, during TSD, ghrelin concentration rose steadily to a plateau in the morning and declined after breakfast. The effect of sleep restriction on ghrelin levels in response to meals has been conflicting. In one study, postprandial ghrelin concentrations and post-meal nadir levels were elevated during PSR as compared with normal sleep [25]. While in another study, ghrelin showed postprandial dips and rebounds during PSR relative to normal sleep [23]. In addition, two studies found that higher nocturnal ghrelin levels occurred during PSR as compared with normal sleep [23,25]. In contrast, another study reported decreased ghrelin levels during the first half the night and an opposing pattern during the second half of the night under TSD as compared with under normal sleep [51]. In the other four studies, no significant effect on hourly ghrelin was observed under PSR [53–56].

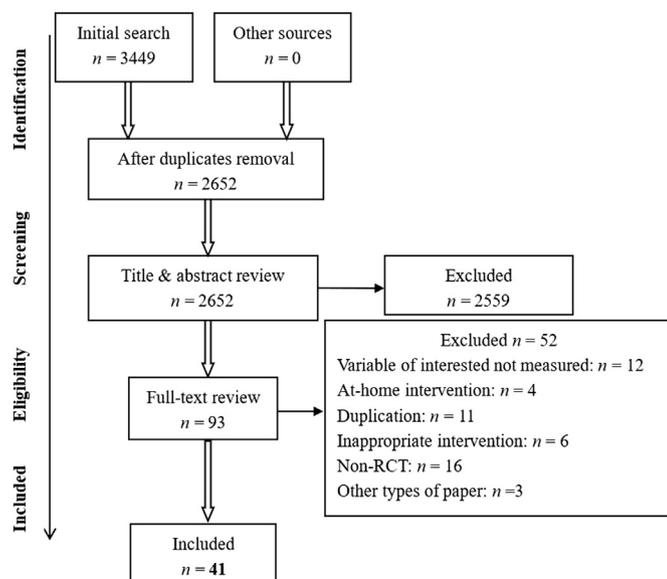


Fig. 1. PRISMA flowchart for study selection.

Table 1
Study and participant characteristics (n = 41).

Author (year)	Participants		Intervention: Duration (washout), sleep condition	Outcome measures				
	N; Male (%)	Age (yrs.); BMI(kg/m ²)		Hunger	Appetite-relating hormones	Insulin sensitivity or resistance	Caloric intake; energy expenditure	Others
Bell et al. (2013) [100]	11; 54.5%	26 ± 3; 23.5 ± 2.3	8d (>3wk) C: 8.5h; E: 5.5h ^d					Weight
Benedict et al. (2011) [51]	14; 100%	22.6 ± 3.0; 23.9 ± 1.9	1d (>4wk) C: 8h; E: TSD	Morning hunger rating ^b	Leptin and ghrelin (24 profile, 15 samples)		^c buffet (late-afternoon); RMR from indirect calorimetry	
Benedict et al. (2012) [60]	12; 100%	23.3 ± 2.1; 22.5 ± 1.7	1d (>2wk) C: 7h; E: TSD	Morning hunger rating (0–9)				fMRI
Brondel et al. (2010) [46]	12; 100%	22.0 ± 3.0; 22.3 ± 1.8	2d (>5d) C: 8h; E: 4h ^d	Morning hunger rating ^b			^c eating (all day); TEE from accelerometer	
Broussard et al. (2015) [30]	19; 100%	23.5 ± 3.0; 23.1 ± 1.7	4d (>4wk) C: 8.5h; E: 4.5h ^d			IVGTT		
Broussard et al. (2016) [25]	19; 100%	23.5 ± 3.0; 23.1 ± 1.7	4d (>4wk) C: 8.5h; E: 4.5h ^d		Leptin and ghrelin (24h profile, sampled every 15–30 min)		^c eating (all day)	Weight
Calvin et al. (2013) [49]	17; 64.7%	24.1 ± 4.5; 22.9 ± 1.8	8d (N/A) C: usual sleep; E: 2/3 usual sleep ^e		Leptin and ghrelin (one fasting sample)		^c eating (all day)	Weight
Cedernaes et al. (2014) [62]	14; 100%	23.3 ± 1.9; 23.4 ± 1.9	1d (>4wk) C: 8.5h; E: TSD	Morning hunger rating ^b				Cognitive control task
Cedernaes & Fanelli et al. (2016) [17]	16; 100%	22.9 ± 2.8; 23.9 ± 2.0	3d (>5wk) C: 8.5h; E: 4:25h ^e	Hunger rating ^b , multiple times	2AG			
Cedernaes & Lampola et al. (2016) [24]	16; 100%	22.9 ± 2.8; 22.9 ± 2.0	3d (>5wk) C: 8.5h; E: 4:25h ^e			HOMA-IR		
Chapman et al. (2013) [57]	14; 100%	23.0 ± 3.0; 23.4 ± 1.9	1d (>4wk) C: 8h; E: TSD				Food purchase	
Donga et al. (2010) [42]	9; 55.6%	44.6 ± 14.7; 23.8 ± 2.4	1d (>3wk) C: 8.5h; E: 4h ^d			Hyperinsulinemic-euglycemic clamp		
Dzaja et al. (2004) [52]	9; 100%	28.0 ± 3.1; 24.0 ± 2.9	1d (>2wk) C: 8h; E: TSD		Ghrelin (24h profile, sampled every 1h)			
Eckel et al. (2015) [29]	16; 50%	22.4 ± 4.8; 22.9 ± 2.4	5d (none) C: 9h; E: 5h ^d			IVGTT		
Fang et al. (2015) [28]	46; 50%	34.7 ± 7.9; 24.8 ± 2.8	1d (N/A) C: 8h; E: TSD				^c eating (all day)	fMRI
Gonzalez-Ortiz et al. (2000) [45]	28; 50%	21.0 ± 2.1; 22.1 ± 1.3	1d (N/A) C: Normal; E: TSD			Insulin suppression test		
Greer et al. (2013) [44]	23; 43.5%	20.5 ± 1.8; 23.0 ± 1.8	1d (>7d) C: 8.2h; E: TSD	Hunger rating ^b				fMRI
Hanlon et al. (2016) [23]	14; 78.6%	23.4 ± 3.0; 23.9 ± 2.6	4d (>4wk) C: 8.5h; E: 4.5h ^d	Hunger rating ^b , multiple times	Leptin and ghrelin (24h profile, sampled every 1h) 2AG		^c buffet (lunch and dinner)	Weight
Hart et al. (2015) [27]	12; 0%	41.7 ± 10.3; 31.0 ± 4.2	2d (>7d) C: 9h; E: 5h ^e	Hunger rating ^b , multiple times	Leptin and ghrelin (one fasting sample)	HOMA-IR	^c buffet (lunch)	
Hibi et al. (2017) [21]	9; 100%	23.0 ± 2.0; 22.2 ± 3.0	3d (>2wk) C: 7h; E: 3.5h ^e	Hunger rating ^b , multiple times	Leptin (one fasting sample)		TEE from indirect calorimetry	
Hogenkamp et al. (2013) [58]	16; 100%	23.6 ± 2.4; 23.0 ± 3.6	1d (>4wk) C: 8h; E: TSD	Hunger rating ^b , multiple times	Ghrelin (one fasting sample)		Portion size task (food choice)	
Markwald et al. (2013) [54]	16; 50%	22.4 ± 4.8; 22.9 ± 2.4	5d (none) C: 9h; E: 5h ^d	Hunger rating ^b , multiple times	Leptin and ghrelin (24h profile, sampled every 1h)		TEE from whole room calorimetry	Weight
McNeil et al. (2016) [22]	18; 66.7%	23.0 ± 4.0; 22.7 ± 2.7	1d (>7d) C: Normal; E:50% restriction ^f				^c eating (all day); TEE from accelerometer	Weight

(continued on next page)

Table 1 (continued)

Author (year)	Participants		Intervention: Duration (washout), sleep condition	Outcome measures				
	N; Male (%)	Age (yrs.); BMI(kg/m ²)		Hunger	Appetite-relating hormones	Insulin sensitivity or resistance	Caloric intake; energy expenditure	Others
McNeil et al. (2017) [20]	18; 66.7%	23.0 ± 4.0; 22.7 ± 2.7	1d (>7d) C: Normal; E:50% restriction ^f	Hunger rating ^b , fasting and post-meal			^c buffet (lunch)	
Nedeltcheva & Kessler et al. (2009) [101]	11; 54.5%	39.0 ± 5.0; 25.5 ± 1.5	14d (>3mo) C: 8.5h; E: 5.5h ^d			IVGTT		
Nedeltcheva & Kilkus et al. (2009) [55]	11; 54.5%	39.0 ± 5.0; 25.5 ± 1.5	14d (>3mo) C: 8.5h; E: 5.5h ^d		Leptin and ghrelin (24h profile, sampled every 30min)		^c eating (all day); TEE and RMR from indirect calorimetry	Weight
Rao et al. (2015) [18]	14; 57.1%	27 ± 5; 24.1 ± 4.1	5d (4–10wk) C: 8h; E: 4h ^d			Hyperinsulinemic- euglycemic clamp	RMR from indirect calorimetry	
Schmid et al. (2007) [102]	10; 100%	25.3 ± 4.4; 23.8 ± 1.6	1day (>2wk) C: 7h; E: TSD	Hunger rating (0–9), multiple times				
Schmid et al. (2008) [65]	9; 100%	24.2 ± 3.0, 23.8 ± 1.8	1d (>2wk) C: 7h; E: 4.5h ^f	Morning hunger rating (0–9)	Leptin and ghrelin (average of two fasting samples collected at 7am and 7:30am)			
Schmid & Jauch-Chara et al. (2009) [64]	10; 100%	25.3 ± 4.4; 23.8 ± 1.6	1d (>2wk) C: 7h; E: 4.5h ^f			HOMA-IR		
Schmid & Hallschmid et al. (2009) [53]	15; 100%	22.9 ± 1.2; 27.1 ± 5.0	2d (>6wk) C: 8h; E: 4h ^d	Hunger rating (0–9), multiple times	Leptin and ghrelin (15h profile, sampled every 1h)		^c eating (all day)	
Schmid et al. (2011) [63]	15; 100%	22.9 ± 1.2; 27.1 ± 5.0	2d (>6wk) C: 8h; E: 4h ^d			Glucose metabolism in response to breakfast		
Shechter et al. (2014) [47]	10; 0%	28.0 ± 7.3, 26.0 ± 1.5	3d (4wk) C: 8h; E: 4h ^d				RMR from indirect calorimetry	
Simpson et al. (2010) ^d [50]	145; 52.2%	30.4; 24.7	5d (N/A) C: 10h; E: 4h ^e		Leptin (one fasting sample)			
Spaeth et al. (2013) ^a [43]	225; 55%	31.3 ± 7.9; 24.8 ± 3.3	5d (N/A) C: 10h; E: 4h ^e				^c eating (all day)	Weight
Spaeth et al. (2015) [26]	47; 55.6%	33.8 ± 9.2; 24.8 ± 3.1	5d (N/A) C: 10h; E: 4h ^e				^c eating (all day); RMR from indirect calorimetry	Weight
Spiegel et al. (2004) [16]	12; 100%	22.0 ± 2.0; 23.6 ± 2.0	2d (>6wk) C: 10h; E: 4h ^d	Hunger rating ^b , multiple times	Leptin and ghrelin (12h profile, sampled every 1h)			
St-Onge et al. (2011) [59]	27; 51.9%	35.3 ± 5.2; 23.6 ± 1.0	5d (>3wk) C: 9h; E: 4h ^d	Hunger rating ^b			^c eating (all day); TEE by doubly labeled water and RMR by indirect calorimetry	
St-Onge & McReynolds et al. (2012) [61]	26; 53.8%	35.1 ± 5.1; 23.6 ± 1.3	5d (>3wk) C: 9h; E: 4h ^d					fMRI
St-Onge & O'Keefe et al. (2012) [56]	27; 51.9%	35.3 ± 5.2; 23.6 ± 1.0	5d (>3wk) C: 9h; E: 4h ^d		Leptin and ghrelin (5 daily fasting samples and 24 profile, 15 samples)	HOMA-IR		Weight
van Leeuwen et al. (2010) [48]	23; 100%	23.1 ± 2.5; 23.3 ± 2.7	5d (N/A) C: 8h; E: 4h ^e	Morning hunger rating (1–5)	Leptin (one fasting sample)	Insulin/glucose ratio		

Notes. C, control condition; E: experimental condition; HOMA-IR, homeostatic model assessment-insulin resistance; N/A, not applicable; IVGTT, intravenous glucose tolerance test; RMR, resting metabolic rate; TEE, total energy expenditure; TSD; total sleep deprivation; 2-AG, 2-arachidonoylglycerol.

^a Cluster randomization was used, one cluster consisted of 4–5 participants.

^b 0–100 mm visual analog was used.

^c *ad libitum* eating.

^d Sleep restriction was achieved by moving the bedtime and wake time proportionally closer together.

^e Sleep restriction was achieved by delaying the bedtime without changing the wake time.

^f Sleep restriction was achieved by advancing the wake time without changing the bedtime.

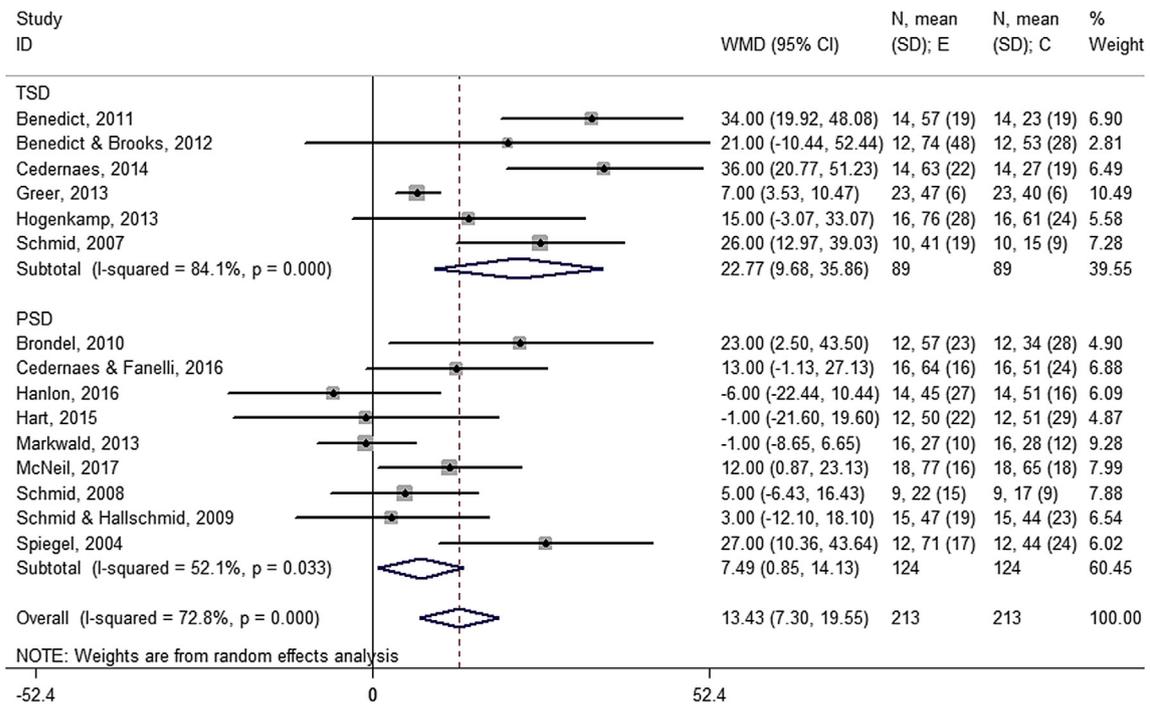


Fig. 2. Forest plots for subjective hunger level (mm): subgroup analysis based on the type of sleep intervention ($n = 15$). Notes. TSD, total sleep deprivation: MD = 22.8, $z = 3.41$, $p = 0.001$. PSR, partial sleep restriction: MD = 7.5, $z = 2.21$, $p = 0.027$. Overall: MD = 13.4, $z = 4.3$, $p < 0.001$.

Similarly, eight studies conducted profile analyses of leptin using hourly samples. Most of the studies did not find a significant effect of sleep restriction on hourly profiles of leptin [25,51,53–56]. Only two studies, a blunted amplitude [23] and consistent reductions in daytime leptin were reported [16]. Two studies [16,23] reported an increased ratio of ghrelin to leptin under PSR.

Endocannabinoids (2-arachidonoylglycerol: 2AG)

Two studies evaluated the effect of sleep restriction on 2AG. One study [17] found that PSR resulted in a higher level of 2AG. In another study [23], although the 24h mean level of 2AG did not differ between conditions, PSR resulted in a higher amplitude and peak.

Effect of sleep restriction on energy balance and weight

Caloric intake

A total of 17 studies examined the effect of sleep restriction on caloric intake (Table 1). All studies measured actual *ad libitum* caloric intake, except in two where indirect caloric intake was measured during food purchase [57] or portion size tasks [58]. Findings from these two studies were excluded from the analysis and 11 studies were included in the meta-analysis. Separate analyses were performed for studies that measured caloric intake over one meal ($n = 3$) and over a day ($n = 8$, all used PSR). Findings from each study are presented in Table S1. Based on Fig. 3 and Table S2, participants under sleep restriction consumed 95.9 (95%CI, -299.8–108.0; $p = 0.36$) less kcal than under normal sleep over one meal. In contrast, participants under PSR consumed 252.8 (95%CI, 59.1–446.5; $p = 0.011$) more kcal than under normal sleep over a day.

Several studies examined the impact of sleep restriction on the macronutrient breakdown of the food, with mixed findings. Sleep restriction resulted in higher proportions of carbohydrates consumption in two studies [25,54], fat consumption in three studies [46,53,59], and protein consumption in one study [27]. Sleep restriction did not exert significant impacts on macronutrient consumption in other studies [20,22,23,26,51,55]. Interestingly,

sleep restriction induced more caloric intake from snacks with an increased carbohydrates consumption [23,25,54,55].

Energy expenditure

Six studies assessed resting metabolic rate using indirect calorimetry (Table 1). Based on the forest plot (Fig. S2) and Table S2, there was no significant effect of sleep restriction on resting metabolic rate (MD = -27.3 kcal/d; 95%CI, -83.4–28.9; $p = 0.341$).

Six studies assessed total energy expenditure using the accelerometer, calorimetry, or doubly labeled water. Due to the large variability in the assessment methods, findings were not meta-analyzed. None of the studies reported a significant effect of sleep restriction on total energy expenditure (Table S1).

Weight

Ten studies (all used PSR) evaluated the effect of sleep restriction on weight. The duration of the intervention ranged from 1 to 14 days, and six studies used a 4d or 5d intervention. Weight change in one study [49] was expressed as median and thus was excluded from the meta-analysis. Weight change from baseline to post-intervention was not reported in two studies [22,25], and therefore the post-intervention value was used. Based on Table S2 and Fig. 4, PSR resulted in a significant weight gain (MD = 0.34 kg; 95% CI, 0.11–0.57; $p = 0.003$).

Effect of sleep restriction on changes in brain activity in response to food stimuli

Five studies assessed the effect of sleep restriction on changes in brain activity in response to food stimuli (Table S1). TSD was associated with greater activation in the right anterior cingulate cortex [60]. After TSD, participants exhibited increased brain connectivity in the salience network, which was involved in reward [28]. The overall neuronal activity in response to food stimuli was greater after restricted sleep than after habitual sleep, and a relative increase in brain activity in areas associated with reward was also

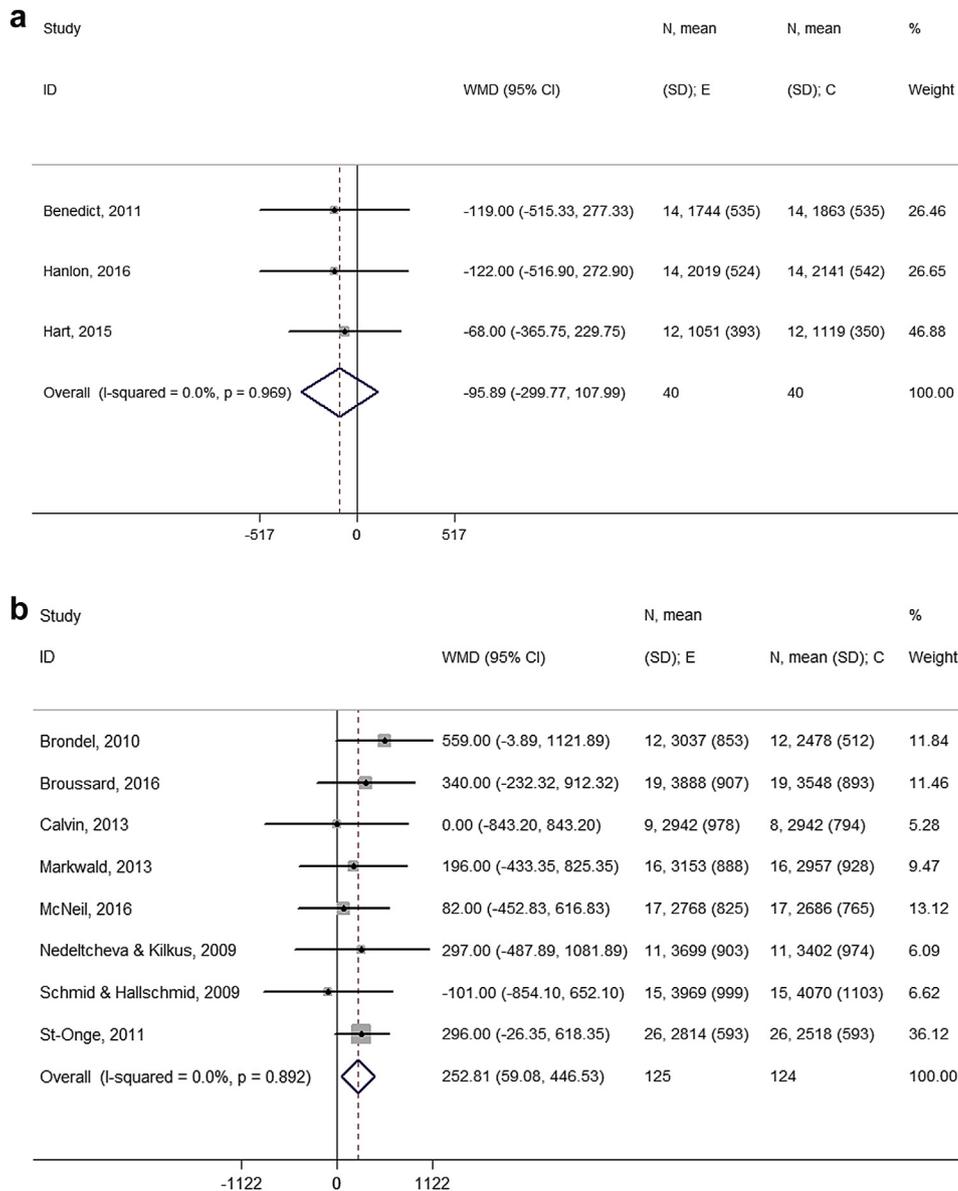


Fig. 3. a) Forest plot for caloric intake (kcal) over one meal ($n = 3$). Notes. MD = -95.9 , $z = 0.92$, $p = 0.357$. b) Forest plot for caloric intake (kcal) over a day ($n = 8$). Notes. MD = 252.8 , $z = 2.56$, $p = 0.011$.

observed [61]. Another study [62] reported less cognitive control over food stimuli under sleep restriction. Sleep restriction also reduced activity in cortical regions, which resulted in the selection of foods most capable of triggering weight-gain [44].

Effect of sleep restriction on insulin sensitivity/resistance

Five studies (all used PSR) reported the impact of sleep restriction on insulin sensitivity. Intravenous glucose tolerance test ($n = 3$) and hyperinsulinemic-euglycemic clamp ($n = 2$) were used (Table 1). Therefore, subgroup analysis based on the methods was conducted. PSR resulted in a significant decrease in insulin sensitivity (overall SMD = -0.70 ; 95%CI, -1.05 to -0.35 ; $p < 0.001$) (Table S2 and Fig. 5). When intravenous glucose tolerance test was used, the SMD was -0.80 ($p < 0.001$).

Eight studies (seven used PSR) reported the impact of sleep restriction on insulin resistance. Table 1 shows the measurements, which varied significantly between studies (e.g.,

homeostatic model assessment of insulin resistance and insulin suppression test). Thus, findings were qualitatively summarized here. Sleep restriction resulted in a significant increase in insulin resistance in five studies [24,42,45,48,63] but not in the other three [27,56,64]. Findings from each study are presented in Table S1.

Sensitivity analysis and publication bias

Three sensitivity analyses (Fig. S3) were conducted for weight change. When the study [43] using cluster RCT design was excluded, the pooled MD was 0.28 kg ($p = 0.019$). Excluding the two studies reporting post-intervention weight did not change the overall effect (MD = 0.34 kg; $p = 0.003$). Excluding the study using a 14-day intervention did not change the overall effect (MD = 0.35 kg, $p = 0.003$). Egger's tests revealed no apparent publication bias (Table S2). Visual inspection also suggested a high degree of funnel plot asymmetry.

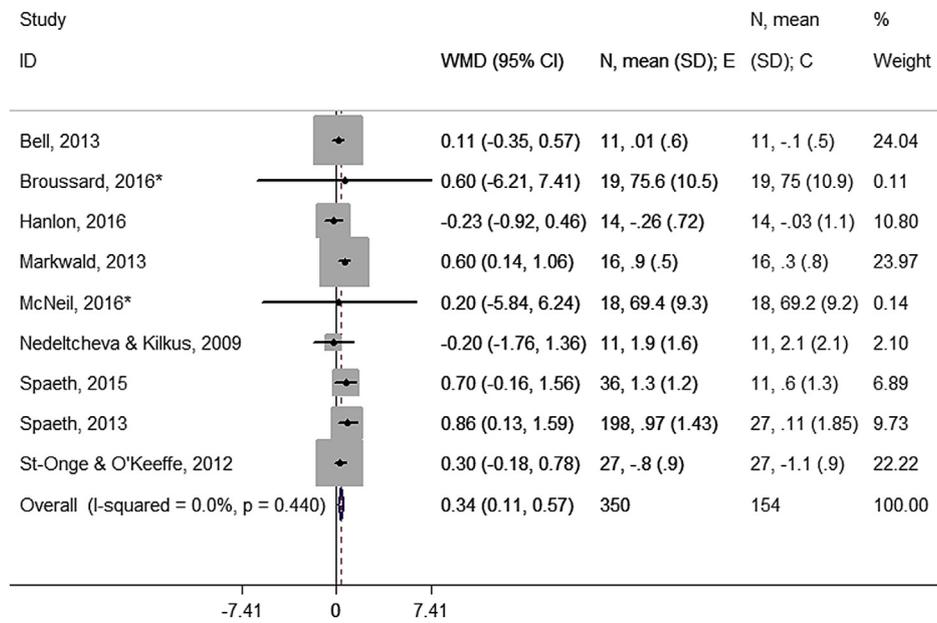


Fig. 4. Forest plot for weight change (kg) (n = 9). Notes. MD = 0.34, z = 2.95, p = 0.003; *post-intervention value was used.

Risk of bias assessment

Table S3 presents the generic risk of bias. Only one study mentioned the use of allocation concealment [49]. Although blinding of participants was not possible, several studies indicated that participants were unaware of the conditions they were assigned to until the beginning of the intervention. Therefore, the risk of performance bias was considered low for these studies. Detection bias was not clear, but it was considered low in studies that included only objective measures. In one study [27], all measures were blinded except for hunger ratings. No apparent attrition and selective bias were detected.

Table S3 also shows the risk of bias related to crossover design. Only one study [65] explicitly stated the rationales for crossover design. All studies included data from both periods. However, only a couple evaluated or mentioned the assessment of carry-over effect. Almost all studies presented data as if they arose from a parallel-group design, except one [46].

Discussion

The aim of this systematic review was to provide an up-to-date, comprehensive examination of the effects of sleep restriction on metabolism-related parameters. We found that

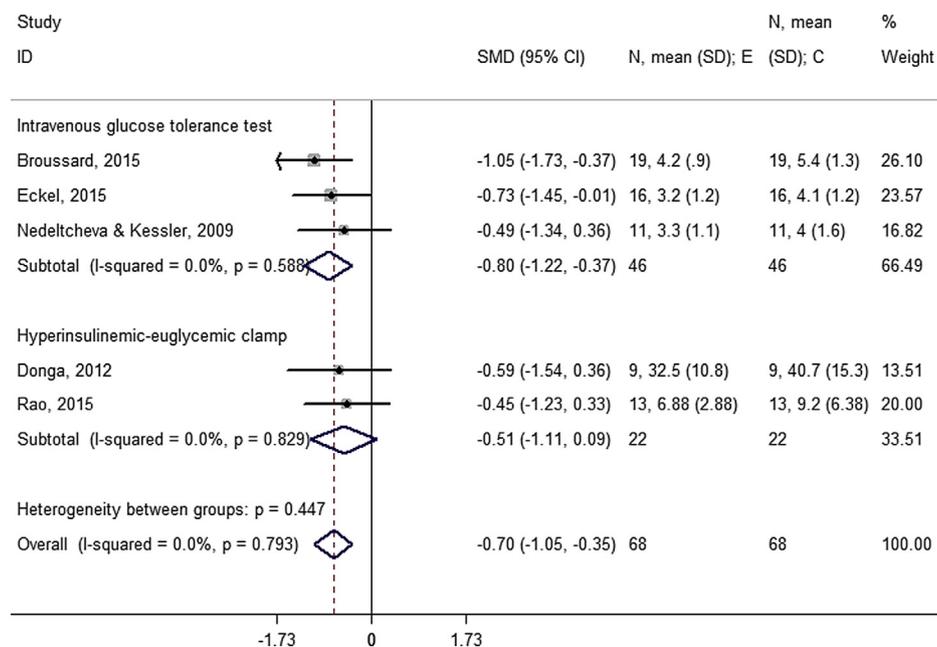


Fig. 5. Forest plot for insulin sensitivity: subgroup analysis based on methods of assessment (n = 5). Notes. Intravenous glucose tolerance test: SMD = -0.80, z = 3.64, p < 0.001. Hyperinsulinemic-euglycemic clamp: SMD = -0.51, z = 1.65, p = 0.098. Overall, SMD = -0.70, z = 3.93, p < 0.001.

sleep restriction resulted in significant increases in subjective hunger, caloric intake, and weight gain, but a decrease in insulin sensitivity. Sleep restriction also elicited changes in brain activities involving reward and cognitive control in response to eating. However, we did not find significant impacts of sleep restriction on total appetite-regulating hormones and energy expenditure. These findings contributed to our knowledge of the impact of sleep restriction on metabolism and provided novel directions in preventing metabolic diseases including obesity and diabetes.

We found strong evidence supporting the detrimental effect of sleep restriction on hunger, and TSD exerted a larger effect than PSR. Hunger level was higher in severe compared with moderate sleep restriction conditions, suggesting that the impact of sleep restriction on hunger may be dose-dependent [66]. This increase in subjective hunger coincided with the increase in calories measured during a portion size task [58] and supermarket purchase test [57]. The mechanisms underlying the relationship between sleep restriction and hunger have not been fully understood. One night of sleep deprivation decreased waking glucose metabolism in multiple regions [67]. According to the Glucostatic Theory of Food Intake Control, reduced glucose utilization in important brain regions may result in increased perception of hunger [68]. Additionally, hunger can be conceptualized from homeostatic and hedonic perspectives. Homeostatic hunger has traditionally been used to describe a biological or subjective state of acute energy depletion. The use of a fasting period (e.g., 8h sleep) creates a state of homeostatic hunger. In contrast, hedonic hunger depends much on the immediate food environment (e.g., palatability of the food) [69]. Despite these distinctions, there are functional and anatomical overlaps between homeostatic and hedonic eating systems. These two systems are likely both activated during all eating situations. In this review, we used hunger levels upon awakening and during fasting. The hunger presented may largely reflect the homeostatic state. Yet, hedonic hunger is also likely involved as supported by the increased consumption of snacks (particularly carbohydrates) [23,25,54,55].

Although sleep restriction resulted in increased hunger, no corresponding changes in overall leptin and ghrelin were observed, which was similar to a previous review [12]. Variability and timing of blood sampling may account for the negative findings. In this review, most studies only had one fasting sample. Rising ghrelin in concert with falling leptin may serve as a critical signal to induce hunger during fasting [70], thus the ratio of the two hormones may be more important than the levels of each alone. Compared to sleep extension, a 2d PSR was associated with an 18% decrease in leptin and a 20% increase in ghrelin in healthy men; the increase in hunger was related to the increase in the ghrelin-to-leptin ratio ($r = 0.87$). Almost 70% of the variance in increased hunger was accounted for by the increase in the ghrelin-to-leptin ratio [16]. The impact of sleep restriction on these hormones likely shows circadian variations. When the 24-hour profile of these hormones was explored, changes were observed during sleep restriction. Hanlon et al. described an increase in the ratio of ghrelin and leptin peak, indicating a shift towards more hunger [23]. Another study found that the nocturnal increase in ghrelin was blunted by TSD and ghrelin levels increased steadily to a plateau in the early morning without a decrease until breakfast. Additionally, the lack of significant changes in leptin may be due to the inert nature of its release, and the duration of sleep restriction may not be sufficient to elicit the slow and gradual decrease in leptin [65].

It worth mentioning that several factors may account for differences between studies in results related to leptin and ghrelin,

including sex, diet, and energy balance. Females had significantly higher circulating leptin level, plasma ghrelin level, and leptin-to-ghrelin than males [71,72]. The impact of sleep restriction on leptin and ghrelin may differ for females and males. In this review, we performed subgroup analyses based on sex. Nonetheless, no significant effect was observed possibly due to the limited number of studies that recruited exclusively females ($n = 2$). In those studies that assessed sex difference, it was reported that PSR increased ghrelin levels in males but not females [56]. Within the PSR condition, females had a greater increase in fasting leptin levels from baseline to PSR than males [50]. Diet may also explain the inconsistent findings between studies. In this review, all procedures were conducted in the controlled laboratory. Although participants received standardized mixed meals, diet composition varied slightly. Dietary composition can induce leptin resistance even without increasing the circulating leptin [73]. In contrast, changes in dietary composition in mixed meals had little effect on ghrelin [74]. Energy balance has been closely related to the change of leptin and ghrelin. Energy deficit typically causes an increase in ghrelin and a decrease in leptin [75]. In this review, participants remained sedentary in the laboratory. They were provided with meals that met their energy need to maintain energy balance. It seems that energy balance status may not have exerted much influence on these hormones.

Significant changes in brain activity in response to food stimuli were observed under sleep restriction, particularly regions related to cognitive control and reward. Previous evidence also found that sleep restriction resulted in a global decrease in brain activity, with larger decreases in the regions mediating higher-order cognitive processes, such as decision-making [76]. Additionally, sleep restriction has resulted in increased activations in food-sensitive regions in the brain [77]. A review [78] suggested that hedonic factors may be more likely to contribute to increased food intake rather than appetite-regulating hormones under sleep restriction. Changes in those brain regions may explain the decreased inhibition over eating and increased hedonic drive to overeat. Recently, Rihm and colleagues [79] found that TSD selectively resulted in an increase in the amygdala, hypothalamus activity, and functional connectivity between these two regions in response to food rewards compared with nonfood rewards. In contrast, no significant changes in hormones were observed. These findings further support that hedonic pathways may be involved in the impact of sleep restriction on food reward.

In this review, we did not observe a significant impact of sleep restriction on total energy expenditure or resting metabolic rate, in line with previous evidence [12,19]. This insignificant finding needs to be interpreted with caution. Sleep loss may not influence energy expenditure in the same magnitude and direction [80]. In addition, despite including more RCTs, the current pooled sample size remained small. Energy metabolism is closely coupled with the circadian system to meet the energy requirement during the biological day and night. Sleep restriction could affect caloric intake in a circadian manner [81]. It could be argued that the effect of sleep restriction on energy expenditure may also exhibit circadian variations. In this review, only a summary of energy expenditure was obtained, which may have masked the significant relationship. Nonetheless, no apparent circadian pattern was observed in previous studies that included 24h hourly assessment of energy expenditure in a metabolic chamber [54,82,83].

When caloric intake over a day was obtained, sleep restriction resulted in a 252.8 kcal increase ($p = 0.011$). This finding is in line with a previous report of a 364 kcal in caloric intake after sleep restriction [19]. In contrast, when caloric intake was measured over one meal, participants under sleep restriction consumed 95.9 ($p = 0.36$) less kcal than under normal sleep. Caloric intake largely

depends on the amount of food available [84]. Therefore, the accumulated effect of sleep restriction on *ad libitum* food consumption would be larger over a day than over one meal. In addition, sleep restriction may not acutely increase caloric intake [53], and one meal is unlikely to capture important eating behaviors that operate over longer periods (e.g., delayed compensation) [85]. Indeed, we found that sleep restriction increased compensatory caloric intake from snacks in this review.

We also found that sleep restriction resulted in a significant weight gain (0.34 kg). In a previous review, sleep restriction resulted in a non-significant weight gain (0.68 kg, 95% CI, -0.09–1.44) [12], which may be explained by the comparatively small sample size. In this review, participants remained in the laboratory and did not engage in physical activity. There was a non-significant change in energy expenditure but a significant increase in energy intake, leading to a positive energy balance. Noteworthy, it is likely that the duration of the intervention in most studies was not long enough to produce larger weight change. Although the amount of weight gain was modest, this change could contribute to increased adiposity over a long period as has been observed previously [86]. On a molecular level, TSD altered genome-wide DNA methylation in adipose tissues to promote adiposity but induced a molecular catabolic signature in skeletal muscle. These changes may favor weight gain [87]. Interestingly, females had a larger increase in energy intake during PSR relative to normal sleep than men [59]. Weight gain under sleep restriction was only observed in females but not males [54]. We observed a significant weight gain despite most participants being males.

Sleep restriction exerted a moderate effect on insulin sensitivity. Multiple pathways underlying the relationship between sleep restriction and glucose metabolism have been summarized. These include decreased brain glucose utilization, increased inflammation, sympathovagal imbalance, and changes in cortisol/growth hormone release under sleep restriction [88]. Studies examining the underlying molecular pathways are also increasing. PSR caused an insulin-resistant state in human peripheral adipocytes [89]. Recently, it was reported that sleep restriction dramatically disrupted the circadian regulation of white adipose tissue transcriptome, resulting in an impairment in carbohydrates metabolism and glucose homeostasis [90]. Building upon previous evidence, we quantified the effect of sleep restriction on insulin sensitivity. The effect size was moderate, interpreted using Cohen's recommendation. To put in comparison, a previous review [91] found a moderate effect of supervised physical activity on insulin sensitivity among healthy adults. Thus, the magnitude of the effect of inadequate sleep on insulin sensitivity seemed similar to that of physical activity, suggesting that this impact is clinically significant. The results are also in agreement with a previous meta-analysis of longitudinal studies demonstrating that the risk of incident diabetes as a result of inadequate sleep was comparable to that of physical inactivity [92].

Overall, our findings support that adequate sleep should be highly recommended by healthcare professionals during patient education and clinical visits, particularly to those at risks for obesity and diabetes. An increasing number of studies has investigated the effect of sleep extension. Tasali et al. [93] found that a two-week sleep extension in the free-living setting resulted in significant decreases in appetite and desire for high-calorie foods. Both in-lab and at-home sleep extension has resulted in improved insulin sensitivity in healthy participants [94,95]. These findings supported the feasibility of sleep extension interventions. Future studies are needed to shed more lights on the effect of sleep extension on various metabolism-related parameters, such as hunger perception, energy intake, and weight.

This review has several strengths and limitations. The causality inference was enhanced by including only RCTs. Sleep intervention was delivered in the closely monitored environment, which improved the fidelity of the intervention. We provided a more comprehensive review by including both types of sleep restriction (i.e., TSD/PSR). Nonetheless, a number of limitations need to be addressed in future studies. In this review, the sum score from both sleep conditions was analyzed as if the trial used a parallel-group design because data required to include a paired analysis were rarely reported. This type of analysis has limitations, such as too wide confidence intervals and too little weight of each trial, which may disguise clinically important heterogeneity. In this review, 10 studies used TSD. Among the 31 studies using PSR, 18 achieved PSR without shifts in circadian phase by moving the usual bedtime and wake time proportionally closer together. The others either delayed the bedtime without changing the wake time ($n = 9$) or advanced the wake time without changing the bedtime ($n = 4$). In the above cases, altered circadian timing may have occurred, as was reported by Markwald et al. [54]. Thus, it is possible that the circadian change resulting from sleep restriction might affect the outcomes of interest. In addition, food intake has been related to the circadian system. However, few studies have partitioned them, precluding us from examining whether sleep restriction affects food intake in a circadian manner. Findings from this review may only be generalized to young, healthy adults, particularly males. Sleep restriction may disrupt metabolism through separate pathways in males and females [96]. Age may moderate the relationship between sleep and metabolic health [97]. Future studies consisting of more representative samples are needed.

In summary, building upon previous evidence, we demonstrated the detrimental effects of sleep restriction on various metabolism-related parameters. Sleep restriction resulted in a significant increase in subjective hunger, caloric intake, and weight gain, but a decrease in insulin sensitivity. Sleep restriction may also affect the rewarding system and cognitive control over eating. These findings may provide novel directions in preventing metabolic diseases including obesity and diabetes. In the meanwhile, more studies are warranted to further unveil the impact of sleep restriction on metabolism-related factors including brain responses to eating and appetite-regulation hormones from the circadian perspective. In addition, future research is needed to shed more lights on the underlying mechanistic pathways involved in the effect of sleep restriction on metabolic health. For instance, sleep restriction may promote metabolic diseases by disrupting the gut microbiome community, though current findings have been mixed [98,99]. Sleep restriction has induced molecular changes in adipose tissues and skeletal muscle [87] and disrupted the circadian regulation of white adipose tissue transcriptome [90]. This emerging evidence offers new insight into the underlying mechanisms.

Practice points

- 1) Inadequate sleep causes an increased sense of hunger.
- 2) Inadequate sleep increases daily caloric intake without changing energy expenditure, leading to overall weight gain.
- 3) Inadequate sleep impairs insulin sensitivity.
- 4) Inadequate sleep may cause brain activity changes in regions involving reward and cognitive control over eating.

Research agenda

- 1) Larger trials using a more representative sample and longer intervention are warranted to confirm the findings.
- 2) More studies are needed to examine the effect of sleep optimization on metabolic health and mechanistic pathways involved.
- 3) Future research is warranted to examine whether sleep loss affects metabolism-related outcomes in a circadian manner, including appetite-regulating hormones and brain response to food stimuli.

Conflicts of interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.smr.2019.02.002>.

References

- [1] Kirov R, Brand S. The memory, cognitive and psychological functions of sleep: update from electroencephalographic and neuroimaging studies. In: Bright P, editor. *Neuroimaging-cognitive and clinical neuroscience*. InTech; 2012. p. 155–80.
- [2] Hirshkowitz M, Whitton K, Albert SM, Alessi C, Bruni O, DonCarlos L, et al. National Sleep Foundation's sleep time duration recommendations: methodology and results summary. *Sleep Health* 2015;1:40–3.
- [3] Harrison Y, Home JA. Should we be taking more sleep? *Sleep* 1995;18:901–7.
- [4] Broman JE, Lundh LG, Hetta J. Insufficient sleep in the general population. *Clin Neurophysiol* 1996;26:30–9.
- [5] Liu Y. Prevalence of healthy sleep duration among adults—United States, 2014. *Morb Mortal Wkly Rep*; 2016. p. 65.
- [6] Centers for Disease Control and Prevention. *Overweight and obesity: adult obesity facts*. Atlanta, GA: Centers for Disease Control and Prevention, U.S. Dept of Health and Human Services; 2017. Retrieved from: <https://www.cdc.gov/obesity/data/adult.html>.
- [7] Centers for Disease Control and Prevention. *National diabetes statistics report*. Atlanta, GA: Centers for Disease Control and Prevention, U.S. Dept of Health and Human Services; 2017. Retrieved from: <https://www.cdc.gov/diabetes/data/statistics/statistics-report.html>.
- *[8] Knutson KL, Spiegel K, Penev P, Van Cauter E. The metabolic consequences of sleep deprivation. *Sleep Med Rev* 2007;11:163–78.
- [9] Itani O, Jike M, Watanabe N, Kaneita Y. Short sleep duration and health outcomes: a systematic review, meta-analysis, and meta-regression. *Sleep Med* 2017;32:246–56.
- *[10] Grandner MA, Seixas A, Shetty S, Shenoy S. Sleep duration and diabetes risk: population trends and potential mechanisms. *Curr Diabetes Rep* 2016;16:106.
- [11] St-Onge M-P. The role of sleep duration in the regulation of energy balance: effects on energy intakes and expenditure. *J Clin Sleep Med* 2013;9:73–80.
- *[12] Capers PL, Fobian AD, Kaiser KA, Borah R, Allison DB. A systematic review and meta-analysis of randomized controlled trials of the impact of sleep duration on adiposity and components of energy balance. *Obes Rev* 2015;16:771–82.
- *[13] Chaput J-P. Short sleep duration promoting overconsumption of food: a reward-driven eating behavior. *Sleep* 2010;33:1135–6.
- [14] Lundahl A, Nelson TD. Sleep and food intake: a multisystem review of mechanisms in children and adults. *J Health Psychol* 2015;20:794–805.
- [15] Chaput J-P. Sleep patterns, diet quality and energy balance. *Physiol Behav* 2014;134:86–91.
- [16] Spiegel K, Tasali E, Penev P, Van Cauter E. Brief communication: sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels, and increased hunger and appetite. *Ann Intern Med* 2004;141:846–50.
- [17] Cedernaes J, Fanelli F, Fazzini A, Pagotto U, Broman JE, Vogel H, et al. Sleep restriction alters plasma endocannabinoids concentrations before but not after exercise in humans. *Psychoneuroendocrinol* 2016;74:258–68.
- [18] Rao MN, Neylan TC, Grunfeld C, Mulligan K, Schambelan M, Schwarz JM. Subchronic sleep restriction causes tissue-specific insulin resistance. *J Clin Endocrinol Metabol* 2015;100:1664–71.
- *[19] Al Khatib HK, Harding SV, Darzi J, Pot GK. The effects of partial sleep deprivation on energy balance: a systematic review and meta-analysis. *Eur J Clin Nutr* 2017;71:614–24.
- [20] McNeil J, Forest G, Hintze LJ, Brunet JF, Finlayson G, Blundell JE, et al. The effects of partial sleep restriction and altered sleep timing on appetite and food reward. *Appetite* 2017;109:48–56.
- [21] Hibi M, Kubota C, Mizuno T, Aritake S, Mitsui Y, Katashima M, et al. Effect of shortened sleep on energy expenditure, core body temperature, and appetite: a human randomised crossover trial. *Sci Rep* 2017;7.
- [22] McNeil J, Doucet E, Brunet J-F, Hintze LJ, Chaumont I, Langlois E, et al. The effects of sleep restriction and altered sleep timing on energy intake and energy expenditure. *Physiol Behav* 2016;164:157–63.
- [23] Hanlon EC, Tasali E, Leproult R, Stuhr KL, Doncheck E, de Wit H, et al. Sleep restriction enhances the daily rhythm of circulating levels of endocannabinoid 2-arachidonoylglycerol. *Sleep* 2016;39:653–64.
- [24] Cedernaes J, Lampola L, Axelsson EK, Liethof L, Hassanzadeh S, Yeganeh A, et al. A single night of partial sleep loss impairs fasting insulin sensitivity but does not affect cephalic phase insulin release in young men. *J Sleep Res* 2016;25:5–10.
- [25] Broussard JL, Kilkus JM, Delebecque F, Abraham V, Day A, Whitmore HR, et al. Elevated ghrelin predicts food intake during experimental sleep restriction. *Obes* 2016;24:132–8.
- [26] Spaeth AM, Dinges DF, Goel N. Resting metabolic rate varies by race and by sleep duration. *Obes* 2015;23:2349–56.
- [27] Hart CN, Carskadon MA, Demos KE, Van Reen E, Sharkey KM, Raynor HA, et al. Acute changes in sleep duration on eating behaviors and appetite-regulating hormones in overweight/obese adults. *Behav Sleep Med* 2015;13:424–36.
- [28] Fang Z, Spaeth AM, Ma N, Zhu SH, Hu SY, Goel N, et al. Altered salience network connectivity predicts macronutrient intake after sleep deprivation. *Sci Rep* 2015;5:8215.
- [29] Eckel RH, Depner CM, Perreault L, Markwald RR, Smith MR, McHill AW, et al. Morning circadian misalignment during short sleep duration impacts insulin sensitivity. *Curr Biol* 2015;25:3004–10.
- [30] Broussard JL, Chapotot F, Abraham V, Day A, Delebecque F, Whitmore HR, et al. Sleep restriction increases free fatty acids in healthy men. *Diabetol* 2015;58:791–8.
- [31] Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.
- [32] Moher D, Liberati A, Tetzlaff J, Altman DG, Prisma Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6:e1000097.
- [33] Hartling L, Featherstone R, Nuspl M, Shave K, Dryden DM, Vandermeer B. Grey literature in systematic reviews: a cross-sectional study of the contribution of non-English reports, unpublished studies and dissertations to the results of meta-analyses in child-relevant reviews. *BMC Med Res Methodol* 2017;17:64.
- [34] Rohatgi A. *WebPlotDigitizer 4.1*. 2015. Retrieved from, <https://apps.automeris.io/wpd/>.
- [35] Higgins JPT, Altman DG, Sterne JAC. Assessing risk of bias in included studies. In: Higgins JPT, Green S, editors. *Cochrane Handbook for systematic reviews of interventions*. 5.1.0. The Cochrane Collaboration; 2011.
- [36] Higgins JPT, Deeks JJ, Altman DG. Special topics in statistics. In: Higgins JPT, Green S, editors. *Cochrane Handbook for systematic reviews of interventions*. Version 5.1.0. The Cochrane Collaboration; 2011.
- [37] Hedges LV. Distribution theory for Glass's estimator of effect size and related estimators. *J Behav Stat* 1981;6:107–28.
- [38] Cohen J. *The t-test for means*. In: Cohen J, editor. *Statistical power analysis for the behavioral sciences*. 2nd ed. New York, NY: Lawrence Erlbaum Associates; 1988. p. 19–66.
- [39] Higgins J, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539–58.
- [40] DerSimonian R, Laird N. Meta-analysis in clinical trials. *Contr Clin Trials* 1986;7:177–88.
- [41] Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–34.
- [42] Donga E, van Dijk M, van Dijk JG, Biermasz NR, Lammers GJ, van Kralingen KW, et al. A single night of partial sleep deprivation induces

* The most important references are denoted by an asterisk.

- insulin resistance in multiple metabolic pathways in healthy subjects. *J Clin Endocrinol Metabol* 2010;95:2963–8.
- [43] Spaeth AM, Dinges DF, Goel N. Effects of experimental sleep restriction on weight gain, caloric intake, and meal timing in healthy adults. *Sleep* 2013;36:981–90.
- [44] Greer SM, Goldstein AN, Walker MP. The impact of sleep deprivation on food desire in the human brain. *Nat Commun* 2013;4:2259.
- [45] Gonzalez-Ortiz M, Martinez-Abundis E, Balcazar-Munoz BR, Pascoe-Gonzalez S. Effect of sleep deprivation on insulin sensitivity and cortisol concentration in healthy subjects. *Diabetes Nutr Metabol* 2000;13:80–3.
- [46] Brondel L, Romer MA, Nougues PM, Touyarou P, Davenne D. Acute partial sleep deprivation increases food intake in healthy men. *Am J Clin Nutr* 2010;91:1550–9.
- [47] Shechter A, Rising R, Wolfe S, Albu JB, St-Onge MP. Postprandial thermogenesis and substrate oxidation are unaffected by sleep restriction. *Int J Obes* 2014;38:1153–8.
- [48] van Leeuwen WMA, Hublin C, Sallinen M, Harma M, Hirvonen A, Porkka-Heiskanen T. Prolonged sleep restriction affects glucose metabolism in healthy young men. *Int J Endocrinol* 2010;1–7.
- [49] Calvin AD, Carter RE, Adachi T, Macedo PG, Albuquerque FN, van der Walt C, et al. Effects of experimental sleep restriction on caloric intake and activity energy expenditure. *Chest* 2013;144:79–86.
- [50] Simpson NS, Banks S, Dinges DF. Sleep restriction is associated with increased morning plasma leptin concentrations, especially in women. *Biol Res Nurs* 2010;12:47–53.
- [51] Benedict C, Hallschmid M, Lassen A, Mahnke C, Schultes B, Schiöth HB, et al. Acute sleep deprivation reduces energy expenditure in healthy men. *Am J Clin Nutr* 2011;93:1229–36.
- [52] Dzaja A, Dalal MA, Himmerich H, Uhr M, Pollmacher T, Schulz A. Sleep enhances nocturnal plasma ghrelin levels in healthy subjects. *Am J Physiol Endocrinol Metabol* 2004;286:E963–7.
- [53] Schmid SM, Hallschmid M, Jauch-Chara K, Wilms B, Benedict C, Lehnert H, et al. Short-term sleep loss decreases physical activity under free-living conditions but does not increase food intake under time-deprived laboratory conditions in healthy men. *Am J Clin Nutr* 2009;90:1476–82.
- [54] Markwald RR, Melanson EL, Smith MR, Higgins J, Perreault L, Eckel RH, et al. Impact of insufficient sleep on total daily energy expenditure, food intake, and weight gain. *Proc Natl Acad Sci* 2013;110:5695–700.
- [55] Nedeltcheva AV, Kilkus JM, Imperial J, Kasza K, Schoeller DA, Penev PD. Sleep curtailment is accompanied by increased intake of calories from snacks. *Am J Clin Nutr* 2009;89:126–33.
- [56] St-Onge MP, O'Keefe M, Roberts AL, RoyChoudhury A, Laferrere B. Short sleep duration, glucose dysregulation and hormonal regulation of appetite in men and women. *Sleep* 2012;35:1503–10.
- [57] Chapman CD, Nilsson EK, Nilsson VC, Cedernaes J, Rangtell FH, Vogel H, et al. Acute sleep deprivation increases food purchasing in men. *Obes* 2013;21:E555–60.
- [58] Hogenkamp PS, Nilsson E, Nilsson VC, Chapman CD, Vogel H, Lundberg LS, et al. Acute sleep deprivation increases portion size and affects food choice in young men. *Psychoneuroendocrinol* 2013;38:1668–74.
- [59] St-Onge MP, Roberts AL, Chen J, Kelleman M, O'Keefe M, RoyChoudhury A, et al. Short sleep duration increases energy intakes but does not change energy expenditure in normal-weight individuals. *Am J Clin Nutr* 2011;94:410–6.
- [60] Benedict C, Brooks SJ, O'Daly OG, Almen MS, Morell A, Aberg K, et al. Acute sleep deprivation enhances the brain's response to hedonic food stimuli: an fMRI study. *J Clin Endocrinol Metabol* 2012;97:E443–7.
- [61] St-Onge MP, McReynolds A, Trivedi ZB, Roberts AL, Sy M, Hirsch J. Sleep restriction leads to increased activation of brain regions sensitive to food stimuli. *Am J Clin Nutr* 2012;95:818–24.
- [62] Cedernaes J, Brandell J, Ros O, Broman JE, Hogenkamp PS, Schiöth HB, et al. Increased impulsivity in response to food cues after sleep loss in healthy young men. *Obes* 2014;22:1786–91.
- [63] Schmid SM, Hallschmid M, Jauch-Chara K, Wilms B, Lehnert H, Born J, et al. Disturbed gluoregulatory response to food intake after moderate sleep restriction. *Sleep* 2011;34:371–7.
- [64] Schmid SM, Jauch-Chara K, Hallschmid M, Schultes B. Mild sleep restriction acutely reduces plasma glucagon levels in healthy men. *J Clin Endocrinol Metabol* 2009;94:5169–73.
- [65] Schmid SM, Hallschmid M, Jauchchara K, Born J, Schultes B. A single night of sleep deprivation increases ghrelin levels and feelings of hunger in normal-weight healthy men. *J Sleep Res* 2008;13:331–4.
- [66] Sargent C, Zhou X, Matthews RW, Darwent D, Roach GD. Daily rhythms of hunger and satiety in healthy men during one week of sleep restriction and circadian misalignment. *Int J Environ Res Public Health* 2016;13:170.
- [67] Thomas M, Sing H, Belenky G, Holcomb H, Mayberg H, Dannals R, et al. Neural basis of alertness and cognitive performance impairments during sleepiness. I. Effects of 24 h of sleep deprivation on waking human regional brain activity. *J Sleep Res* 2000;9:335–52.
- [68] Chapat JP, Tremblay A. The glucostatic theory of appetite control and the risk of obesity and diabetes. *Int J Obes* 2009;33:46.
- [69] Lowe MR, Butryn ML. Hedonic hunger: a new dimension of appetite? *Physiol Behav* 2007;91:432–9.
- [70] Saper CB, Chou TC, Elmquist JK. The need to feed: homeostatic and hedonic control of eating. *Neuron* 2002;36:199–211.
- [71] Williams RL, Wood LG, Collins CE, Morgan PJ, Callister R. Energy homeostasis and appetite regulating hormones as predictors of weight loss in men and women. *Appetite* 2016;101:1–7.
- [72] Makovey J, Naganathan V, Seibel M, Sambrook P. Gender differences in plasma ghrelin and its relations to body composition and bone-an opposite-sex twin study. *Clin Endocrinol* 2007;66:530–7.
- [73] Vasselli JR, Scarpace PJ, Harris RB, Banks WA. Dietary components in the development of leptin resistance. *Adv Nutr* 2013;4:164–75.
- [74] Gannon MC, Nuttall FQ. Effect of a high-protein diet on ghrelin, growth hormone, and insulin-like growth factor-I and binding proteins 1 and 3 in subjects with type 2 diabetes mellitus. *Metabolism* 2011;60:1300–11.
- [75] Lockie SH, Andrews ZB. The hormonal signature of energy deficit: increasing the value of food reward. *Mol Metabol* 2013;2:329–36.
- [76] Killgore WDS, Balkin TJ, Wesensten NJ. Impaired decision making following 49 h of sleep deprivation. *J Sleep Res* 2006;15:7–13.
- [77] Katsunuma R, Oba K, Kitamura S, Motomura Y, Terasawa Y, Nakazaki K, et al. Unrecognized sleep loss accumulated in daily life can promote brain hyperreactivity to food cue. *Sleep* 2017. PMID: 28958004.
- *[78] Chapat J-P, St-Onge M-P. Increased food intake by insufficient sleep in humans: are we jumping the gun on the hormonal explanation? *Front Endocrinol* 2014;5:116.
- [79] Rihm JS, Menz MM, Schultz H, Bruder L, Schilbach L, Schmid SM, et al. Sleep deprivation selectively up-regulates an amygdala-hypothalamic circuit involved in food reward. *J Neurosci* 2018. PMID: 30559151.
- [80] Klingenberg L, Sjodin A, Holmback U, Astrup A, Chapat JP. Short sleep duration and its association with energy metabolism. *Obes Rev* 2012;13:565–77.
- [81] McHill AW, Wright Jr KP. Role of sleep and circadian disruption on energy expenditure and in metabolic predisposition to human obesity and metabolic disease. *Obes Rev* 2017;18(Suppl 1):15–24.
- [82] Shechter A, Rising R, Albu JB, St-Onge MP. Experimental sleep curtailment causes wake-dependent increases in 24-h energy expenditure as measured by whole-room indirect calorimetry. *Am J Clin Nutr* 2013;98:1433–9.
- [83] Klingenberg L, Chapat JP, Holmback U, Jennum P, Astrup A, Sjodin A. Sleep restriction is not associated with a positive energy balance in adolescent boys. *Am J Clin Nutr* 2012;96:240–8.
- [84] Raynor HA, Wing RR. Package unit size and amount of food: do both influence intake? *Obesity* 2007;15:2311–9.
- [85] de Castro JM. Eating behavior: lessons from the real world of humans. *Nutrition* 2000;16:800–13.
- [86] Vikdahl M, Carlsson M, Linder J, Forsgren L, Haglin L. Weight gain and increased central obesity in the early phase of Parkinson's disease. *Clin Nutr* 2014;33:1132–9.
- [87] Cedernaes J, Schonke M, Westholm JO, Mi J, Chibalin A, Voisin S, et al. Acute sleep loss results in tissue-specific alterations in genome-wide DNA methylation state and metabolic fuel utilization in humans. *Sci Adv* 2018;4:eaar8590.
- *[88] Reutrakul S, Van Cauter E. Sleep influences on obesity, insulin resistance, and risk of type 2 diabetes. *Metabolism* 2018. PMID: 29510179.
- [89] Broussard JL, Ehrmann DA, Van Cauter E, Tasali E, Brady MJ. Impaired insulin signaling in human adipocytes after experimental sleep restriction: a randomized, crossover study. *Ann Intern Med* 2012;157:549–57.
- [90] Wilms B, Leineweber EM, Molle M, Chamorro R, Pommerenke C, Salinas-Riester G, et al. Sleep loss disrupts morning-to-evening differences in human white adipose tissue transcriptome. *J Clin Endocrinol Metabol* 2018. PMID: 30535338.
- [91] Conn VS, Koopman RJ, Ruppert TM, Phillips LJ, Mehr DR, Hafdahl AR. Insulin sensitivity following exercise interventions: systematic review and meta-analysis of outcomes among healthy adults. *J Prim Care Community Health* 2014;5:211–22.
- *[92] Anothaisintawee T, Reutrakul S, Van Cauter E, Thakkinstian A. Sleep disturbances compared to traditional risk factors for diabetes development: systematic review and meta-analysis. *Sleep Med Rev* 2016;30:11–24.
- *[93] Tasali E, Chapotot F, Wroblewski K, Schoeller D. The effects of extended bedtimes on sleep duration and food desire in overweight young adults: a home-based intervention. *Appetite* 2014;80:220–4.
- [94] Killick R, Hoyos CM, Melehan KL, Dungan 2nd GC, Poh J, Liu PY. Metabolic and hormonal effects of 'catch-up' sleep in men with chronic, repetitive, lifestyle-driven sleep restriction. *Clin Endocrinol* 2015;83:498–507.
- [95] Leproult R, Delyens G, Gilson M, Peigneux P. Beneficial impact of sleep extension on fasting insulin sensitivity in adults with habitual sleep restriction. *Sleep* 2015;38:707–15.
- [96] Rangtell FH, Schmidt F, Wurffel J, Karamchedu S, Andersson P, Vogel H, et al. Morning enzymatic activity of DPP-4 is differentially altered by sleep loss in women and men. *Diabetes Care* 2018;41:e10–1.
- [97] Titova OE, Lindberg E, Elmstahl S, Lind L, Schiöth HB, Benedict C. Associations between the prevalence of metabolic syndrome and sleep parameters vary by age. *Front Endocrinol* 2018;9:234.
- [98] Benedict C, Vogel H, Jonas W, Woting A, Blaut M, Schurmann A, et al. Gut microbiota and glucometabolic alterations in response to recurrent partial

- sleep deprivation in normal-weight young individuals. *Mol Metabol* 2016;5:1175–86.
- [99] Zhang SL, Bai L, Goel N, Bailey A, Jang CJ, Bushman FD, et al. Human and rat gut microbiome composition is maintained following sleep restriction. *Proc Natl Acad Sci* 2017;114:e1564–71.
- [100] Bell LN, Kilkus JM, Booth 3rd JN, Bromley LE, Imperial JG, Penev PD. Effects of sleep restriction on the human plasma metabolome. *Physiol Behav* 2013;122:25–31.
- [101] Nedeltcheva AV, Kessler L, Imperial J, Penev PD. Exposure to recurrent sleep restriction in the setting of high caloric intake and physical inactivity results in increased insulin resistance and reduced glucose tolerance. *J Clin Endocrinol Metabol* 2009;94:3242–50.
- [102] Schmid SM, Hallschmid M, Jauch-Chara K, Bandorf N, Born J, Schultes B. Sleep loss alters basal metabolic hormone secretion and modulates the dynamic counterregulatory response to hypoglycemia. *J Clin Endocrinol Metabol* 2007;92:3044–51.