THE EFFECTS OF SLEEP EXTENSION ON CARDIOMETABOLIC RISK FACTORS: A SYSTEMATIC REVIEW

Short title: **SLEEP EXTENSION AND CARDIOMETABOLIC RISK FACTORS**

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Summary

Studies have shown bidirectional relationships between short- or long-sleep duration and risk for obesity, non-communicable diseases, all-cause mortality and cardiovascular disease mortality. Increasing sleep duration may be an appropriate strategy to reduce cardiometabolic risk in short-sleeping individuals. The aim is to review the effects of sleep extension interventions on cardiometabolic risk in adults. The PubMed and Scopus databases were searched for relevant, English, peer-reviewed scientific publications (until August 2018). Seven studies that aimed to increase sleep duration in adults by any sleep extension intervention and described at least one cardiometabolic risk factor were included. These studies had a combined sample size of 138 participants who were either healthy (n=14), healthy short-sleeping (n=92), overweight short-sleeping (n=10), or pre- and or hypertensive short-sleeping (n=22) individuals. The durations of the sleep extension interventions ranged from three days to six weeks and all successfully increased total sleep time by between 21 and 177min. Sleep extension was associated with improved direct and indirect measures of insulin sensitivity, decreased leptin and peptide tyrosine-tyrosine, and reductions in overall appetite, desire for sweet and salty foods, intake of daily free sugar, and percentage of daily caloric intake from protein. This review provides preliminary evidence for a role for sleep extension to improve cardiometabolic outcomes and directive towards future studies in the field of cardiometabolic health and sleep.

Key words: sleep duration, non-communicable diseases, obese, cardiovascular disease, insulin sensitivity, metabolic syndrome.

INTRODUCTION

It was estimated that non-communicable diseases (NCDs) accounted for 38 million deaths globally in 2012 (World Health Organization, 2015) and are projected to further increase to 52 million by 2030 (Mathers and Loncar, 2006). Currently, the main contributor to NCD mortality is cardiovascular disease ~~(CVD)~~, which accounts for 37% of all NCD deaths globally (World Health Organization, 2015). The prevalence of obesity, a major NCD risk factor, and type II diabetes mellitus (T2DM) are also increasing each year. Globally 10.8% of males and 14.9% of females were obese in 2014 and these numbers are estimated to rise to 18% and 21% in males and females respectively by 2025 (NCD-RisC, 2016a). Similarly, the prevalence of T2DM was 9.0% and 7,9% in 2014 in males and females respectively and it is estimated that 12.8% and 10.4% of men and women globally ~~will be diabetic~~will be diagnosed with T2DM by 2025 (NCD-RisC, 2016b). To decrease the current and future burden of NCDs, especially obesity and cardiometabolic diseases ~~(CMD)~~, new interventions are being developed, assessed and validated.

Mounting evidence is available to suggest that sleep is key to an individual's health. Prospective studies and meta-analyses have shown that both short and long sleep durations (self-reported) increase risk for mortality and developing, or dying from, coronary heart disease and stroke (Cappuccio et al., 2011; Cappuccio et al., 2010; Gallicchio and Kalesan, 2009; Kripke et al., 2002). While we recognise that both short and long sleep are associated with health risks, for the purpose of this review we will focus solely on short sleep, defined as <7h per night, unless otherwise specified.

Epidemiological studies report consistent relationships between short sleep duration and increased risk for mortality, T2DM~~diabetes~~, hypertension, cardiovascular disease, stroke, coronary heart disease, overweight and obesity, weight gain, hyperglycaemia and impaired glucose tolerance (Anothaisintawee et al., 2016; Bliwise et al., 2017; Cappuccio et al., 2008; Chao et al., 2011; Gottlieb et al., 2005; Gottlieb et al., 2006; Itani et al., 2017; Knutson et al., 2009; Patel and Hu, 2008; Roda et al., 2016; Sasaki et al., 2016; Sperry et al., 2015; Walatara

et al., 2016; Wu et al., 2014). Furthermore, poor lifestyle factors such as smoking (Wang et al., 2017), lack of physical exercise (Wang et al., 2017) and alcohol use (Galli et al., 2013) are more common in short-sleeping individuals, presumably compounding their risk for developing NCDs. Both short and long sleep have also been associated with depression (Zhai et al., 2015), and depression severity has been associated with metabolic syndrome components (Hiles et al., 2016).

Recognising that epidemiological evidence does not infer causality, examination of studies using acute sleep restriction protocols may shed light on the direction of the association between sleep duration and cardiometabolic risk factors. It seems likely that sleep restriction may alter energy balance. For example, participants subjected to five nights of sleep restriction (4h per night) displayed greater neuronal activation of brain regions sensitive to food stimuli and food intake in response to unhealthy food compared to when allowed a week of habitual of sleep (7-9h) (St-Onge et al., 2013). Indeed, increased caloric intake ~~and/~~and~~or~~ subsequent weight gain has been observed in participants following eight nights of sleep restriction (two-thirds of habitual sleep duration) (Calvin et al., 2013), five consecutive nights of sleep restriction (4h per night) (Spaeth et al., 2013) and just five or four nights of sleep restriction (Bosy-Westphal et al., 2008; Markwald et al., 2013). Additionally, restricting sleep to 4.3h for two nights (Bromley et al., 2012) or 5.5h for two weeks (Schmid et al., 2009) ~~Schmid et al., 2009~~ reduces the intensity and amount of physical activity participants choose to do.

Sleep restriction has also been shown to negatively affect other aspects of cardiometabolic health. Two randomized crossover-controlled trials demonstrated that four or five nights of sleep restriction (4.5h or 4h per night respectively) reduced insulin sensitivity compared to longer sleep (8.5h or 8h sleep respectively) (Broussard et al., 2012; Rao et al., 2015). Likewise, just two days of sleep restriction (4h per night) resulted in higher insulin and glucose peak responses to breakfast intake, suggesting an impairment of glucose tolerance, possibly caused by a decreased insulin sensitivity (Schmid et al., 2011). Similar results have been found

in other studies with various study designs and cohorts (Buxton et al., 2010; Donga et al., 2010; Reynolds et al., 2012; Sweeney et al., 2017; Wang et al., 2016). Finally, five nights of sleep restriction (4h per night) increased lymphocyte activation and the production of proinflammatory cytokines, which have been associated with an increased risk for developing cardiovascular diseases (van Leeuwen et al., 2009).

In light of the association between short sleep duration and risk for NCDs and the effect of acute sleep restriction on cardiometabolic function, interventions aimed at increasing sleep duration are being trialled as a new approach to reducing risk for obesity and NCDs. One study reviewed the feasibility and effectiveness of sleep extension for weight management and cardiometabolic disease prevention, and concluded that prolonging sleep may improve cardiometabolic risk in short sleepers (Pizinger et al., 2018). However, the authors did not adopt a systematic approach, which increases the risk for bias, and only studies on short-sleeping participants were included, which ignores the potential benefit or risk of sleep-extension in normal-sleepers. Therefore, the aim of this study was to systematically review the effects of sleep extension interventions on cardiometabolic risk factors in adults regardless of habitual sleep duration.

METHODS

Literature search

Peer-reviewed original studies in which sleep extension interventions were used, and cardiometabolic risk factors were measured as outcomes, were assessed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009). Articles were included if all of the following criteria were met: participants were adults (18 years or older); the study used a sleep extension intervention (i.e. any intervention aimed at increasing participants' habitual sleep duration); outcomes were measured before and after the sleep extension intervention; reported outcomes included at least one cardiometabolic risk factor (i.e. blood pressure, blood markers of fasting cholesterol, triglycerides or glucose, body

mass index (BMI), waist circumference) or other outcomes related to these risk factors; and originally published in English (or an English translation of the article was available). Exclusion criteria were: reviews, commentaries, letters, editorials, conference proceedings, case reports, conference abstracts or non-peer reviewed articles. No exclusions were made for the design of the reviewed study.

The databases PubMed and Scopus were searched for articles published up to August 2018. The initial electronic search strategy included the following terms: “sleep-extension” or “sleep extension” or “extended sleep” or “extend sleep” or “increase sleep” or “bed time extension” or “time-in-bed extension” or “time in bed extension” or “tib extension” and “blood pressure” or “hypertension” or “cholesterol” or “glucose” or “weight” or “waist circumference” or “body mass index” or “BMI” or “metabolic syndrome” or “cardiovascular disease” or “cvd” or “non-communicable disease” or “ncd” or “cardiometabolic” in the title or abstract of the paper. This initial search strategy identified 38 items in PubMed and 36 items in Scopus. When the search was repeated with only the terms related to sleep extension, thus excluding the risk factors, 199 items were identified in PubMed and 217 in Scopus. To assure that no papers that measured cardiometabolic risk factors were excluded from this systematic review, only sleep extension related terms were included in the final search strategy. The final search terms for the PubMed and Scopus databases are presented in **Table 1**. The following filters were applied; Species: Humans; Language: English.

[preferred location Table 1]

Study selection

In the first round, articles were screened on title and abstract only. The second round involved assessing the eligibility criteria. RH and PP screened the results and tested eligibility separately. Cases of conflicts were discussed with DR and LR who served as arbitrators. The item in question was then included or excluded accordingly.

RESULTS

The article search process is depicted in **Figure 1**. The initial search identified 416 items using the search criteria described above. One hundred and fifty-seven duplicates were removed and the titles and abstracts of the remaining 259 items were screened. Of these, 236 items were excluded and 23 tested for eligibility. A further 16 items were excluded for reasons mentioned in **Figure 1**. Seven studies met the inclusion criteria set to review the effect of a sleep extension intervention on cardiometabolic risk factors. The citations in these items were also subjected to screening and eligibility testing, but none were included for reasons described in **Figure 1**.

[preferred location Figure 1]

Study characteristics

Three of the seven included studies are randomized controlled trials ~~(RCTs)~~ (Haack et al., 2013; Al Khatib et al., 2018; Reynold et al., 2014), two are cross-over trials (Killick et al., 2015; Kubo et al., 2011), and two are descriptive observational studies (Leproult et al., 2015; Tasali et al., 2014). The sample sizes of the included studies range from 10 to 42 participants. The participants comprised healthy adults (Al Khatib et al., 2018; Reynold et al., 2014), healthy, short-sleeping (<6.5h or <7h per night) adults (Killick et al., 2015; Leproult et al., 2015), ~~overweight,~~ short-sleeping (<6.5h per night) adults who were overweight (Tasali et al., 2014), short-sleeping (<6h per night) factory workers (Kubo et al., 2011) and pre- or~~and~~ hypertensive adults (Haack et al., 2013). The sleep extension intervention strategies were either (i) time-in-bed extensions or (ii) personalised sleep consultation or behaviour counselling with sleep hygiene tips, or a combination of the two. The intervention durations ranged from three days to six weeks, and sleep duration was extended successfully in all studies by 21 to 177min. Outcome variables included blood pressure, anthropometric variables, glucose, insulin and insulin sensitivity indices, appetite and hormones that influence appetite, and inflammatory markers.

Results of individual studies

Sleep extension strategy types and efficacy

The sleep extension strategies and the efficacy of the interventions in each of the included studies are summarized in **Table 2**. In the study with the longest intervention duration (6 weeks), prehypertensive and stage-1 hypertensive participants were randomized into sleep extension (n=13) and sleep maintenance (n=9) groups (Haack et al., 2013). The sleep extension group received sleep hygiene information and instructions to prolong time-in-bed by 60min daily for six weeks. Specifically, participants were instructed to go to sleep 30min earlier and rise 30min later than their usual bed and wake-up times. The sleep maintenance group also received sleep hygiene information, but was instructed to maintain their habitual bedtimes for six weeks. Total sleep time was extended by 35±9min to ~6.9h in the sleep extension group and by 4±9 min to ~6.3h in the sleep maintenance group as assessed by actigraphy (p=0.03, group-by-time interaction effect). Participants with shorter total sleep times at baseline increased sleep duration more during the sleep extension phase (r=-0.71, p<0.01).

Leproult *et al*. (2015) made use of a five- to six-week individualised sleep schedule aimed at increasing sleep duration by 60min (Leproult et al., 2015). The 16 healthy ~~non obese,~~ short-sleeping (<7h) adult participants who were not obese met with the study staff every two weeks to discuss potential difficulties with their schedules, and solutions to overcome these difficulties. The participants were also able to contact the investigators via email or telephone for further support if necessary. The study staff advised each participant to avoid physical activity within two hours of bedtime. This sleep extension strategy increased mean actigraphy-assessed sleep duration on weekdays by 44±34min from 6.0±0.5h ~~6.3±0.5h to 7.4±0.7h~~ (p<0.001). This effect was not observed on weekends, presumably because the participants' pre-intervention weekend total sleep time was already >7h.

Tasali *et al.* (2014) made use of a two-week sleep extension intervention in which ten adults who were overweight, but otherwise healthy ~~adults who~~and usually slept less than 6.5h per

night were given tips on sleep hygiene and received individualized behavioural counselling on the first day of sleep extension (Tasali et al., 2014). A follow-up visit was planned at the end of the first week. The aim of the intervention was to extend time-in-bed to 8.5h and total sleep time to 7-8h per night. On average, the participants went to bed 75min earlier and got up 30min later. Mean sleep duration assessed by actigraphy increased from 5.6±0.1h to 7.1±0.1h (p<0.001).

In another study, 14 apparently healthy participants with self-reported sleep durations of 6-9h per night and no sleep complaints were randomized to a time-in-bed extension group (n=8) and a control group (n=6) (Reynold et al., 2014). The time-in-bed extension group was instructed to increase time-in-bed by 180min per night for one week by adhering to a fixed sleep schedule. The control group was instructed to maintain their median habitual time-in-bed through a fixed sleep schedule. To avoid unintended change based on the participants' expectations, the participants were told that the intervention could have a positive effect, a negative effect or no effect. Sleep duration was assessed using actigraphy. Participants in the sleep extension group extended their sleep duration by 120min from 6.8±0.6h to 8.8±0.9h whereas those in the sleep maintenance group decreased their sleep duration by 16min from 6.9±0.4h to 6.7±0.2h (p<0.001) (Reynold et al., 2014).

In a more recent study, f~~F~~orty-two ~~non-obese,~~ healthy, habitually short-sleeping (<7h) participants who were not obese were randomized into a sleep extension group (n=21) and a control group (n=21) (Al Khatib et al., 2018). The control group was requested to keep their lifestyle, including their bedtime and get-up times, as usual, but they were offered the intervention upon completion of the study. The sleep extension group received a 45min sleep consultation session with a health psychologist. During this session, the participant was introduced to the importance of sleep, current recommendations of sleep duration, and the concept of sleep hygiene. The psychologist would then provide and talk the participant through a list of common sleep hygiene tips. The participant would select at least four tips that they thought were applicable to them, and easily implementable. These tips, barriers thereof,

implementation intentions, and agreed-upon bedtimes were then added into a contract. Participants received diaries in which they noted whether they were successful in implementing the changes on each day of the four-week intervention period (Al Khatib et al., 2018). Sleep duration, assessed by actigraphy, increased by 21min (95% CI: 6-36min) for the intervention group, which was significantly more than for the control group (-11min, 95% CI: -26-4min, p=0.004).

Kubo *et al.* (2011) applied a non-conventional sleep extension strategy; instead of extending sleep on every day of the week, sleep extension was attempted only on weekend nights (Friday, Saturday and Sunday), while the habitually short sleep during weekdays (<6h) was maintained throughout the sleep extension period of three weeks (Kubo et al., 2011). Twenty-six daytime employees in a manufacturing industry were included in this cross-over controlled trial and were instructed to stay in bed for at least 8h between 22h00 and 09h00 without taking naps during the day. Sleep duration (assessed by actigraphy) increased by 60-120min (p<0.001) on weekend days. However, sleep duration during weekdays remained at baseline level, which was approximately 5h per night. Because significant time-by-group interactions were observed for bedtime (p<0.001), but not for wake~~rising~~ time, the increased total sleep time was mainly attributed to the change in bedtime (Kubo et al., 2011).

Lastly, the study by Killick et al. (2015) was performed in a controlled environment with 10h of forced time-in-bed (Killick et al., 2015). Although this study design is indeed that of sleep extension, this intervention is not regarded as an appropriate strategy to increase habitual sleep duration. This study shall therefore not be discussed further in this section.

In summary, sleep extension strategies included ~~once-off~~single or ~~repeated~~ multiple personalized sleep consultation sessions~~s~~ (4), sleep hygiene recommendations (3), and time-in-bed extension with or without bedtime recommendations (6). Interventions with a duration of more than one week, consistently included personalized sleep counselling and generally had a less prescriptive time-in-bed extension approach (e.g. personalized bedtime recommendations). In comparison, short-term interventions (≤1 week) included a more

instructive approach to achieve time-in-bed extension (e.g. forced time-in-bed), and did not include personalized counselling. The shorter interventions produced greater extensions in time-in-bed duration compared to the longer interventions.

[preferred location Table 2]

Effect of sleep extension interventions on cardiometabolic risk factors

The effects of the various sleep extension interventions utilised in the seven included studies on outcome variables are summarised in **Table 3**.

Anthropometry

Body weight, BMI, waist circumference and percent body fat were outcome variables in the studies reviewed. Of these, two assessed changes in body weight (Al Khatib et al., 2018; Leproult et al., 2015), two assessed BMI (Haack et al., 2013; Al Khatib et al., 2018), two assessed body fat (Haack et al., 2013; Al Khatib et al., 2018) and one assessed waist circumference (Al Khatib et al., 2018) before and after the intervention. No change in mean body weight was observed following a six-week sleep extension intervention in 16 healthy~~,~~ ~~non-obese~~ adults who were not obese (Leproult et al., 2015). Likewise, four weeks of sleep extension did not change body weight in 21 short-sleeping (<7h) adults (*p*-value not reported) (Al Khatib et al., 2018). No changes were found for BMI in 12 pre- or~~and~~ hypertensive individuals who received sleep extension for six weeks (Haack et al., 2013). In neither of the two studies that reported on total body fat as an outcome variable did total body fat change as a result of the sleep extension intervention (Haack et al., 2013; Al Khatib et al., 2018). Lastly, no change in waist circumference was observed in healthy, short-sleeping (<7h) adults, following a four-week sleep extension intervention (Al Khatib et al., 2018).

Resting blood pressure and heart rate

Resting systolic blood pressure (SBP) and diastolic blood pressure (DBP) were assessed in three of the included studies (Haack et al., 2013; Kubo et al., 2011; Reynold et al., 2014) and resting heart rate (RHR) in two of the studies (Haack et al., 2013; Reynold et al., 2014). While prehypertensive and stage 1 hypertensive individuals both experienced reductions in resting SBP (14±3 mmHg, $p<0.001$) and DBP (8±3 mmHg, $p<0.02$) following sleep extension (Haack et al., 2013), the extent of this reduction was not different to that experienced by an active control group (SBP and DBP decreased by 7±5 and 3±4 mmHg respectively, $p=0.03$ for time effect, $p=0.15$ for group-by-time interaction effect) that was given sleep hygiene information. Reynold *et al.* (2014) found no changes in SBP or DBP (no *p*-value reported) in 14 healthy sleepers following a one-week sleep extension intervention (Reynold et al., 2014). Kubo *et al.* (2011) measured blood pressure in daytime factory workers on a Monday and Thursday prior to a weekend sleep extension strategy, and on the same days after the intervention (Kubo et al., 2011). No changes in either SBP or DBP were found as a result of the intervention. Neither Haack *et al.* (2013) nor Reynold *et al.* (2014) found changes in RHR following sleep extension ($p=0.87$, *p*-value not reported respectively) (Haack et al., 2013; Reynold et al., 2014).

Fasting blood glucose, ~~and~~ insulin and C-peptide levels

Fasting blood glucose, insulin and measures of insulin resistance were outcome variables in two of the reviewed studies (Killick et al., 2015; Leproult et al., 2015). A three-day sleep extension intervention did not affect fasting blood glucose in 19 healthy, short-sleeping (<6.5h) male adults ($p>0.05$) (Killick et al., 2015). Likewise, Leproult *et al*. (2015) found no effect on fasting blood glucose in 16 healthy, ~~non-obese~~ adults who were not obese following a 5-6 week sleep extension intervention (*p*-value not reported) (Leproult et al., 2015). However, changes in fasting blood glucose correlated with changes in sleep duration assessed by actigraphy ($r=0.65$, $p=0.017$), and with changes in total sleep time assessed by polysomnography ($r=0.53$, $p=0.041$) (Leproult et al., 2015), suggesting that fasting blood

glucose increases as sleep duration and total sleep time increases. Fasting plasma insulin levels in habitually short-sleeping (<6.5h) males were significantly lower following three nights of extended sleep (10h) compared to three nights of sleep restriction (6h, p<0.05) (Killick et al., 2015). Levels of serum C-peptide, a polypeptide that is required in the insulin synthesis pathway and used as a measure of insulin secretion in individuals with diabetesics (Jones and Hattersley, 2013), also decreased significantly (p<0.05) (Killick et al., 2015).

Another study found that sleep extension did not significantly change affect fasting insulin levels in 16 healthy, non-obese adults who were not obese, however, the author reported that changes in both polysomnography-assessed total sleep time (r=-0.60, p=0.025), and actigraphy-assessed sleep duration (r=-0.57, p=0.053) correlated with changes in fasting insulin levels with moderate effect sizes, despite although the correlation of the latter not being significant p-value for the latter was 0.053 (r=0.57) (Leproult et al., 2015). Changes in total sleep time as assessed by polysomnography following sleep extension, correlated with changes in the insulin-to-glucose ratio (p=0.009) and the Quantitative Insulin Sensitivity Check Index (QUICKI) (p=0.002) (Leproult et al., 2015). QUICKI was also significantly improved following 10h of sleep, as opposed to the habitual 6h of sleep in the study by Killick *et al.* (2017), as well as other measures of insulin sensitivity, such as the homeostatic model assessmentHOMA for insulin resistance (HOMA-IR) (p<0.05) and β-cell function (HOMA-β) (p<0.05). Lastly, a three-day sleep extension intervention significantly increased insulin sensitivity as determined by the oral glucose tolerance test (OGTT) in healthy, short-sleeping (<6.5h) male adults (p<0.05) (Killick et al., 2015).

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Physical activity

Of the seven identified studies, two reported on physical activity outcomes, namely step counts (Reynold et al., 2014) and physical activity intensity as percentage of awake time (Al Khatib et al., 2018). The sleep extension group in the first study increased average daily step counts from 6,442±1,772 to 7,413±2,281 steps, whereas the step count in the sleep maintenance

group increased from 5,662±1,625 to 6,246±1,583, which was reported as not significant (no *p*-value reported) (Reynold et al., 2014). The second study reported that the intervention had no effect on the percentages of awake-time spent in sedentary behaviour, or vigorous, moderate or low physical activity intensities ($p>0.05$).

To summarize, the sleep extension interventions used in the included studies resulted in no measurable changes in any of the anthropometric, cardiovascular or physical activity outcomes assessed. The twothree studies which did measure glucose and insulin-related outcomes provide preliminary evidence that increasing sleep duration may improve glucose control or insulin sensitivity. The results were inconsistent, however, indicating that more research is needed in this area.these studies have demonstrated that extension of sleep may improve fasting insulin, insulin sensitivity and serum C-peptide levels. These changes results were solely only observed in the study by Killick *et al.* (2015),two studies which took place in a controlled environment and may not be reflective of real world situations (Killick et al., 2015)and more research is needed to confirm and better understand the effect of sleep extension on these outcome variables. The sleep extension interventions used in the included studies produced resulted in nto measurable changes in any of the anthropometric, cardiovascular or physical activity outcomes assessed.

Other observations

This section describes three outcomes of sleep extension interventions that do not fall directly under the World Health Organisation's cardiometabolic risk factors for NCDs, but may influence cardiometabolic health indirectly.

Macronutrient and caloric Dietary intake

Two outcomes that areDietary intake is indirectly associated with an increased cardiometabolic risk are macronutrient and caloric intake, since itthey may contribute to overweight and obesity. Two studies assessed the effect of sleep extension on these outcome variablesdietary intake

(Haack et al., 2013; Al Khatib et al., 2018). Haack *et al*. (2013) assessed changes in daily caloric and sodium intake in prehypertensive and stage 1 hypertensive individuals and found that at the end of a six-week sleep extension intervention neither outcome changed (Haack et al., 2013). In another study, free sugar intake was reduced in the sleep extension group (by 9.6 g/day) but did not change in the control group (0.7g/day) indicating a significant time-by-group effect of the intervention on sugar intake (p=0.042) (Al Khatib et al., 2018). Additionally, the percentage of daily energy intake from protein increased in the sleep extension group (by 1.6%) and decreased~~reduced~~ in the control group (-1.9%, p=0.018 for time-by-group effect). However, no changes were observed in daily intake of carbohydrate, total sugar, total fat, saturated fat or fibre (Al Khatib et al., 2018).

~~Tasali *et al.* (2014) did not measure macronutrient or caloric~~dietary ~~intake, however, in the ten short-sleeping (<6.5h) young overweight participants~~ who are overweight~~, appetite decreased by 14% (p=0.03) in response to the intervention (Tasali et al., 2014). Moreover, while their desire for fruits, vegetables and protein-rich nutrients remained unchanged, their desire for sweet and salty foods decreased by 62% (p=0.017).~~

Satiety and appetite ~~regulators~~

Satiety and appetite arei~~s~~ partially regulated by neuronal and hormonal signals originating from the gastro-intestinal tract and adipose tissue, thereby contributingon~~on~~ to a healthy energy balance. These regulators may therefore influence energy intake and maytherefor~~e~~ contribute to weight gain and obesity. However, only Killick *et al.* (2015) reported satiety and appetite regulatory hormones as outcome variables in response to sleep extension. Significant decreases were found for plasma leptin (a hormone that increases satiety, p<0.05) and peptide tyrosine-tyrosine (PYY, a peptide that reduces appetite, p<0.05) following sleep extension, but not for ghrelin (a hormone that induces hunger, p-value not reported) (Killick et al., 2015).

Finally, in ten short-sleeping (<6.5h) young participants who were overweight, appetite decreased by 14% (p=0.03) in response to the intervention. Moreover, while their desire for fruit, vegetables and protein-rich nutrients remained unchanged, their desire for sweet and salty foods decreased by 62% (p=0.017) (Tasali et al., 2014). (Tasali *et al.* (2014).

Depression and anxiety

One study included measures of depression and anxiety as outcome variables (Reynold et al., 2014). Extending sleep duration for one week increased the Beck Depression Inventory (BDI) score from 2.4±1.8 to 5.3±4.4, suggesting an increase in depression symptoms severity, in 14 physically and mentally healthy adults, whereas the BDI score in the sleep maintenance group increased from 4.8±6.3 to 6.0±9.2. While no p-value was reported, the authors report this difference (i.e. greater increase in BDI score in the sleep maintenance group) to be non-significant (Reynold et al., 2014). In the same study, anxiety as assessed by the State-Trait Anxiety Inventory (STAI) increased from 31.3±7.4 to 33.5±9.7 in the intervention group, and decreased from 35.2±14.0 to 33.0±12.9 in the sleep maintenance group; but the difference in these changes were reported to be non-significant (Reynold et al., 2014).

Inflammatory, sympatho-adrenal, and metabolic markers

Many inflammatory, sympatho-adrenal and metabolic markers have been associated with an increased risk for cardiovascular and metabolic diseases. For example, high levels of the inflammatory marker C-reactive protein (CRP) and white blood cells (WBC) may be associated with a higher risk for coronary heart disease (Danesh et al., 1998); interleukin (IL)-6, a protein involved in both inflammatory and cardiometabolic pathways, has been linked to type 2 diabetes mellitusT2DM (Spranger et al., 2003); noradrenaline (NE) has been associated with an increased risk for mortality, especially from progressive heart failure (Cohn et al., 1984); adiponectin has been identified as an independent risk factor for metabolic syndrome (Renaldi et al., 2009); and the inflammatory marker tumour necrosis factor alpha (TNF-α) has been

shown to play a role in obesity-linked insulin resistance (Hotamisligil et al., 1993). Three of the seven studies explored the effects of sleep extension on these markers (Haack et al., 2013; Killick et al., 2015; Reynold et al., 2014). Killick *et al.* (2015) reported no significant changes in cortisol (a hormone which is released in response to stress and hypoglycaemia, *p*-value not reported) (Killick et al., 2015). Likewise, sleep extension did not significantly improve ~~WBC~~ white blood cell count, IL-6, CRP or NE in twelve pre- or~~and~~ hypertensive participants (Haack et al., 2013), and~~. Similarly,~~ a one-week time-in-bed extension intervention in healthy sleepers did not change CRP, IL-6, adiponectin or TNF-α levels (Reynold et al., 2014)

Resting metabolic rate

Resting metabolic rate (RMR) may be regarded as an indirect cardiometabolic risk factor due to its association with long-term weight gain (Ravussin et al., 1988). One study reported on the effect of sleep extension on RMR as assessed by indirect calorimetry and found that RMR did not increase more in the sleep extension group than in the sleep maintenance group ($p>0.05$) (Al Khatib et al., 2018).

Collectively, these studies have shown that sleep extension may decrease daily free sugar intake, increase daily energy intake from proteins, decrease leptin and PYY levels, and reduce appetite and desire for sweet and salty foods, all of which combined may contribute to a reduced energy intake and promote a healthy weight. Neither depression, anxiety, inflammatory, sympatho-adrenal, metabolic markers nor resting metabolic rate changed in response to the sleep extension interventions implemented in the reviewed studies.

[preferred location Table 3]

DISCUSSION

The aim of this ~~study~~ systematic review was to examine the effects of sleep extension interventions on cardiometabolic risk factors in adults. Based on the seven studies reviewed, three categories of outcome variables changed in response to sleep extension: those related to insulin sensitivity (Killick et al., 2015), to dietary~~energy~~ intake (Al Khatib et al., 2018; Killick et al., 2015) and to appetite (Tasali et al., 2014).

Since ~~Previous~~ previous studies have shown that short sleep is associated with higher fasting glucose and insulin concentrations (Ford et al., 2013) and reduced insulin sensitivity (Matthews et al., 2012), it~~.~~ ~~Thus it~~ seems plausible to hypothesise that increasing sleep duration may improve these metabolic indices. ~~Two studies provide some support for the hypothesis that sleep extension may improve insulin sensitivity in individuals with habitually short sleep but who are otherwise healthy (Killick et al 2015, Leproult et al 2015).~~ ~~However, i~~It is intriguing that Killick *et al.* (2015) reported significant improvements in insulin sensitivity-related outcomes (HOMA-IR, HOMA-β, QUICKI) and fasting insulin in ~~healthy~~ short-sleeping (<6.5h) ~~males~~ participants whose indices were within the healthy range at baseline. Furthermore, these changes were measured in response to the shortest sleep extension strategy (three days) reviewed. While these results may be attributed to the impressive sleep extension recorded ~~(±177min, the largest of the reviewed studies)~~, these data must be interpreted with care as sleep extension was achieved by forced time-in-bed in a controlled environment which may not be translatable to a real-world situation. Given the short intervention period, these findings do not shed light on long-term improvements in insulin sensitivity-related outcomes, and future research is needed to confirm whether similar effects are observed in ~~insulin resistant or diabetic~~ short-sleeping individuals with insulin resistance or diabetes.

At first glance the Leproult *et al.* (2015) study does not appear to provide support for sleep extension being a successful intervention for improving insulin sensitivity ~~sensitivity in healthy non-obese, individuals~~. ~~Their observation that individuals who had larger increases in sleep duration (actigraphy) and/or total sleep time (polysomnography) over the 5-6 week study period were more likely to have larger reductions in insulin-to-glucose ratio, and fasting glucose~~

and insulin levels and a larger increase in QUICKI (Leproult et al., 2015) However, the correlations between change in sleep duration and change in insulin sensitivity-related outcomes indicates some role for increasing sleep duration. While there this study are certainly had limitations to the Leproult *et al.* (2015) study (no control group, no direct assessment of insulin sensitivity in response to a glucose challenge (Leproult et al., 2015)(Leproult *et al.* (2015)), the extent to which fasting glucose levels wereas reduced was similar to that observed in overweight and obese individuals who arewere overweight or obese and who undertook 12 weeks of high intensity interval training (HIIT) (Batacan et al., 2016). Although comparisons between the two interventions are difficult because of the differences in populations studied and reporting of the data, one might speculate that a sleep extension intervention may be as effective in improving fasting glucose and insulin levels as exercise, specifically high intensity interval trainingHIIT.

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Conflicting findings exist between the two reviewed studies that reported on energy intake, with one finding Of the two studies which reported on outcome variables that were related to energy intake (Haack et al., 2013; Al Khatib et al., 2018), only one observed an effect of the sleep extension intervention. In this study, a four-week intervention resulted in a concurrent reduction in energy intake from free sugars and an increase in energy intake from protein in non obese, healthy, short sleeping (<7h) adults (Al Khatib et al., 2018). The findings of thea reduction in energy intake from free sugars, and an increase in energy intake from protein in response to the sleep extension interventionin the study by() and the other reporting no such changes (Haack et al., 2013) (). One might speculate that the reason for Haack *et al.* (2013) not observing any similar finding relates to the pre- orand hypertensive nature of the participants studied. Without any normotensive control group, one cannot ascertain whether hypertension hads any confounding effect on dietaryenergy intake.

The outcome variables that were related to appetite can be divided in appetite and desire for certain foods, and levels of hunger, satiety and appetite regulatory hormones and peptides. Tasali *et al.* (2014) demonstrated that two weeks of sleep extension in overweight, short-

~~sleeping (<6.5h) young adults reduced overall appetite as well as desire for sweet and salty food.~~ There is resonance between the observations ~~latter~~ ~~finding~~that sleep extension ~~of~~ reduces~~d~~ overall appetite and desire for sweet and salty food (Tasali et al., 2014)~~in the study by~~(~~observation resonates well with the finding~~and ~~of~~ reduced~~tion~~ ~~in~~ daily free sugar intake ~~reported by~~(~~Al Khatib *et al.* (2018)~~). These studies ~~thus~~ suggest that short-sleeping adults may benefit from sleep extension in cases where appetite-control and food choice are desired behaviour changes relating to weight loss. However, there is no evidence to support that this may translate to a reduction in daily caloric intake, especially in light of the two studies included in this review which showed no change in caloric intake in response to sleep extension (Haack et al., 2013; Al Khatib et al., 2018). Furthermore, since Tasali *et al.* (2014) included~~had~~ no control group, one cannot conclude that sleep extension alone was responsible for the outcome observed. ~~it remains unknown whether the findings by Tasali et al. (2014) are a result of the sleep extension alone or of other factors, as no control group was included.~~ Additionally, since ~~the~~ overall appetite and desire for sweet and salty food were only assessed in the morning, and since food desirability has been shown to be affected by time-of-day (Spaeth et al., 2013), one may speculate that appetite and desire for certain foods may be different in the evening. This is especially important since caloric intake and consumption of calories during late-night hours in chronically sleep-restricted individuals may ~~cause~~ result susceptibility to weight gain (Spaeth et al., 2013).

Since leptin and PYY are understood to inhibit hunger (Batterham et al., 2002; Joannic et al., 1998), the observation of ~~The reductions in~~reduced leptin and PYY (but not ghrelin) following sleep extension (Killick et al., 2015) ~~in the study ()~~appears to be at odds with ~~the findings~~that of reduced appetite (Tasali et al., 2014)~~in the study by()~~.~~,~~ On one hand, since neither study measured both variables, ~~since leptin and PYY are understood to inhibit hunger A third study in short-sleeping (<6.5h) healthy males reported reductions in leptin and PYY, but not in ghrelin, in response to three days of sleep extension (Killick et al., 2015). Leptin and PYY are understood to inhibit hunger (Batterham et al., 2002; Joannic et al., 1998). Wh~~, thus lower

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~~levels of leptin and PYY may increase hunger, which appears to be at odds with the findings of reduced appetite (Tasali et al., 2014). Whether these~~one cannot conclude that lower levels of leptin and PYY translates to ~~actually~~ increased appetite ~~in the study by Killick *et al.* (2015) was not assessed, although no difference in energy intake was observed~~. Differences in study design and participants may also account for these seemingly contradictory findings~~,~~. ~~for example, Tasali *et al.* (2014) assessed food desirability only in the morning, and did not include a control group and could therefore not account for confounding factors.~~ Previous studies have found that sleep restriction increases plasma leptin, resulting in an increase in energy intake (Spiegel et al., 2004), while others have found that sleep restriction increases energy intake despite a decrease in plasma leptin and PYY (Markwald et al., 2013). Thus the mechanisms behind any association between sleep, appetite, leptin and PYY appear to be more complicated and require further investigation.

Given the large body of evidence that suggests that short sleep duration is associated with weight gain (Patel and Hu, 2008), overweight (Roda et al., 2016) and obesity (Wu et al., 2014), it is surprising that so few studies have explored the effect of sleep extension on body composition. Of the three that did so in this review, ~~None~~ not one ~~of the studies reviewed~~ found significant improvements in any anthropometric outcomes following sleep extension (Haack et al., 2013; Al Khatib et al., 2018; Leproult et al., 2015). A possible explanation for two of these studies may be that the participants were of healthy weight or not ~~n~~ obese ~~weight~~ when recruited (Al Khatib et al., 2018; Leproult et al., 2015)~~,~~, thus improvements in anthropometric outcomes may have been unlikely. ~~(Al Khatib et al., 2018; Leproult et al., 2015).~~ Additionally, one might speculate that the intervention durations of these three studies (4-6 weeks) may have been too short for reductions in weight or total body fat to occur, or co-interventions such as exercise and diet may be required. While the findings of the reviewed studies do not support the hypothesis that sleep extension interventions improve body weight, BMI ~~and/~~or body fat, ~~interventions~~ studies in participants ~~who are obese~~with obesity are needed before the hypothesis can be rejected. ~~Given the large body of evidence that suggests that short sleep~~

~~duration is associated with weight gain (Patel and Hu, 2008), overweight (Roda et al., 2016) and obesity (Wu et al., 2014), it is surprising that so few studies have explored the effect of sleep extension on body composition.~~

~~Sleep extension did not improve blood pressure or RHR outcomes in any of the three included studies which measured these outcomes (Haack et al., 2013; Kubo et al., 2011; Reynold et al., 2014). One explanation for the lack of response in blood pressure and RHR in two of the studies (Kubo et al., 2011; Reynold et al., 2014)~~

The participants in two of the three studies that assessed blood pressure and RHR in response to sleep extension were ~~may be that the participants were~~ normotensive on average, and baseline RHR was within the normal (60-100 bpm) range[1] ~~(Haack et al., 2013;~~ Kubo et al., 2011; Reynold et al., 2014).~~.~~ It was therefore unlikely for improvements in these variables to occur. Furthermore, the intervention durations of these two studies (3 days to a week) may not have been sufficiently long to invoke any change in blood pressure. To the best of our knowledge, no study has reported a decrease in SBP or DBP with any non-pharmacological intervention after just one week. On the other hand, Haack *et al.* (2013) had a longer sleep extension period of six weeks, and only included prehypertensive and stage 1 hypertensive participants, and still, no significant improvement in blood pressure was observed. However, the reductions in ~~systolic~~ SBP and ~~diastolic blood pressure~~DBP observed between the start and end of the sleep extension intervention (14mmHg and 8mmHg respectively) in the intervention group, although not significant, were similar to those observed in other lifestyle interventions, albeit in a shorter time frame (Blumenthal et al., 2010; Somers et al., 1991). For example, a six-month endurance training programme was shown to reduce resting SBP and DBP by 10mmHg and 7mmHg respectively (Somers et al., 1991). Likewise, in a study in which both dietary and exercise interventions were implemented, SBP and DBP decreased by 10mmHg and 5mmHg respectively (Blumenthal et al., 2010). Therefore, one explanation for the absence of any significant change may be the study's lack of statistical power due to a small sample size, rather than a lack of clinical change in blood pressure. Collectively these

data suggest that sleep extension is unlikely to benefit normotensive individuals by reducing resting blood pressure. More research with medium- or long-term sleep extension interventions are required to establish the effect on lowering resting blood pressure in short-sleeping individuals with hypertension.

None of the included studies found significant improvements in any physical activity-related outcomes following sleep extension. ~~Of the two studies which measured physical activity as an outcome, neither showed any effect of sleep extension (1-4 weeks) on daily step count, time spent in either moderate or vigorous physical activity, or sedentary behaviour as a percentage of active time in healthy individuals (Reynold et al., 2014) or non-obese short-sleepers (<7h) (Al Khatib et al., 2018).~~ Limitations in the study by Reynold *et al.* (2014) were that the effect-size between the two groups was calculated independently of the other group, and the results of hypothesis testing were not reported. Nevertheless, these findings are in line with studies conducted on individuals with sleep disorders (Kline et al., 2014; West et al., 2009). For example, Kline *et al.* (2014) used brief behavioural therapy to improve sleep quality in older adults with insomnia reported no change in daytime physical activity levels (Kline et al., 2014), and West *et al.* (2009) observed that continuous positive airway pressure ~~(CPAP)~~ treatment did not increase physical activity in patients with obstructive sleep apnoea, despite improvements in daytime sleepiness (West et al., 2009). More research is required to definitively conclude whether or not a sleep extension intervention plays any role in increasing voluntary moderate to vigorous physical activity levels, or reducing sedentary time in short-sleeping adults. In addition, the effect of extending sleep duration on compliance to supervised physical activity programs should also be investigated.

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~~Only one of the reviewed studies measured markers of depression and anxiety in response to sleep extension, and by sleep extension in the study by Reynold *et al.* (2014), yet the authors postulated that depression worsened following the intervention.~~ The worsening of markers of depression and anxiety in the study by Reynold et al. (2014) ~~latter~~ is an unexpected finding; one would expect depression to improve in response to such an intervention since depression

has been associated with both short and long sleep (Zhai et al., 2015). The authors speculated that by extending time-in-bed to ±10h, and sleep to almost 9h, a scenario of forced sleep was created, which may have contributed to the alleged worsening of depression. It must be noted, however, that the increase in BDI score following the time-in-bed extension is minimal, since the BDI score ranges from 0 to 63, and scores below 9 (as observed in this study) are thought to reflect “minimal” depression. The difference between the baseline and follow-up BDI scores may not be clinically relevant as both indicate an absence of depression, even if the effect was significant. Furthermore, the sleep extension and sleep maintenance groups were not matched for depression and the analyses for one group was performed independently of the other (Reynold et al., 2014). The interactions between depression, cardiometabolic risk factors and sleep are complex and it is not fully understood whether sleep and depression are independent or overlapping risk factors for cardiometabolic disease (Mezick et al., 2011). Future studies on sleep extension in short-sleeping individuals with symptoms of depression and anxiety may shed more light on the relationships between depression, cardiometabolic risk factors and sleep.

The hypothesis that sleep extension might improve inflammatory, sympatho-adrenal and metabolic markers (i.e. cortisol, IL-6, CRP, adiponectin, NE, TNF-α levels or white blood cell~~WBC~~ count) are not supported by the reviewed studies. Study design may explain the lack of findings in these studies. First, two of the studies may have been underpowered due to the small sample size, and therefore not able to detect changes in these markers (Haack et al., 2013; Reynold et al., 2014). Second, the extent to which sleep duration was increased (Haack et al., 2013) or the short duration of the intervention (Reynold et al., 2014) may have been insufficient for changes in these markers to occur. Third, the blood markers were all within a normal range at baseline; thus the effect of any non-pharmacological intervention that attempts to ‘normalise’ behaviour may not affect these markers. Future studies with larger sample sizes longer interventions in short-sleeping individuals with inflammatory, sympatho-adrenal and

metabolic markers outside of the normal range at baseline may help elucidate the effect of sleep extension on these markers.

Lastly, ~~one reviewed study included RMR as an outcome variable, and it was found not to be affected by sleep extension. T~~to the best of our knowledge, only one study has investigated the relationship between sleep duration and RMR and found that RMR did not differ between short (5-6h), average (7-8h) and long (9-10h) sleepers (Chaput et al., 2008). T~~hus t~~he finding~~s~~ by Al Khatib *et al.* (2018) that RMR was not affected by sleep extension is ~~are~~ thus in line with this observation.

Of the seven different sleep extension strategies employed, those that reported the largest increases in total sleep time were achieved by extending time-in-bed by 2-4h. It remains to be seen, however, whether these strategies are sustainable over an extended period of time. Indeed, of the reviewed studies, those that extended total sleep time by the most also had the shortest study periods (Killick et al., 2015; Kubo et al., 2011; Reynold et al., 2014). Kubo *et al.* (2011) reported that after the time-in-bed extension, the participants immediately returned to their habitual sleep duration suggesting that long-term, and drastic sleep extension may be difficult to achieve. Tasali *et al.* (2014) included sleep hygiene tips and behaviour change counselling in their time-in-bed extension strategy and successful increased sleep duration over a longer period (two weeks). Thus time-in-bed extension alone, without any personalized counselling or improvement of sleep hygiene, may not result in sustainable changes in sleep duration in the long term. Furthermore, since none of the included studies performed long-term follow-ups, the sustainability of these interventions is unknown. Long-term sleep extension may not have been the aim of these studies and it is likely that different sleep extension interventions may be better suited for different populations of desired outcomes. Instructive time-in-bed extension may increase total sleep time dramatically from the first night, which is ideal for studies in which the effect of acute short-term sleep extension is investigated, while interventions that include sleep hygiene and bedtime routine may increase total sleep time less dramatically initially, but may increase compliance over an extended period of time. Therefore,

for the purpose of improving cardiometabolic health, suggestive, rather than instructive, personalized sleep extension strategies that include sleep hygiene education may be most appropriate and sustainable.

Limitations

In addition to the limitations present in the reviewed studies, this systematic literature review has its own limitations. First, only papers in the English language were included. Any relevant papers written in other languages that were not translated to English are therefore not included in this review. Second, the search terms used to describe the sleep extension intervention may not cover all terminology used for this type of intervention. It is therefore possible that papers by authors who describe the intervention differently are not included. However, the terminology used in the included articles and the papers in the reference lists of the included articles were also assessed without any other terminology of the sleep extension intervention mentioned. Finally, this review focuses on the extension of sleep duration, not the quality thereof. Thus, the results are not applicable to interventions such as Cognitive Behavioural Therapy for Insomnia that aim to improve sleep in general (i.e. improve quality and quantity of sleep).

CONCLUSION

Evidence from this systematic review indicates that increasing sleep duration over a 3-day to 6-week period is a viable, implementable intervention which may improve direct and indirect measures of insulin sensitivity, as well as appetite and dietary intake. However, no changes were observed in other cardiometabolic risk factors such as anthropometric outcomes, blood pressure, inflammatory, sympatho-adrenal or metabolic markers, depression and anxiety, physical activity and resting metabolic rate. These findings may be relevant to researchers, medical practitioners, dieticians, exercise physiologists and other professionals who are involved in weight loss and preventive medicine.

~~Since all seven studies successfully increased sleep duration over periods of 3 days to 6 weeks, however, sleep extension appears to be a viable intervention to explore in short-sleeping adults. Indeed, it has been shown to be effective in collegiate athletes (Mah et al., 2011).~~ The current evidence to support the role of sleep extension interventions to reduce risk for cardiometabolic disease risk is sparse, however, and the diversity of study designs and participants used make the data difficult to synthesise. Future studies assessing sleep extension strategies in larger cohorts, encompassing children, teenagers, older adults and diseased populations are still required, however, as well as evidence supporting the long term sustainability of such interventions.

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Figure 1. Outline of the literature search procedure and article selection.

Table 1. Final search terms used to search the Pubmed and Scopus databases.

Database	Search term
PubMed	(“Sleep-extension” [Title/Abstract] OR “Sleep extension”[Title/Abstract] OR “extended sleep”[Title/Abstract] OR “extend sleep”[Title/Abstract] OR “increase sleep”[Title/Abstract] OR “bed time extension”[Title/Abstract] OR “time-in-bed extension”[Title/Abstract] OR “time in bed extension”[Title/Abstract] OR “tib extension”[Title/Abstract])
Scopus	TITLE-ABS ("Sleep-extension") OR TITLE-ABS ("Sleep extension") OR TITLE-ABS ("extended sleep") OR TITLE-ABS ("extend sleep") OR TITLE-ABS ("increase sleep") OR TITLE-ABS ("bed time extension") OR TITLE-ABS ("time-in-bed extension") OR TITLE-ABS ("time in bed extension") OR TITLE-ABS ("tib extension")

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Table 2. An overview of the sleep extension strategies and efficacy in each of the included studies, in order of intervention duration.

Citation	Study design	Population	Group	Sample size	Strategy	Duration of intervention	Sleep duration			*P*-value
							From (h)	To (h)	Difference (min)	
Haack *et al.* (2013)	RCT	Prehypertensive or stage 1 hypertensive adults (<7h sleep duration)	Intervention	13	Go to bed 30min earlier and 30min later (+60min) Sleep hygiene recommendations Weekly contact to discuss problems	6 weeks	6.3±0.2	~6.9	35±9	0.03 (GxT)
			Comparison	9	Maintain habitual bedtimes Sleep hygiene recommendations		6.2±0.3	~6.3	4±9	
Leproult *et al.* (2015)	DOS	Healthy adults who were not obese (<7h sleep duration and weekend catch-up sleep)	Intervention	16	Personalized sleep schedule to increase sleep by 60min per day Biweekly meeting to discuss difficulties, apply improvements to schedule Ability to contact investigators via phone or email	5-6 weeks	6.03±0.5	~6.77.4±0.7	44±34	<0.0001 (G)
Al Khatib *et al.* (2018)	RCT	Healthy adults who were not obese (5-7h habitual sleep duration)	Intervention	21	Personalized sleep consultation session Sleep hygiene recommendations Personalized bedtime recommendations	4 weeks	5.5 (95% CI: 5.8-6.3)	~5.8	21 (95% CI: 6-36)	0.004 (GxT)
			Comparison	21	Maintain habitual short sleep (<7h)		5.9 (95% CI: 5.6-6.2)	~5.7	-11 (95% CI: -26-4)	
Tasali *et al.* (2014)	DOS	Young adults who were overweight (<6h sleep duration)	Intervention	10	Individualized behavioral counseling on sleep hygiene on first day of intervention period: all social and environmental factors discussed; Counseling on modifiable factors and other barriers; Time in bed extension to 8.5h; Further counseling provided if needed after 1 week.	2 weeks	5.6±0.1	7.1±0.1	~96	<0.001 (T)
Reynold *et al.* (2014)	RCT	Healthy adults (6-9h sleep duration, no sleep complaints)	Intervention	8	Fixed personalized sleep schedule to spend an additional 180min in bed each night TIB must be spent trying to sleep (no distractions)	1 week	6.8±0.6	8.8±0.9	+120 effect-size: 2.66	NA
			Comparison	6	Fixed habitual bedtime schedule		6.9±0.4	6.7±0.2	-16 effect-size: 0.91	
Kubo *et al.* (2011)	COT	Adult daytime industrial workers (6h sleep duration)	Intervention	26	Stay in bed for at least 8h between 22h00-09h00 on Friday, Saturday and Sunday	3 days	~<6	~<8	~120	<0.001 (GxT)

			Comparison (crossover)		Keep habitual sleep-wake patterns					
Killick *et al.* (2015)	COT	Healthy male adults (<6.5h weeknight sleep duration and weekend catch-up sleep)	Intervention	8	Time-in-bed extension to 10h in sleep lab	3 days	6.2±0.1	~9.2	~177	NA
			Comparison (crossover)	8	Time-in-bed restriction to 6h in sleep lab	3 days	6.2±0.1	~5.8	~-23	NA

COT: cross-over trial; DOS: descriptive observational study; G: group-effect; GxT: group and time interaction; RCT: randomized control trial; T: time-effect. Values following '~' are converted from text when no actual values were available. For example, "~<6h360 min" means that the approximate total sleep time is less than 6h360 min, because the inclusion criteria was sleeping less than 6h each night, and for "~6.9h413", the post-intervention total sleep time was not reported, so the difference was added to or subtracted from the pre-intervention total sleep time.

Table 3. The effect of sleep extension on outcome variables.

	Citation	Study design	Population	Sample size*	Sleep extension	Effect	*P*-Value
Adiponectin	Reynold *et al.* (2014)	RCT	Healthy adults (6-9h sleep duration)	8/14	↑ 120±19min in 1 week	↔	NS, (ES=-0.08)
Alcohol	Al Khatib *et al.* (2018)	RCT	HNon-obese healthy adults who were not obese (< 7h sleep duration)	21/42	↑ 2 min in 4 weeks	↔	0.226 (GxT)
Appetite	Tasali *et al.* (2014)	DOS	Overweight Sshort-sleeping (<6.5h) young adults who were overweight	10/10	↑ 96min in 2 weeks	Overall appetite: ↓ 14%	0.03 (T)
						Desire for sweet and salty foods: ↓ 62%	0.017 (T)
						Desire for fruits: ↔	0.632 (T)
						Desire for vegetables: ↔	0.478 (T)
						Desire for protein-rich nutrients: ↔	0.764 (T)
Blood pressure	Haack *et al.* (2013)	RCT	Pre- orand hypertensive adults (<7h sleep duration)	13/22	↑ 35±9min for 6 weeks	SBP: ↔	<0.001 (T) 0.15 (GxT)
						DBP: ↔	<0.02 (T) 0.21 (GxT)
	Kubo *et al.* (2011)	COT	Short-sleeping (≤6h) daytime industrial workers	26/26	↑ 60-120min for 3 days	SBP: ↔	0.171 (GxT)
						DBP: ↔	0.869 (GxT)

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	Citation	Study design	Population	Sample size*	Sleep extension	Effect	*P*-Value
	Reynold *et al.* (2014)	RCT	Healthy adults (6-9h sleep duration)	8/14	↑ 120±19min in 1 week	SBP: ↔	NS, (ES=-0.07)
						DBP: ↔	NS, (ES=0.02)
Body fat	Haack *et al.* (2013)	RCT	Pre- or~~and~~ hypertensive adults (<7h sleep duration)	13/22	↑ 35±9min for 6 weeks	↔	0.74 (GxT)
	Al Khatib *et al.* (2018)	RCT	~~Non-obese, H~~healthy adults who were not obese (5-7h sleep duration)	21/42	↑ 21min in 4 weeks	↔	NS (GxT)
BMI	Haack *et al.* (2013)	RCT	Pre- or~~and~~ hypertensive adults (<7h sleep duration)	13/22	↑ 35±9min for 6 weeks	↔	0.14 (GxT)
	Al Khatib *et al.* (2018)	RCT	Healthy adults who were not obese (5-7h sleep duration)~~Non-obese, healthy adults (5-7h sleep duration)~~	21/42	↑ 21min in 4 weeks	↔	NS (GxT)
Body weight	Leproult *et al.* (2015)	DOS	Healthy ~~non-obese~~ adults who were not obese (<7h sleep duration)	-/16	↑ 44±34min in 5-6 weeks	↔	0.81 (G)
	Al Khatib *et al.* (2018)	RCT	Healthy adults who were not obese (5-7h sleep duration)~~Non-obese, healthy adults (5-7h sleep duration)~~	21/42	↑ 21min in 4 weeks	↔	NS (GxT)
Cortisol	Killick *et al.* (2015)	COT	Healthy male adults (<6.5h sleep duration)	8/8	↑ 177min in 3 days	↔	>0.05 (G)
C-peptide	Killick *et al.* (2015)	COT	Healthy male adults (<6.5h sleep duration)	8/8	↑ 177min in 3 days	↓	<0.05 (G)
C-reactive protein	Haack *et al.* (2013)	RCT	Pre- or~~and~~ hypertensive adults (<7h sleep duration)	13/22	↑ 35±9min for 6 weeks	↔	0.12 (GxT)
	Reynold *et al.* (2014)	RCT	Healthy adults (6-9h sleep duration)	8/14	↑ 120±19min in 1 week	↔	NS, (ES=-0.04)
Depression & anxiety	Reynold *et al.* (2014)	RCT	Healthy adults (6-9h sleep duration)	8/14	↑ 120±19min in 1 week	BDI: ↔	NS, (ES=-0.86)
						STAI: ↔	NS, (ES=-0.26)
Dietary intake	Haack *et al.* (2013)	RCT	Pre- or~~and~~ hypertensive adults (<7h sleep duration)	13/22	↑ 35±9min in 6 weeks	Daily Caloric intake: ↔	0.56 (GxT)
						Daily Sodium intake: ↔	0.39 (GxT)
						Daily carbohydrate intake: ↔	>0.10 (GxT)
						Daily fat intake: ↔	>0.10 (GxT)
						Daily protein intake: ↔	>0.10 (GxT)

	Citation	Study design	Population	Sample size*	Sleep extension	Effect	*P*-Value
	Al Khatib *et al.* (2018)	RCT	Healthy adults who were not obese (5-7h sleep duration)~~Non-obese, healthy adults (5-7h sleep duration)~~	21/42	↑ 21min in 4 weeks	Free sugars intake g/day: ↓; %cal: ↔	0.042; 0.181 (GxT)
						Caloric intake g/day: ↔	0.259 (GxT)
						Protein intake g/day: ↔; %cal: ↑	0.570; 0.018 (GxT)
						Carbohydrate intake g/day: ↔; %cal: ↔	0.083; 0.898 (GxT)
						Total sugar intake g/day: ↔; %cal: ↔	0.164; 0.867 (GxT)
						Fiber intake g/day: ↔	0.329 (GxT)
						Fat intake g/day: ↔; %cal: ↔	0.162; 0.074 (GxT)
						Saturated fat intake g/day: ↔; %cal: ↔	0.390; 0.421 (GxT)
Ghrelin	Killick *et al.* (2015)	COT	Healthy male adults (<6.5h sleep duration)	8/8	↑ 177min in 3 days	↔	>0.05 (G)
Glucose (fasting)	Leproult *et al.* (2015)	DOS	Healthy adults who were not obese (<7h sleep duration)~~Healthy non-obese adults (<7h sleep duration)~~	16/16	↑ 44±34min in 5-6 weeks	↔	>0.05 (G)
	Killick *et al.* (2015)	COT	Healthy male adults (<6.5h sleep duration)	8/8	↑ 177min in 3 days	↔	>0.05 (G)
Heart rate	Haack *et al.* (2013)	RCT	Pre- or~~and~~ hypertensive adults (<7h sleep duration)	13/22	↑ 35±9min in 6 weeks	↔	0.87 (GxT)
	Reynold *et al.* (2014)	RCT	Healthy adults (6-9h sleep duration)	8/14	↑ 120±19min in 1 week	↔	NS, (ES=0.19)
Insulin (fasting)	Leproult *et al.* (2015)	DOS	Healthy adults who were not obese (<7h sleep duration)~~Healthy non-obese adults (<7h sleep duration)~~	16/16	↑ 44±34min in 5-6 weeks	↔	>0.05 (G)
	Killick *et al.* (2015)	COT	Healthy male adults (<6.5h sleep duration)	8/8	↑ 177min in 3 days	↓	<0.05 (G)
Insulin sensitivity	Leproult *et al.* (2015)	DOS	Healthy adults who were not obese (<7h sleep duration)~~Healthy non-obese adults (<7h sleep duration)~~	16/16	↑ 44±34min in 5-6 weeks	Insulin-to-glucose ratio: ↔	>0.05 (G)
						QUICKI: ↔	>0.05 (G)
						HOMA-IR: ↔	>0.05 (G)
	Killick *et al.* (2015)	COT	Healthy male adults (<6.5h sleep duration)	8/8	↑ 177min in 3 days	Insulin sensitivity (OGTT, minimal model analysis): ↑	<0.05 (G)

	Citation	Study design	Population	Sample size*	Sleep extension	Effect	*P*-Value
						HOMA-IR: ↓	<0.05 (G)
						HOMA-β: ↓	<0.05 (G)
						QUICKI: ↑	<0.05 (G)
Interleukin-6	Haack *et al.* (2013)	RCT	Pre- or~~and~~ hypertensive adults (<7h sleep duration)	13/22	↑ 35±9min for 6 weeks	↔	0.61 (GxT)
	Reynold *et al.* (2014)	RCT	Healthy adults (6-9h sleep duration)	8/14	↑ 120±19min in 1 week	↔	NS, (ES=-0.65)
Leptin	Killick *et al.* (2015)	COT	Healthy male adults (<6.5h sleep duration)	8/8	↑ 177min in 3 days.	↓	<0.05 (G)
Norepinephrine	Haack *et al.* (2013)	RCT	Pre- or~~and~~ hypertensive adults (<7h sleep duration)	13/22	↑ 35±9min for 6 weeks	↔	0.92 (GxT)
Peptide YY	Killick *et al.* (2015)	COT	Healthy male adults (<6.5h sleep duration)	8/8	↑ 177min in 3 days	↓	<0.05 (G)
Physical activity	Reynold *et al.* (2014)	RCT	Healthy adults (6-9h sleep duration)	8/14	↑ 120±19min in 1 week	Average daily steps: ↔	NS, (ES: -0.48)
	Al Khatib *et al.* (2018)	RCT	Healthy adults who were not obese (5-7h sleep duration)~~Non-obese, healthy adults (5-7h sleep duration)~~	21/42	↑ 21min in 4 weeks	Physical activity intensity: ↔	NS (GxT)
Resting metabolic rate	Al Khatib *et al.* (2018)	RCT	Healthy adults who were not obese (5-7h sleep duration)~~Non-obese, healthy adults (5-7h sleep duration)~~	21/42	↑ 21min in 4 weeks	↔	NS (GxT)
Tumor necrosis factor alpha	Reynold *et al.* (2014)	RCT	Healthy adults (6-9h sleep duration)	8/14	↑ 120±19min in 1 week	↔	NS, (ES: -0.09)
Waist circumference	Al Khatib *et al.* (2018)	RCT	Healthy adults who were not obese (5-7h sleep duration)~~Non-obese, healthy adults (5-7h sleep duration)~~	21/42	↑ 21min in 4 weeks	↔	NS (GxT)
White blood cell count	Haack *et al.* (2013)	RCT	Pre- or~~and~~ hypertensive adults (<7h sleep duration)	13/22	↑ 35±9min in 6 weeks	↔	0.88 (GxT)

BDI: Beck Depression Inventory II; COT: cross-over trial; DBP: diastolic blood pressure; DOS: descriptive observational study; ES: effect size; G: group-effect; GxT: group and time interaction; HOMA-IR: homeostatic model assessment for insulin resistance; HOMA-β: homeostatic model assessment for β-cell function; NS: not significant; OGTT: oral glucose tolerance test; QUICKI: Quantitative Insulin Sensitivity Check Index; RCT: randomized control trial; SBP: systolic blood pressure; STAI: State-Trait Anxiety Inventory; T: time-effect; %cal: as percentage of daily caloric intake. ↔: no significant change; ↓: significant decrease; ↑: significant increase. *Sample size reported as sleep extension group / total sample size.