A SLEEP BEHAVIOUR INTERVENTION TO IMPROVE CARDIOMETABOLIC HEALTH IN ADULTS WITH OVERWEIGHT AND OBESITY

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Declaration of author's work

Plagiarism is to use another person's work and pretend that it is one's own. The author knows plagiarism is wrong.

The author declares that this thesis is his own work and is in his own words. Each contribution to this thesis from the work of others has been attributed, cited and referenced.

The study was conceptualized by the author's supervisor Dr Dale Rae and co-supervisor A/Prof Laura Roden. The application for approval by the University of Cape Town Human Rights Ethic Committee was compiled by the author's supervisors and him.

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The recruitment of participants for Chapter 3, Chapter 4, Chapter 5, and the associated administration and communication were carried out by the author. Most procedures, including the home-based polysomnography and phlebotomy were performed by the author. Only the dual x-ray absorptiometry scans and blood analyses were done by others, namely by a private radiologist and a commercial blood analysis lab respectively. The author also performed the data analyses, drafting of figures, and discussion of findings. These chapters were reviewed by the author's supervisors. At the time of thesis submission, the manuscript for these chapters were being prepared for publication.

Finally, the formulation of ideas in Chapter 6 are the author's view and in the author's own words and the chapter was also reviewed by the author's supervisors.

Signed by candidate

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About the Author

Rob Henricus Petrus Henst was born on the 12th of March in Schaijk, the Netherlands. He graduated from pre-vocational secondary education (VMBO) in 2005 and continued to study process and laboratory technology at an intermediate vocational educational (MBO) institution. In 2009, Rob started with a Bachelor of Science degree, majoring in Life Science with a minor in Exercise Science. For his undergraduate thesis in 2012, he moved to South Africa where he was introduced to chronobiology in exercise science. In 2013, Rob continued to study in South Africa for his Master of Science (Exercise Science) degree and published his first peer-reviewed article in the *Journal of Biological Rhythms*. He then developed an interest in sleep and cardiometabolic health, specifically in the context of public health. In 2015, these interests were combined and lead to his current PhD thesis on a sleep behaviour intervention for the betterment of cardiometabolic health. In this year, he also co-founded the business unit *Sleep Science* within the Sports Science Institute of South Africa to help individuals sleep better. In 2019, Rob moved back to the Netherlands to write the final pages of his PhD thesis.

Contents

Abbreviations

ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
BDI	Beck Depression Inventory
BMI	Body Mass Index
BP	Blood Pressure
CMD	Cardiometabolic Disease
CON	Control Group
CPSS	Cohen's Perceived Stress Scale
CRP	C-reactive Protein
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
ECG	Electrocardiography
EDS	Excessive Daytime Sleepiness
EEG	Electroencephalography
EMG	Electromyography
EOG	Electrooculography
ES	Effect Size
ESS	Epworth Sleepiness Scale
HbA1c	Glycated Haemoglobin
HDL	High-density Lipoprotein
HÖ-MEQ	Horne-Östberg Morningness-Eveningness Personality Questionnaire
HOMA2-IR	Homeostatic Model Assessment 2 for Insulin Resistance
HWP	Healthy Weight Programme group
IL	Interleukin
IQR	Interquartile Range

LDL	Low-density Lipoprotein
LEAN	Lean Control Group
MetS	Metabolic Syndrome
NCD	Non-communicable Disease
NE	Norepinephrine
NREM	Non-rapid Eye Movement
NS	Not Significant
OR	Odds Ratio
OSA	Obstructive Sleep Apnoea
PSG	Polysomnography
PSQI	Pittsburgh Sleep Quality Index
PYY	Peptide Tyrosine-tyrosine
QUICKI	Quantitative Insulin Sensitivity Check Index
REM	Rapid Eye Movement
REMOL	REM Onset Latency
RHR	Resting Heart Rate
RMR	Resting Metabolic Rate
SBI	Sleep Behaviour Intervention Group
SBP	Systolic Blood Pressure
SCN	Suprachiasmatic Nuclei
SE	Sleep Efficiency
SOL	Sleep Onset Latency
SRI	Sleep Regularity Index
sSRI	Simplified Sleep Regularity Index
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
TC	Total Cholesterol

TG	Triglycerides
TiB	Time-in-Bed
TNF	Tumour Necrosis Factor
TST	Total Sleep Time
WASO	Wake After Sleep Onset
WC	Waist Circumference
WHtr	Waist-to-Height ratio

Abstract

Introduction

Cardiometabolic diseases (CMD) such as cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM), pose a major health burden on the world's population. Moreover, cardiometabolic morbidity and mortality rates are expected to increase over the following decades. Sleep duration, sleep fragmentation, sleep timing and sleep architecture have been associated with cardiometabolic health and obesity, and warrant exploration as targets for reducing CMD risk.

Aim and Objectives

The purpose of this thesis was to evaluate the efficacy of a sleep behaviour intervention and consequent effect on cardiometabolic health. A commercial lifestyle intervention programme in the Cape Town metropole served as the setting in which the sleep behaviour intervention was applied. The participants of this lifestyle intervention programme received psychological support, dietary advice and regular group exercise sessions, which, at least in part, controlled for those factors, making this a suitable setting for the sleep behaviour intervention study.

The purpose of this thesis was achieved by the following aims:

1. To systematically review the effects of sleep extension interventions on cardiometabolic risk factors in adults.
2. To describe and compare the sleep characteristics of adults who are lean, overweight and class I obese, and class II obese and to determine the extent to which sleep characteristics were associated with cardiometabolic health.
3. To determine whether the sleep characteristics of individuals with overweight and obesity were altered as a result of participation in an eight-week diet and exercise lifestyle intervention programme.
4. To measure the effects of a sleep behaviour intervention within an eight-week diet and exercise lifestyle intervention programme on sleep and cardiometabolic health in individuals with overweight and obesity, and to determine whether changes in sleep were associated with changes in cardiometabolic health.

Methods

For the first aim, the PubMed and Scopus databases were searched for relevant, English, peer-reviewed scientific publications that described the effects of sleep extension on cardiometabolic health outcomes in adults (until August 2018). For the second aim, the body mass index (BMI),

waist circumference (WC), waist-to-height ratio (WHtr), blood pressure (BP), fasting glucose and total cholesterol (TC) levels, Cohen's perceived stress scale (CPSS) score, and habitual sleep characteristics (questionnaire, actigraphy and polysomnography; PSG) of individuals who were lean (LEAN), overweight or class I obese (OW-OBI) and class II obese (OBII) were assessed and compared. For the third aim, the BMI, WC, WHtr, BP, fasting glucose and TC levels, CPSS score, and habitual sleep characteristics (questionnaire and actigraphy) of participants of a diet and exercise lifestyle intervention programme who were overweight or obese (HWP) and of individuals who did not participate in a lifestyle intervention programme (CON) were assessed and compared at baseline and eight weeks later at follow-up. For the fourth and final aim, BMI, WC, WHtr, total body fat, lean mass, BP, fasting measures of insulin resistance, lipids, resting metabolic rate (RMR) and habitual sleep characteristics (questionnaire and actigraphy) of participants of a lifestyle intervention programme with overweight or obesity who were randomly assigned to undergo a sleep behaviour intervention (SBI) or not (CON), were assessed and compared at baseline and eight weeks later at follow-up.

Results and Discussion

The systematic review observed that sleep extension is a viable, implementable intervention which may improve measures of insulin sensitivity, appetite and dietary intake. The review provides preliminary evidence for a role of sleep extension to improve cardiometabolic outcomes, but also highlights the need for studies assessing sleep improvement strategies in larger and more diverse cohorts, as well as the long-term sustainability of these interventions.

In the second study, it was found that the OBII individuals in the intervention component of this thesis (n=63) had shorter actigraphy-measured time-in-bed (TiB), shorter total sleep time (TST) and lower sleep efficiency (SE) than the OW-OBI group (n=50, TiB: p=0.033; TST: p=0.002; SE: p=0.002) and the LEAN group (n=39, TiB: p=0.003; TST: p<0.001; SE: p=0.003). In addition, the OBII group had more awakenings >5 min (p=0.028), later bedtimes (p=0.019), less regular sleep (p=0.004), and less non-rapid eye movement stage 3 (NREM3) sleep (p=0.006) than the LEAN group. Finally, the OW-OBI and OBII groups had higher Pittsburgh Sleep Quality Index (PSQI, OW-OBI: p=0.003; OBII: p<0.001) and Epworth Sleepiness Scale (ESS, OW-OBI: p=0.003; OBII: p=0.008) scores than the LEAN group. Thus, individuals with class II obesity had more fragmented and irregular sleep, shorter sleep durations, less NREM3 sleep, worse subjective sleep quality, and more daytime sleepiness than their counterparts with overweight and class I obesity and those who are lean. This sleep impairment may put them at risk for future cardiometabolic complications, which in turn may perpetuate sleep impairment.

In the third study, the HWP group (n=31) reduced their BMI (effect size (ES): 1.015, $p<0.001$), WC (ES: 1.075, $p<0.001$) WHtr (ES: 1.073, $p<0.001$) and CPSS score (ES: 0.530, $p=0.009$) compared to the CON group (n=23), while no measurable changes in their sleep characteristics were observed. It was thus concluded that the eight-week lifestyle intervention programme does not *per se* cause changes in sleep, despite improvements in anthropometric measures. Since these findings suggest that participation in a diet and exercise lifestyle intervention programme alone does not halt or reverse the vicious cycle between poor sleep and cardiometabolic impairment, it must be explored whether the inclusion of a sleep behaviour intervention may confer additional benefits.

In the final study, the SBI group (n=15) demonstrated earlier get-up times (ES: -0.811, $p=0.035$) and midpoints of sleep (ES: -0.815, $p=0.034$) than the CON group (n=15) in response to the intervention. Changes in sleep duration, sleep fragmentation or sleep timing were not different between the SBI and CON groups. SBP (ES: 0.627, $p=0.039$) and RMR (ES: 1.110, $p=0.007$) increased, and glycated haemoglobin (HbA1c) decreased (ES: -0.784, $p=0.049$) in the SBI group over the course of the programme. Furthermore, with the SBI and CON groups combined, change in TC and change in RMR correlated with change in SRI (TC: $\rho=0.565$, $p=0.002$, n=27; RMR: $\rho=0.612$, $p<0.001$, n=27). These findings suggest that sleep modulation in individuals with overweight and obesity may result in cardiometabolic benefits, and that HbA1c, RMR and SBP may be more sensitive to changes in sleep timing than anthropometric measures and lipids.

Conclusion

The findings in this thesis support a role for sleep improvement strategies to improve cardiometabolic health. Before implementing a sleep behaviour intervention in new or existing lifestyle, wellness or incentive programmes, aspects such as format and content, participant selection, and screening for underlying sleep disorders and psychological conditions must be considered in order to maximise the efficacy of the sleep intervention. Further research is needed to confirm the findings of the present study in alternative settings, and to determine how participants who may benefit from a sleep behaviour intervention for the betterment of cardiometabolic health may be identified.

Chapter 1

Introduction

1.1 Introduction and scope of the thesis

Cardiometabolic diseases (CMD) such as cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM), pose a major health burden on the world's population. Recent global statistics indicate that 17.9 million and 5.0 million people die annually from CVD and T2DM respectively. CMD morbidity and mortality are expected to increase globally in the next few decades due to changes towards a more sedentary lifestyle and higher rates of urbanisation. These numbers of CMD morbidity are also expected to increase due to increasing life expectancy of individuals with CMD, and availability of more accurate and complete data (Cho et al., 2018). An important risk factor for these and other non-communicable diseases (NCD) is obesity, which is estimated to account for 3.4 million deaths annually world-wide (World Health Organization, 2015).

An overwhelming amount of evidence has been published to suggest that cardiometabolic health is associated with sleep health (Rangaraj and Knutson, 2016). Generally, these studies show that individuals with poor cardiometabolic health and CMD are more likely to have impaired sleep, which may lead to further deterioration of their cardiometabolic health, thus perpetuating the vicious cycle between cardiometabolic health and poor sleep (Lucassen et al., 2012). This thesis focused on the improvement of sleep for the betterment of cardiometabolic health. Despite sleep encompassing a wide range of measures, this thesis will predominantly focus on measures that directly relate to cardiometabolic health, specifically sleep duration, fragmentation, timing, and architecture.

1.2 An introduction to sleep and sleep health

Carskadon and Dement (2011) defined sleep as "a reversible behavioural state of perceptual disengagement from and unresponsiveness to the environment" (Carskadon and Dement, 2011). Sleep is recurring, essential and covers approximately one-third of the human life span. One explanation for why we sleep may be to undertake essential biological activities to allow for optimal performance during the period we are best adapted to, namely daytime (Foster, 2018). These activities may be more efficient, or only possible, when the body is at rest, the sensory input is low, and the energy-requirement for other activities is decreased, which is the case during sleep. It makes sense that these activities occur at the time-of-day to which we are poorly adapted, namely night-time, and that we are thus adapted to sleep during this period.

1.2.1 Function of sleep

Because the effects of insufficient sleep may manifest in multiple ways, it is likely that sleep does not serve one, but several different functions (Krueger et al., 2016). Our current understanding about functions of sleep have been reviewed by Krueger et al. (2017) and include ensuring proper immune function, reducing caloric use, replenishing energy stores in the brain, clearing waste products of neural metabolism from the brain, restoring cognitive and behavioural performance degradation induced by wakefulness, and allowing brain plasticity and memory consolidation (Krueger et al., 2016). Insufficient and poor quality sleep have also been associated with cardiometabolic impairments, which are discussed in **Section 1.5**.

1.2.2 Regulation of sleep

The regulation of normal sleep has been described as the product of two interacting mechanisms, the homeostatic process and the circadian process, and is referred to as the two-process model of sleep regulation (Borbely et al., 2016). The homeostatic process represents an increasing propensity to sleep during wakefulness. This sleep propensity then decreases during sleep. The circadian process counteracts the sleep homeostat by regulating alertness in a time-of-day-based sinusoidal matter. For most individuals, sleepiness sets in during the evening, when the homeostatic sleep propensity is at its highest, and the circadian alerting is diminished, which will lead to the preparation for bedtime and ultimately sleep (Borbely et al., 2016). Together, these two processes ensure that sleep occurs at approximately the same time-of-day, which is referred to as the regularity of sleep timing, which may be measured with the sleep regularity index (SRI) (Phillips et al., 2017). The interaction of the circadian and homeostatic processes also decreases the chance that sleep is interrupted. This unintentional discontinuation of sleep may be referred to as sleep fragmentation, and is often measured through sleep efficiency (SE, percentage of time-in-bed (TiB) spent sleeping), wake after sleep onset (WASO, time spent awake between initial sleep onset and final awakening), and the number of awakenings (expressed in duration or in occurrences per hour of sleep time) (Berry et al., 2018).

1.2.3 Sleep architecture

During a typical night, human adults cycle through different types of sleep with distinguishable electroencephalographic (EEG) patterns called sleep stages. The distribution and duration of these sleep stages within each sleep period is called sleep architecture. These sleep stages can be categorized into rapid eye movement (REM) and non-rapid eye movement (NREM) sleep stages

(McCarley, 2007). NREM sleep may be further divided in three sleep stages with increasing arousal thresholds (i.e. the intensity of stimuli required to wake up), namely NREM1, NREM2, and NREM3 sleep.

NREM1 sleep is characterised by low-amplitude, mixed frequency (predominantly 4-7 Hz) EEG activity, and slow eye movements. Upon progression into NREM2 sleep, short bursts of fast oscillations (11-16 Hz) called sleep spindles, and single slow wave forms, called K-complexes, become visible on the EEG channel, specifically over the frontal and central brain regions. These K-complexes become more common as sleep progresses into NREM3 sleep, until slow wave activity (0.5-2 Hz) predominates the EEG channel. Due to these slow oscillations, NREM3 sleep is also referred to as slow wave sleep (Berry et al., 2018). The last sleep stage is REM sleep, which is not only characterized by rapid movements of the eye, but also by muscle atonia.

Transitions to a lighter sleep stage, or to wakefulness, can occur from any sleep stage. When such transitions are paired with a sudden increase in EEG frequency, and, if a transition from REM sleep occurs, a concurrent increase in chin electromyography (EMG) activity, they are called 'arousals' (Berry et al., 2018).

1.2.4 Sleep health

To ensure optimal mental and physical health, good sleep health is essential. While it is recommended that human adults sleep for 7–9 h in a 24-h period (Hirshkowitz et al., 2015), sleep duration alone is not sufficient to define good sleep health. Other dimensions of sleep are important too. While a global definition of sleep health is work in progress, it was suggested that such measure should incorporate sleep satisfaction, alertness/sleepiness, sleep timing, sleep continuity (a measure of how interrupted sleep is), and duration (Buysse, 2014). The American National Sleep Foundation recommends criteria that constitute good sleep quality, which may be used to determine sleep health (Ohayon et al., 2017). The difference between sleep quality and sleep health is that the first describes how good or bad sleep itself is, whereas the latter takes into account the effects of sleep on health and daytime functioning, such as satisfaction and sleepiness. As such, sleep quality is an important component of sleep health.

Sleep is mainly an unconscious process, meaning that individuals have no direct control over the onset of sleep, the depth of sleep, or unwanted awakenings. However, certain behaviours may positively influence these aspects of sleep, and are called sleep hygiene. Common sleep hygiene recommendations include: avoiding or minimizing caffeine, nicotine and alcohol intake at specific times-of-day; exercising regularly, but not too close to bedtime; managing and avoid stress during

the day, so it can be kept out of the bedroom; minimizing noise in the bedroom; ensuring regular bedtimes and get-up times; and avoiding daytime napping (Irish et al., 2015).

1.3 Measurement of sleep

Because of the complexity of sleep, no single measure of sleep exists. Instead, various behavioural, neurological and subjective measures may be used to describe aspects of sleep.

1.3.1 Polysomnography

The gold standard method for determining sleep architecture is polysomnography (PSG), which, relies on EEG to detect brain activity, electrooculography (EOG) to detect eye-movements and EMG to detect muscle activity during sleep. The PSG recording of the entire sleep period is divided into epochs (usually 30 s in duration), which are scored individually based on rules originally set by Rechtschaffen and Kales (Rechtschaffen et al., 1968) or varieties thereof. The most commonly-used set of rules to score sleep, especially in sleep medicine, are those by the American Academy of Sleep Medicine (Berry et al., 2018). In additional to EEG, EOG, and EMG, other channels such as electrocardiography (ECG), pulse oximetry, nasal and oral airflow, thorax and abdominal respiration, may be included in PSG depending on the test requirements. These additional channels are usually included to detect sleep disorders such as sleep-disordered breathing. Although PSG is the gold standard for assessing sleep, PSG is invasive, costly, and not representative of habitual sleep, especially when done in the clinical environment of a sleep laboratory, which is often the case.

1.3.2 Actigraphy

A common tool for the assessment of habitual sleep is actigraphy, which involves the detection of movements, usually via a wrist-worn accelerometer. Since actigraphy is cost-effective and non-invasive, it can be used to monitor several days or weeks of sleep. This makes actigraphy superior for assessing habitual sleep patterns, including timing and regularity. Actigraphy relies only on body movement, and since the absence of movement does not always imply sleep, actigraphy-assessed sleep duration is usually over-predicted compared to PSG-assessed sleep duration (Jackson et al., 2018). On-device annotation and sleep diaries are often used to increase accuracy of defining bedtimes and get-up times of the main sleep period. Actigraphy is not suitable to measure or predict sleep architecture as sleep stages cannot be accurately distinguished by movements alone.

1.3.3 Subjective sleep measures

In addition to the objective aspects of sleep, sleep can also be assessed subjectively. Subjective sleep measures may relate to the perceived quality of sleep, daytime sleepiness or fatigue, risk for sleep disorders, or self-reported measures of sleep timing, duration, latency or disturbances. While many subjective tools have been developed, it is beyond the scope of this thesis to present tools other than those used in the experimental chapters.

Subjective sleep quality is difficult to define as many elements contribute to "good" sleep. A widely-used tool for the assessment of subjective sleep quality is the Pittsburgh Sleep Quality Index (PSQI) questionnaire, which comprises 19 questions relating to sleep habits and provides scores on seven components, as well as a global sleep quality score (sum of the component scores) and self-reported bedtime, get-up time, sleep onset latency (SOL), and sleep duration (Buysse et al., 2002). Another subjective measure, which is used to assess the effect of habitual sleep on daytime sleepiness, is the Epworth Sleepiness Scale (ESS) (Johns, 1991). Based on the likeliness of dozing off in eight different scenarios, the ESS assigns each individual a 'sleepiness score' between 0 and 24, with higher scores indicating greater levels of daytime sleepiness.

Lastly, subjective sleep measures may be used to assess an individual's sleep duration, SOL, or number and duration of awakenings, usually in response to a single question. Although self-reported sleep assessments are cost-efficient and simple to use, they may overestimate sleep duration compared to objectively measured sleep duration, especially when sleep fragmentation is high (Cespedes et al., 2016, Jackson et al., 2018).

1.4 An introduction to circadian rhythms

Most physiological processes including metabolism (Huang et al., 2011), bowel movement (Hoogerwerf, 2006), cell regeneration (Huang et al., 2011), and hormone secretion (Moore and Klein, 1974, Moore and Eichler, 1972) exhibit circadian (i.e. approximately 24 h) variation. These so-called circadian rhythms are controlled by a system of molecular clocks, which can be found in virtually all cells (Patke et al., 2020), and which oscillate with a period of about 24 h. The circadian clocks in cells that share a common function (e.g. liver cells, heart cells) oscillate in unison, which allows the time-dependent physiological processes in organs to be aligned (Rietveld, 1992). The rhythms of these peripheral clocks are orchestrated by two clusters of cells in the hypothalamus, called the suprachiasmatic nuclei (SCN), which allows for the alignment between the circadian rhythms in organs (Rietveld, 1992) and synchronisation to the external light environment. The function of the system of circadian clocks is to anticipate time-of-day-related changes to the

environment, and to regulate physiological processes on a molecular, cellular, organ and organism level. For example, circadian rhythms make the suppression of bowel movement and urine secretion at night possible to allow uninterrupted nocturnal sleep (Hoogerwerf, 2006, Cho et al., 2011). Circadian rhythms also allow an increase in metabolic activity during the day in anticipation of food intake (Huang et al., 2011).

The circadian clocks oscillate endogenously and can be synchronised or entrained to the environment through external time cues, commonly referred to as *zeitgebers*. The most important time cue for the SCN is light, which is captured by the photopigment melanopsin found in the intrinsically photosensitive retinal ganglion cells in the retina (Berson, 2007). Information about light exposure is then projected to the SCN via the retinohypothalamic tract, where it may delay or advance the phase (i.e. timing) of the SCN's circadian rhythm, allowing alignment with the light-dark cycle resulting from the Earth's rotation around its own axis. Other time cues include food intake (Feillet et al., 2006), exercise (Mrosovsky, 1996), and possibly social interactions (Grandin et al., 2006).

Naturally, some variation in the timing of circadian clocks relative to environmental and social time exists between individuals (Roenneberg et al., 2003). This characteristic is observed behaviourally as one's chronotype, or diurnal preference. Those with a strong preference for mornings (i.e. retiring and rising earlier) are on one end of the chronotype spectrum, those without a strong preference for either mornings or evenings are in the middle of the spectrum, while those with a strong preference for evenings (i.e. retiring and rising later) are on the other end of the spectrum. Various tools have been developed to asses a person's chronotype, such as the Horne-Östberg morningness-eveningness personality questionnaire (HÖ-MEQ) (Horne and Ostberg, 1976), and the Munich chronotype questionnaire (Roenneberg et al., 2003).

1.4.1 Circadian disruption

When an individual's system of circadian clocks does not appropriately anticipate time-of-day, resulting in impaired daytime functioning or health, we speak of circadian disruption. One form of circadian disruption may be caused by an extremely late or early chronotype, such that an individual's circadian clock is anticipating night-time during daytime and *vice versa*. In more extreme cases, an individual may be diagnosed with a circadian rhythm disorder, such as advanced or delayed sleep phase disorder. Individuals with later chronotypes are more likely to develop cardiometabolic impairment (Merikanto et al., 2013), which is further discussed in **Section 1.5.4**.

Another form of circadian disruption is social jet lag, which is the misalignment between the circadian clock time, or chronotype, and social time (related to social obligations such as work and family) (Wittmann et al., 2006). Social jet lag is the difference between the time of the midpoint of sleep on working days, mainly driven by the social clock, and the time of the midpoint of sleep on free days, mainly driven by the circadian clock. The larger social jet lag is, the higher the misalignment between circadian and social time, and the higher the risk of daytime sleepiness and sleep deprivation. Social jet lag has been associated with obesity (Roenneberg et al., 2012) and other aspects of cardiometabolic health, which are also further discussed in **Section 1.5.4**.

To ensure proper circadian functioning, circadian rhythms must be of sufficient amplitude, so that differences between the peak and trough of the circadian rhythm of any physiological process or behaviour is prominent. For example, when the circadian amplitude of alertness is attenuated, not only could the individual be less alert during the day but also more alert during night-time, which may impair nocturnal sleep. Indeed, sleep disturbances have been associated with a decreased circadian amplitude of melatonin (Pandi-Perumal et al., 2009). Moreover, attenuated circadian amplitudes of body temperature and heart rate have been associated with T2DM (Gubin et al., 2017).

Circadian disruption may have an external origin, related to zeitgebers, or have an internal origin, related to the zeitgeber reception or circadian clock. For example, circadian disruption may be caused by exposure to zeitgebers at the wrong time-of-day (e.g. exposure to bright light in the middle of the night) or by weak zeitgebers (e.g. working in an office with low-intensity lights), which makes the synchronisation of the circadian clock to the Earth's light-dark cycle difficult. On the other hand, independent of zeitgebers, blindness (Sack et al., 1992), eye lens opacity (Kessel et al., 2010), neurodegeneration (Videnovic et al., 2014), and mutations in the genes involved in circadian regulation (Barnard and Nolan, 2008), may also result in circadian disruption. Where circadian disruption has an external origin, behavioural factors such as night-time bright-light exposure, caffeine consumption, and irregular bedtimes may be addressed to improve circadian health (Swanson and Burgess, 2017).

1.5 Cardiometabolic impairment and poor sleep: a vicious cycle

1.5.1 Cardiometabolic health

Risk factors that predispose an individual to CMD include abdominal obesity, hypertension, hyperglycaemia, hyperlipidaemia, and hypertriglyceridaemia (Eckel et al., 2005). The co-occurrence

of three or more of these CMD risk factors considerably increases an individual's risk of developing CMD, and is historically referred to as the metabolic syndrome (MetS), or simply 'high cardiometabolic risk' (Grundy et al., 2005). The associations between CMD and risk factors thereof for four aspects of sleep; sleep duration, sleep fragmentation, sleep timing, and sleep architecture, will be summarized in the sections below.

1.5.2 Cardiometabolic health and sleep duration

Studies that report on the associations between short sleep duration and cardiometabolic outcomes may either refer to chronic (i.e. habitual) or acute (i.e. sleep restriction) short sleep duration. With regards to the association between habitual short sleep duration and cardiometabolic health, evidence from both cross-sectional and prospective studies are available.

In cross-sectional studies, both self-reported and objective short sleep duration have been associated with metabolic disturbances, including the development of obesity, hypertension, diabetes and cardiovascular disease (Taheri et al., 2004, Lauderdale et al., 2009, Buxton and Marcelli, 2010). Higher levels of glycated haemoglobin (HbA1c) were associated with self-reported short sleep duration (<6 h) in T2DM outpatients, independent of known confounding factors (Martorina and Tavares, 2019). Another study found that the association between self-reported short sleep duration and increased adiposity was stronger in women than in men (St-Onge et al., 2010). Likewise, women, but not men, who reported sleeping ≤5 h per night were at a greater risk for hypertension (blood pressure (BP) ≥140/90 mmHg) or using hypertensive medication than those who reported sleeping for 7 h per night (Cappuccio et al., 2007). This increased hypertensive risk was also found in women who reported sleeping <6 h per night compared to women who reported sleeping ≥6 h per night, and this association was stronger in premenopausal than postmenopausal women (Stranges et al., 2010). Lastly, women who reported short sleep durations (≤5 h) had elevated levels of high-sensitivity C-reactive protein (CRP) a marker of acute-phase inflammation (Miller et al., 2009).

Prospective cohort studies have shown that a self-reported short sleep duration (≤5 h (Yeo et al., 2013) or <6 h (Magee et al., 2013) per night) was associated with higher all-cause and CVD mortality. Moreover, women who reported sleeping ≤5 h or <6 h per night, had an increased risk of developing hypertension within the following 5 years, compared to women who reported sleeping 7 h per night (Cappuccio et al., 2007).

Acute short sleep duration, or sleep restriction, has also been associated with cardiometabolic impairment in various experimental design studies. For example, sleep deprivation for only one

night was associated with elevated afternoon/evening cortisol levels, which in turn was associated with abdominal obesity and insulin resistance, both major risk factors for T2DM (Omisade et al., 2010). Moreover, two nights of sleep restriction (4 h TiB) in twelve healthy men resulted in a reduction in leptin (appetite-supressing hormone), an increase in ghrelin (appetite-stimulating hormone), and an increase in hunger and appetite (Spiegel et al., 2004c), which may increase food intake, and subsequently increase risk for weight-gain and obesity. Lastly, five nights of sleep restriction (4 h TiB) decreased whole-body and skeletal muscle and adipose tissue-specific insulin resistance in 14 healthy men and women (Rao et al., 2015).

Knutson and Van Cauter (2008) and Lucassen *et al.* (2012) have proposed similar models to explain how short sleep duration may be related to the development of obesity and T2DM. The authors suggested that on one hand, short sleep duration could result in an increase in sympathetic nervous system activity as well as an increase in evening cortisol, night time growth hormone levels and pro-inflammatory cytokines, all of which may contribute to increasing insulin resistance and decreasing glucose tolerance, which in turn may lead to T2DM. On the other hand, short sleep duration has been associated with increased orexin and ghrelin levels (Taheri et al., 2004), and decreased leptin levels (Mullington et al., 2003). This may increase appetite, which, in addition to short sleep duration leaving a person more time to eat, could potentially increase food intake, which contributes to the development of obesity if energy expenditure remains low (Knutson & Van Cauter, 2008; Lucassen et al., 2012).

1.5.3 Cardiometabolic health and sleep fragmentation

Sleep fragmentation has been associated with anthropometric measures and other aspects of cardiometabolic health. For example, various studies have shown that obesity and a higher body mass index (BMI) are associated with measures of sleep fragmentation, such as the fragmentation index (amount of interruption of sleep measured by physical movement)(van den Berg et al., 2008, Lauderdale et al., 2009) and frequency of awakenings (Corbalan-Tutau et al., 2012). Moreover, middle-aged women, but not men, who reported waking up several times per night were more likely to experience major weight gain (>5 kg) over the following five to seven years than those who did not report any frequent sleep problems (Lyytikäinen et al., 2010). Sleep fragmentation may not only be associated with weight gain, it may also make weight-loss more difficult. For example, women with overweight and obesity who had five or more wake episodes per night (from actigraphy) experienced less weight loss in response to a seven-month weight-loss intervention compared to those with less than five wake episodes per night (Sawamoto et al., 2014).

Interestingly, sleep fragmentation seems to be associated with waist circumference (WC), independent of BMI, suggesting that different mechanisms link sleep fragmentation with general and abdominal adiposity (Mezick et al., 2014). This association was only found in women, however, and there may be important sex differences in the association between sleep fragmentation and adiposity. Higher SE, a measure that correlates with sleep fragmentation, has also been associated with adverse cardiometabolic health, namely obesity and higher diastolic BP (DBP) (Resta et al., 2003, Corbalan-Tutau et al., 2012).

Moreover, two days of experimentally induced sleep fragmentation in individuals who were healthy decreased insulin sensitivity and glucose effectiveness (the insulin-independent and glucose-dependent uptake of glucose and suppression of glucose production), while morning cortisol levels and sympathetic nervous system activity increased (Stamatakis and Punjabi, 2010). Furthermore, experimentally-induced sleep fragmentation increased insulin secretion, decreased glucagon-like peptide 1 (stimulates insulin secretion, reduces appetite (Holst, 2007)), reduced fat oxidation and increased carbohydrate oxidation in healthy males (Gonnissen et al., 2013, Hursel et al., 2011).

An important cause of sleep fragmentation is obstructive sleep apnoea (OSA) which may be found in 9 to 38% of individuals in populations of many industrialised regions around the globe excluding Africa (Senaratna et al., 2017). OSA is a condition where the flow of air into the lungs repeatedly decreases or ceases completely as a result of narrowing of the upper airway. This cessation in airflow results in frequent oxygen desaturation, followed by an arousal from sleep, often accompanied with gasps for air. OSA has been associated with obesity (Punjabi, 2008), hypertension (Kapa et al., 2008), cardiovascular disease (Newman et al., 2001), insulin resistance (Ip et al., 2002), and all-cause mortality (Marshall et al., 2008). It remains unknown whether intermittent hypoxia, sleep fragmentation, or both drive cardiovascular impairment in OSA. On one hand, sleep fragmentation was found to be independently associated with dyslipidaemia in patients with OSA (Qian et al., 2016), suggesting that sleep fragmentation alone may impair the lipid profile. Moreover, experimentally induced sleep fragmentation in mice, without intermittent hypoxia, resulted in higher counts of monocytes and neutrophils, which suggests an increased pro-inflammatory state, and more severe atherosclerosis (McAlpine et al., 2019). Indeed, sleep fragmentation in humans was linked to a higher neutrophil count and higher coronary artery calcification (Vallat et al., 2020). Sleep fragmentation without intermittent hypoxia has also been shown to increase sympathetic nervous system activation (Ferreira et al., 2020), vascular endothelial dysfunction and BP (Carreras et al., 2014). On the other hand, however, 30 days of experimentally induced sleep fragmentation did not alter structural or functional echocardiographic outcomes in mice (Cabrera-Aguilera et al., 2019). Moreover, the pathway for

intermittent hypoxia-driven cardiometabolic impairment is evident and well understood (Levy et al., 2015). In conclusion, the contribution of intermittent hypoxia and sleep fragmentation to cardiometabolic impairment in OSA is complex and may differ between specific types of cardiovascular and metabolic impairment, between different levels of hypoxia and sleep fragmentation severity, and between different durations of the presence of hypoxia and sleep fragmentation (e.g. months or years).

While extensive work has been carried out on the association between cardiometabolic health and OSA, more research is needed on the association between cardiometabolic health and other dimensions of sleep. Therefore, this thesis will focus on sleep duration, sleep fragmentation, sleep architecture, and sleep timing separately from OSA.

1.5.4 Cardiometabolic health and sleep timing

Another important factor in the relationship between cardiometabolic health and sleep is sleep timing and derivatives thereof. For example, one study showed that individuals who prefer later bedtimes are more likely to have T2DM and arterial hypertension than individuals who prefer earlier bedtimes, independent of sleep duration (Merikanto et al., 2013). Another study found that later sleep timing (midpoint of sleep ≥5:30) was associated with more calories consumed after 20:00, but not with BMI, after adjusting for sleep duration (Baron et al., 2011). On the other hand, advancing bedtime resulted in an increased intake of low glycaemic index foods, fruit and dairy in adolescents (Asarnow et al., 2017).

Moreover, sleep/wake pattern regularity has also been associated with measures of cardiometabolic health. For example, a larger variability in bedtime was associated with an higher BMI and insulin resistance in middle-aged women (Taylor et al., 2016), and a lower SRI in older adults was associated with an increased ten-year risk of CVD, T2DM, obesity, hypertension, and higher levels of fasting glucose and HbA1c (Lunsford-Avery et al., 2018).

Lastly, social jet lag has been identified as a contributor to poor cardiometabolic health as well. This circadian misalignment has been associated with a higher BMI (Roenneberg et al., 2012), higher prevalence of being overweight or obese (Mota et al., 2017, Parsons et al., 2015), higher fasting glucose levels (Mota et al., 2017), the metabolic syndrome (Parsons et al., 2015), and the presence of more cardiometabolic risk factors (Wong et al., 2015).

Sleep timing, sleep regularity and social jet lag are associated with cardiometabolic health because they relate to circadian health, which has been shown to be associated with adverse cardiometabolic health. For example, a simulated shift work protocol, leading to circadian

misalignment, resulted in increased waketime BP and 24 h average SBP and DBP, and increased inflammatory markers interleukin (IL)-6, C-reactive protein (CRP), resistin, and tumour necrosis factor (TNF)-α (Morris et al., 2016, Morris et al., 2017). Other endocrinologic consequences of circadian disruption includes decreased leptin levels, which has been shown in 14 healthy participants following 25 light-dark cycles of 24.6 h (the duration of a day on Mars) (Nguyen and Wright, 2010). Forced-desynchrony, a method of inducing circadian disruption by exposing individuals to a non-24 h light-dark cycle, thus preventing circadian alignment, resulted in increased blood glucose and insulin levels, reversed daily cortisol rhythm, and increased arterial pressure in a study with ten adults (Scheer et al., 2009). Circadian misalignment may also impair autonomic nervous system function, which has also been associated with CVD risk (Grimaldi et al., 2016). Experimentally-induced circadian disruption in humans and mice has also been associated with altered rhythms of composition and function of the intestinal microbiota, resulting in glucose intolerance and obesity (Thaiss et al., 2014). Furthermore, polymorphisms within the genes that are involved in circadian rhythmicity (*CLOCK*, *BMAL1* and *PER2*) have been associated with obesity, metabolic syndrome, eating disorders and T2DM (Garaulet and Madrid, 2009, Garaulet et al., 2010, Garaulet et al., 2011, Sookoian et al., 2008).

Lifestyle-driven circadian disruption, such as that seen in shift workers and those with social jet lag, has also been associated with poor cardiometabolic health. For example, shift work has been associated with an increased risk for obesity and cardiometabolic impairment (Di Lorenzo et al., 2003, Karlsson et al., 2001), and coronary heart disease (Vetter et al., 2016). An additional effect of circadian disruption, however, is disrupted sleep, which, as has been discussed in the previous sections and following section, may further contribute to cardiometabolic impairment (Dijk and von Schantz, 2005). Moreover, circadian disruption in combination with sleep restriction, which often occurs in shift workers, decreases resting metabolic rate (RMR) and pancreatic insulin secretion after a meal, which lead to increased blood glucose level (Buxton et al., 2012). In addition, individuals with social jet lag have an increased risk for obesity and CMD (Roenneberg et al., 2012, Wong et al., 2015). Thus, sleep timing and derivatives thereof, as they relate to circadian disruption are directly linked to cardiometabolic health.

1.5.5 Cardiometabolic health and sleep architecture

Sleep architecture has been associated with cardiometabolic health in cross-sectional studies. For example, community-dwelling older (≥65 y) men with the least time spent in NREM3 sleep had increased odds for obesity compared to those with the most time spent in NREM3 sleep (Rao et

al., 2009). Moreover, in obese adolescents, less NREM3 was associated with decreased insulin secretion following an intravenous glucose tolerance test, even after correcting for degree of obesity, pubertal stage, sex and obstructive sleep apnoea (Koren et al., 2011).

Experimental studies have also shown associations between cardiometabolic health and sleep architecture. For example, in a cross-over trial, Tasali *et al.* (2008) demonstrated that NREM3 sleep suppression lead to decreased insulin sensitivity in healthy adults, suggesting that NREM3 sleep is important for maintaining normal glucose homeostasis (Tasali et al., 2008). Furthermore, experimental reductions in NREM3 and REM sleep have been shown to increase appetite, carbohydrate and fat consumption, and energy intake in apparently healthy adults (Shechter et al., 2012). Experimental NREM3 suppression in healthy men resulted in reduced insulin sensitivity, while experimental REM sleep disturbance did not affect glucose tolerance (Herzog et al., 2013). Combined, these cross-sectional and experimental studies suggest that compromised sleep architecture, specifically decreased NREM3 sleep, may increase risk for obesity and T2DM.

1.6 Lifestyle intervention programmes

A range of interventions have been explored to curb the rise of obesity and ultimately reduce risk for CMD, of which nutrition and exercise modulation are possibly the most common (Fontana et al., 2007). Both interventions aim to induce an energy deficit via strategies such as calorie restriction, increased energy expenditure and boosting of metabolic rate, and have been shown to be successful in improving body composition, blood lipids and insulin sensitivity in healthy (Fontana et al., 2007, Wu et al., 2009), and diabetic populations (Kelley et al., 1993). Despite effective short-term improvements in weight loss and cardiometabolic health, adherence and partial weight regain are common challenges in both nutrition and exercise interventions, and necessitate exploring alternative or additional interventions (Wu et al., 2009).

Given the associations between short sleep duration, sleep fragmentation, delayed and irregular sleep timing and decreased NREM3 sleep with an increased likelihood for developing obesity and CMD, an intriguing question is whether or not improving these aspects of sleep might reverse some of the associated cardiometabolic risk factors. Surprisingly few studies have studied the effects of sleep modulation on reducing risk for developing obesity and CMD (Haack et al., 2013, Leproult et al., 2015, Al Khatib et al., 2018, Tasali et al., 2014, Reynold et al., 2014, Kubo et al., 2011). In one study, experimental extension of sleep duration by almost 3 h per night, lead to an increase in insulin sensitivity, assessed with the oral glucose tolerance test, in short-sleeping (<6.5 h) healthy male adults (Killick et al., 2015). Others found that advancing the bedtime of adolescents

resulted in increased intake of low glycaemic index foods, fruit and dairy (Asarnow et al., 2017). While this topic is discussed in more detail in **Chapter 2**, more research is needed to assess whether improving sleep in individuals who are at risk for developing CMD could improve their cardiometabolic health.

1.7 Purpose of thesis

The aim of this thesis is to investigate whether a sleep behaviour intervention, aimed at improving nocturnal sleep over a period of eight weeks, can improve anthropometric measures of BMI, WC, waist-to-height ratio (WHtr), total body fat and lean mass, and improve cardiometabolic health outcomes in individuals with overweight and obesity (**Chapter 5**). This aim will be achieved by first systematically reviewing the literature about sleep extension interventions to improve cardiometabolic health, by describing their strengths and weaknesses and identifying knowledge gaps (**Chapter 2**). Next, the sleep habits of individuals with overweight and obesity recruited from the location where the sleep behaviour intervention study takes place will be described (**Chapter 3**). Since this research project makes use of an eight-week diet and exercise lifestyle intervention programme open to the public as the setting for the sleep behaviour intervention, any effects this lifestyle programme may have on sleep characteristics will be assessed (**Chapter 4**).

Chapter 2

The Effects of Sleep Extension on Cardiometabolic Risk Factors: a Systematic Review

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This chapter is presented with minor modifications from the publication in conformity with the thesis.

The co-authors have agreed that the publication may be included in this thesis.

2.1 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% respectively of men and women globally 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 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 <7 h per night, unless otherwise specified.

Epidemiological studies report consistent relationships between short sleep duration and increased risk for mortality, T2DM, hypertension, CVD, 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 individuals with short sleep duration, 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 (4 h 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 (7-9 h) (St-Onge et al., 2013). Indeed, increased caloric intake and 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 (4 h per night) (Spaeth et al., 2013) and just four or five nights of sleep restriction (Bosy-Westphal et al., 2008, Markwald et al., 2013). Additionally, restricting sleep to 4.3 h for two nights (Bromley et al., 2012) or 5.5 h for two weeks (Schmid et al., 2009) reduced 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 (4.5 h or 4 h per night respectively) reduced insulin sensitivity compared to longer sleep (8.5 h or 8 h sleep respectively) (Broussard et al., 2012, Rao et al., 2015). Likewise, just two days of sleep restriction (4 h 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 (4 h per night) increased lymphocyte activation and the production of proinflammatory cytokines, which have been associated with an increased risk for developing CVDs (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 CMD 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.

2.2 Methods

2.2.1 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 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, BP; blood markers of cholesterol; triglycerides, TG, or glucose; body mass index, BMI; or waist circumference, WC) 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 2.1**. The following filters were applied; Species: Humans; Language: English.

Table 2.1. 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")

2.2.2 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.

2.3 Results

2.3.1 Literature

The article search process is depicted in **Figure 2.1**. 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 2.1**. 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 2.1**.

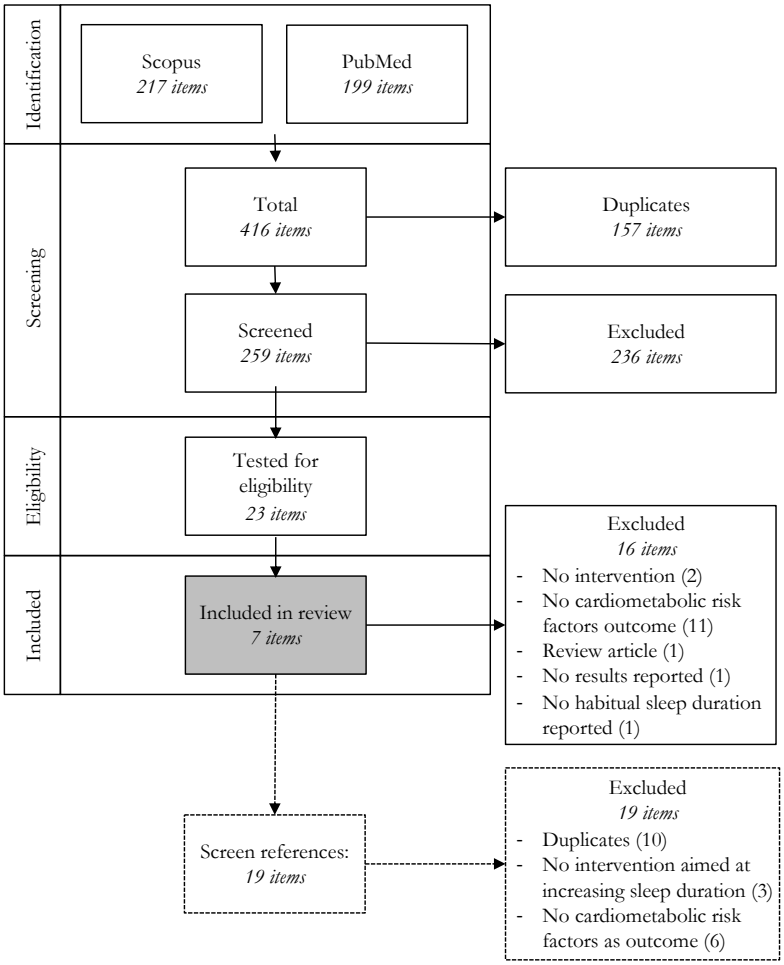

Figure 2.1. Outline of the literature search procedure and article selection.

2.3.2 Study characteristics

Three of the seven included studies are randomized controlled trials (Haack et al., 2013, Al Khatib et al., 2018, Reynolds et al., 2012), two are crossover trials (Killick et al., 2015, Kubo et al., 2011), and two are intervention studies without concurrent control groups (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 (<6.5 h or <7 h per night) adults (Killick et al., 2015, Leproult et al., 2015), short-sleeping (<6.5 h per night) adults who were overweight (Tasali et al., 2014), short-sleeping (<6 h per night) factory workers (Kubo et al., 2011) and pre- or hypertensive adults (Haack et al., 2013). The sleep extension intervention strategies were either time-in-bed (TiB) extensions, or 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 177 min. Outcome variables included BP, anthropometric

variables, glucose, insulin and insulin sensitivity indices, appetite and hormones that influence appetite, and inflammatory markers.

2.3.3 Results of individual studies

2.3.3.1 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 2.2**. 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 TiB by 60 min daily for six weeks. Specifically, participants were instructed to go to sleep 30 min earlier and rise 30 min later than their usual bed and get-up times. The sleep maintenance group also received sleep hygiene information, but was instructed to maintain their habitual bedtimes for six weeks. TST was extended by 35±9 min to ~6.9 h in the sleep extension group and by 4±9 min to ~6.3 h in the sleep maintenance group as assessed by actigraphy (p=0.03, group-by-time interaction effect). Participants with shorter TST 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 60 min (Leproult et al., 2015). The 16 healthy short-sleeping (<7 h) 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 2 h of bedtime. This sleep extension strategy increased mean actigraphy-assessed sleep duration on weekdays by 44±34 min from 6.0±0.5 h (p<0.001). This effect was not observed on weekends, presumably because the participants' pre-intervention weekend TST was already >7 h.

Tasali *et al.* (2014) made use of a two-week sleep extension intervention in which ten adults who were overweight, but otherwise healthy and usually slept less than 6.5 h 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 TiB to 8.5 h and TST to 7-8 h per night. On average, the

participants went to bed 75 min earlier and got up 30 min later. Mean sleep duration assessed by actigraphy increased from 5.6±0.1 h to 7.1±0.1 h (p<0.001).

In another study, 14 apparently healthy participants with self-reported sleep durations of 6-9 h per night and no sleep complaints were randomized to a TiB extension group (n=8) and a control group (n=6) (Reynold et al., 2014). The TiB extension group was instructed to increase TiB by 180 min per night for one week by adhering to a fixed sleep schedule. The control group was instructed to maintain their median habitual TiB 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 120 min from 6.8±0.6 h to 8.8±0.9 h whereas those in the sleep maintenance group decreased their sleep duration by 16 min from 6.9±0.4 h to 6.7±0.2 h (p<0.001) (Reynold et al., 2014). It must be noted that this was the only included study where the participants did not have short sleep at baseline. The authors hypothesised detrimental effects of sleep extension on the outcome measures.

In a more recent study, 42 healthy, habitually short-sleeping (<7 h) 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 45 min 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 21 min (95% CI: 6-36 min) for the intervention group, which was significantly more than for the control group (-11 min, 95% CI: -26-4 min, 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 (<6 h) 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 crossover-controlled trial and were instructed to stay in bed for at least 8 h between 22:00 and 09:00 without taking naps during the day. Sleep duration (assessed by actigraphy) increased by 60-120 min (p<0.001) on weekend days. However, sleep duration during weekdays remained at baseline level, which was approximately 5 h per night. Because significant time-by-group interactions were observed for bedtime (p<0.001), but not for wake time, the increased TST 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 10 h of forced TiB (Killick et al., 2015). Although this study design was indeed that of sleep extension, this intervention was 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 single or multiple personalized sleep consultation sessions (4), sleep hygiene recommendations (3), and TiB extension with or without bedtime recommendations (6). Interventions with a duration of more than one week, consistently included personalized sleep counselling and the TiB extension approach (e.g. personalized bedtime recommendations) was generally less prescriptive. In comparison, short-term interventions (≤1 week) included a more instructive approach to achieve TiB extension (e.g. forced TiB), and did not include personalized counselling. The shorter interventions produced greater extensions in TiB duration compared to the longer interventions.

Table 2.2. 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 (<7 h sleep duration)	Intervention	13	Go to bed 30 min earlier and 30 min later (+60 min) 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)	IWOC	Healthy adults who were not obese (<7 h sleep duration and weekend catch-up sleep)	Intervention	16	Personalized sleep schedule to increase sleep by 60 min per day Biweekly meeting to discuss difficulties, apply improvements to schedule Ability to contact investigators via phone or email	5-6 weeks	6.0±0.5	~6.7	44±34	<0.0001 (G)
Al Khatib *et al.* (2018)	RCT	Healthy adults who were not obese (5-7 h 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 (<7 h)		5.9 (95% CI: 5.6-6.2)	~5.7	-11 (95% CI: -26-4)	

Citation	Study design	Population	Group	Sample size	Strategy	Duration of intervention	Sleep duration			*p*-value
							From (h)	To (h)	Difference (min)	
Tasali *et al.* (2014)	IWOC	Young adults who were overweight (<6 h sleep duration)	Intervention	10	Individualized behavioural counselling on sleep hygiene on first day of intervention period: all social and environmental factors discussed; Counselling on modifiable factors and other barriers; TiB extension to 8.5 h; Further counselling 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 (6-9 h sleep duration, no sleep complaints)	Intervention	8	Fixed personalized sleep schedule to spend an additional 180 min in bed each night TiB must be spent trying to sleep (no distractions)	1 week	6.8±0.6	8.8±0.9	+120 ES: 2.66	NA
			Comparison	6	Fixed habitual bedtime schedule		6.9±0.4	6.7±0.2	-16 ES: 0.91	
Kubo *et al.* (2011)	COT	Adult daytime industrial workers (6 h sleep duration)	Intervention	26	Stay in bed for at least 8 h between 22:00-09:00 on Friday, Saturday and Sunday	3 days	~<6	~<8	~120	<0.001 (GxT)
			Comparison (crossover)		Keep habitual sleep-wake patterns					

Citation	Study design	Population	Group	Sample size	Strategy	Duration of intervention	Sleep duration			*p*-value
							From (h)	To (h)	Difference (min)	
Killick *et al.* (2015)	COT	Healthy male adults (<6.5 h weeknight sleep duration and weekend catch-up sleep)	Intervention	8	TiB extension to 10 h in sleep lab	3 days	6.2±0.1	~9.2	~177	NA
			Comparison (crossover)	8	TiB restriction to 6 h in sleep lab	3 days	6.2±0.1	~5.8	~-23	NA

CI: Confidence interval; COT: crossover trial; ES: effect size; G: group-effect; GxT: group and time interaction; IWOC: intervention study without control group; NA: not applicable; RCT: randomized controlled trial; T: time-effect; TiB: time-in-bed. Values following '~' are converted from text when no actual values were available. For example, "~<6 h" means that the approximate TST is less than 6 h, because the inclusion criteria was sleeping less than 6 h each night, and for "~6.9 h", the post-intervention TST was not reported, so the difference was added to or subtracted from the pre-intervention TST.

2.3.4 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 2.3**.

2.3.4.1 Anthropometric measures

Weight, BMI, WC and total 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 total body fat (Haack et al., 2013, Al Khatib et al., 2018) and one assessed WC (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 adults who were not obese (Leproult et al., 2015). Likewise, four weeks of sleep extension did not change body weight in 21 short-sleeping (<7 h) adults (*p*-value not reported)(Al Khatib et al., 2018). No changes were found for BMI in 12 individuals with pre- or hypertension 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 WC was observed in adults who were healthy and short-sleeping (<7 h), following a four-week sleep extension intervention (Al Khatib et al., 2018).

2.3.4.2 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 individuals with prehypertension and stage 1 hypertension 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 BP 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).

2.3.4.3 Fasting blood glucose, 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 (<6.5 h) male adults (p>0.05) (Killick et al., 2015). Likewise, Leproult *et al.* (2015) found no effect on fasting blood glucose in 16 healthy, 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 TST assessed by polysomnography (PSG; r=0.53, p=0.041) (Leproult et al., 2015), suggesting that fasting blood glucose increases as sleep duration and TST increases. Fasting plasma insulin levels in habitually short-sleeping (<6.5 h) males were significantly lower following three nights of extended sleep (10 h) compared to three nights of sleep restriction (6 h, 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 diabetes (Jones and Hattersley, 2013), also decreased significantly (p<0.05) (Killick et al., 2015). Another study found that sleep extension did not significantly change fasting insulin levels in 16 healthy, adults who were not obese, however, the author reported that changes in both PSG-assessed TST (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 size (ES), despite the correlation of the latter not being significant (Leproult et al., 2015). Changes in TST as assessed by PSG 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 10 h of sleep, as opposed to the habitual 6 h of sleep in the study by Killick *et al.* (2017), as well as other measures of insulin sensitivity, such as the homeostatic model assessment for insulin resistance (p<0.05) and β-cell function (p<0.05) (Killick et al., 2015). Lastly, sleep extension significantly increased insulin sensitivity as determined by the oral glucose tolerance test in healthy, short-sleeping (<6.5 h) male adults (p<0.05) (Killick et al., 2015).

2.3.4.4 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 6442±1772 to 7413±2281 steps, whereas the step count in the sleep maintenance group increased from 5662±1625 to 6246±1583 steps, 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 two studies which did measure glucose and insulin-related outcomes provided 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.

2.3.4.5 Other observations

This section describes 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.

2.3.4.5.1 Dietary intake

Dietary intake is indirectly associated with an increased cardiometabolic risk, since it may contribute to overweight and obesity. Two studies assessed the effect of sleep extension on dietary intake (Haack et al., 2013, Al Khatib et al., 2018). Haack *et al.* (2013) assessed changes in daily caloric and sodium intake in individuals with prehypertension and stage 1 hypertension 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 (0.7 g/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 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).

2.3.4.5.2 Satiety and appetite

Satiety and appetite are partially regulated by neuronal and hormonal signals originating from the gastro-intestinal tract and adipose tissue, thereby contributing to a healthy energy balance. These regulators may therefore influence energy intake and may 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. Namely, significant decreases were found for plasma leptin (a hormone that increases satiety, $p<0.05$) and 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 (<6.5 h) 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).

2.3.4.5.3 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 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).

2.3.4.5.4 Inflammatory, sympatho-adrenal, and metabolic markers

Several 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 CRP and white blood cells 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 T2DM (Spranger et al., 2003); norepinephrine (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 MetS (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 white blood cell count, IL-6, CRP or NE in twelve pre- or hypertensive participants (Haack et al., 2013), and a one-week TiB extension intervention in healthy sleepers did not change CRP, IL-6, adiponectin or TNF-α levels (Reynold et al., 2014).

2.3.4.5.5 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 RMR changed in response to the sleep extension interventions implemented in the reviewed studies.

Table 2.3. Effect of sleep extension on outcome variables.

Outcome variable	Citation	Study design	Population	Sample size [a]	Sleep extension	Effect	*p*-value
Adiponectin	Reynold et al. (2014)	RCT	Healthy adults (6-9 h sleep duration)	8/14	↑ 120±19 min in 1 week	↔	NS, (ES=-0.08)
Alcohol	Al Khatib et al. (2018)	RCT	Healthy adults who were not obese (< 7 h sleep duration)	21/42	↑ 2 min in 4 weeks	↔	0.226 (GxT)
Appetite	Tasali et al. (2014)	IWOC	Short-sleeping (<6.5 h) young adults who were overweight	10/10	↑ 96 min 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)
BP	Haack et al. (2013)	RCT	Pre- or hypertensive adults (<7 h sleep duration)	13/22	↑ 35±9 min for 6 weeks	SBP: ↔	<0.001 (T) 0.15 (GxT)
						DBP: ↔	<0.02 (T) 0.21 (GxT)
	Kubo et al. (2011)	COT	Short-sleeping (≤6 h) daytime industrial workers	26/26	↑ 60-120 min for 3 days	SBP: ↔	0.171 (GxT)
						DBP: ↔	0.869 (GxT)
	Reynold et al. (2014)	RCT	Healthy adults (6-9 h sleep duration)	8/14	↑ 120±19 min in 1 week	SBP: ↔	NS, (ES=-0.07)
						DBP: ↔	NS, (ES=0.02)
Total body fat	Haack et al. (2013)	RCT	Pre- or hypertensive adults (<7 h sleep duration)	13/22	↑ 35±9 min for 6 weeks	↔	0.74 (GxT)
	Al Khatib et al. (2018)	RCT	Healthy adults who were not obese (5-7 h sleep duration)	21/42	↑ 21 min in 4 weeks	↔	NS (GxT)
BMI	Haack et al. (2013)	RCT	Pre- or hypertensive adults (<7 h sleep duration)	13/22	↑ 35±9 min for 6 weeks	↔	0.14 (GxT)
	Al Khatib et al. (2018)	RCT	Healthy adults who were not obese (5-7 h sleep duration)	21/42	↑ 21 min in 4 weeks	↔	NS (GxT)

Outcome variable	Citation	Study design	Population	Sample size [a]	Sleep extension	Effect	*p*-value
Body weight	Leproult et al. (2015)	IWOC	Healthy adults who were not obese (<7 h sleep duration)	-/16	↑ 44±34 min in 5-6 weeks	↔	0.81 (G)
	Al Khatib et al. (2018)	RCT	Healthy adults who were not obese (5-7 h sleep duration)	21/42	↑ 21 min in 4 weeks	↔	NS (GxT)
Cortisol	Killick et al. (2015)	COT	Healthy male adults (<6.5 h sleep duration)	8/8	↑ 177 min in 3 days	↔	>0.05 (G)
C-peptide	Killick et al. (2015)	COT	Healthy male adults (<6.5 h sleep duration)	8/8	↑ 177 min in 3 days	↓	<0.05 (G)
CRP	Haack et al. (2013)	RCT	Pre- or hypertensive adults (<7 h sleep duration)	13/22	↑ 35±9 min for 6 weeks	↔	0.12 (GxT)
	Reynold et al. (2014)	RCT	Healthy adults (6-9 h sleep duration)	8/14	↑ 120±19 min in 1 week	↔	NS, (ES=-0.04)
Depression & anxiety	Reynold et al. (2014)	RCT	Healthy adults (6-9 h sleep duration)	8/14	↑ 120±19 min in 1 week	BDI: ↔	NS, (ES=-0.86)
						STAI: ↔	NS, (ES=-0.26)
Dietary intake	Haack et al. (2013)	RCT	Pre- or hypertensive adults (<7 h sleep duration)	13/22	↑ 35±9 min 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)
	Al Khatib et al. (2018)	RCT	Healthy adults who were not obese (5-7 h sleep duration)	21/42	↑ 21 min 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)

Outcome variable	Citation	Study design	Population	Sample size [a]	Sleep extension	Effect	*p*-value
						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 (<6.5 h sleep duration)	8/8	↑ 177 min in 3 days	↔	>0.05 (G)
Glucose (fasting)	Leproult et al. (2015)	IWOC	Healthy adults who were not obese (<7 h sleep duration)	16/16	↑ 44±34 min in 5-6 weeks	↔	>0.05 (G)
	Killick et al. (2015)	COT	Healthy male adults (<6.5 h sleep duration)	8/8	↑ 177 min in 3 days	↔	>0.05 (G)
Heart rate	Haack et al. (2013)	RCT	Pre- or hypertensive adults (<7 h sleep duration)	13/22	↑ 35±9 min in 6 weeks	↔	0.87 (GxT)
	Reynold et al. (2014)	RCT	Healthy adults (6-9 h sleep duration)	8/14	↑ 120±19 min in 1 week	↔	NS, (ES=0.19)
Insulin (fasting)	Leproult et al. (2015)	IWOC	Healthy adults who were not obese (<7 h sleep duration)	16/16	↑ 44±34 min in 5-6 weeks	↔	>0.05 (G)
	Killick et al. (2015)	COT	Healthy male adults (<6.5 h sleep duration)	8/8	↑ 177 min in 3 days	↓	<0.05 (G)
Insulin sensitivity	Leproult et al. (2015)	IWOC	Healthy adults who were not obese (<7 h sleep duration)	16/16	↑ 44±34 min 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 (<6.5 h sleep duration)	8/8	↑ 177 min in 3 days	Insulin sensitivity (OGTT, minimal model analysis): ↑	<0.05 (G)
						HOMA-IR: ↓	<0.05 (G)
						HOMA-β: ↓	<0.05 (G)
						QUICKI: ↑	<0.05 (G)
IL-6	Haack et al. (2013)	RCT	Pre- or hypertensive adults (<7 h sleep duration)	13/22	↑ 35±9 min for 6 weeks	↔	0.61 (GxT)

Outcome variable	Citation	Study design	Population	Sample size [a]	Sleep extension	Effect	*p*-value
	Reynold et al. (2014)	RCT	Healthy adults (6-9 h sleep duration)	8/14	↑ 120±19 min in 1 week	↔	NS, (ES=-0.65)
Leptin	Killick et al. (2015)	COT	Healthy male adults (<6.5 h sleep duration)	8/8	↑ 177 min in 3 days.	↓	<0.05 (G)
NE	Haack et al. (2013)	RCT	Pre- or hypertensive adults (<7 h sleep duration)	13/22	↑ 35±9 min for 6 weeks	↔	0.92 (GxT)
PYY	Killick et al. (2015)	COT	Healthy male adults (<6.5 h sleep duration)	8/8	↑ 177 min in 3 days	↓	<0.05 (G)
Physical activity	Reynold et al. (2014)	RCT	Healthy adults (6-9 h sleep duration)	8/14	↑ 120±19 min in 1 week	Average daily steps: ↔	NS, (ES: -0.48)
	Al Khatib et al. (2018)	RCT	Healthy adults who were not obese (5-7 h sleep duration)	21/42	↑ 21 min in 4 weeks	Physical activity intensity: ↔	NS (GxT)
RMR	Al Khatib et al. (2018)	RCT	Healthy adults who were not obese (5-7 h sleep duration)	21/42	↑ 21 min in 4 weeks	↔	NS (GxT)
TNF-α	Reynold et al. (2014)	RCT	Healthy adults (6-9 h sleep duration)	8/14	↑ 120±19 min in 1 week	↔	NS, (ES: -0.09)
WC	Al Khatib et al. (2018)	RCT	Healthy adults who were not obese (5-7 h sleep duration)	21/42	↑ 21 min in 4 weeks	↔	NS (GxT)
White blood cell count	Haack et al. (2013)	RCT	Pre- or hypertensive adults (<7 h sleep duration)	13/22	↑ 35±9 min in 6 weeks	↔	0.88 (GxT)

Data are presented as mean ± SD. BDI: Beck Depression Inventory II; BMI: body mass index; BP: blood pressure; COT: crossover trial; CRP: C-reactive protein; DBP: diastolic blood pressure; 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; IL: interleukin; IWOC: intervention study without control group; NE: norepinephrine; NS: not significant; OGTT: oral glucose tolerance test; PYY: peptide tyrosine-tyrosine; QUICKI: Quantitative Insulin Sensitivity Check Index; RCT: randomized controlled trial; RMR: resting metabolic rate; SBP: systolic blood pressure; STAI: State-Trait Anxiety Inventory; T: time-effect; TNF: tumour necrosis factor; WC: waist circumference; %cal: as percentage of daily caloric intake. ↔: no significant change; ↓: significant decrease; ↑: significant increase. a Sample size reported as sleep extension group / total sample size.

2.4 Discussion

The aim of this 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 intake (Al Khatib et al., 2018, Killick et al., 2015) and to appetite (Tasali et al., 2014).

Since previous studies have shown that short sleep is associated with higher fasting glucose levels and insulin levels (Ford et al., 2013) and reduced insulin sensitivity (Matthews et al., 2012), it seems plausible that increasing sleep duration may improve these metabolic indices. 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 short-sleeping (<6.5 h) participants whose indices were within the healthy range at baseline (Killick et al., 2015). 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, these data must be interpreted with care as sleep extension was achieved by forced TiB 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 individuals with short sleep duration and insulin resistance or T2DM.

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. However, the correlations between change in sleep duration and change in insulin sensitivity-related outcomes indicate some role for increasing sleep duration. While this study certainly had limitations (no control group, no direct assessment of insulin sensitivity in response to a glucose challenge (Leproult et al., 2015), the extent to which fasting glucose levels were reduced was similar to that observed in individuals who were overweight or obese and undertook 12 weeks of high intensity interval training (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 training.

Conflicting findings exist between the two reviewed studies that reported on energy intake, with one finding a reduction in energy intake from free sugars, and an increase in energy intake from

protein in response to the sleep extension intervention (Al Khatib et al., 2018) 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- or hypertensive nature of the participants studied. Without any normotensive control group, one cannot ascertain whether hypertension had any confounding effect on dietary intake.

There is resonance between the observations that sleep extension reduces overall appetite and desire for sweet and salty food (Tasali et al., 2014) and reduces daily free sugar intake (Al Khatib et al., 2018). These studies 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 no control group, one cannot conclude that sleep extension alone was responsible for the outcome observed. Additionally, since 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 individuals with chronic sleep-restriction may result in 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 reduced leptin and PYY (but not ghrelin) following sleep extension (Killick et al., 2015) appears to be at odds with that of reduced appetite (Tasali et al., 2014). On one hand, since neither study measured both variables, one cannot conclude that lower levels of leptin and PYY translates to increased appetite. Differences in study design and participants may also account for these seemingly contradictory findings. Previous studies have found that sleep restriction increases plasma leptin, resulting in an increase in energy intake (Spiegel et al., 2004c), 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, not one 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 obese when recruited (Al Khatib et al., 2018, Leproult et al., 2015), thus improvements in anthropometric outcomes may have been unlikely. 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 or total body fat, studies in participants with obesity are needed before the hypothesis can be rejected.

The participants in two of the three studies that assessed BP and RHR in response to sleep extension were normotensive on average, and baseline RHR was within the normal (60-100 bpm) range (Kubo et al., 2011, Reynold et al., 2014). It was therefore unlikely for improvements in these variables to occur. Since the participants in the Reynold *et al.* (2014) study did not have short sleep at baseline, the authors did not hypothesise that either BP or RHR would improve. Furthermore, the intervention durations of these two studies (three days to a week) may not have been sufficiently long to invoke any change in BP. To the best of my 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 BP was observed. However, the reductions in SBP and DBP observed between the start and end of the sleep extension intervention (14 mmHg and 8 mmHg 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 10 mmHg and 7 mmHg respectively (Somers et al., 1991). Likewise, in a study in which both dietary and exercise interventions were implemented, SBP and DBP decreased by 10 mmHg and 5 mmHg 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 BP. Collectively these data suggest that sleep extension is unlikely to benefit individuals who are normotensive by reducing resting BP. More research with medium- or long-term sleep extension interventions are required to establish the effect on lowering resting BP in individuals with short sleep duration and hypertension.

None of the included studies found significant improvements in any physical activity-related outcomes following sleep extension. Limitations in the study by Reynold *et al.* (2014) were that the

ES 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 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.

The worsening of markers of depression and anxiety in the study by Reynold et al. (2014) may be regarded as 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 hypothesised, however, that by extending TiB to ±10 h, and sleep to almost 9 h, a scenario of forced sleep was created, which may worsen depression, as was indeed the case. It must be noted that the increase in BDI score following the TiB 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 CMD (Mezick et al., 2011). Future studies on sleep extension in individuals with short sleep duration and 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 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 intervention durations, and with individuals with short sleep duration and 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, to the best of my knowledge, only one study has investigated the relationship between sleep duration and RMR and found that RMR did not differ between short (5-6 h), average (7-8 h) and long (9-10 h) sleepers (Chaput et al., 2008). The finding by Al Khatib *et al.* (2018) that RMR was not affected by sleep extension is thus in line with this observation (Al Khatib et al., 2018).

Of the seven different sleep extension strategies employed, those that reported the largest increases in TST were achieved by extending TiB by 2-4 h. 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 TST 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 TiB 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 TiB extension strategy and successful increased sleep duration over a longer period (two weeks). Thus, TiB 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 TiB extension may increase TST 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 TST 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.

2.4.1 Study 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 only on the extension of sleep duration, not on the improvements of other aspects of sleep, such as sleep fragmentation, sleep timing, or sleep architecture. Thus, the results are not applicable to sleep behaviour interventions such as Cognitive Behavioural Therapy for Insomnia that aim to improve sleep in general (i.e. improve quality and quantity of sleep).

2.5 Conclusion

Evidence from this systematic review indicates that increasing sleep duration over a three-day to six-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, BP, inflammatory, sympatho-adrenal or metabolic markers, depression and anxiety, physical activity and RMR. These findings may be relevant to researchers, medical practitioners, dieticians, exercise physiologists and other professionals who are involved in weight loss and preventive medicine. The current evidence to support the role of sleep extension interventions to reduce risk for CMD 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.

Chapter 3

A Comparison of Sleep Characteristics between adults who are Lean, Overweight and Class I Obese, and Class II Obese

3.1 Introduction

Obesity and cardiometabolic impairment have been associated with sleep and circadian disturbances in populations around the world (Rangaraj and Knutson, 2016, Parsons et al., 2015) (see **Section 1.5** for a summary). In light of the overarching purpose of this thesis, it is first necessary to describe the sleep characteristics and associated cardiometabolic risk in the population that will be studied in the intervention component of this thesis. Especially since the nature of the sleep-cardiometabolic risk relationship may well vary between population groups.

A study on the self-reported sleep characteristics of individuals from Austria, Belgium, Brazil, China, Germany, Japan, Portugal, Slovakia, Spain, and South Africa, showed that the individuals from South Africa reported longer times to fall asleep, had the second highest prevalence of individuals who reported 'they do not sleep well' and the second highest prevalence of individuals who rated at least 6 on the Athens Insomnia Scale (Soldatos et al., 2005). Additionally, the individuals from South Africa reported to be 'Very sleepy' and 'Dangerously sleepy' most frequently, while bedtime, get-up time, sleep duration, and nap prevalence and duration in these individuals were similar to those from the other countries (Soldatos et al., 2005). In addition, a study on self-reported sleep duration among older adults in South Africa found that 11.6% reported sleeping less than 6 h, and 23.5% reported sleeping more than 10 h per night (Peltzer, 2012). In contrast, a study with older adults from the United States of America found that more than 30% had self-reported sleep durations of less than 6 h, and less than 5% reported sleep durations of more than 9 h (Xiao et al., 2019). Furthermore, in the study by Peltzer (2012), white, mixed ancestral, and Indian-Asian ethnicities were associated with short sleep duration (<6 h), while lower wealth and hypertension were associated with long sleep duration (>10 h) (Peltzer, 2012). Given the ethnic and socioeconomic diversity in South Africa, sleep duration and other sleep characteristics may vary depending on the demographic characteristics of the cohort. Lastly, our research group recently described lower body mass index (BMI), waist circumference (WC) and better insulin resistance in young African-origin South African women sleeping <7 h compared to those sleeping 7-9 h (self-reported) (Rae et al., 2018). This finding was in contrast with findings of similar studies in the United States of America and Europe, where shorter sleep duration was associated with increased adiposity and worse insulin resistance (Buxton and Marcelli, 2010, Donat et al., 2013, López-García et al., 2008, Bjorvatn et al., 2007). Thus, while these studies report that South Africa has a high prevalence of individuals who report poor sleep and long sleep duration, most of the above-mentioned studies on South Africans reported on the sleep duration and quality of individuals from low income settings and of African-origin.

The intervention component of this thesis will be performed on individuals who sign up for a commercial diet and exercise lifestyle intervention programme. It is prudent to first describe the sleep characteristics in a similar group of individuals, and to assess whether sleep disturbances in these individuals, if they exist at all, are related to obesity severity.

Therefore, the aim of this study is to describe and compare the sleep characteristics between individuals who are lean (LEAN), individuals who are overweight and class I obese (OW-OBI), and those who are class II obese (OBII) and to determine the extent to which sleep characteristics are associated with cardiometabolic health in this sample, specifically in adults representative of the population that would be studied in the intervention component of this thesis. The first objective is to describe and compare actigraphy and polysomnography (PSG)-derived sleep characteristics (bedtime, get-up time, midpoint of sleep, time-in-bed (TiB), total sleep time (TST), sleep onset latency (SOL), awakening index, wake after sleep onset (WASO), sleep efficiency (SE), awakenings >5 min, simplified sleep regularity index (sSRI) and social jet lag), and subjective sleep characteristics (sleep quality, daytime sleepiness, and chronotype) between the three groups. The second objective is to describe and compare anthropometric (BMI, WC, waist-to-height ratio; WHtr), cardiometabolic (blood pressure (BP), fasting glucose and total cholesterol (TC) levels), and perceived stress characteristics between the three groups. The third objective is to explore associations between the anthropometric, cardiometabolic and sleep characteristics within the three groups. It is hypothesised that the OW-OBI and OBII groups will have later bedtimes, get-up times and midpoints of sleep, shorter sleep durations, longer SOL, more sleep fragmentation, more daytime sleepiness, worse subjective sleep quality and later chronotypes than the LEAN group. Lastly, it is hypothesised that unfavourable anthropometric and cardiometabolic outcomes will be associated with unfavourable sleep outcomes in all groups.

3.2 Methods

3.2.1 Participants

Adults with overweight or obesity and a WC>88 cm (females) or >102 cm (males), 20 years of age or older and of all ethnicities were recruited near the sites in the Cape Town metropole where the sample for the intervention component of this thesis was recruited. Participants with a BMI >25 $kg \cdot m^{-2}$ and ≤35 $kg \cdot m^{-2}$ comprised the overweight and class I obesity group (OW-OBI). Those with a BMI >35 $kg \cdot m^{-2}$ comprised the class II obesity group (OBII). The decision to combine the overweight and class I obesity group was made *post-hoc* due to the unbalanced nature of the groups.

The participants were recruited through the local gym (e.g. newsletter, active recruitment), advertisement in local newspapers and by word-of-mouth in the Cape Town suburbs of Newlands and surroundings. Exclusion criteria were being diagnosed with a sleep disorder (excluding insomnia or mild obstructive sleep apnoea, OSA); exposure to any extrinsic factors that preclude normal nocturnal sleep (e.g. currently breastfeeding, parents of young children who routinely wake up in the night, shift work); transmeridian travel exceeding three time zones in the previous two months; participation in any sport or physical activity for which regular training is required (more than four times per week). Additionally, individuals who were lean and apparently healthy were recruited for the LEAN group from the same sites where the OW-OBI and OBII groups were recruited. Participants had a BMI ≤25 $kg \cdot m^{-2}$ and a WC ≤88 cm (females) or ≤102 cm (males), were 20 years of age or older, and of all ethnicities. The exclusion criteria were the same as for the OW-OBI and OBII groups.

3.2.2 Study design

In this descriptive cross-sectional study, the LEAN, OW-OBI, and OBII groups were compared with respect to the variables of interest. All volunteers completed a questionnaire detailing their demographics, medical history, sleep characteristics and perceived stress. The participants also had their weight, height, WC, resting BP, fasting glucose and TC levels measured. Over the following seven days, the participants wore a wrist actigraph, which, together with a diary, was used to assess their sleep habits. The testing took place between 06:00 and 10:00 to account for possible time-of-day variation in some of the variables. The participants were instructed not to exercise in the morning of the assessment prior to testing and to refrain from eating and drinking anything but water from 22:00 the previous night until after the assessment. The participants were asked the time of their last meal and if they had not fasted since 22:00 the previous night, the appointment was rescheduled.

3.2.3 Detailed procedures

3.2.3.1 Demographic and lifestyle assessments

The demographic, occupational, travel, and medical history questions in the questionnaire served to characterize the participants, as well as to ensure their eligibility for the study. Due to the fact that the city in which the study took place (Cape Town) is home to multiple ethnic groups, the demographic section of the questionnaire included one question asking participants to self-identify

their ethnicity (Black/African, White, Mixed Ancestry (coloured), Indian, Asian, or Other). Smoking status was categorized as 'never', 'past', or 'current'. The participants were asked how many standard drinks containing alcohol they drink on a typical weekend/day-off day, and on a typical week/working day, from which the alcohol consumption in units per week was estimated. Alcohol consumption was categorized as 'none' if the participant did not consume alcohol at all, 'low' if one to seven units per week for females or one to 14 units per week for males were consumed, 'moderate' if seven to 14 units per week for females or 14 to 21 units per week for males were consumed, and 'high' if more than 14 units for females or more than 21 units for males were consumed. For physical activity, participants were asked what their average total exercise time for the week was. Individuals were placed into one of three physical activity level categories based on the hours of exercise they regularly performed per week prior to the study: low levels of physical activity (<1 h of exercise per week), moderate (1-3 h of exercise per week), or high (>3 h of exercise per week).

3.2.3.2 Anthropometric measures

Each participant's height (cm) was measured using a portable stadiometer (Seca 213, Seca Deutschland, 22089 Hamburg, Germany). Body weight (kg) was measured using a digital platform scale (Peninsula Scales, Killarney Gardens, Cape Town, South Africa) which was calibrated twice a year. The participants were instructed to empty their pockets, remove their shoes, and take off any loose clothing such as scarves, jackets and sweaters. Each participant's BMI ($kg \cdot m^{-2}$) was calculated by dividing their weight in kilograms by the square of their height in metres. For WC, participants were asked to stand up straight with their feet as close together as physically possible. A metal anthropometric tape (Cescorf Equipment Ltd., Porto Elegre, Brazil) was used to measure the narrowest circumference between the tenth rib and iliac crest at the end of a normal exhalation. Measurements were taken in duplicates and averaged. WHtr was calculated by dividing WC in cm by height in cm. Outcome variables were height (cm), weight (kg), BMI ($kg \cdot m^{-2}$), WC (cm), and WHtr.

3.2.3.3 Blood pressure

After 10 minutes of seated rest, diastolic blood pressure (DBP) and systolic blood pressure (SBP) readings were taken three times at 1-minute intervals from the upper arm of each participant using an appropriately-sized cuff and an automated blood pressure monitor (Omron HEM-907, Omron Health Care, Kyoto, Japan). The three measurements were alternated between the left and right

arms. The two DBP readings that were closest together were averaged and the same was done for the SBP measurements. If the median DBP or SBP measurement was as close to the lowest as it was to the highest measurement, the median measurement was used (i.e. the average of the three measurements). Outcome variables were resting DBP and SBP (mmHg).

3.2.3.4 Fasting glucose and total cholesterol levels

The index or middle finger was punctured with a spring-loaded safety blade lancet. The first droplet of blood was removed with a swab and discarded, and the second drop was placed on a Accutrend Plus device testing strip (Roche Products, Randburg, South Africa). The linear measuring range for fasting glucose was between 1.1 and 33.3 mmol·L^{-1}, and for TC between 3.88 and 7.76 mmol·L^{-1}. If the result was below or above these ranges as indicated by the device with "Lo" or "Hi" respectively, the upper or lower limit was used for the analysis. Outcome variables were fasting glucose (mmol·L^{-1}) and TC (mmol·L^{-1}) levels.

3.2.3.5 Perceived stress

Perceived stress was assessed with the 14-item Cohen's Perceived Stress Scale (CPSS), which provides a score between 0 and 56, where higher scores indicate higher levels of perceived stress (Cohen et al., 1983).

3.2.3.6 Cardiometabolic risk factors

Cardiometabolic risk factors were defined as follows: elevated WC (WC >88 cm for females, or WC >102 cm for males; elevated BP (DBP ≥130 mmHg, SBP ≥90 mmHg, or on antihypertensive medication); elevated fasting glucose levels (fasting glucose level ≥5.6 mmol·L^{-1}) (Grundy et al., 2005), and elevated TC levels (TC level ≥5.2 mmol·L^{-1}) (Lloyd-Jones et al., 2010).

3.2.3.7 Actigraphy

Participants wore an actigraphy device (Actiwatch AW2, Philips Respironics, Bend, OR, USA) for seven consecutive nights and days on the wrist of their non-dominant hand. The participants were instructed to press and hold the marker button on the side of the Actiwatch for 3 s when they: 1) decided to close their eyes and try to sleep at the beginning of each nocturnal resting period, and 2) woke to rise for the day or decided not to try to sleep any further. Participants were also instructed to keep a sleep diary, in which they would record bedtime and get-up time and any factors that may have disturbed their sleep (e.g. barking dog, use the toilet at night, stressful day).

For a dataset to be valid, a minimum of three weekday nights (Sunday – Thursday) and one weekend night (Friday or Saturday) was required. Philips Actiware software (version 6.0.9, Respironics Inc., Murrysville, PA, USA) was used to analyse the recordings. The researcher would manually set the start and end of each nocturnal resting period based on the activity and light levels and event markers, as previously described (Chow et al., 2016), and confirmed by the diary if needed. The wake threshold was set at 40 activity counts and the sleep interval detection algorithm was set at 10 min for sleep onset and 10 min for sleep end, as per default settings. The software predicted when the participant was awake or asleep for each 15 s epoch of the resting period. A simplified version of the sleep regularity index (SRI), a measure of sleep/wake pattern regularity (Phillips et al., 2017), was calculated as per equation 1, where n is day, and bedtime and get-up time are expressed in 24 h clock time, with minutes as a fraction of hours (e.g. 23.75 for 23:45). Where bedtime was later than 24:00, 24 h was added to the bedtime (e.g. 25.50 for 01:30).

$$sSRI_n\ (\%) = 100 \times \frac{(|\Delta_{Bedtime_n - Bedtime_{n-1}}| + |\Delta_{Get-up\ time_n - Get-up\ time_{n-1}}|)}{1440} \times 100 \qquad (1)$$

Social jet lag was calculated as the absolute difference between mean midpoint of sleep on weekdays and mean midpoint of sleep on weekend days (Wittmann et al., 2006). If sleep duration was longer on weekend days than weekdays, half the difference between TST on weekend days and weekdays was subtracted from social jet lag to correct for catch-up sleep (Jankowski, 2017). The outcome variables were actigraphy-derived bedtime (hh:mm), get-up time (hh:mm), TiB (h), TST (h), SOL (min), SE (%, TST divided by TiB multiplied by 100), WASO (min), number of awakenings >5 min (count), awakening index (number of awakenings of any duration divided by TST), sSRI (%), midpoint of sleep (hh:mm), and corrected social jet lag (min). All variables were averaged over all days of actigraphy monitoring, with the exception of corrected social jet lag.

3.2.3.8 Polysomnography

A subset of participants who participated in the intervention component of this thesis underwent two consecutive nights of home-based PSG (Easy Ambulatory 2, Cadwell Industries, Inc., Kennewick, WA, USA). The first night served as a familiarisation night and was used only if the second night of PSG could not be used (e.g. when device malfunctioned). PSG was performed according to the American Academy of Sleep Medicine's recommended electrode montages: electroencephalography (EEG): frontal (F3-M2, F4-M1), central (C3-M2, C4-M1) and occipital (O1-M2, O2-M1); electrooculography (EOG) (E1-M2, E2-M1); submental electromyography (EMG); electrocardiography (ECG); and body position (Berry et al., 2018). Data were sampled at 200 Hz, the high and low-cut frequency filters were set at 35 Hz and 0.53 Hz respectively, and the

notch filter was set at 50 Hz. Sleep stages and arousals were scored according to the standard criteria of the American Academy of Sleep Medicine (Berry et al., 2018). Chest and abdominal respiratory inductance plethysmography; airflow pressure transducer; pulse oximetry; and body position were also recorded to assess sleep-disordered breathing, however, owing to technical and human errors, these data could not be used. Lights-on and lights-off were captured by the participant using an annotation button on the PSG device. If the participant did not annotate lights-on or lights-off, the EEG, EOG and body position channels were used to estimate these times. Outcome variables were SOL (min), rapid eye movement onset latency (REMOL, min), WASO (min, wake time after at least three epochs of sleep have occurred), SE (%), sleep stages (time relative to TST (%) spent in non-REM (NREM)1, NREM2, NREM3 and REM sleep), and arousal index (number of cortical arousals per hour of sleep).

3.2.3.9 Subjective sleep assessments

Subjective sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI) questionnaire, which provides scores from 0 to 3 on seven components (subjective sleep quality, SOL, sleep duration, habitual SE, sleep disturbances, use of sleeping medication, and daytime dysfunction) and a global sleep quality score (sum of the component scores) (Buysse et al., 2002). Daytime sleepiness was assessed with the Epworth Sleepiness Scale (ESS) which assigns a score between 0 and 24 to indicate levels of daytime sleepiness (Johns, 1991). Diurnal preference, or chronotype, was assessed with the Horne-Östberg morningness-eveningness personality questionnaire (HÖ-MEQ) where lower scores (16-41) indicate eveningness and higher scores (59-86) morningness (Horne and Ostberg, 1976).

3.2.3.10 Sleep health

Five binary values for sleep duration, fragmentation, regularity, social jet lag and daytime sleepiness, and a sleep health score were created. For sleep duration, the American National Sleep Foundation's recommendations for sleep duration for adults (7-9 h) was used (Hirshkowitz et al., 2015). This recommendation is mainly based on self-reported sleep duration, however, which has been shown to be approximately 48 min higher than objective sleep duration measured in a group of young adults in the USA (Lauderdale et al., 2008). Therefore, 48 min was subtracted from this recommendation. Thus, participants were assigned a 1 if TST <6.2h, or a 0 if TST ≥6.2h. High sleep fragmentation was defined based on the American National Sleep Foundation's sleep quality recommendations (Ohayon et al., 2017) for SE (<85%), WASO (>20 min), and awakenings >5 min (>1 awakening). If any two of these conditions were met, participants were assigned a 1 for

sleep fragmentation, or a 0 if not. High sSRI was defined based on the study by Lunsford-Avery *et al.* (Lunsford-Avery et al., 2018), where irregular sleepers were defined as those with a SRI below the 20th percentile of their cohort, namely 61%. However, since the sSRI is by definition higher than SRI, as it ignores nocturnal awakenings and daytime naps, the 20th percentile of the present cohort was used as a cut-off point, namely 90%. Participants were assigned a 1 if sSRI was less than this cut-off value, or a 0 if not. The participants were assigned a 1 for social jet lag if the corrected social jet lag was more than 60 min, or a 0 if not (Mota et al., 2017). The four objective indicators of sleep health were based on actigraphy. Participants with excessive daytime sleepiness (EDS), which was defined as having an ESS score >10, were assigned a 1, and those without EDS a 0. Lastly, the poor sleep health indicators that were present in each individual were summed and reported as the sleep health score.

3.2.4 Data and statistical analyses

All data were reported as mean ± standard deviation or median with interquartile range (IQR). To test for differences of the continuous outcome variables between groups, the one-way analysis of covariance (ANCOVA) with age as a covariate was used if the group × age interaction effect was not statistically significant, and the model residuals were normally distributed. Otherwise, if the group × age interaction effect in the ANCOVA model was statistically significant, the one-way analysis of variance (ANOVA) with Bonferroni *post-hoc* test was used if the model's residuals were normally distributed. If the residuals of the ANCOVA or ANOVA were not normally distributed, the data was transformed, or the Kruskal-Wallis one-way ANOVA with the Bonferroni-adjusted Dunn's *post-hoc* test was used (Dunn, 1964).

Categorical distributions were analysed using Pearson's chi-squared. The *p*-values for the chi-squared *post-hoc* test were calculated from the adjusted residuals, and were Bonferroni-adjusted (*p*-value times number of cells of the contingency table).

For the association analyses, linear regressions between variables of interest were used while correcting for age if the predictor variable × age interaction effect was not statistically significant, and the model's residuals were normally distributed. If the residuals for the linear regression were not normally distributed, ordered logistic regression between the quintiles of the outcome variables and the continuous predictor variables (including age) were used. If the assumption for proportionality of odds for the ordered logistic regressions were not met, generalized ordered logistic regressions were used. The *p*-values for the linear and (generalized) ordered logistic

regressions were Bonferroni-adjusted. Statistical significance was accepted when $p<0.05$. Data were analysed using Stata (v15.1, StataCorp, Texas USA).

3.3 Results

3.3.1 Participants

One-hundred and seventy-one individuals consented to participate in the study. Of these, 13 did not meet the eligibility criteria, and another six were excluded because of actigraphy data acquisition errors. The remaining participants comprised the LEAN group (n=39), OW-OBI group (n=50) and OBII group (n=63). Of the included participants, none reported a previous diagnosis of insomnia.

3.3.2 Demographic and lifestyle characteristics

The demographic and lifestyle characteristics of the three groups are presented in **Table 3.1**. The OW-OBI group was significantly older than the LEAN ($p=0.044$) and OBII ($p<0.001$) groups. The OBII group had fewer White ($p<0.001$) and more mixed ancestral ($p<0.001$) individuals than the expected frequencies. Fewer participants in the LEAN group reported 'low' levels of physical activity ($p=0.036$), and more participants reported 'high' levels of physical activity ($p=0.001$) than the expected frequency, while more participants reported 'low' levels of physical activity than the expected frequency in the OBII group ($p=0.049$).

Table 3.1. Demographic and lifestyle characteristics of the LEAN, OW-OBI, and OBII groups.

	LEAN (n=39)	OW-OBI (n=50)	OBII (n=63)	Between-group comparison *p*-value
Age (y)	41.4 (28.0)	53.8 (15.6) [a]	42.5 (14.1)	**0.002**
Gender				0.910
Female	31 (80%)	38 (76%)	48 (76%)	
Male	8 (20%)	12 (24%)	15 (24%)	
Ethnicity				**<0.001**
White	31 (80%)	41 (82%)	32 (51%) [*]	
Mixed ancestry	4 (10%)	5 (10%)	28 (44%) [*]	
Black	2 (5%) [b]	3 (6%) [b]	1 (2%) [b]	
Indian	2 (5%) [b]	-	2 (3%) [b]	
Other	-	1 (2%) [b]	-	
Smoking status				0.067

Never	32 (82%)	33 (66%)	39 (62%)	
Past	4 (10%)	15 (30%)	17 (27%)	
Current	3 (8%) [b]	2 (4%) [b]	7 (11%) [b]	
Alcohol consumption				0.249
None	12 (31%)	15 (30%)	31 (49%)	
Low	22 (56%)	27 (54%)	26 (41%)	
Moderate	4 (10%)	7 (14%)	6 (10%)	
Heavy	1 (3%) [b]	1 (2%) [b]	-	
Physical activity level				**0.001**
Low	10 (25%) *	22 (44%)	37 (59%) *	
Moderate	12 (31%)	19 (38%)	19 (30%)	
High	17 (44%) *	9 (18%)	7 (11%)	

Data are presented as median (interquartile range) or count (percentage). LEAN: lean control group; OBII: class II obese group; OW-OBI: overweight-class I obese group. The *p*-values for the between-group comparisons were determined using the Kruskal-Wallis ANOVA with Dunn's *post-hoc* test, or Chi-squared tests. The cells indicated with * are significantly different to the expected frequency. [a] The OW-OBI group was significantly older than the LEAN and OBII groups. The cells indicated with [b] were excluded from the analyses as expected cell frequency <5.

3.3.3 Anthropometric, cardiometabolic and perceived stress outcomes

The anthropometric, cardiometabolic and perceived stress characteristics of the three groups are presented in **Table 3.2**. One observation for each of the OW-OBI and OBII groups was missing for the fasting glucose and TC tests due to the inability to obtain blood because of poor blood perfusion to the fingers. TC levels were higher than the linear measuring range for two participants in the LEAN group, one participant in the OW-OBI group, and two participants in the OBII group, and thus 7.76 $mmol \cdot L^{-1}$ was used. In addition, TC levels were lower than the linear measuring range for one participant in the LEAN group, three participants in the OW-OBI group and two participants in the OBII group, and thus 3.88 $mmol \cdot L^{-1}$ was used. By design, the OW-OBI group was heavier and had higher BMI, larger WC, and larger WHtr than the LEAN group, and the OBII group had a higher BMI, larger WC, and larger WHtr than both the LEAN and OW-OBI groups. The OBII group had higher DBP than the OW-OBI and LEAN groups. Both OW-OBI and OBII groups had higher fasting glucose levels than the LEAN group.

Finally, the OBII had a higher prevalence of elevated WC ($p<0.001$) and BP ($p=0.009$), while the LEAN group had a lower prevalence of elevated WC ($p<0.001$) and BP ($p=0.021$) than the expected frequencies (**Table 3.3**). Although the prevalence of elevated fasting glucose level was different between the groups, the difference could not be detected with *post-hoc* tests.

Table 3.2. Anthropometric, cardiometabolic and perceived stress characteristics of the LEAN, OW-OBI, and OBII groups.

	LEAN	n	OW-OBI	n	OBII	n	Between-group comparison *p*-value	LEAN v OW-OBI	OW-OBI v OBII	OBII v LEAN
Anthropometric measures										
Height (cm)	168.9±7.3	39	168.6±8.7	50	166.6±8.2	63	0.233	NA	NA	NA
Weight (kg)	61.8 (11.2)	39	90.3 (17.6)	50	111.7 (29.1)	63	**<0.001** [t]	**<0.001** [t]	**<0.001** [t]	**<0.001** [t]
BMI ($kg \cdot m^{-2}$)	22.2 (3.0)	39	31.8 (3.9)	50	39.2 (6.9)	63	**<0.001** [†]	**<0.001** [†]	**<0.001** [†]	**<0.001** [†]
WC (cm)	72.1±6.3	39	95.1±9.6	50	111.5±12.4	63	**<0.001**	**<0.001**	**<0.001**	**<0.001**
WHtr	0.43±0.03	39	0.56±0.04	50	0.67±0.07	63	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Blood pressure										
DBP (mmHg)	71.0 (15.0)	39	77.0 (11.5)	50	82.5 (16.0)	63	**<0.001**	0.117	**0.016**	**<0.001**
SBP (mmHg)	114.0 (13.5)	39	115.5 (22.0)	50	118.5 (23.5)	63	0.751 [†]	NA	NA	NA
Fingerprick tests										
Fasting glucose ($mmol \cdot L^{-1}$)	4.5 (0.8)	39	5.0 (1.1)	49	5.3 (1.2)	62	**<0.001** [†]	**0.012** [†]	0.075 [†]	**<0.001** [†]
TC ($mmol \cdot L^{-1}$)	5.4 (1.5)	39	5.9 (1.7)	49	5.4 (1.7)	62	0.315 [†]	NA	NA	NA
CPSS	16.3±6.2	39	19.0±6.4	50	17.9±5.9	63	0.062	NA	NA	NA

Data are presented as mean ± standard deviation or median (interquartile range). BMI: body mass index; CPSS: Cohen's perceived stress scale; DBP: diastolic blood pressure; LEAN: lean control group; NA: not applicable; OBII: class II obese group; OW-OBI: overweight-class I obese group; SBP: systolic blood pressure; TC: total cholesterol; WC: waist circumference; WHtr: waist-to-height ratio. The *p*-values for the between-group comparisons were determined using the ANCOVA with age as a covariate, with ([t]) or without (no superscript symbol) transformation to achieve normal distribution of ANCOVA residuals, or the Kruskal-Wallis ANOVA ([†]) with Dunn's *post-hoc* test.

Table 3.3 Prevalence of cardiometabolic risk factors in the LEAN, OW-OBI and OBII groups.

	LEAN	n	OW-OBI	n	OBII	n	Between-group comparison *p*-value
Elevated WC	0 (0%) *	39	40 (80%)	50	62 (98%) *	63	**<0.001**
Elevated BP	7 (18%) *	39	17 (34%)	50	33 (52%) *	63	**0.002**
Elevated fasting glucose	5 (13%)	39	12 (24%)	49	24 (39%)	62	**0.015** [a]
Elevated TC	24 (62%)	39	34 (69%)	49	38 (61%)	62	0.632

Data are presented as count (percentage). BP: blood pressure; LEAN: lean control group; OBII: class II obese group; OW-OBI: overweight-class I obese group; TC: total cholesterol; WC: waist circumference. The *p*-values for the between-group comparisons were determined using Chi-squared tests. The cells indicated with * are significantly different to the expected frequency. [a] *Post-hoc* analyses were not sensitive enough to detect differences between groups.

3.3.4 Actigraphy, polysomnography and subjective sleep outcomes

The actigraphy, PSG and sleep questionnaire outcomes are presented in **Table 3.4**. Two observations are missing for the actigraphy measures that depend on accelerometer data, due to an accelerometer calibration error. Bedtime, get-up time and derivatives were not affected by this error.

From actigraphy, the OBII group had shorter TiB and TST and lower SE than the OW-OBI and LEAN groups. The OBII group had more awakenings >5 min than the LEAN group. Of the sleep timing-related measures, bedtime was delayed in the OBII group compared to the LEAN group, and the OBII group had a lower sSRI than the LEAN group. With all three groups combined, sSRI correlated with age (ρ=0.307, p<0.001). However, due to the non-normal distribution of the ANCOVA residuals for sSRI, even after data transformation, age could not be adjusted for.

PSG sleep characteristics were only different for NREM3 sleep, such that the OBII had less NREM3 sleep than the LEAN group. Although PSG TST was longer in the OW-OBI group than in the OBII group, these variables were only reported for descriptive purposes, and will not be discussed further. Rather actigraphy-derived TST is used since it is more representative of habitual sleep duration.

The OW-OBI and OBII groups reported higher PSQI scores than the LEAN group. Specifically, the distribution of habitual SE (component 4 of the PSQI) and sleep disturbances (component 5 of the PSQI) were different between the groups (**Table 3.5**). However, Bonferroni-adjusted *post-hoc* analyses could not detect significance between groups. Lastly, the OW-OBI and OBII groups had higher ESS scores than the LEAN group.

Of the five indicators of poor sleep health, only the prevalence of short sleep duration and high sleep fragmentation were different between the groups (**Table 3.6**). More individuals in the OBII group (p<0.001), and fewer individuals in the LEAN group (p=0.039) had short sleep duration

than the expected frequencies. *Post-hoc* analyses lacked sensitivity to detect between-group differences in the prevalence of high sleep fragmentation. The sleep health score was higher (i.e. worse sleep health) in the OBII group than in the LEAN and OW-OBI groups.

Because the groups were not similar in physical activity level and because physical activity is known to affect sleep, the associations of these characteristics with the sleep variables were assessed. With all three groups combined, sSRI was lower in those reporting to be 'low' physically active (median=91.7, interquartile range (IQR)=4.2, n=69), than in those who report being "moderate" physically active (median=93.2, IQR=4.0, n=50, p=0.017) or "high" physically active (median=93.9, IQR=2.9, n=33, p=0.005). None of the other sleep measures were different between levels of physical activity (data not shown).

Table 3.4. Actigraphy, PSG, and subjective sleep characteristics of the LEAN, OW-OBI, and OBII groups.

	LEAN	n	OW-OBI	n	OBII	n	Between-group comparison *p*-value	LEAN v OW-OBI	OW-OBI v OBII	OBII v LEAN
Actigraphy										
TiB (h)	7.6 (1.0)	39	7.6 (1.2)	50	7.3 (1.2)	63	**0.008**	0.377	**0.033**	**0.003**
TST (h)	7.0±0.6	39	6.7±0.8	50	6.3±0.8	61	**<0.001**	0.295	**0.002**	**<0.001**
SOL (min)	7.0 (7.5)	39	5.5 (7.5)	50	7.9 (9.5)	61	0.177 [t]	NA	NA	NA
SE (%)	90.1 (5.2)	39	90.2 (4.2)	50	87.5 (6.1)	61	**0.001** [†]	1.000 [†]	**0.002** [†]	**0.003** [†]
WASO (min)	23.3 (13.6)	39	25.6 (14.3)	50	28.4 (18.2)	61	0.106 [t]	NA	NA	NA
Awakenings > 5 min	0.43 (0.55)	39	0.46 (0.80)	50	0.67 (1.14)	61	**0.050** [† a]	0.660 [†]	0.146 [†]	**0.028** [†]
Awakening index	5.6 (2.5)	39	5.5 (2.3)	50	5.7 (2.1)	61	0.148 [t]	NA	NA	NA
Bedtime (hh:mm)	22:49 (0:50)	39	22:49 (1:05)	50	23:16 (1:08)	63	**0.027** [†]	0.765 [†]	0.078 [†]	**0.019** [†]
Get-up time (hh:mm)	06:32 (0:51)	39	06:28 (1:04)	50	06:29 (0:43)	63	0.802 [†]	NA	NA	NA
sSRI (%)	94.2 (5.6)	39	93.2 (4.1)	50	92.2 (3.7)	63	**0.010** [†]	0.335 [†]	0.101 [†]	**0.004** [†]
Midpoint of sleep (hh:mm)	02:44 (0:44)	39	02:41 (1:05)	50	02:54 (0:49)	63	0.505 [t]	NA	NA	NA
Corrected social jet lag (min)	31.1 (54.8)	39	29.2 (29.6)	50	47.1 (42.5)	61	0.587 [t]	NA	NA	NA
Polysomnography										
TiB (h)	7.6 (0.6)	12	7.3 (1.2)	14	6.6 (1.3)	16	0.053 [t]	NA	NA	NA
TST (h)	6.6±1.0	12	6.8±0.9	14	5.9±1.1	16	**0.045**	0.705	**0.020**	0.062
SOL (min)	4.5 (5.3)	12	4.3 (6.5)	14	3.8 (3.8)	16	0.448 [†]	NA	NA	NA
REMOL (min)	102.3 (85.8)	12	67.0 (20.0)	14	73.3 (84.8)	16	0.379 [t]	NA	NA	NA
WASO (min)	28.8 (34.3)	12	17.5 (19.0)	14	27.3 (49.3)	16	0.066	NA	NA	NA
SE (%)	93.5 (10.0)	12	93.5 (3.0)	14	93.0 (11.0)	16	0.690 [†]	NA	NA	NA
NREM1 (%TST)	11.0 (9.7)	12	10.1 (7.9)	14	13.4 (9.1)	16	0.474 [t]	NA	NA	NA
NREM2 (%TST)	47.8±6.8	12	48.5±7.4	14	52.0±9.5	16	0.224	NA	NA	NA
NREM3 (%TST)	22.0±8.4	12	17.7±10.2	14	12.8±8.0	16	**0.020**	0.191	0.111	**0.006**
REM (%TST)	17.6±6.8	12	21.1±5.2	14	20.2±4.8	16	0.300	NA	NA	NA
Arousal index	11.5 (10.2)	12	10.8 (13.9)	14	10.3 (9.1)	16	0.862 [t]	NA	NA	NA

	LEAN	n	OW-OBI	n	OBII	n	Between-group comparison *p*-value	LEAN v OW-OBI	OW-OBI v OBII	OBII v LEAN
Questionnaires										
PSQI	4.0 (4.0)	39	7.0 (4.0)	50	7.0 (4.0)	63	**<0.001** [t]	**0.002** [t]	0.546 [t]	**<0.001** [t]
ESS	7.0 (6.0)	39	8.0 (6.0)	50	8.0 (5.0)	63	**0.006** [t]	**0.003** [t]	0.602 [t]	**0.008** [t]
HÖ-MEQ	62.0 (13.0)	39	58.5 (16)	50	56.0 (11.0)	63	0.174 [t]	NA	NA	NA

Data are presented as mean ± standard deviation or median (interquartile range). ESS: Epworth Sleepiness Scale; HÖ-MEQ: Horne-Östberg morningness-eveningness personality questionnaire; LEAN: lean control group; NA: not applicable; NREM: non rapid eye movement sleep; OBII: class II obese group; OW-OBI: overweight-class I obese group; PSQI: Pittsburgh Sleep Quality Index; REM: rapid eye movement sleep; REMOL: REM onset latency; SE: sleep efficiency; SOL: sleep onset latency; sSRI: simplified sleep regularity index; TiB: time-in-bed; TST: total sleep time; WASO: wake after sleep onset. The *p*-values for the between-group comparisons were determined using the ANCOVA with age as a covariate, with ([t]) or without (no superscript symbol) transformation to achieve normal distribution of ANCOVA residuals, or the Kruskal-Wallis ANOVA ([†]) with Dunn's *post-hoc* test. [a] *p*-value was 0.0495, but was rounded up to 0.05.

Table 3.5. Score categories for components 4 and 5 of the PSQI for the LEAN, OW-OBI, and OBII groups.

	LEAN (n=39)	OW-OBI (n=50)	OBII (n=63)	Between-group comparison *p*-value
Component 4: Habitual SE				**0.024** [b]
0	28 (72%)	20 (40%)	34 (54%)	
1	5 (13%)	16 (32%)	12 (19%)	
2	5 (13%)	9 (18%)	6 (10%)	
3	1 (3%)	5 (10%)	11 (17%)	
Component 5: Sleep disturbances				**0.016** [b]
0	2 (5%) [a]	0 (0%) [a]	1 (2%) [a]	
1	27 (69%)	24 (48%)	28 (44%)	
2	10 (26%)	26 (52%)	30 (48%)	
3	0 (0%) [a]	0 (0%) [a]	4 (6%) [a]	

Data are presented as count (percentage). LEAN: lean control group; OBII: class II obese group; OW-OBI: overweight-class I obese group; PSQI: Pittsburgh sleep quality index; SE: sleep efficiency. Higher component scores indicate worse sleep. The *p*-values for the between-group comparisons were determined using Chi-squared tests. The cells indicated with [a] were excluded from the *post-hoc* test as expected cell frequency <5. [b] *Post-hoc* analyses were not sensitive enough to detect differences between groups.

Table 3.6. Prevalence of poor sleep health indicators and sleep health score in the LEAN, OW-OBI and OBII groups.

	LEAN	n	OW-OBI	n	OBII	n	Between-group comparison *p*-value
Short sleep duration	5 (13%) *	39	10 (20%)	50	30 (49%) *	61	**<0.001**
High sleep fragmentation	5 (13%) [b]	39	13 (26%) [b]	50	24 (39%) [b]	61	**0.015**
High sSRI	9 (23%)	39	11 (22%)	50	16 (25%)	63	0.910
High corrected social jet lag	11 (28%)	39	7 (14%)	50	17 (28%)	61	0.161
EDS	4 (10%)	39	14 (28%)	50	14 (22%)	63	0.120
Sleep health score	0.0 (2.0)	39	1.0 (2.0)	50	2.0 (1.0) [c]	61	**0.003** †

Data are presented as count (percentage) or median (interquartile range). EDS: excessive daytime sleepiness; LEAN: lean control group; OBII: class II obese group; OW-OBI: overweight-class I obese group; sSRI: simplified sleep regularity index. The *p*-values for the between-group comparisons were determined using Chi-squared tests (no superscript symbol) or the Kruskal-Wallis ANOVA (†) with Dunn's *post-hoc*. The cells indicated with * are significantly different to the expected frequency. [b] *Post-hoc* analyses were not sensitive enough to detect differences between groups. [c] Significantly different to LEAN ($p<0.001$) and OW-OBI ($p=0.029$) groups.

3.3.5 Association analyses

Association analyses were performed combining data from all three groups and adjusting for age. Higher BMI, WC, and WHtr were associated with lower TST, and higher PSQI and ESS scores were associated with a higher CPSS score (**Fig 3.1**). Additionally, higher quintiles of WHtr were associated with lower actigraphy SE, more awakenings >5 min, and higher PSQI score, and higher quintiles of WC were also associated with lower actigraphy SE, more awakenings >5 min (**Fig 3.2**). Lastly, individuals in the lowest WC quintile were more likely to have lower PSQI scores than those in the other four WC quintiles (**Fig 3.3**). No other associations were found between parameters.

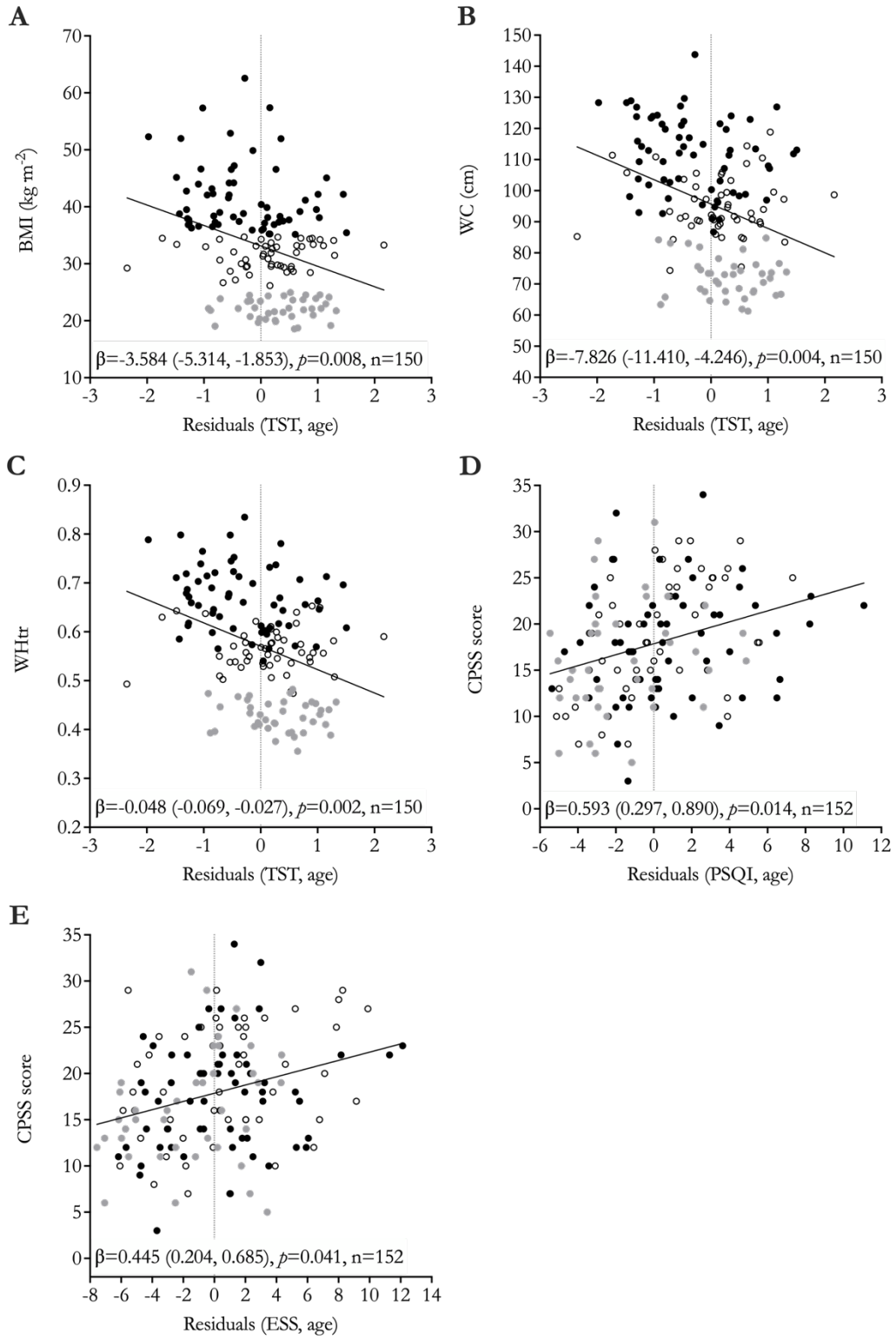

Figure 3.1. Linear regression plots for BMI and TST (**A**), WC and TST (**B**), WHtr and TST (**C**), CPSS and PSQI (**D**), and CPSS and ESS (**E**). ●: lean control group (LEAN); ○: overweight-class I obese group (OW-OBI); ●: class II obese group (OBII). BMI: body mass index; CPSS: Cohen's perceived stress scale; ESS: Epworth sleepiness scale; PSQI: Pittsburgh sleep quality index; TST: total sleep time; WC: waist circumference; WHtr: waist-to-height ratio. All TST is actigraphy-based. Data are presented as beta coefficients (95% confidence interval) and *p*-values shown were determined using multiple linear regression analyses correcting for age.

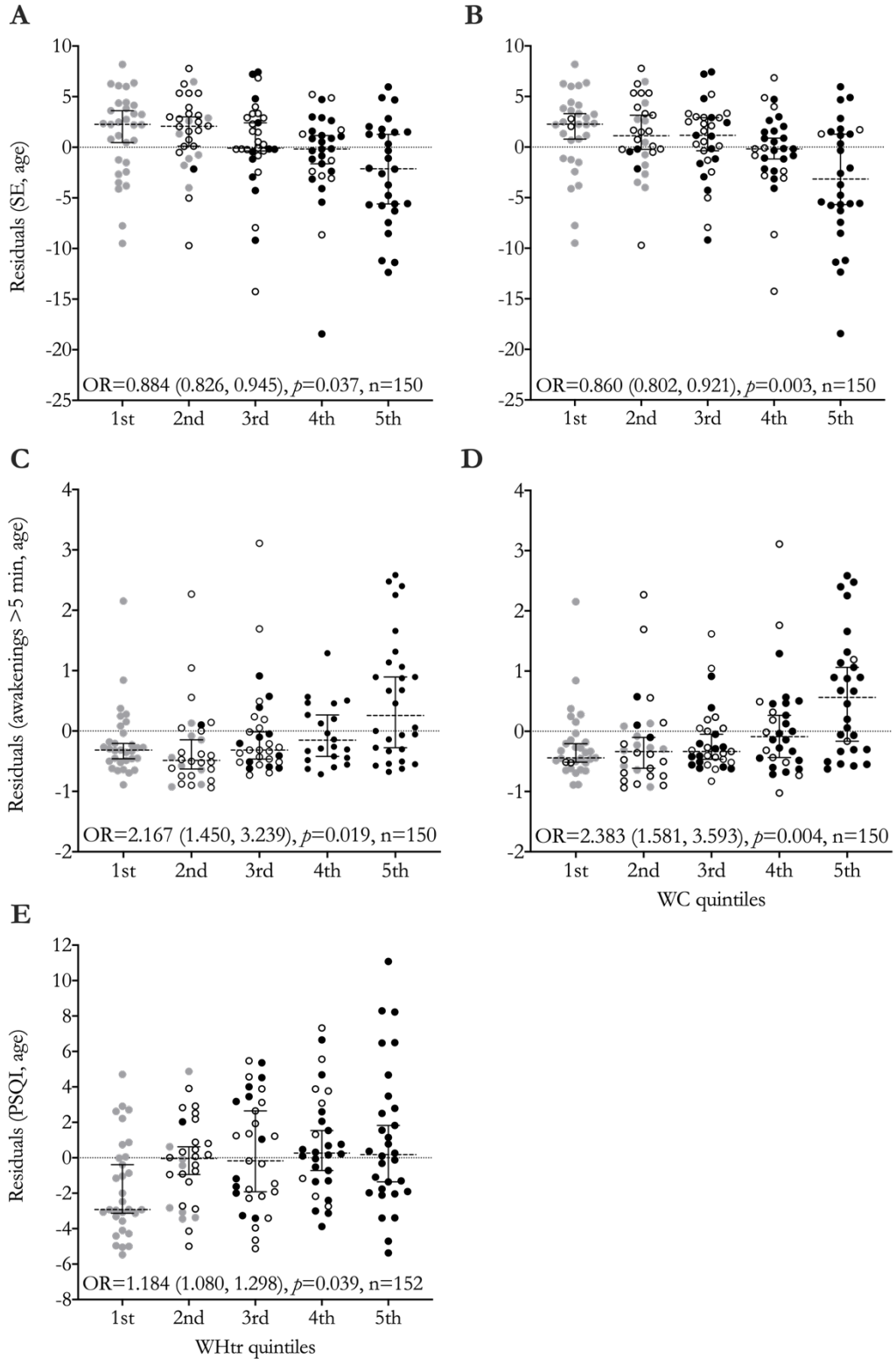

Figure 3.2. Dot plots for the residuals of SE for each WHtr (A) and WC (B) quintile, residuals of awakenings >5 min for each WHtr (C) and WC (D) quintile, and residuals of PSQI for each WHtr quintile (E). ●: lean control group (LEAN); ○: overweight-class I obese group (OW-OBI); ●: class II obese group (OBII). OR: odds ratio; PSQI: Pittsburgh sleep quality index; SE: sleep efficiency; WC: waist circumference; WHtr: waist-to-height ratio. SE and awakenings >5 min are actigraphy-based. The OR (95% confidence interval) and *p*-values were determined using ordered logistic regression analyses correcting for age.

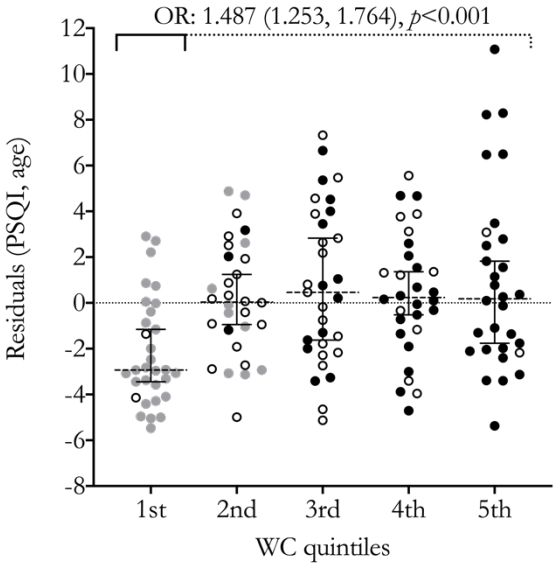

Figure 3.3. Dot plots for the residuals of PSQI for each WC quintile. ●: lean control group (LEAN); ○: overweight-class I obese group (OW-OBI); ●: class II obese group (OBII). OR: odds ratio; PSQI: Pittsburgh sleep quality index; WC: waist circumference. The OR (95% confidence interval) and *p*-values were determined using generalized ordered logistic regression analyses correcting for age, and represent the odds for having lower PSQI scores in the quintile below the solid bracket compared to those in the dotted bracket.

3.4 Discussion

Anthropometric and cardiometabolic health, and actigraphy, polysomnographic, and subjective sleep characteristics of individuals who are lean, individuals with overweight or class I obesity, and individuals with class II obesity were investigated and compared. The main finding was that the OBII group had less TiB and TST, and lower SE than the OW-OBI and LEAN groups. The OBII group also had more awakenings >5 min, later bedtimes, lower sSRI, and less NREM3 sleep than the LEAN group, but not the OW-OBI group. Furthermore, the OW-OBI and OBII groups had worse subjective sleep quality and levels of daytime sleepiness than the LEAN group. Additionally, the prevalence of short sleep duration in the OBII group was higher, and that of the LEAN group was lower, than the expected frequencies. Over and above the between-group differences in anthropometric measures by study design, the OBII group had higher DBP than the OW-OBI and LEAN groups, and the OBII and OW-OBI groups had higher levels of fasting glucose than the LEAN group. Likewise, the prevalence of elevated BP in the OBII group was higher, and that of the LEAN group was lower than the expected frequencies. Higher WC and WHtr were associated with shorter TST, lower SE, more awakenings >5 min, and higher PSQI scores (worse sleep quality), and higher BMI was associated with lower TST. Finally, higher CPSS scores were associated with higher PSQI and ESS scores.

Interestingly, differences in objective measures of sleep were observed between the LEAN and OBII groups, but not between the LEAN and OW-OBI groups. This finding suggests that mere overweight and class I obesity may not affect objective sleep measurably, and that true differences in sleep start to be detectable only in class II obesity. However, since the OW-OBI group had worse subjective sleep quality and daytime sleepiness than the LEAN group, other measures of impaired sleep, not assessed by actigraphy or PSG may exist in the OW-OBI.

The finding of increased sleep fragmentation and prevalence of high sleep fragmentation in the OBII group, and the correlation of WC and WHtr with SE, and awakenings >5 min in the pooled cohort, are in line with studies that show associations between sleep fragmentation and BMI or obesity (van den Berg et al., 2008, Lauderdale et al., 2009, Stamatakis and Punjabi, 2010, Mezick et al., 2014). Moreover, sleep fragmentation may lead to reductions in NREM3 sleep (Hursel et al., 2011), which was indeed observed in the OBII group. Both reduced NREM3 sleep and sleep fragmentation (possibly through a reduction in NREM3 sleep) have been associated with impaired glucose homeostasis and insulin resistance (Tasali et al., 2008, Herzog et al., 2013, Koren et al., 2011, Stamatakis and Punjabi, 2010, Gonnissen et al., 2013). This may, at least in the OBII group, contribute to the higher fasting glucose levels observed. Moreover, sleep fragmentation has been associated with increased blood pressure (Corbalan-Tutau et al., 2012), which is consistent with the finding of higher SBP in the OBII group.

In addition to the increased sleep fragmentation, the OBII group also had later bedtimes and consequently shorter TiB. The decision to retire later and spend less time sleeping may either be conscious, driven by deprioritising sleep over other activities such as entertainment (e.g. watching TV, reading) and socializing, or subconscious, driven by a decreased sleep propensity (i.e. feeling less sleepy) or sleep need (i.e. requiring less sleep). Given the higher levels of daytime sleepiness in the OBII group, it is more likely that, if subconscious, the difference in TiB is not driven by a decreased sleep need, but rather by a decreased sleep propensity at night.

Based on the two-process model of sleep regulation (Borbely et al., 2016), the suggested decrease in sleep propensity may be explained by two different mechanisms: one that involves the homeostatic process and one that involves the circadian process.

First, although sleep outside of the nocturnal sleep period (i.e. daytime naps) was not captured in this study, it is possible that the OBII group napped during the day, thereby affecting the homeostatic process, subsequently decreasing night-time sleep propensity, resulting in later bedtimes and shorter TiB. In addition, day-to-day variation in napping occurrence and duration,

influenced by work and social commitments, may have caused variation in night-time sleep propensity, and could thus also explain the decreased sSRI.

Second, if one assumes that daytime napping did not occur, and given that the OBII group spent less time asleep and had more fragmented sleep, they presumably had longer episodes of wakefulness in a 24 h period than the LEAN group. One may therefore speculate that the homeostatic process drives an increase in sleep propensity, and that the OBII would retire earlier, not later as is observed in the present study. It is thus plausible that rather the circadian process, and not the homeostatic process, plays a larger role in this observation. Furthermore, since neither midpoint of sleep nor chronotype were different between the groups, the lower sleep propensity is unlikely to be explained by changes in the phase (i.e. timing) of the circadian process, but rather by the amplitude of the circadian process. That is, the circadian amplitude of alerting in the OBII group is suppressed, not only resulting in decreased alertness during the day, but also decreased sleepiness at night. However, to the best of my knowledge, no studies have compared the circadian rhythm amplitude of melatonin, core body temperature or measures of sleepiness or alertness of individuals who are obese and individuals who are lean using constant routine or forced desynchrony protocols to support this observation. On the other hand, studies assessing diurnal variation under entrained conditions have shown that the amplitude of the leptin rhythm is attenuated in individuals with obesity (Saad et al., 1998), and inversely associated with weight gain (Matkovic et al., 1997), while the diurnal rhythms of melatonin (Brambilla et al., 1988) and core body temperature (Heikens et al., 2011) were not different in obese compared to individuals who were lean. Additionally, the shorter sleep duration may also explain a change in the circadian process; sleep restriction has been shown to decrease the diurnal amplitude of leptin (Spiegel et al., 2004a), the Stanford sleepiness scale rating, oral temperature (Taub, 1981) and the circadian amplitude of gene expression (Moller-Levet et al., 2013). Others have suggested that the phase-advancing effect of light is attenuated when sleep need is high following sleep restriction (Burgess, 2010). These mutual influences of the homeostatic and circadian processes, and their mechanisms are well known and have been described in detail elsewhere (Borbely et al., 2016).

Regardless of the potential mechanisms described above, the lower sSRI observed in the OBII group may be indicative of a decreased circadian amplitude on its own. Namely, as sleep propensity becomes less driven by time-of-day (i.e. the circadian process) it becomes more dependent on time awake and the accumulation of sleep debt (i.e. homeostatic process), which varies more between days. Others found that SRI was associated with delayed sleep timing, increased daytime sleep and sleepiness, reduced light exposure and cardiometabolic risk in a cohort of older adults (Lunsford-Avery et al., 2018). Future intervention studies focusing on improving sleep regularity in individuals

with overweight and obesity may shed more light on the direction of the association between circadian amplitude and cardiometabolic risk.

The between-group difference in sSRI may also be explained by the difference in levels of physical activity between the groups. Those who reported lower levels of physical activity had lower sSRI, irrespective of their groups. Indeed, regular exercise has been shown to be associated with rest-activity rhythm consolidation and regularity in healthy elderly males (Van Someren et al., 1997). Moreover, children with higher weekday-weekend sleep regularity had more consistent and more intensive activity than children with lower sleep regularity (Stone et al., 2013). A possible mechanism for this observation in humans may have been found in mice, namely, spontaneous exercise during the active period was shown to increase suprachiasmatic nuclei (SCN) activity amplitude (van Oosterhout et al., 2012). Thus, a higher SRI may be caused by an increased circadian amplitude that results from more regular activity and resting behaviour. The differences in sSRI between the LEAN and OBII groups may thus not be exclusively dependent on adiposity.

The decreased TiB and increased sleep fragmentation in the OBII group compared to the LEAN group, ultimately resulted in the shorter TST in the OBII group. This finding, and the correlation between anthropometric measures and TST, are in line with studies that have shown associations between short sleep duration and BMI (Taheri et al., 2004, Lauderdale et al., 2009), and obesity (Cappuccio et al., 2008, Rasmussen et al., 2008). Furthermore, others have shown that individuals with short sleep durations (≤5 h) may be at a greater risk of weight gain over the following 6 to 16 years (Patel et al., 2006, Chaput et al., 2008), and thus individuals in the present study who are obese and with short sleep durations may also be at risk of further weight gain. However, the sleep durations of the participants in OBII group in the present study were not as short as that of those in the aforementioned studies. As such, it is possible that the participants of the present study may be protected against further weight gain, provided that sleep duration does not decrease further. Short sleep duration has also been associated with type 2 diabetes mellitus (T2DM) (Xu et al., 2010, Cappuccio et al., 2009), and 14 days of sleep restriction (5.5 h) in individuals who are healthy and non-obese has been shown to lead to reduced glucose tolerance and insulin sensitivity (Nedeltcheva et al., 2009). Again, although the sleep duration of the individuals with obesity in the present study is not as short as that of the cited studies, the participants may be protected against developing (further) insulin resistance.

Despite no differences in objective sleep between the OW-OBI and LEAN groups, the OW-OBI group reported higher levels of daytime sleepiness. The objective measures of sleep assessed in the present study may thus not explain these differences. Although the participants were excluded if they were diagnosed with OSA or received treatment for OSA, participants were not systematically

subjected to a sleep study to confirm the absence of sleep-disordered breathing. Given that obesity is a risk factor for OSA and the high estimated number of undiagnosed OSA cases (Kapur et al., 2002), it cannot be assumed that all participants did not have OSA. Therefore, undiagnosed OSA may explain the increased levels of daytime sleepiness in some of the individuals in the OW-OBI group. However, sleepiness in individuals with obesity and OSA might only be partially explained by sleep apnoea. For example, the apnoea-hypopnoea index and ESS score are only moderately correlated (Serafini et al., 2001, Kingshott et al., 1995), and a proportion of individuals with OSA and daytime sleepiness continue to experience sleepiness after receiving continuous positive airway pressure therapy (Antic et al., 2011, Pepin et al., 2009). Moreover, bariatric surgery in individuals with obesity and OSA seems to decrease daytime sleepiness dramatically, without addressing OSA (Holty et al., 2011, Fritscher et al., 2007). Together, these findings suggest that adiposity itself, regardless of the presence of OSA, is associated with daytime sleepiness. Others have suggested that these mechanisms may be associated with metabolic or circadian disturbances, and more research is needed to confirm these findings (Vgontzas et al., 1998). It must also be noted that although the OW-OBI and OBII groups had ESS scores that were statistically higher than those of the LEAN group, the difference is small and may not be clinically relevant or noticeable in everyday life. Moreover, the groups did not differ in the prevalence of EDS, regarded as the severity at which sleepiness becomes debilitating.

Although the OW-OBI and OBII groups had higher PSQI scores, which indicates worse sleep quality, it cannot be assumed that these participants are less satisfied with their sleep than the individuals in the LEAN group, since, the groups did not differ in the first component of the PSQI, i.e. rating of subjective sleep quality. Instead, the PSQI components that were different between the groups were sleep disturbance and habitual SE, which only confirms the between-group difference in actigraphy-assessed sleep fragmentation.

Finally, despite the differences in sleep characteristics between the groups of the present study, it must be noted that the prevalence of poor sleep health indicators and the sleep health score was generally low, even in the highest adiposity group (OBII). Therefore, not all individuals with cardiometabolic impairment or class II obesity may have impaired sleep, and thus not all individuals in this category may benefit from sleep improvement categories.

3.4.1 Study limitations

This study had several limitations. First, by not including daytime naps and dozing, it cannot be assumed that participants with less total nocturnal sleep time did not nap during the day and

ultimately extend 24 h TST, which could subsequently decrease sleep propensity in the evening. While instructed to annotate naps, the participants were inconsistent with annotating naps in their diaries and automatic or visual detection of naps without these annotations are guesses at best. It was therefore decided to only include the nocturnal sleep period in the analysis. Second, only a subset of participants in each group underwent PSG, leading to decreased power in the analyses of these variables. Third, the common disconnection of the finger pulse oximeter and nasal cannula of the PSG device made the data unsuitable for the detection of sleep-disorder breathing. It could therefore not be determined whether or not the participants had undiagnosed sleep-disordered breathing, or whether the sleep impairment observed in the OBII group was due to their adiposity alone and not compounded by sleep-disordered breathing. Fourth, while both cardiometabolic health and sleep have been associated with socioeconomic status (Ogunsina et al., 2018, Grandner et al., 2010), measures of the latter were not included in the data collection or analysis of the present study. To minimize differences in socioeconomic status between individuals, all participants were recruited from the same site in the Cape Town metropole. Therefore, this convenience sample is not generalizable to the larger Cape Town Metropole. Fifth, due to scheduling and time constraints, some of the actigraphy nights overlapped with the PSG nights. Because PSG is considered invasive and may alter normal sleep, it is possible that allowing the actigraphy and PSG nights to overlap may have affected the actigraphy data. However, since the actigraphy data shown is the average over four to seven nights, the impact of the PSG nights on these data is minimal. Indeed, when all overlap nights were removed from the analysis, the significance did not change (data not shown).

3.5 Conclusion

Combined, these findings suggest that the individuals with class II obesity experienced more sleep fragmentation, which may have led to a decrease in NREM3 sleep, more irregular sleep, and shorter sleep duration than individuals who are lean. This sleep impairment may put them at risk for worsening of their cardiometabolic health, including additional weight gain and insulin resistance, which in turn, may perpetuate sleep impairment. These findings are in line with those from other cohorts around the world. Future research should investigate whether sleep improvement strategies may prevent or mitigate cardiometabolic impairment in individuals with overweight and obesity and especially in those with class II obesity.

Chapter 4

The Effect of an eight-week Diet and Exercise Lifestyle Intervention Programme on the Sleep Characteristics of Adults with Overweight and Obesity

4.1 Introduction

Short sleep duration (Lucassen et al., 2012, Cappuccio et al., 2011), sleep fragmentation (van den Berg et al., 2008, Lauderdale et al., 2009), delayed and irregular sleep timing (Merikanto et al., 2013, Taylor et al., 2016), social jet lag (Mota et al., 2017), and decreased non-rapid eye movement (NREM)3 sleep (Rao et al., 2009, Tasali et al., 2008) have been bidirectionally associated with obesity and worse cardiometabolic health in populations around the globe (see **Chapter 1** for a full discussion). In **Chapter 3**, it was found that South African individuals with class II obesity had shorter sleep duration, less regular sleep timing, more sleep fragmentation, and less NREM3 sleep compared to individuals who are lean. Their sleep habits may put them at an increased risk of further weight gain and future insulin resistance and may thus perpetuate the vicious cycle of poor sleep and impaired cardiometabolic health.

Traditionally, weight-loss interventions primarily consist of nutritional modulation or exercise, or a combination thereof, to increase energy expenditure and decrease energy intake. The aim is to induce a negative energy balance which increases reliance on fat metabolism, thereby reducing fat stores and body weight. The effects of these interventions on cardiometabolic health are well-described. For example, a twelve-month weight-loss lifestyle intervention with nutritional modulation and exercise reduced fasting glucose, triglycerides (TG), insulin resistance, glycated haemoglobin (HbA1c) and leptin, and increased high-density lipoprotein (HDL) levels in adults with overweight and obesity with the metabolic syndrome (MetS) (Salas-Salvado et al., 2019). Likewise, another twelve-month lifestyle intervention resulted in reductions in HbA1c, systolic blood pressure (SBP), diastolic blood pressure (DBP), TG, and an increase in HDL in 5,145 individuals with overweight and obesity and type 2 diabetes mellitus (T2DM) (Look Ahead Research Group, 2007).

The effect of sleep modulation, most commonly sleep extension, on cardiometabolic health has also been described, albeit to a lesser extent (see **Chapter 2** for a full discussion). For example, three weekend nights of catch-up sleep has been shown to improve insulin sensitivity in men with chronic sleep restriction (Killick et al., 2015). In contrast, six weeks of sleep extension was found to be ineffective for improving body mass index (BMI), total body fat, or blood pressure (BP) in pre- or hypertensive adults (Haack et al., 2013). Likewise, BMI and total body fat were not affected in short-sleeping healthy adults following four weeks of sleep extension (Al Khatib et al., 2018).

Thus, both diet and exercise, and sleep modulation may improve cardiometabolic health. However, to the best of my knowledge, no studies have described the effect of a diet and exercise lifestyle

intervention programme on sleep, or the interplay between sleep and cardiometabolic health within lifestyle interventions. The effects of exercise on sleep in isolation, however, have been investigated, and these studies can be divided into three categories.

In the first category are the studies with cohorts of individuals with diagnosed insomnia. Studies in this category were recently reviewed systematically (Banno et al., 2018). The authors concluded that exercise may indeed improve sleep quality (assessed with the Pittsburgh Sleep Quality Index, PSQI; and Insomnia Severity Index) without any notable adverse effects in patients with diagnosed insomnia (Banno et al., 2018). For example, a six-month moderate-intensity aerobic training protocol (three 50-min sessions per week) decreased sleep onset latency (SOL) and wake after sleep onset (WASO), and increased sleep efficiency (SE) and subjective sleep quality (PSQI) in sedentary adults with chronic primary insomnia (Passos et al., 2011). Similarly, insomnia symptom severity (Insomnia Severity Index) in inactive adults with diagnosed insomnia decreased following 6 months of moderate- to vigorous intensity physical activity (≥150 min per week) (Hartescu et al., 2015). The authors of the review paper also mentioned that the effect of exercise on sleep may be greater in individuals with diagnosed insomnia than in those without diagnosed insomnia but with sleep complaints (Banno et al., 2018).

The second category of studies comprises those on individuals without diagnosed insomnia but with insomnia symptoms or sleep complaints. These studies have also been systematically reviewed, albeit less recently, and only cohorts of middle-aged and older adults were included (Yang et al., 2012). Nevertheless, when the results of the six included papers were combined, it was found that exercise training improved subjective sleep quality (PSQI) in these cohorts (Yang et al., 2012). For example, one of the included papers reported that 16 weeks of aerobic exercise (four 10-40 min sessions per week), in combination with sleep hygiene education, improved self-reported SOL, increased sleep duration, and subjective sleep quality (PSQI) in healthy sedentary adults with insomnia symptoms (Reid et al., 2010). A more recent study, not included in the review paper, reported that SOL (piezoelectric bed sensor) and self-reported difficulty initiating sleep improved in a group of participants with chronic insomnia symptoms, most of whom were overweight or obese, following a six-month aerobic exercise programme (one to five 30-60 min session(s) per week) (Tan et al., 2016). In this study, differences between baseline and follow-up measures were also observed for WASO, SE and subjective sleep quality in the exercise group, although not significantly different to those found in the control group (Tan et al., 2016). Thus, although evidence is available to suggest that exercise may change, and more specifically improve, sleep, it is important to note that the participants of these studies had diagnosed insomnia or insomnia symptoms.

For the last category, which includes studies with individuals who were not specifically recruited for having diagnosed insomnia or symptoms thereof, no review papers are available. However, one original study found that 12 weeks of aerobic exercise and resistance training (180 min weekly) increased sleep duration and SE in obese adolescents with no diagnosed insomnia or sleep complaints (Mendelson et al., 2016). On the other hand, in a randomized controlled trial with middle-aged women with low levels of physical activity, four months of walking or yoga did not affect subjective sleep quality (PSQI) (Elavsky and McAuley, 2007).

Lastly, another systematic review, which only included randomized controlled trials, found that resistance training, especially when combined with aerobic exercise improved sleep quality (assessed with various tools, including PSQI and the Insomnia Severity Index) (Kovacevic et al., 2018). However, this review included both clinical and nonclinical populations with and without insomnia, and effect-differences between cohorts with and without insomnia were not unpacked. Thus, while sufficient evidence is available to suggest that exercise may improve insomnia symptoms or sleep complaints in individuals with insomnia, evidence to support a role of exercise in improving sleep in individuals without sleep complaints is less abundant.

Little is known about the effect of nutritional modulation on sleep. Studies have found that some foods such as cherries and kiwi fruit improve aspects of sleep, possibly due to their rich contents of circadian phase-advancing substances, e.g. melatonin, serotonin, tryptophan (Garrido et al., 2010, Lin et al., 2011). Moreover, the glycaemic index, carbohydrate and fat contents of diets have also been shown to affect sleep. For example, SOL was reduced in healthy participants who had eaten a meal with a high glycaemic index 4 h before bedtime compared to those who had eaten a meal with a low glycaemic index (Afaghi et al., 2007). Additionally, an older study found that a high-carbohydrate/low-fat diet resulted in less NREM3 sleep than a low-carbohydrate/high-fat diet or a balanced diet, and that both high-carbohydrate/low-fat diets and low-carbohydrate/high-fat diets resulted in more rapid eye movement (REM) sleep than a balanced diet (Phillips et al., 1975). Another older study found that three days of high-carbohydrate bedtime food supplementation resulted in more REM sleep (three-day average) than carbohydrate-free or low-carbohydrate bedtime food supplementation (Porter and Horne, 1981). Similarly, and more recently, a short-term very low-carbohydrate diet resulted in an acute decrease in REM sleep and an acute increase in NREM3 sleep (Afaghi et al., 2008). Thus, evidence seems to suggest that both exercise and diet modulation in isolation may affect sleep. However, little is known about the combined effect of exercise and diet modulation, such as seen in lifestyle intervention programmes may affect sleep.

Therefore, the aim of this study was to determine whether the sleep characteristics of individuals with overweight and obesity were altered as a result of participation in an eight-week diet and exercise lifestyle intervention programme. The first objective was to compare actigraphy-derived sleep characteristics (bedtime; get-up time; midpoint of sleep; time-in-bed, TiB; total sleep time, TST; SOL; awakening index; WASO; awakenings >5 min; SE; and simplified sleep regularity index, sSRI), and subjective sleep characteristics (PSQI; Epworth sleepiness scale, ESS; and the Horne-Östberg morningness-eveneningness personality questionnaire, HÖ-MEQ) score in individuals with overweight and obesity measured before and after participation in an eight-week diet and exercise lifestyle intervention programme to those measured in BMI-matched individuals not participating in the programme (i.e. control group). The second objective was to determine whether any changes in sleep characteristics were associated with changes in anthropometric or cardiometabolic measures over the eight-week period. The hypothesis was that individuals with overweight and obesity participating in the eight-week diet and exercise lifestyle intervention programme would advance their bedtimes, increase their sleep durations, decrease sleep fragmentation, become earlier chronotypes, and improve subjective sleep quality and daytime sleepiness to a greater extent than a control group at the end of the eight-week period. It was also hypothesised that capacity for improvements in anthropometric and cardiometabolic measures depends on the baseline sleep measures, and that the extent to which sleep changes from baseline will determine the extent to which anthropometric and cardiometabolic measures change in response to the intervention.

4.2 Methods

4.2.1 Participants

Participants were recruited from the pool of individuals with overweight and obesity who voluntarily enrolled in a commercial eight-week diet and exercise lifestyle intervention programme, called 'the Healthy Weight Programme' (HWP group). Participants who enrolled in the programme were informed about the study via an email after enrolment, via their individual goal-setting session, and via the workshop in the first week of the programme. Additionally, participants with overweight and obesity who did not enrol in the eight-week lifestyle intervention programme, were recruited from the same area in the Cape Town metropole for the control (CON) group. Participants in both groups had a BMI >27.5 $kg \cdot m^{-2}$ and abdominal obesity (waist circumference (WC) >88 cm for females, or >102 cm for males); were 20 years of age or older; and of all ethnicities. Participants with a narrower WC, but a BMI >28.5 $kg \cdot m^{-2}$ were also included.

Participants were not eligible if they had been diagnosed with a sleep disorder (excluding insomnia or mild obstructive sleep apnoea, OSA); were exposed to any extrinsic factor that precludes normal nocturnal sleep (e.g. currently breastfeeding, parents of young children who routinely wake up in the night, shift work); had undergone transmeridian travel exceeding three time zones in the previous two months; or participated in any sport or physical activity for which regular (more than four times per week) training was required.

4.2.2 Study design

In this natural experiment, participants of the HWP group were compared to the age and gender-matched CON group with respect to change in the variables of interest over an eight-week period. During this period, the HWP group participated in the lifestyle intervention programme, while the CON group did not. Both groups underwent baseline and follow-up assessments. During the baseline assessment, the participants completed a questionnaire detailing their demographics, medical history, and various sleep questionnaires and a perceived stress questionnaire. The participants also had their weight, height, WC, resting BP, and fasting glucose and TC levels measured. Over the following seven days, the participants wore a wrist actigraph, which, together with a diary, was used to assess their habitual sleep habits. This assessment was repeated after eight weeks. Both baseline and follow-up assessments took place between 06:00 and 10:00 to account for possible time-of-day variation in some of the variables. Within this timeframe, however, the baseline and follow-up assessment may not have been at exactly the same time *per se*. The participants were instructed not to exercise in the morning of the assessment and to refrain from eating and drinking anything but water from 22:00 the previous night until after the assessment. The participants were asked the time of their last meal the night before, and if they had not fasted since 22:00 the previous night, the appointment was rescheduled.

4.2.3 Lifestyle intervention programme

The aim of the commercial lifestyle intervention programme, called the *Healthy Weight Programme*, was to make sustainable lifestyle modifications (exercise and diet) for the individuals to reduce their weight and improve their health. In the first week, the HWP group received a goal setting session with a psychologist and a dietary consultation session (including an individualised eating plan) with a dietician. The participants also attended a workshop to improve knowledge about diet and exercise and to learn skills to reduce and manage their weight. Over the following eight weeks, the participants attended periodized group exercise sessions specifically for individuals with

overweight and obesity three to four times per week. Each participant's diet and exercise were closely monitored, and adjusted if necessary, by the programme dieticians and biokineticists (clinical exercise physiologists). Although recruited from the same suburbs of the Cape Town metropole, the participants of the lifestyle intervention programme had to pay a considerable fee and may thus have been of higher socioeconomic status than the control participants.

4.2.4 Detailed procedures

The detailed procedures were identical to those described in **Section 3.2.3**, with the exception of the PSG assessment which was not included in this study.

4.2.5 Data and statistical analyses

All data were reported as mean ± standard deviation or median with interquartile range. A Student's t-test or Kruskal-Wallis analysis of variance (ANOVA) was used to compare the characteristics of the two groups at baseline. To test if the changes in outcome variables from baseline to follow-up assessments were different between the groups, an analysis of covariance (ANCOVA) was used with baseline as a covariate if the group × baseline interaction was not significant. If the group × baseline interaction was significant, this assumption for ANCOVA was violated, and a one-way ANOVA was used instead. If the residuals of the ANCOVA or ANOVA were not normally distributed, the Kruskal-Wallis ANOVA was used. Cohen's effect size (ES) was reported if change in the outcome variable was significantly different between groups. ES was considered small if less than 0.5, moderate if 0.5 or higher and less than 0.8, and large if 0.8 or higher. Categorical distributions at baseline and follow-up were analysed using Pearson's chi-squared or Fisher's exact tests. For the analyses of change in the binary cardiometabolic and sleep conditions between baseline and follow-up, participants were first categorized as '0' if they did not have the condition at baseline and follow-up, '1' if they did not have the condition at baseline, but did have the condition at follow-up, '2' if they had the condition at baseline, but did not have the condition at follow-up, and '3' if they had the condition at baseline and follow-up. The distributions of these new categorical variables were then analysed with the Pearson's chi-squared or Fisher's exact tests. The *p*-value for the chi-squared *post-hoc* test was calculated from the adjusted residuals and were Bonferroni adjusted (*p*-value times number of cells of the contingency table). Correlations between baseline and change in anthropometric and cardiovascular health outcomes and sleep variables were analysed using Pearson's (for parametric data) and Spearman's (for non-

parametric data) correlations as appropriate. The *p*-value for the significance was accepted when $p<0.05$. Data were analysed using Stata (v15.1, StataCorp, Texas USA).

4.3 Results

4.3.1 Participants

Forty-four participants who enrolled for the eight-week lifestyle intervention programme were recruited and tested at baseline. Of these, eleven participants were lost to follow-up and two were lost due to technical errors with the Actiwatch. One female participant with a WC of 84.6 cm but a BMI of 28.7 $kg \cdot m^{-2}$ was also included in the HWP group. The final sample size for the HWP group was 31. In addition, 30 CON individuals who did not, and never had, participated in the lifestyle intervention programme were recruited and tested at baseline. Of these, three participants were lost to follow-up, three due to technical errors with the Actiwatch, and one for not collecting sufficient actigraphy data. One female participant with a WC of 86.0 cm and BMI of 33.1 $kg \cdot m^{-2}$ was included in the CON group. The final CON group comprised 23 individuals. None of the included participants reported a previous diagnosis of insomnia.

The participants of the HWP group were also included in the OW-OBI (n=10) or OBII (n=21) groups of **Chapter 3**, and participants of the CON group were also included in the OW-OBI (n=14) or OBII (n=9) groups of **Chapter 3**.

4.3.2 Demographic and lifestyle characteristics

The demographic and lifestyle characteristics of the CON and HWP groups at baseline and at follow-up are presented in **Table 4.1**. There were no differences between the two groups in any of these characteristics at baseline. At follow-up, however, as a consequence of the exercise component of the lifestyle intervention, more participants in the HWP group reported 'high' levels of physical activity, and fewer participants reported 'low' levels of physical activity compared to the CON group. The groups were not different in smoking status or alcohol consumption at follow-up.

4.3.3 Anthropometric, cardiometabolic and perceived stress outcomes

The baseline and change in anthropometric, cardiometabolic and perceived stress characteristics of the HWP and CON groups are presented in **Table 4.2**. One HWP and two CON BP

observations were lost as the pulse was too weak to be detected with the automatic BP monitor. One HWP observation and two CON observations were lost for fasting glucose, while two HWP and one CON TC observations were lost due to poor blood perfusion to the fingers. TC levels were higher than the linear measuring range for one participant in the HWP group at baseline, and for one participant in the CON group at baseline and follow-up, and thus 7.76 $mmol \cdot L^{-1}$ was used. In addition, TC levels were lower than the linear measuring range for three participants in the CON group at baseline and thus 3.88 $mmol \cdot L^{-1}$ was used. The groups did not differ in any of the anthropometric or cardiometabolic variables at baseline. The HWP group had a significantly larger change in BMI, WC, WHtr and CPSS than the CON group over the eight-week period. The ES for BMI, WC, and WHtr were large, and that of CPSS was moderate. Neither change in DPB and SBP, nor change in fasting glucose and TC levels were different between the groups.

The prevalence of cardiometabolic risk factors are presented in **Table 4.3**. Neither elevated WC, BP, fasting glucose levels or TC were different between the groups at baseline or follow-up. Change in prevalence of cardiometabolic risk factors from baseline to follow-up was also not different between the groups for any of the variables.

Table 4.1. Demographic and lifestyle characteristics of the CON and HWP groups at baseline and follow-up.

	CON (n=23)		HWP (n=31)		Between-group comparison at baseline	Between-group comparison at follow-up
	Baseline	Follow-up	Baseline	Follow-up	*p*-value	*p*-value
Age (y)	47.9±11.1	-	44.5±11.4	-	0.284	-
Gender					0.220	-
Female	19 (83%)	-	20 (65%)	-		
Male	4 (17%)	-	11 (35%)	-		
Ethnicity					0.074	-
White	16 (70%)	-	16 (52%)	-		
Mixed ancestry	4 (17%)	-	14 (45%)	-		
Black	2 (9%) [b]	-	1 (3%) [b]	-		
Other	1 (4%) [b]	-	0 (0%) [b]	-		
Smoking status					1.000	0.574
Never	15 (65%)	13 (57%)	18 (58%)	18 (58%)		
Past	8 (35%)	10 (43%)	11 (36%)	11 (36%)		
Current	0 (0%) [a]	0 (0%) [a]	2 (6%) [a]	2 (6%) [a]		
Alcohol consumption					0.573	0.776
None	9 (39%)	9 (39%)	14 (45%)	13 (42%)		
Low	12 (52%)	12 (52%)	13 (42%)	14 (46%)		
Moderate	2 (9%) [a]	2 (9%) [a]	4 (13%) [a]	2 (6%) [a]		
Heavy	0 (0%) [a]	0 (0%) [a]	0 (0%) [a]	2 (6%) [a]		
Physical activity level					0.374	**<0.001**
Low	9 (39%)	9 (39%) *	18 (58%)	1 (3%) *		
Moderate	9 (39%)	9 (39%)	9 (29%)	4 (13%)		
High	5 (22%)	5 (22%) *	4 (13%)	26 (84%) *		

Data are presented as mean ± standard deviation or count (percentage). CON: control group; HWP: Healthy Weight Programme group. The *p*-values for the between-group comparisons were determined using the Student's t-test, or Fisher's exact test. The cells indicated with * are significantly different to the expected frequency. The cells indicated with [a] were excluded from the analysis as expected cell frequency was too low.

Table 4.2. Anthropometric, cardiometabolic and perceived stress characteristics of the CON and HWP groups at baseline, and change from baseline to follow-up.

	CON			HWP			Between-group comparison at baseline	Between-group comparison of change	
	Baseline	Change	n	Baseline	Change	n	*p*-value	ES	*p*-value
Anthropometric measures									
Height (cm)	164.5 (9.0)	-	23	168.7 (12.4)	-	31	0.088[†]	-	-
Weight (kg)	97.1 (22.3)	-0.2 (2.6)	23	105.2 (29.4)	-2.3 (3.3)	31	0.089	**0.928**	**0.002** [bl]
BMI (kg·m^{-2})	34.5 (6.0)	-0.1 (1.1)	23	37.1 (7.4)	-0.8 (1.1)	31	0.431	**1.015**	**<0.001** [bl]
WC (cm)	98.3 (15.2)	0.1 (4.2)	23	109.3 (22.6)	-3.1 (2.4)	31	0.073[†]	**1.075**	**<0.001**[†]
WHtr	0.61 (0.08)	0.00 (0.02)	23	0.64 (0.12)	-0.02 (0.01)	31	0.187[†]	**1.073**	**<0.001**[†]
Blood pressure									
DBP (mmHg)	81.6±9.3	-4.7±6.2	21	80.7±10.5	-3.4±6.9	30	0.741	-0.189	0.566 [bl]
SBP (mmHg)	121.0±14.3	-6.6±10.2	21	121.6±18.2	-3.5±11.6	30	0.902	-0.281	0.171 [bl]
Fingerprick tests									
Fasting glucose (mmol·L^{-1})	4.8 (1.0)	0.2 (1.1)	21	5.4 (1.1)	0.1 (1.0)	30	0.356	0.174	0.867 [bl]
TC (mmol·L^{-1})	5.7 (2.2)	-0.1 (0.7)	22	5.4 (1.1)	0.0 (0.8)	29	0.865	-0.194	0.478 [bl]
CPSS	18.0 (11.0)	1.0 (6.0)	23	18.0 (10.0)	-3.0 (5.0)	31	0.930[†]	**0.530**	**0.009**[†]

Data are presented as mean ± standard deviation or median (interquartile range). BMI: body mass index; CON: control group; CPSS: Cohen's perceived stress scale; DBP: diastolic blood pressure; ES: effect size; HWP: Healthy Weight Programme group; SBP: systolic blood pressure; TC: total cholesterol; WC: waist circumference; WHtr: waist-to-height ratio. The *p*-values for the between-group comparisons at baseline were determined using the Student's t-test (no superscript symbol) or Kruskal-Wallis ([†]), and those for the between group comparisons of change were determined using the ANCOVA adjusted for baseline values ([bl]), Student's t-test (no superscript symbol) or Kruskal-Wallis([†]). The ES represents Cohen's *d*.

Table 4.3. Prevalence of cardiometabolic risk factors in the CON and HWP groups at baseline and follow-up.

	CON				HWP				Between-group comparison at baseline	Between-group comparison at follow-up
	Baseline		Follow-up	n	Baseline		Follow-up	n	*p*-value	*p*-value
Elevated WC	22 (96%)	↔	22 (96%)	23	29 (94%)	↓	25 (81%)	31	1.000	0.218
Elevated BP	11 (52%)	↓	5 (24%)	21	16 (53%)	↓	11 (37%)	30	1.000	0.375
Elevated fasting glucose	5 (24%)	↔	5 (24%)	21	13 (43%)	↓	11 (37%)	30	0.234	0.375
Elevated TC	13 (59%)	↓	12 (55%)	22	17 (59%)	↓	16 (55%)	29	1.000	1.000

Data are presented as count (percentage). BP: blood pressure; CON: control group; HWP: Healthy Weight Programme group; TC: total cholesterol; WC: waist circumference. ↑ indicates prevalence increased, ↓ indicates prevalence decreased, and ↔ indicates prevalence did not change between baseline and follow-up. The *p*-values for the between-group comparisons were determined using the Fisher's exact test.

4.3.4 Actigraphy and subjective sleep outcomes

The baseline and change in actigraphy and subjective sleep characteristics of the HWP and CON groups are presented in **Table 4.4**. Two HWP observations for some of the actigraphy variables were lost due to data acquisition errors, which resulted in only bedtime, get-up time and their derivatives being retrievable. None of the sleep characteristics were different at baseline between the groups and none of the sleep variables changed differently between the two groups over the eight-week period.

The prevalence of poor sleep health indicators and the sleep health score are presented in **Table 4.5**. In both groups, most (>50%) of the individuals did not have poor sleep health at baseline or follow-up. Prevalence of poor sleep health indicators was not different between the groups at baseline or follow-up. Likewise, change in the prevalence of poor sleep health indicators or in the sleep health score from baseline to follow-up was not different between the groups for any of the variables.

Table 4.4. Actigraphy and subjective sleep characteristics of the CON and HWP groups at baseline, and change from baseline to follow-up.

	CON			HWP			Between-group comparison at baseline	Between-group comparison of change	
	Baseline	Change	n	Baseline	Change	n	*p*-value	ES	*p*-value
Actigraphy									
TiB (h)	7.6±1.0	-0.3±1.0	23	7.2±0.6	0.1±0.8	31	0.150	-0.518	0.438 [bl]
TST (h)	6.6±0.8	-0.3±0.9	23	6.3±0.7	0.1±0.7	29	0.247	-0.402	0.148 [bl]
SOL (min)	8.0 (9.2)	-0.6 (10.2)	23	6.5 (10.7)	1.0 (8.0)	29	0.971[†]	-0.088	0.537 [†]
SE (%)	88.3 (6.0)	0.1 (4.6)	23	88.4 (4.1)	-0.6 (4.1)	29	0.992	-0.310	0.273
WASO (min)	29.6 (25.9)	-1.0 (13.2)	23	27.3 (9.5)	-0.4 (10.0)	29	0.314	-0.406	0.311 [bl]
Awakenings >5 min	0.6 (1.0)	0.0 (1.0)	23	0.4 (0.9)	0.0 (0.6)	29	0.157	-0.073	0.955 [bl]
Awakening index (awakenings/h of TST)	6.3 (3.5)	0.0 (0.7)	23	5.6 (2.9)	0.1 (1.6)	29	0.832[†]	0.070	0.876 [†]
Bedtime (hh:mm)	23:01±0:40	0:08±0:47	23	23:10±0:42	0:04±0:37	31	0.455	0.110	0.974 [bl]
Get-up time (hh:mm)	6:34 (1:23)	-0:08 (1:05)	23	6:22 (0:36)	0:01 (0:43)	31	0.409	-0.450	0.108
sSRI (%)	92.5±2.9	0.0±3.8	23	92.5±2.7	-0.5±3.8	31	0.940	0.151	0.586
Midpoint of sleep (hh:mm)	2:47±0:37	0:00±0:29	23	2:46±0:37	0:06±0:29	31	0.912	-0.202	0.465
Corrected social jet lag (min)	33.0±25.3	6.1±41.9	23	45.2±33.3	-7.1±42.6	29	0.151	0.312	0.269
Questionnaires									
PSQI	7.4±3.1	-0.3±1.7	23	6.5±3.2	-1.6±3.2	31	0.279	0.490	0.081
ESS	8.7±3.7	-0.7±2.6	23	8.3±4.2	-0.7±3.0	31	0.706	-0.018	0.949
HÖ-MEQ	60.5±9.9	0.5±3.2	23	56.8±9.6	1.5±5.1	31	0.179	-0.234	0.817 [bl]

Data are presented as mean ± standard deviation or median (interquartile range). CON: control group; ES: effect size ESS: Epworth sleepiness scale; HÖ-MEQ: Horne-Östberg morningness-eveningness personality questionnaire; HWP: Healthy Weight Programme group; PSQI: Pittsburgh sleep quality index; SE: sleep efficiency; SOL: sleep onset latency; sSRI: simplified sleep regularity index; TiB: time-in-bed; TST: total sleep time; WASO: wake after sleep onset. The *p*-values for the between-group comparisons at baseline were determined using the Student's t-test (no superscript symbol) or Kruskal-Wallis ([†]), and those for the between group comparisons of change were determined using the ANCOVA adjusted for baseline values ([bl]), Student's t-test (no superscript symbol) or Kruskal-Wallis([†]). The ES represents Cohen's *d*.

Table 4.5. Prevalence of poor sleep health indicators and sleep health score in the CON and HWP groups.

	CON				HWP				Between-group comparison at baseline	Between-group comparison at follow-up
	Baseline		Follow-up	n	Baseline		Follow-up	n	*p*-value	*p*-value
Short sleep duration	7 (30%)	↑	11 (48%)	23	11 (38%)	↑	12 (41%)	29	0.770	0.780
High sleep fragmentation	9 (39%)	↓	7 (30%)	23	11 (38%)	↔	11 (38%)	29	1.000	0.770
High sSRI	4 (17%)	↓	3 (13%)	23	6 (19%)	↑	8 (26%)	31	1.000	0.319
High corrected social jet lag	3 (13%)	↑	5 (22%)	23	7 (24%)	↓	6 (21%)	29	0.482	1.000
EDS	6 (26%)	↔	6 (26%)	23	9 (29%)	↓	7 (23%)	31	1.000	1.000

	CON			HWP			Between-group comparison at baseline	Between-group comparison of change
	Baseline	Change	n	Baseline	Change	n	*p*-value	*p*-value
Sleep health score	1.0 (2.0)	0.0 (0.0)	23	1.0 (2.0)	0.0 (2.0)	29	0.510	0.859 [bl]

Data are presented as count (percentage) or median (interquartile range). CON: control group; EDS: excessive daytime sleepiness; HWP: Healthy Weight Programme group; sSRI: simplified sleep regularity index. ↑ indicates prevalence increased, ↓ indicates prevalence decreased, and ↔ indicates prevalence did not change between baseline and follow-up. The *p*-values for the between-group comparisons of the binary variables were determined using the Fisher's exact test, for the between-group comparison of sleep health score at baseline with the Student's t-test, and for the between-group comparisons of change between baseline and follow-up with the ANCOVA adjusted for baseline values ([bl]). The ES (Cohen's *d*) for poor sleep health indicators was 0.110.

4.3.5 Association analyses

At baseline, TST correlated with WC (**Fig 4.1A**) and WHtr (**Fig 4.1B**). Change in anthropometric and cardiometabolic health characteristics did not correlate with sleep characteristics at baseline (data not shown). No correlations were found between change in anthropometric and cardiometabolic health characteristics in response to the lifestyle intervention programme and change in sleep characteristics (data not shown).

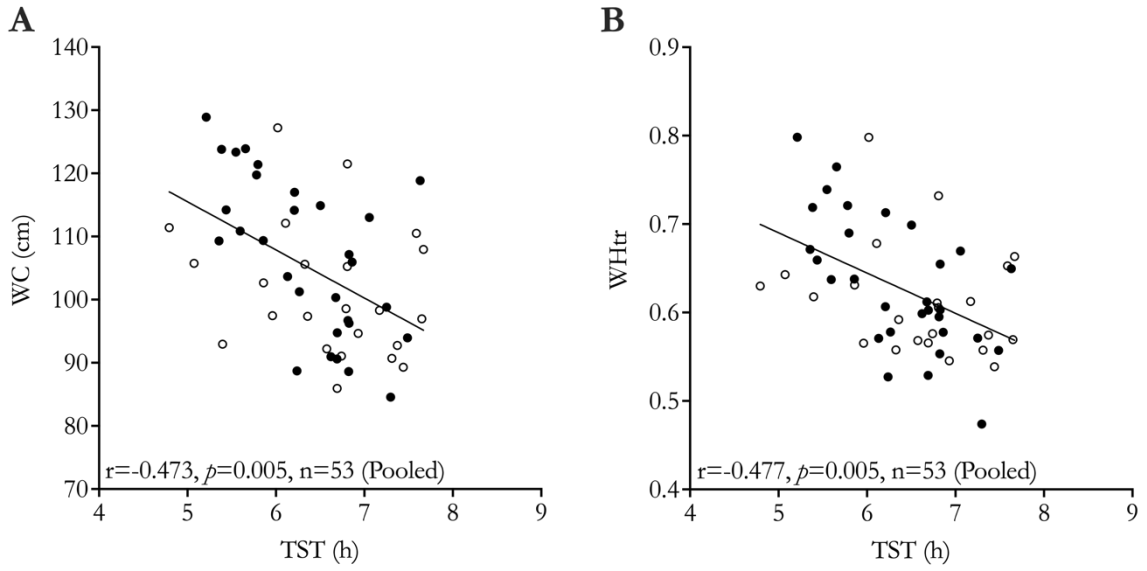

Figure 4.1. Correlation plots for WC and TST (**A**), and WHtr and TST (**B**) at baseline. ○ control group (CON); ● Healthy Weight Programme group (HWP). TST: total sleep time; WC: waist circumference; WHtr: waist-to-height ratio. The coefficients and *p*-values were determined using Pearson's correlation.

4.4 Discussion

In this study, the effects of an eight-week diet and exercise lifestyle intervention programme on the cardiometabolic health and sleep characteristics of individuals with overweight and obesity were described. The main finding was that participation in the lifestyle intervention programme aimed at weight-loss, improving fitness and improving cardiometabolic health, does not *per se* lead to concomitant changes in actigraphy-derived and subjective sleep characteristics, despite improving anthropometric measures and perceived stress.

Research suggests a role for both exercise and diet in isolation on sleep (see **Section 4.1**). To the best of my knowledge, however, the present study is the first to describe the effect of a combined diet and exercise lifestyle intervention programme, designed for weight-loss, on sleep.

As discussed in **Section 4.1**, most evidence for a role of exercise in improving sleep comes from studies of which participants had either insomnia or symptoms thereof. Although insomnia symptoms were not measured in the participants of the present study, none reported being previously diagnosed with insomnia, and they did also not have poor sleep health in particular, which may explain the lack of effect observed in the present study. Despite the potential effect of some foods and diet on sleep, any change in the individual's dietary intake in the present study, if they occurred at all, in combination with the effects of other exposures from the intervention, did not measurably affect sleep. It must be noted, however, that the dietary advice was different for each participant of the intervention programme, and that dietary intake was not assessed throughout the intervention. Therefore, any discussion in this regard is speculative at best, and is beyond the scope of this study.

Evidence of a bidirectional association between anthropometric measures and aspects of sleep is abundant. Even in the current cohort of individuals with overweight and obesity, WC and WHtr were associated with TST. It was therefore surprising that sleep was not affected by an improvement in the anthropometric measures in the present study. There are several possible non-mutually exclusive reasons for the absence of an improvement in sleep following the intervention.

First, as the sleep health score was low in both the HWP and CON groups, participants may not have had a particularly poor sleep health to begin with, and improvements in sleep may have thus been an unlikely outcome for the majority of participants. In addition, these findings show that despite the association between adiposity and poor sleep, it cannot be assumed that all participants of a lifestyle intervention programme who are overweight or obese have poor sleep. The effect of the intervention on sleep may have been more profound if all participants had poor sleep at baseline. This was not, however, an objective of the present study.

Second, the duration of the intervention (eight weeks) may have been too short for any spontaneous changes in sleep to occur, following changes in dietary modulation, exercise, and cardiometabolic health. Although changes in sleep have been observed following shorter-duration sleep-improvement interventions (Suzuki et al., 2008, Chen et al., 2010), sleep improvement through weight-loss interventions may require more time. That is, weight-loss intervention-mediated changes in sleep may occur through both changes in lifestyle (i.e. diet and exercise) and

changes in cardiometabolic health (e.g. weight-loss). The effect of changes in cardiometabolic health on sleep, however, may require more time.

Third, it is also possible that in order to halt the vicious cycle of adiposity and poor sleep, more weight-loss than what was achieved during the lifestyle intervention of the present study is required, or other aspects of cardiometabolic health must improve. It is also possible that although adiposity and poor cardiometabolic health may drive an individual to have disrupted sleep, weight-loss in combination with sleep modulation are required to restore sleep. It may be difficult, if possible at all, to investigate the effect of weight-loss, without the effect of diet and exercise, on sleep. To the best of my knowledge, no such studies have been published.

Evidence suggests that weight-loss is dependent on sufficient sleep. For example, one study found that adults with overweight and obesity who were experimentally sleep-restricted, lost less total fat mass following eight weeks of caloric restriction than adults with overweight or obesity who could sleep *ad libitum* (Wang et al., 2018). Another study reported that adolescents with obesity who lost more than 1 $kg \cdot m^{-2}$ of their BMI following a multidisciplinary weight management programme, had longer sleep duration at baseline than those who lost less than 1 $kg \cdot m^{-2}$ of their BMI (Sallinen et al., 2013). These studies are in line with a study of American Indian and Alaska Native participants of a lifestyle intervention focussing on diet, exercise and behaviour modification, where short sleep duration (≤6 h) predicted less weight-loss (Nuyujukian et al., 2016). A lifestyle intervention programme in combination with a sleep intervention programme may thus not only improve aspects of sleep, but also improve weight-loss and possibly other aspects of cardiometabolic health. In the present study, however, changes in anthropometric measures were independent of how the participants were sleeping at baseline. The predominantly good sleep health in the majority of the participants of the present study may have disassociated sleep at baseline from change in cardiometabolic health. More research is needed to explore whether good sleep health supports weight-loss and improvements in cardiometabolic health in lifestyle intervention programmes.

Finally, the decrease in perceived stress following the lifestyle intervention programme may be the result of the programme's exercise sessions. Other studies found that perceived stress reduced following four and twelve weeks of aerobic gymnastic exercise in postnatal women (Yang and Chen, 2018), and in older adults following a ten-week physical activity intervention (Starkweather, 2007). Higher levels of perceived stress have been associated with shorter sleep duration and worse sleep quality (Doolin et al., 2018, Rawat et al., 2016), and higher CPSS scores were also associated with higher PSQI and ESS scores in **Chapter 3**. If a reason for sleep disturbance originates from

high levels of perceived stress, it is likely that improving stress levels may improve sleep quality. In the present study, however, improvements in perceived stress were not associated with changes in sleep. These findings may suggest that the perceived stress did not affect the participant's sleep, or, as mentioned above, sleep was of good duration and quality in the first place.

4.4.1 Study limitations

The participants in this natural experiment did not have particularly poor sleep to start with, and thus were unlikely to improve on this aspect. The findings of this study may thus not apply to participants of lifestyle intervention programmes who have poor sleep health. Another limitation is the modest sample size, which may increase the chance of type II error, following the Bonferroni-adjustment. Namely, the alpha-level for the *post-hoc* test and correlations were Bonferroni-adjusted to avoid the multi-comparison problem (chance of type I errors increases with the number of tests performed). However, this Bonferroni-adjustment has been suggested to be too conservative, and thus increasing the chance of type II error (Rothman, 1990, Perneger, 1998), especially in combination with the small sample size in the present study. To illustrate, no associations were found between sleep indices at baseline and change in anthropometric or cardiometabolic measures with Bonferroni-adjustment, while without Bonferroni-adjustment, change in SBP correlated with corrected social jet lag and HÖ-MEQ score, such that those with less corrected social jet lag and earlier chronotypes at baseline experienced the highest reduction in SBP. Those with earlier chronotypes and worse sleep quality at baseline had the largest reduction in fasting glucose levels. Lastly, those with the lower corrected social jet lag at baseline experienced larger decreases in TC levels. Further research on larger cohorts is required to confirm that the absence of an association between baseline sleep and change in anthropometric and cardiometabolic measures are indeed true negatives. Furthermore, a larger sample size would allow for the adjustment of confounding factors such as age and participation or compliance. Other factors may include those that have not been assessed and may therefore be listed as additional study limitations. One of these factors may be knowledge of sleep hygiene, which may have been assessed with the Sleep Hygiene Index; a tool which tests the presence of 13 common poor sleep hygiene behaviours (Mastin et al., 2006). Another of those confounding factors may be dietary intake, which may have been assessed with a food diary. Lastly, the study was designed as a natural experiment and not as a randomized controlled trial. The sample was drawn from the same area, but separately from one another. For the HWP group, the sample was drawn from a population of individuals from the Cape Town metropole who had enrolled for the commercial diet and exercise lifestyle intervention programme. The CON group was drawn from a population from

the Cape Town metropole who had not enrolled for the commercial lifestyle intervention programme. To match the two groups for age and sex, the CON group was recruited after the HWP group. This setting did therefore not allow for randomisation. Due to this limitation, it is possible that the two groups differed by other factors, not accounted for in the current study, that may explain some of the outcomes. For example, it cannot be ruled out that the changes in anthropometric measures and CPSS score were not due to factors that also affected the decision to enrol for the lifestyle intervention programme, rather than the intervention itself.

4.5 Conclusion

This study showed that a commercial eight-week lifestyle intervention programme with nutritional modulation and exercise does not lead to concomitant changes in sleep in individuals with overweight and obesity. The relatively good sleep health and cardiometabolic health of the majority of participants upon entering the programme and the duration or efficacy of the lifestyle intervention programme may explain the findings of the present study. Further research should investigate whether the addition of a sleep behaviour intervention to lifestyle intervention programmes improves the participants' sleep and cardiometabolic health.

Chapter 5

A Sleep Behaviour Intervention to Improve Cardiometabolic Health in Adults with Overweight and Obesity: a Randomized Controlled Trial

5.1 Introduction

Cardiometabolic disease (CMD), and an important risk factor thereof, obesity, pose a major health burden on the world's population (World Health Organization, 2015). Poor sleep has been associated with cardiometabolic impairment in populations around the world (see **Chapter 1**). As shown in **Chapter 3**, individuals with class II obesity recruited from the population studied in the intervention component of this thesis, had shorter sleep duration, more sleep fragmentation, delayed bedtime, less regular sleep and less non-rapid eye movement (NREM)3 sleep than those who were overweight or had class I obesity.

Although evidence for the association between sleep and cardiometabolic health is abundant, surprisingly few studies have looked into the effect of improving sleep as a means to improve cardiometabolic health. For example, only seven studies have looked at the effect of sleep extension specifically on cardiometabolic health (see **Chapter 2**). Collectively, these studies described improvements in insulin sensitivity, a decrease in leptin and peptide tyrosine-tyrosine (PYY), and change in appetite and food intake following sleep extension interventions. However, due to the small number of studies, small study cohorts, and disparities between findings, evidence to support a role for sleep improvement interventions in reducing risk for CMD is promising but inconclusive. Another reason for the discrepancies between the findings of these studies may be that diet and exercise have been insufficiently controlled for.

Therefore, the aim of this randomized controlled trial was to measure the effects of a sleep behaviour intervention within an eight-week diet and exercise lifestyle intervention programme on sleep and cardiometabolic health in individuals with overweight and obesity, and to determine whether changes in sleep were associated with changes in cardiometabolic health outcomes. The reason for applying the sleep behaviour intervention within the setting of this lifestyle intervention was to ensure that both diet and exercise were controlled for, at least to some extent, so that any confounding effects on cardiometabolic outcomes might be minimised. It was hypothesised that the sleep behaviour intervention would improve participants' sleep (e.g. increase sleep duration, reduce sleep fragmentation, and decrease social jet lag) and that these improvements would be associated with improvements in markers for cardiometabolic health.

5.2 Methods

5.2.1 Participants

Men and women with overweight or obesity who enrolled in a commercial eight-week lifestyle intervention programme were invited to participate in this study. Participants were eligible if their body mass index (BMI) was ≥25 $kg \cdot m^{-2}$, their waist circumference (WC) was >88 cm (females) or >102 cm (males) and their age was >20 years. Participants with narrower WC were also included provided their BMI was >28.5 $kg \cdot m^{-2}$. Participants were not eligible if they had been diagnosed with a sleep disorder (excluding insomnia or mild obstructive sleep apnoea, OSA); used hypnotic drugs on a regular basis; were exposed to any other factor that precludes normal nocturnal sleep (e.g. currently breastfeeding, parents of young children who routinely wake up in the night, shift work); had undergone transmeridian travel exceeding three time zones in the two months leading up to the baseline assessment or before the follow-up assessment; or participated in any sport or physical activity for which regular training is required (more than four times per week). Eligible participants were randomly assigned to either the CON or the SBI group.

5.2.2 Study design

This study was a randomized controlled trial. The participants voluntarily enrolled in a commercial eight-week lifestyle intervention programme where they underwent a goal-setting session with a psychologist and a dietary consultation session (including an individualised eating plan) with a dietician (see **Section 4.2.3**). The participants had baseline and follow-up measurements taken which included a questionnaire, one week of actigraphy and measures of cardiometabolic health and perceived stress. The assessments were performed within two weeks of the start and end of the lifestyle intervention programme. All questionnaire, anthropometric and clinical measurements took place in the morning between 06:00 and 10:00 to avoid diurnal variation bias of these variables. Within this timeframe, however, the baseline and follow-up assessments may not have been at exactly the same time *per se*. The participants were instructed not to exercise in the morning before the assessment and to refrain from eating and drinking anything but water from 22:00 the previous night until after the assessment to ensure an 8-h fast. The participants were asked the time of their last meal. If participants were not fasted since 22:00 the previous night, the appointment was rescheduled. Following the baseline assessment, but still within two weeks of the start of the programme, the participants were randomly assigned to either the CON or SBI group by means of drawing. Participants in the SBI group underwent a sleep behaviour intervention

aimed at improving nocturnal sleep over the duration of the lifestyle intervention programme. Participants in the CON group were asked not to change their sleep habits or patterns during the eight-week period and did not receive the sleep behaviour intervention.

5.2.3 Sleep behaviour intervention

The aim of the intervention was to improve nocturnal sleep, i.e. ensure optimal sleep-timing, fall asleep with ease, stay asleep throughout the night, wake up at desired wake-up time and acquire sufficient sleep. The intervention comprised of individualized, one-on-one, consultation sessions with techniques borrowed from motivational interviewing (e.g. open questions, affirmation, listening, reflection, and summaries). The intervention was based on four principles. First, awareness, which related to making the participant cognizant of the need for behaviour change. Second, education or transfer of information, which related to the education about sleep in general, the consequences of poor sleep, and an introduction to tools that may help one sleep better. The third principle related to the individual's intrinsic motivation to change. The last principle on which the intervention was based is support with behaviour change itself, and may involve affirmation to progress made, and addressing challenges the individuals may experience with behaviour change. During the first session, the participant and researcher identified challenges that the participant had with their sleep, including social and environmental barriers to sleep. Baseline actigraphy data were used to evoke the participant's realisation of suboptimal sleep (e.g. if sleep duration was less than 6.5 h, or sleep onset latency (SOL) was longer than 30 min). The participant also received verbal education about sleep in general and the importance of sleep. At the end of this session, which took approximately 60 min, a plan of action was agreed upon, which the participant tried to implement at home. Typical action points were related to sleep hygiene and included maintaining regular bedtime and get-up times; avoiding electronic screen time from 20:00 in the evening; having their evening meal before 19:00; and using relaxation techniques. During each successive session, which took between 30 and 60 min, the progress and obstacles to the suggested behavioural changes were discussed and new suggestions were made accordingly. This process was repeated weekly for the duration of the lifestyle intervention programme at the participant's discretion.

5.2.4 Detailed procedures

The detailed procedures for demographic and lifestyle assessments, anthropometric measurements, blood pressure (BP), perceived stress, actigraphy and subjective sleep assessments were as those described in **Section 3.2.3**.

5.2.4.1 Dual X-ray absorptiometry

A whole-body dual X-ray absorptiometry scan (Discovery-W, Hologic Inc., Bedford, MA, USA) was used to determine total body fat (as a percentage of total weight) and lean mass (kg) (Micklesfield et al., 2012).

5.2.4.2 Insulin resistance and lipids

Fasting blood samples were taken from all participants for the assessment of glucose, insulin, glycated haemoglobin (HbA1c), and blood lipid levels. All blood samples were analysed by a medical diagnostic laboratory (Lancet Laboratories, Century City, Cape Town, South Africa). The homeostatic model assessment 2 for insulin resistance (HOMA2-IR) calculator (v2.2.3, Diabetes Trials Unit, University of Oxford) was used to determine insulin resistance from fasting glucose and insulin levels (Levy JC, 1998). Outcome variables were fasting glucose ($mmol \cdot L^{-1}$) and insulin levels, HOMA2-IR, HbA1c (%), TC ($mmol \cdot L^{-1}$), low-density lipoprotein (LDL, $mmol \cdot L^{-1}$), high-density lipoprotein (HDL, $mmol \cdot L^{-1}$), as well as triglyceride (TG, $mmol \cdot L^{-1}$) levels.

5.2.4.3 Resting metabolic rate

Resting metabolic rate (RMR) was determined by indirect calorimetry using the ventilated hood technique in a fasted state (Quark RMR, Cosmed, Rome, Italy). Participants were asked to lie still in a supine position and be quiet but remain awake for the duration of the RMR assessment. Oxygen uptake and carbon dioxide production were measured at 5 s intervals for 20 min, or until a steady state was achieved for at least 10 min (<5% change in respiratory exchange ratio). The last 10 min of data where steady state was achieved was used for the analysis. Before each assessment, the gas analyser was calibrated with a 3-L syringe and standard gas mixtures of oxygen (26% O_2 with the balance nitrogen) and carbon dioxide (4% CO_2, 16% O_2 and the balance nitrogen) (BOC Special Gas, Afrox, Cape Town, South Africa). The gas analyser was validated by ethanol burns every two weeks. The outcome variable was RMR ($kcal \cdot kg \cdot day^{-2}$).

5.2.4.4 Cardiometabolic risk

The cardiometabolic risk factor criteria defined by the American Heart Association and the National Heart, Lung, and Blood Institute were used (Grundy et al., 2005). Elevated WC was defined as having a WC >88 cm for females, or WC >102 cm for males. Elevated TG was defined as having triglyceride levels ≥1.7 mmol·L^{-1}. Reduced HDL was defined as having HDL levels <1.30 mmol·L^{-1} for females, or <1.03 mmol·L^{-1} for males, or taking medication for hyperlipidaemia. Elevated BP was defined as having systolic blood pressure (SBP) ≥130 mmHg, diastolic blood pressure (DBP) ≥85 mmHg, or being on antihypertensive medication. Elevated fasting glucose was defined as fasting glucose levels ≥5.6 mmol·L^{-1}. Participants were classified as being at high cardiometabolic risk if at least three of these cardiometabolic risk factors were present (Grundy et al., 2005).

5.2.5 Data and statistical analyses

All data were reported and analysed as described in **Section 4.2.5**.

5.3 Results

5.3.1 Participants

Forty-six participants consented to participate of whom 30 were included in the final analysis (SBI: n=15, CON: n=15). Eight participants had insufficient actigraphy data due to technical errors, seven were lost at follow-up, and one participant did not meet the eligibility criteria. The SBI group included one female participant with a WC of 86.7 cm but a BMI of 36.1 kg·m^{-2}. The CON group included three female participants with WC of 75.5, 83.5, and 84.9 cm but a BMI of 29.1, 31.5, and 29.9 kg·m^{-2} respectively. None of the participants reported a previous diagnosis of insomnia.

Participants in both groups attended a similar number of exercise classes during the eight-week lifestyle intervention programme (SBI: 19.7±5.6, CON: 19.1±6.0, p=0.780). Participants in the SBI group also attended 3.7±1.0 (range: 2-5 sessions) sleep behaviour intervention sessions during the trial.

The participants in the SBI group were included in the OW-OBI (n=7) or OBII (n=8) groups of **Chapter 3**, and the participants of the CON group were also included in the OW-OBI (n=6) or OBII (n=9) groups of **Chapter 3**.

5.3.2 Demographic and lifestyle characteristics

Baseline and follow-up demographic and lifestyle characteristics of the two groups are presented in **Table 5.1**. The groups were not different in any of the demographic and lifestyle characteristics at baseline, nor at follow-up.

Table 5.1. Demographic and lifestyle characteristics of the CON and SBI groups at baseline and follow-up.

	CON (n=15)		SBI (n=15)		Between-group comparison at baseline	Between-group comparison at follow-up
	Baseline	Follow-up	Baseline	Follow-up	*p*-value	*p*-value
Age (y)	46.7±12.2	-	47.4±11.0	-	0.722	-
Gender					1.000	-
Female	11 (73%)	-	11 (73%)	-		
Male	4 (27%)	-	4 (27%)	-		
Ethnicity					0.700	-
White	10 (66%)	-	9 (60%)	-		
Mixed ancestry	4 (27%)	-	6 (40%)	-		
Indian	1 (7%) [a]	-	0 (0%) [a]	-		
Smoking status					0.678	0.683
Never	9 (60%)	9 (60%)	10 (67%)	9 (60%)		
Past	5 (33%)	5 (33%)	3 (20%)	3 (20%)		
Current	1 (7%) [a]	1 (7%) [a]	2 (13%) [a]	3 (20%) [a]		
Alcohol consumption					0.440	0.688
None	4 (26%)	4 (26%)	6 (40%)	5 (33%)		
Low	10 (67%)	9 (60%)	7 (46%)	7 (47%)		
Moderate	1 (7%) [a]	1 (7%) [a]	1 (7%) [a]	2 (13%) [a]		
Heavy	0 (0%) [a]	1 (7%) [a]	1 (7%) [a]	1 (7%) [a]		
Physical activity level					1.000	1.000
Low	7 (47%)	1 (7%) [a]	7 (47%)	1 (7%) [a]		
Moderate	7 (47%)	2 (13%)	6 (40%)	3 (20%)		
High	1 (6%) [a]	12 (80%)	2 (13%) [a]	11 (73%)		

Data are presented as mean ± standard deviation or count (percentage). CON: control group; SBI: sleep behaviour intervention group. The *p*-values represent the between-group comparisons determined using the Student's t-test, Fisher's exact or Chi-squared tests. The cells indicated with [a] were excluded from the analysis as expected cell frequency was too low.

5.3.3 Actigraphy and subjective sleep outcomes

Baseline and change from baseline to follow-up actigraphy and subjective sleep characteristics are presented in **Table 5.2**. The only variable that differed between the groups at baseline was awakening index, which was higher in the SBI group than in the CON group. From baseline to follow-up, get-up time advanced more in the SBI group than in the CON group. Additionally, while the midpoint of sleep advanced in the SBI group, it delayed in the CON group. The effect size (ES) for both get-up time and midpoint of sleep were large.

The prevalence of poor sleep health indicators and the sleep health score are presented in **Table 5.3**. The prevalence of indicators of poor sleep health was low (<50%) in both groups. The groups were not different in the prevalence of poor sleep health indicators at baseline or in change from baseline to follow-up (p>0.05). Likewise, the sleep health score at baseline or change from baseline to follow-up was not different between the groups.

Table 5.2. Actigraphy and subjective sleep characteristics of the CON and SBI groups at baseline and change from baseline to follow-up.

	CON			SBI			Between-group comparison at Baseline	Between-group comparison of Change	
	Baseline	Change	n	Baseline	Change	n	*p*-value	ES	*p*-value
Actigraphy									
TiB (h)	7.2±0.9	0.2±0.6	15	7.7±1.1	0.0±1.0	15	0.145	-0.198	0.573 [bl]
TST (h)	6.4±0.9	0.2±0.6	15	6.8±1.0	0.2±0.9	15	0.239	-0.085	0.543 [bl]
SOL (min)	8.9 (23.4)	-0.6 (11.4)	15	7.7 (9.6)	-0.4 (15.6)	15	0.445	0.307	0.408
SE (%)	88.6±4.6	1.3±4.8	15	88.1±2.7	2.0±4.9	15	0.736	0.142	0.807 [bl]
WASO (min)	20.9 (11.0)	2.5 (11.9)	15	30.1 (13.7)	1.7 (29.0)	15	0.070	-0.492	0.188
Awakenings >5 min	0.57 (0.71)	-0.14 (0.90)	15	0.60 (1.00)	0.19 (0.98)	15	0.964	0.094	0.798
Awakening index (awakenings/h of TST)	5.2 (1.4)	0.3 (1.4)	15	6.1 (1.3)	-0.2 (2.0)	15	**0.046**	-0.526	0.411 [bl]
Bedtime (hh:mm)	23:26±1:08	0:04±0:33	15	23:12±0:59	-0:20±0:56	15	0.542	-0.519	0.166
Get-up time (hh:mm)	6:37 (0:39)	-0:03 (0:51)	15	6:49 (2:16)	-0:18 (0:37)	15	0.404	-0.811	**0.035**
Midpoint of sleep (hh:mm)	3:02±0:50	0:08±0:31	15	3:04±0:55	-0:20±0:40	15	0.947	-0.815	**0.034**
sSRI (%)	93.0 (4.1)	-1.8 (4.7)	15	92.2 (4.3)	-0.5 (4.2)	15	0.263[†]	0.533	0.147[†]
Corrected social jet lag (min)	38.2±20.7	-3.6±25.0	15	41.5±26.7	2.8±40.8	15	0.702	0.189	0.609
Sleep questionnaires									
PSQI	7.3±3.1	-2.1±3.3	15	7.5±3.0	-2.5±2.5	15	0.905	-0.158	0.669
ESS	7.0 (7.0)	0.0 (2.0)	15	9.0 (3.0)	-2.0 (3.0)	15	0.251	-0.333	0.750 [bl]
HÖ-MEQ	55.0 (13.0)	1.0 (4.0)	15	56.0 (15.0)	2.0 (6.0)	15	0.880	0.481	0.147 [bl]

Data are presented as mean ± standard deviation or median (interquartile range). CON: control group; ES: effect size; ESS: Epworth sleepiness scale; HÖ-MEQ: Horne-Östberg morningness-eveningness personality questionnaire; PSQI: Pittsburgh sleep quality index; SBI: sleep behaviour intervention group; SE: sleep efficiency; SOL: sleep onset latency; sSRI: simplified sleep regularity index; TiB: time-in-bed; TST: total sleep time; WASO: wake after sleep onset. The *p*-values for the between-group comparisons at baseline were determined using the Student's t-test (no superscript symbol) or Kruskal-Wallis ([†]), and those for the between group comparisons of change were determined using the ANCOVA, adjusted for baseline values ([bl]), Student's t-test (no superscript symbol) or Kruskal-Wallis([†]). The ES represents Cohen's *d*.

Table 5.3. Prevalence of poor sleep health indicators and sleep health score in the SBI and CON groups.

	CON				SBI				Between-group comparison at baseline	Between-group comparison at follow-up
	Baseline		Follow-up	n	Baseline		Follow-up	n	*p*-value	*p*-value
Short sleep duration	7 (47%)	↓	5 (33%)	15	4 (27%)	↓	1 (7%)	15	0.450	0.169
High sleep fragmentation	4 (27%)	↓	3 (20%)	15	4 (27%)	↑	5 (33%)	15	1.000	0.682
High sSRI	3 (20%)	↑	4 (27%)	15	4 (27%)	↓	3 (20%)	15	1.000	1.000
High corrected social jet lag	2 (13%)	↓	1 (7%)	15	4 (27%)	↓	3 (20%)	15	0.651	0.598
EDS	2 (13%)	↔	2 (13%)	15	3 (20%)	↓	1 (7%)	15	1.000	1.000

	CON			SBI			Between-group comparison at baseline	Between-group comparison of change
	Baseline	Change	n	Baseline	Change	n	*p*-value	*p*-value
Sleep health score	1.2±1.0	-0.2±1.2	15	1.3±0.8	-0.4±1.2	15	0.843	0.650

Data are presented as count (percentage) or mean ± standard deviation. CON: control group; EDS: excessive daytime sleepiness; SBI: sleep behaviour intervention group; sSRI: simplified sleep regularity index. ↑ prevalence increased, ↓ prevalence decreased, and ↔ prevalence did not change between baseline and follow-up. For poor sleep health at follow-up, analysis was not performed as expected cell frequency was <1 in two cells. The *p*-values for the between-group comparisons of the binary variables were determined using the Fisher's exact test, and for the between-group comparison of the sleep health score at baseline and change between baseline and follow-up with the Student's t-test. The ES (Cohen's *d*) for poor sleep health indicators was -0.167.

5.3.4 Anthropometric, cardiometabolic and perceived stress outcomes

Baseline and change in anthropometric measures, BP, fasting glucose, insulin and lipid levels are presented in **Table 5.4**. The weight of one individual in the CON group exceeded the dual X-ray absorptiometry scanner's weight limit, and thus one observation was missing for total body fat and lean mass. Blood could not be obtained from two participants in the CON group, which resulted in two observations missing for the fasting glucose, insulin, and blood lipids outcomes. One additional observation was missing in the CON group for blood lipids outcomes due to human error. Lastly, one observation was missing for RMR in the SBI group, and two observations were missing in the CON group, due to human and technical errors. The groups were not different in any of the anthropometric or cardiometabolic health outcomes at baseline.

In response to the intervention, SBP increased in the SBI group, while it decreased in the CON group. The ES was moderate. Moreover, participants in the SBI group had a greater reduction in HbA1c than those in the CON group following the intervention. The ES was found to be moderate. Lastly, RMR increased in the SBI group, while it decreased in the CON group, and the ES was large.

The prevalence of cardiometabolic risk factors and high cardiometabolic risk in the SBI and CON groups at baseline and follow-up are presented in **Table 5.5**. The groups did not differ in prevalence of cardiometabolic risk factors or high cardiometabolic risk at baseline or follow-up. Change from baseline to follow-up for these variables were also not different between the two groups.

Table 5.4. Anthropometric and cardiometabolic characteristics of the CON and SBI groups at baseline and the change from baseline to follow-up.

	CON			SBI			Between-group comparison at Baseline	Between-group comparison of Change	
	Baseline	Change	n	Baseline	Change	n	*p*-value	ES	*p*-value
Anthropometric measures									
Height (cm)	169.4 (14.6)	-	15	167.7 (15.8)	-	15	0.443 †	-	-
Weight (kg)	105.7 (53.0)	-1.3 (2.4)	15	99.1 (16.1)	-1.9 (2.9)	15	0.494 †	-0.271	0.373 †
BMI (kg·m^{-2})	38.8±9.8	-0.7±0.9	15	36.0±6.0	-0.9±0.5	15	0.348	-0.290	0.509 bl
WC (cm)	103.9 (36.3)	-1.9 (2.6)	15	103.3 (14.6)	-3.1 (2.9)	15	0.756 †	-0.477	0.152 †
WHtr	0.62 (0.20)	-0.01 (0.02)	15	0.62 (0.09)	-0.02 (0.01)	15	0.950 †	-0.471	0.085 †
Total body fat (%)	47.2±4.9	-0.3±1.5	14	46.7±5.4	-1.1±2.0	15	0.813	-0.460	0.232 bl
Lean mass (kg)	53.9±12.7	-2.4±2.7	14	52.5±8.8	-2.7±1.7	15	0.730	-0.160	0.642 bl
Blood pressure									
DBP (mmHg)	78.2±12.9	-1.4±7.2	15	82.8±9.9	-2.1±9.6	15	0.289	-0.083	0.791 bl
SBP (mmHg)	116.0±22.1	-2.8±11.3	15	118.5±15.9	4.8±12.8	15	0.732	0.627	**0.039 bl**
Glucose and Insulin									
Fasting glucose (mmol·L^{-1})	5.2 (0.8)	0.2 (0.9)	13	5.3 (0.9)	0.1 (0.5)	15	0.593	0.136	0.723
Fasting insulin (mU·L^{-1})	14.9 (14.1)	1.3 (8.0)	13	17.2 (11.2)	1.0 (5.0)	15	0.311 †	-0.327	0.713 †
HOMA2-IR	1.9 (1.9)	0.2 (1.1)	13	2.3 (1.6)	0.1 (0.6)	15	0.869	-0.284	0.481 bl
HbA1c (%)	5.1 (0.6)	0.1 (0.1)	13	5.4 (0.6)	-0.1 (0.3)	15	0.282	-0.784	**0.049**
Blood lipids									
TC (mmol·L^{-1})	5.3 (1.2)	-0.3 (1.1)	12	5.8 (1.5)	-0.1 (0.6)	15	0.626 †	-0.226	0.922 †
LDL (mmol·L^{-1})	3.4 (1.5)	-0.2 (1.1)	12	3.6 (1.0)	0.0 (0.7)	15	0.555	-0.071	0.840 bl
HDL (mmol·L^{-1})	1.3 (0.4)	0.0 (0.1)	12	1.2 (0.5)	0.0 (0.2)	15	0.625	0.204	0.602 bl
TG (mmol·L^{-1})	1.4±0.5	0.2±0.5	12	1.7±0.7	-0.1±0.3	15	0.342	-0.740	0.077 bl
RMR (kcal·kg·day^{-2})	16.3±1.0	-0.7±1.6	13	16.4±2.7	0.9±1.3	13	0.879	1.110	**0.007 bl**
CPSS	15.7±5.9	-2.7±2.7	15	19.2±5.9	-4.6±4.2	15	0.111	-0.531	0.510 bl

Data are presented as mean ± standard deviation or median (interquartile range). BMI: body mass index; CON: control group; CPSS: Cohen's perceived stress scale; DBP: diastolic blood pressure; ES: effect size; HbA1c: glycated haemoglobin; HDL: high-density lipoprotein; HOMA2-IR: homeostatic model assessment 2 for insulin resistance; LDL: low-density lipoprotein; RMR: resting metabolic rate; SBI: sleep behaviour intervention group; SBP: systolic blood pressure; TC: total cholesterol; TG: triglycerides; WC: waist circumference; WHtr: waist-to-height ratio. The *p*-values for the between-group comparisons at baseline were determined using the Student's t-test (no superscript symbol) or

Kruskal-Wallis ([†]), and those for the between group comparisons of change were determined using the ANCOVA adjusted for baseline values ([bl]), Student's t-test (no superscript symbol) or Kruskal-Wallis([†]). The ES represents Cohen's *d*.

Table 5.5. Prevalence of cardiometabolic risk factors and high cardiometabolic risk in the CON and SBI groups at baseline and follow-up.

	CON				SBI				Between-group comparison at baseline	Between-group comparison at follow-up
	Baseline		Follow-up	n	Baseline		Follow-up	n	*p*-value	*p*-value
Elevated WC	12 (80%)	↔	12 (80%)	15	14 (93%)	↓	12 (80%)	15	0.598	1.000
Elevated BP	5 (33%)	↓	4 (27%)	15	9 (60%)	↓	7 (47%)	15	0.272	0.450
Elevated fasting glucose	3 (23%)	↔	3 (23%)	13	4 (27%)	↔	4 (27%)	15	1.000	1.000
Reduced HDL	4 (33%)	↑	5 (42%)	12	9 (60%)	↓	8 (53%)	15	0.707	0.707
Elevated TG	3 (25%)	↑	4 (33%)	12	6 (40%)	↓	5 (33%)	15	0.683	1.000
High cardiometabolic risk	3 (25%)	↔	3 (25%)	12	6 (40%)	↓	5 (33%)	15	0.704	1.000

Data are presented as count (percentage). BP: blood pressure; CON: control group; HDL: high-density lipoprotein; SBI: sleep behaviour intervention group; TG: triglycerides; WC: waist circumference. ↑ indicates prevalence increased, ↓ indicates prevalence decreased, and ↔ indicates prevalence did not change between baseline and follow-up. The *p*-values for the between-group comparisons were determined using the Fisher's exact test.

5.3.5 Association analyses

When the groups were pooled, change in sSRI correlated with change in TC (**Fig 5.1A**) and with change in RMR (**Fig 5.1B**), such that an increase in sSRI was associated with a decrease in TC and an increase in RMR. However, these correlations were lost when the groups were split. Moreover, one individual in the SBI group experienced a much larger change in sSRI than the other individuals in the SBI and CON groups. After removing this observation, significance is lost for the correlation between change in sSRI and TC (ρ=-0.513, p=0.111, n=26), but not that of change in sSRI and RMR (ρ=0.590, p=0.029, n=26). No other changes in sleep measures correlated with changes in cardiometabolic health measures.

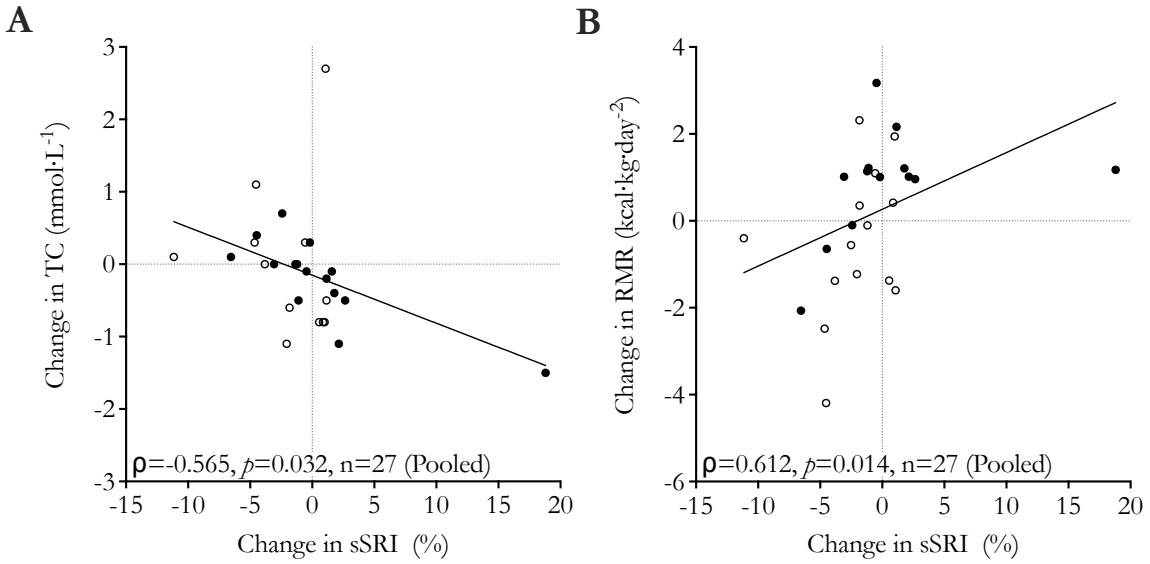

Figure 5.1. Correlation plots for change in sSRI and change in TC (A) and between sSRI and change in RMR. ○: control group (CON); ●: sleep behaviour intervention (SBI) group. RMR: resting metabolic rate; sSRI: simplified sleep regularity index; TC: total cholesterol. Significance was determined using Spearman's correlation.

5.4 Discussion

The effects of a sleep behaviour intervention within a diet and exercise lifestyle intervention programme designed to improve cardiometabolic health in individuals with overweight and obesity were described. The SBI group advanced get-up time and midpoint of sleep, demonstrated increased RMR and decreased HbA1c, and improvements in sSRI were associated with improvements in TC and RMR.

Besides the improvements in RMR and HbA1c, the advancement of midpoint of sleep and get-up time in the present study, may also be beneficial to the participants from a cardiometabolic perspective. For instance, delayed sleep timing has been associated with increased caloric intake after 20:00 and type 2 diabetes mellitus (T2DM) (Merikanto et al., 2013, Baron et al., 2011). It must be noted, however, that changes in bedtime, get-up time and midpoint of sleep were not associated with measures of cardiometabolic health in the present study.

One explanation for change in sleep timing-related behaviour, but not in other aspects of sleep, in the present study, may be that sleep timing is reflected immediately, whereas changes related to other aspects of sleep are indirect. For example, to advance midpoint of sleep, one would only need to consciously retire and get-up earlier, whereas changes in TST require a shorter SOL and increased maintenance of sleep, which are unconscious processes, and may be more difficult to achieve. Moreover, twenty-two healthy men and women who were classified as late chronotypes based on the Munich Chronotype Questionnaire advanced their midpoint of sleep on free days by approximately 2 h by receiving sleep hygiene recommendations, which included instructions to advance bedtime and get-up times (Valshtein et al., 2019). These findings demonstrate that even in late chronotypes, sleep hygiene instructions, even without individualized counselling can induce significant changes in sleep timing. One study was successful in increasing commitment to bedtime procrastination using a self-regulatory intervention in undergraduate students who were concerned about their delayed bedtimes (Valshtein et al., 2019). Although no subjective or objective measures of sleep timing were taken, the difference between self-reported planned and actual bedtime was significantly less in the intervention group than in the control group. The findings also suggest that changes to sleep timing, or at least aligning planned and actual bedtime, are relatively easy to make.

Although the changes that occurred in sleep timing in the present study must thus not be underappreciated, it was surprising that the other measures of poor sleep health that were observed in the OBII group of **Chapter 3**, such as short sleep duration and sleep fragmentation were not affected by the sleep behaviour intervention in the present study. The findings of the present study were aligned, however, to those of a four-session sleep behaviour intervention study with adolescents, where changes in objective sleep characteristics were not different to that of a control group (Cain et al., 2011). While the intervention by Cain *et al.* incorporated aspects to increase participant motivation, further support to behavioural change was lacking, which might have contributed to the lack of response in their objective sleep measures. The authors did report improvements in motivation of the adolescents to change, which may be an important first step to actual behaviour change. Unfortunately, no measures of motivation were taken in the present study, and thus the two studies cannot be compared in this regard.

While not observed in the present study, others have found that sleep duration and sleep fragmentation change in response to similar sleep behaviour interventions. For example, a four-session sleep intervention in older adults with sleep difficulties in a non-residential day care facility improved actigraphy-assessed sleep efficiency (SE), awakenings and wake after sleep onset (WASO), but not TST and PSQI scores (Martin et al., 2017). Additionally, a sleep extension intervention in short-sleeping adults increased time-in-bed (TiB), TST, SE, awakening index and PSQI scores, but not SOL (Al Khatib et al., 2018).

In contrast to the aforementioned studies, the participants in the present study were not subjected to sleep-related inclusion criteria, except for not being exposed to external factors which may affect sleep (e.g. shift work, parents of young children), and for not being diagnosed with moderate to severe obstructive sleep apnoea (OSA). Thus, one explanation for the absence of changes in sleep fragmentation and duration in the present study may be that the participants were sleeping well in the first place. Indeed, only 4 out of 15 participants of the SBI group had short sleep duration, high sleep fragmentation, high sSRI, and high corrected social jet lag at baseline, while EDS was only found in 3 out of 15 participants in the SBI group at baseline. As such, the participants of the SBI groups were not particularly poor sleepers, which may make it more challenging to improve sleep. In fact, attempting sleep modulation in individuals with good sleep health may be detrimental. For example, forced TiB extension in healthy sleepers resulted in an increase in depression, interleukin (IL)-6 levels, and ESS score (Reynold et al., 2014).

Another explanation as to why improvements in sleep measures were modest may be that the participants in the present study were participating in a lifestyle intervention programme with nutritional and exercise modulation and were thus already implementing changes to their lifestyle. Making changes to sleep in addition may have been overwhelming to the participants and may have decreased compliance, which was not quantitatively measured throughout the intervention. Building on this, participants took part in the lifestyle intervention programme to lose weight, improve fitness and improve health and were told that the sleep behaviour intervention may either result in more weight loss, less weight loss, or have no effect at all. Therefore, the participants may have been less incentivised to make changes to sleep-related behaviour, than to make changes related to diet and exercise, which also may affect compliance to the sleep behaviour intervention.

Additionally, the association of cardiometabolic health with short sleep duration and poor sleep quality is thought to be bidirectional (Lucassen et al., 2012). Lifestyle and stress factors, depression, sleep disordered breathing, decreased circadian amplitude, and – where diabetes mellitus is involved – thirst, nocturia and rapid declines in blood glucose levels have all been suggested to

explain how obesity may result in poor sleep (Lucassen et al., 2012). It may therefore be challenging to improve sleep in individuals with obesity without first addressing these psychological and physical factors. Although others were successful in improving sleep in individuals who were overweight (Tasali et al., 2014), to the best of my knowledge, the present study is the first to attempt sleep improvement in individuals who are predominantly obese. Since individuals with class II obesity experience more sleep disturbances than individuals with overweight and class I obesity (see **Chapter 3**), sleep in individuals with severe obesity may also be more difficult to improve than sleep in those with moderate or mild obesity. This may thus further explain why increasing sleep duration and decreasing sleep fragmentation, in this cohort of individuals who are predominantly obese, may be more difficult to achieve than initially hypothesised. Differences in response to the sleep behaviour intervention between the various obesity categories would ideally have been explored but could not be done due to the small sample size.

Sleep duration and quality may not have improved in the participants due to reasons specific to the intervention. Previously, our research group recommended applying suggestive, rather than instructive, personalised strategies that include sleep hygiene education for the purpose of improving cardiometabolic health through sleep extension (Henst et al., 2019). Notwithstanding that the aim of the present intervention was general nocturnal sleep improvement, and not sleep extension specifically. Indeed, sleep hygiene education is an important aspect of cognitive behavioural therapy for insomnia (CBT-I), which is the preferred treatment for primary insomnia (Morgenthaler et al., 2006), however, as one may expect, sleep hygiene education in isolation has been found to be ineffective for the treatment of clinical insomnia (Schutte-Rodin et al., 2008). Furthermore, evidence to support the role of sleep hygiene recommendations in improving sleep in nonclinical populations is lacking (Irish et al., 2015). The present study suggests that personalized sleep hygiene recommendations in individuals with overweight and obesity who do not have a poor sleep health *per se* may not affect sleep noticeably outside of the clinical setting.

Moreover, these sleep hygiene recommendations were communicated with techniques borrowed from motivational interviewing, which is an elaborative and evocative counselling style to resolve ambivalence, and was originally designed to help individuals with drinking addictions by finding intrinsic motivators to drive change (Rollnick and Miller, 1995). This technique may thus be suitable if the participants of the present study were ambivalent about changing their sleep behaviour and have intrinsic motivation. However, less so without intrinsic motivators, for example if the participants did not believe they had a problem with their sleep, or they did not see the benefit of making sleep-related behaviour changes. Therefore, an instructive approach may have resulted in more drastic changes in sleep, however, its long-term efficacy is undetermined.

Finally, the short intervention duration was unlikely to have played a role, as others have been successful in changing measures of sleep with interventions of shorter durations, namely of three days to six weeks (Haack et al., 2013, Al Khatib et al., 2018, Killick et al., 2015, Kubo et al., 2011, Leproult et al., 2015, Reynold et al., 2014, Tasali et al., 2014). Likewise, the number of intervention sessions in the present study was similar to, or higher than, those of other sleep intervention strategies which successfully increased sleep duration and does therefore not explain the lack of effect following the sleep behaviour intervention in the present study (Al Khatib et al., 2018, Leproult et al., 2015, Tasali et al., 2014).

It was also hypothesised that the sleep behaviour intervention would improve anthropometric and cardiometabolic measures. Indeed, favourable effects of the sleep behaviour intervention were observed for HbA1c and RMR. The observed improvement in HbA1c is not surprising, given the association of increased HbA1c with both short and long sleep duration, and poor subjective sleep quality in patients with T2DM (Lee et al., 2017). Additionally, patients with T2DM who underwent a diabetes sleep education program and thereby improved their sleep hygiene, decreased their PSQI scores and Hba1c levels more than those who did not undergo the programme (Li et al., 2018). Since all but one of the participants in the present study did not have T2DM, the finding of improved HbA1c is all the more convincing. Furthermore, HbA1c has been associated with sleep duration and sleep quality (Knutson et al., 2006), and others have suggested that HbA1c may be a target for interventions to improve sleep quality in individuals with T1DM (Martyn-Nemeth et al., 2018). Since poor and short sleep have been associated with a decrease in insulin sensitivity (Stamatakis and Punjabi, 2010), the reverse may have occurred following the sleep behaviour intervention in the present study, resulting in an increased insulin sensitivity and consequently decreased average blood glucose levels, and thus HbA1c. However, measures of these mechanisms were not taken and therefore this speculation cannot be confirmed in the present study.

The present study is the first to report an increase in RMR following a sleep behaviour intervention. This finding is favourable since lower RMR has been associated with weight gain (Buscemi et al., 2005), and higher RMR has been associated with weight maintenance after weight-loss (Vogels et al., 2005). While short sleep duration has been associated with reduced RMR in at least two studies (Benedict et al., 2011, Spaeth et al., 2015), the present study is the first to suggest a relationship between measures of sleep timing and RMR. First, RMR improved in the SBI group, where advances in get-up time and midpoint of sleep were also observed. Second, RMR was associated with sSRI when the SBI and CON groups were combined. Furthermore, despite the evidence for an association between RMR and sleep duration, RMR did not change following sleep extension in another study (Al Khatib et al., 2018).

As mentioned above, in the present study, those that experienced the largest increase in RMR also had the largest increase in sSRI (i.e. sleep timing became more regular). However, since sSRI was not affected by the sleep behaviour intervention, change in sSRI may be explained by the same mechanisms that caused the increase in RMR. For instance, regular sleep timing is an indicator of a robust circadian clock, i.e. the circadian amplitude of the biological processes that exhibit circadian variation are high, including those that influence an individual's sleep onset and wake-up times. Since RMR exhibits circadian variation (Zitting et al., 2018), an increase in sleep regularity may be paralleled by a higher circadian amplitude of RMR. This, in combination with an advancement of the circadian clock, possibly indicated by the advanced midpoint of sleep in the present cohort, may result in a higher RMR at the time-of-day the indirect calorimetry was performed (i.e. between 06:00 and 10:00). Future research is needed to confirm the association between RMR and measures of sleep timing.

Despite no changes in sSRI or TC in response to the intervention, those with the highest increase in sSRI experienced the highest reduction in TC when the groups were pooled. Although this correlation was no longer significant after removal of an outlier for change in sSRI, Spearman's rho was minimally affected. This correlation is independent of group, and thus unrelated to the sleep behaviour intervention. Moreover, TC was unaffected by the lifestyle intervention programme in **Chapter 4**, and did also not correlate with sSRI, or any other sleep outcomes in that study. To the best of my knowledge, the current study is the first to find an association between sleep regularity and TC. More research is needed to confirm this finding, and to explore possible mechanisms.

In addition to the favourable effects of HbA1c, RMR, and cardiometabolic risk, an unfavourable effect was observed for SBP, which increased in response to the sleep behaviour intervention. Although this finding was surprising, it must be noted that the ES was only moderate, the average SBP was still below normal clinical range after the intervention, and the prevalence of elevated BP in the SBI group dropped from nine to seven. The significance of this finding on cardiometabolic health is therefore debatable. To the best of my knowledge, this is the first study to demonstrate an increase in single-recording SBP following sleep modulation. One week of extending sleep duration by 1 h, however, decreased SBP by 7.0±3.0 mmHg in healthy undergraduate students (Stock et al., 2019). Other studies using sleep extension interventions (Kubo et al., 2011, Haack et al., 2013, Reynold et al., 2014) and a web-delivered sleep hygiene, stimulus control, and cognitive behavioural therapy intervention (McGrath et al., 2017) found no effects on DBP or SBP. Likewise, a diabetes sleep education programme reported a decrease in SBP, but not DBP, although this effect was lost after adjustment for covariates (Li et al., 2018).

Lastly, the effect of the sleep behaviour intervention on cardiometabolic measures may only become apparent after an extended period of time. For example, delayed midpoint of sleep has been associated with weight regain following an exercise intervention in postmenopausal women (McNeil et al., 2019), possibly due to an increased energy intake in the evening (Baron et al., 2011). Therefore, one may speculate that the advanced midpoint of sleep in the participants of the SBI may reduce the chance of weight regain, and the participants may thus only experience the benefits of the sleep behaviour intervention sometime after the programme. However, the long-term benefit of the sleep behaviour intervention was outside the scope of this study.

Contrary to the hypothesis, anthropometric variables, measures of insulin resistance and blood lipids were not affected by the sleep behaviour intervention. One explanation may be the limited effect of the intervention on sleep itself. That is, if these measures of cardiometabolic health were expected to improve in response to changes in sleep following the sleep behaviour intervention, then changes in sleep must occur for changes in cardiometabolic health to happen. Changes in sleep timing alone may not be sufficient to drive change in these measures of cardiometabolic health. Indeed, the associations with cardiometabolic health are most frequently found for sleep duration (see **Section 1.5.2**) and sleep fragmentation (see **Section 1.5.3**), and less so for sleep timing (Baron et al., 2011). Second, although the participants were overweight or obese, not all participants were in poor cardiometabolic health *per se*. Specifically, 9 out of 15 participants of the SBI group had elevated BP or reduced HDL, but only 4 and 6 out of 15 participants had elevated fasting glucose and elevated TG levels respectively. Furthermore, only 6 out of 15 participants of the SBI group at baseline met the criteria for being at high cardiometabolic risk. Therefore, changes in these outcomes may have been unlikely for the majority of participants.

5.4.1 Study limitations

These results must be interpreted in context of the limitations of this study, which are a small sample size; not having a measure of compliance to the sleep behaviour intervention; and the exclusion of analyses of naps, food intake and exercise. The small sample size may increase the chance of type II errors and decrease the representability of the sample to the general population. In addition, a larger sample size would allow for the adjustment for factors such as exercise and intervention session attendance, which may have decreased the unexplained variance of the models. Such information may also explain whether the absence of an effect on the sleep variables were due to the poor compliance, or because of the minimal impact of these changes on sleep. Another analysis that may be performed with a larger sample size is the comparison of responders

versus non-responders. Moreover, the intervention may have affected other aspects of sleep which were not measured, for example napping frequency and duration. Although the participants wore an actigraphy device throughout the day, the participants were not instructed to annotate naps in the present study. The same can be said about food intake, since factors affecting food intake such as appetite and circulating levels of leptin and ghrelin are associated with sleep (Taheri et al., 2004, Spiegel et al., 2004a, Spiegel et al., 2004b). Another limitation is that, while one of the reasons for using the diet and exercise lifestyle intervention programme as the setting for the sleep behaviour intervention was to attempt to control for exercise, exercise exposure was not measured. It is thus possible that inter-individual differences in exercise frequency, intensity and duration might have impacted the findings of this study. Lastly, as mentioned in **Section 3.2.3.8**, the participants in the present study who were included in **Chapter 3** of this thesis underwent PSG. Due to insufficient PSG data available, it was decided to exclude the PSG analysis from the present study. However, due to scheduling and time constraints, some of the actigraphy nights from the present study overlapped with the PSG nights. Because PSG is considered invasive and may alter normal sleep, it is possible that allowing the actigraphy and PSG nights to overlap may have affected the actigraphy data. However, since the actigraphy data shown are the average over four to seven nights, the impact of the PSG nights on these data is minimal. Indeed, when all overlapping nights were removed from the analysis, the significance did not change (data not shown).

5.5 Conclusion

These findings add to the limited available literature that describe sleep modulation as a candidate for interventions to improve cardiometabolic health. Evidence to support this statement is scarce and more studies are needed before sleep modulation is readily applied to existing or new lifestyle interventions. I suggest that future research should be focused on participants with cardiometabolic impairment and poor sleep, as changes in cardiometabolic health, sleep duration and sleep fragmentation are more likely to occur and more necessary. Moreover, studies are needed to explore the long-term benefits of sleep behaviour interventions on cardiometabolic health, specifically on weight regain. I also suggest that measures of appetite, satiety, hunger and timing of food and food intake are included, as these are likely candidates for change. Finally, studies with larger sample sizes are needed to allow for adjustment of cofounders, including compliance.

Chapter 6

General Discussion and Future Considerations

The findings of the studies described in this thesis suggest that sleep behaviour interventions are a promising strategy to mitigate the global burden of cardiometabolic disease (CMD). More research is needed, however, to better understand who may benefit from such interventions, and how these individuals may be identified. In this chapter, practical implementations and recommendations for the implementation of sleep behaviour interventions for the betterment of cardiometabolic health are discussed and directives for future research are provided.

6.1 Practical implications and recommendations

The findings of this thesis suggest that developers of lifestyle intervention programmes and their participants may benefit from a sleep behaviour intervention, especially when decreased glycated haemoglobin (HbA1c) and increased resting metabolic rate (RMR) are desirable. Moreover, good sleep health may be necessary to support weight-loss and cardiometabolic health improvements. For example, following participation in a weight-loss intervention, women with overweight and obesity and higher sleep fragmentation lost less weight than those with less sleep fragmentation (Sawamoto et al., 2014). As such, the addition of sleep behaviour interventions may make lifestyle intervention programmes more effective.

6.1.1 Other stakeholders

Sleep behaviour interventions may not only be implementable or valuable to lifestyle intervention programmes. Other stakeholders that may benefit from sleep behaviour intervention programmes are patient or hospital wellness programmes, employee wellness programmes, schools, and health and life insurance providers.

6.1.1.1 Patient or hospital wellness programmes

Patients with cardiometabolic impairment and impaired sleep, who are under supervision of their general practitioner or specialist doctor may benefit from participation in a sleep behaviour intervention. Regardless of cardiometabolic health, general practitioners in the United Kingdom prefer alternative strategies to prescribing hypnotic drugs to patients with sleep problems, such as personal counselling, raising awareness around sleep, and sleep interventions at workplaces and schools (Siriwardena et al., 2010).

6.1.1.2 Employee wellness programmes

Employers and employees may also benefit from sleep interventions as part of an employee wellness programme. Sleep-related workplace productivity loss and associated costs in the United States have been calculated to be hundreds of dollars per employee (Rosekind et al., 2010). Workplace wellness programmes have been found to improve employee health in the United States, and for every dollar spent on such programmes medical costs drop by $3.27 and absenteeism costs drop by $2.73 (Baicker et al., 2010). The addition of sleep behaviour interventions to existing employee wellness programmes may improve sleep health, absenteeism and presenteeism, and have been reviewed recently (Redeker et al., 2019).

6.1.1.3 Schools

Sleep education programmes with subsequent sleep behaviour interventions may be offered at schools, at least to inform children and adolescents about the importance of sleep, and to equip them with tools to ensure good sleep behaviour now and at a later stage of life. Note, however, that two studies by the same group (one with, and one without a motivational aspect) on adolescents who underwent a sleep behaviour intervention programme did not find any subjective or objective improvements in sleep (Cain et al., 2011, Moseley and Gradisar, 2009). Moreover, a pilot with nine female adolescents with poor sleep quality (Pittsburgh sleep quality index (PSQI) score ≥9, except for one individual with a PSQI score of 5) who underwent a six-session sleep behaviour intervention programme showed effect size-based improvements in objective sleep measures (Bei et al., 2013). Since no control group was included in the latter study, it is difficult to comment on the true effectiveness of the programme.

6.1.1.4 Health and life insurance providers

Health and life insurers may benefit from sleep behaviour intervention programmes for their clients, as good sleep health may decrease medical costs associated with sleep deprivation and cardiometabolic health. For example, short sleep duration has been associated with higher CMD risk (Knutson, 2010, Kronholm et al., 2011), and addressing poor sleep health among clients with increased CMD risk may decrease morbidity, and thus cost for health insurers. Likewise, long sleep onset latencies, high sleep fragmentation, and short sleep duration have been associated with CMD and all-cause mortality (Hublin et al., 2007, Gallicchio and Kalesan, 2009, Dew et al., 2003, Heslop et al., 2002, Cappuccio et al., 2010), and addressing sleep disturbances of clients, may decrease the cost to life insurers. An incentive-based programme to increase physical activity in clients of health

insurer in South Africa, has already been shown to decrease hospital admission and cost (Patel et al., 2011). By addressing poor sleep health among clients at risk, in addition to other health-promotion programmes, morbidity risk may be decreased, life may be prolonged and thus costs to health and life insurance may be saved.

6.1.2 Identifying participants of health and wellness programmes

Not all participants, students, clients, patients and employees of the stakeholders mentioned above may benefit from a sleep behaviour intervention, however. By identifying individuals who may benefit from a sleep behaviour intervention within an existing programme (e.g. lifestyle intervention programme, school education programme, or employee wellness programme), and only offering it to those who may, efficacy may be improved while reducing costs. Individuals may fall into one of four categories based on their sleep health and CMD risk. These categories will be discussed in the following sections.

6.1.2.1 Healthy individuals

Individuals without sleep or cardiometabolic impairment are the least likely to benefit from a sleep behaviour intervention to improve sleep and cardiometabolic health. That is, improvements in sleep and cardiometabolic health may both be unnecessary and unfeasible. Individuals who fall into this category may therefore not be offered a sleep behaviour intervention, and with that, relieving pressure from sleep consultants or coaches, and reduce the cost of the programme.

6.1.2.2 Individuals with poor sleep health

Individuals with sleep impairment but good cardiometabolic health may benefit from a sleep behaviour intervention for reasons other than their cardiometabolic health. For example, higher PSQI scores (i.e. worse subjective sleep quality) were associated with higher Cohen's perceived stress scale (CPSS) scores in **Chapter 3** of this thesis, and impaired sleep has been associated with an increased risk of anxiety under stress (Kalmbach et al., 2019) and susceptibility to the common cold (Prather et al., 2015). Furthermore, it is plausible that individuals in this category are at risk for developing future cardiometabolic impairment because of their sleep impairment. For this group of individuals, it may be important to monitor cardiometabolic health and include them in the sleep behaviour intervention programme.

6.1.2.3 Individuals with increased cardiometabolic risk

In the third category are those with cardiometabolic impairment, but good sleep health. These individuals are more likely to benefit from traditional lifestyle intervention programmes that focus on diet and exercise. However, as these individuals may be at risk for developing sleep impairment, driven by their decreased cardiometabolic health, their sleep should be monitored closely. If a deterioration in sleep health occurs, they may have progressed to the fourth category.

6.1.2.4 Individuals with increased cardiometabolic risk and poor sleep health

Individuals in the fourth category have both cardiometabolic and sleep impairment and may benefit most from sleep behaviour intervention to improve cardiometabolic health. Participants in this category should thus always be offered to be included in a sleep behaviour intervention.

Participants of the study described in **Chapter 5** were recruited for their adiposity but only 25% of the CON group, and 40% of the SBI group had a high cardiometabolic risk. Furthermore, as the study was a natural experiment, the participants were recruited regardless of their sleep health, as long as external factors that may impair sleep (e.g. nocturnal family or work commitments, hypnotic medication use), or sleep-disordered breathing and previously diagnosed insomnia were absent. Thus, the participants in the SBI and CON groups of **Chapter 5** may have been categorized in either of the four categories, and the effect of the sleep behaviour intervention on sleep and cardiometabolic outcomes may have been dependent on the category each participant fell under. This type of categorisation of the participants in the present study, however, was not possible due to the small sample size. Regardless, the findings of the present study highlight the importance of screening participants, patients, clients and employees for sleep health risk, to stratify individuals based on needs. Future research is needed to assess the precise effect of sleep improvement interventions on cardiometabolic health in each of these categories. Classification into these categories may be done with the cardiometabolic risk factors described in **Section 3.2.3.6**, which were based on definitions by Grundy et al. (2005) and Lloyd-Jones et al. (2010), or **Section 5.2.4.4**, which was based on Grundy et al. (2005). Categorisation of sleep health may be done with the indicators of poor sleep health and the sleep health score as described in **Section 3.2.3.10**, or by using cut-off values which have been proposed before (Brindle et al., 2019). However, more research is needed to improve and validate the criteria of poor sleep health, such as the work by Buysse and colleagues (Brindle et al., 2019, Buysse, 2014, Dong et al., 2019, DeSantis et al., 2019).

6.1.3 Screening for obstructive sleep apnoea

Another consideration is the screening of participants, patients, clients and employees for OSA, which has been shown to exacerbate cardiometabolic risk, especially in individuals with obesity and the metabolic syndrome (MetS) (Drager et al., 2013). Because participants of lifestyle intervention programmes aimed at weight-loss are likely to be overweight or obese, and given that high BMI is a risk factor for OSA (Chung et al., 2008), a high prevalence of OSA among the participants is expected. This makes the setting of a lifestyle intervention programme specifically suitable for OSA screening. For example, participants may be screened for OSA with the STOP-Bang questionnaire which has been shown to have a high sensitivity and good specificity (Chung et al., 2014). Those who screen positive for OSA may be referred to their general practitioner who may refer them for formal diagnosis and medical treatment of their condition. This is not to say, however, that individuals with OSA may not benefit from a sleep behaviour intervention. In fact, individuals with OSA were found to have poor sleep hygiene as assessed with the Sleep Hygiene Index (SHI), which may not aid good sleep health, especially in combination with OSA (Lee et al., 2015). Moreover, 68.3% of patients who were on positive airway pressure treatment for OSA complained of insomnia symptoms before treatment, which persisted for two years after starting treatment (Bjornsdottir et al., 2013). For this reason, participants who screen positive for a sleep-disordered breathing condition may specifically benefit from a sleep behaviour intervention, which can be tailored to the needs of these individuals. Moreover, since compliance to positive airway pressure treatment is often poor, sleep intervention programmes may include positive airway pressure treatment support if needed (Sawyer et al., 2011).

6.1.4 Screening for psychological conditions

The fourth and last consideration is the screening for psychological conditions that underlie poor sleep health. For example, the most common symptom of anxiety disorders such as generalized anxiety disorder and post-traumatic stress disorder is insomnia (Saletu-Zyhlarz et al., 1997, McLay et al., 2010). Individuals with sleep impairment that may originate from such psychological conditions may be referred to a psychologist, as sleep consultants may not be equipped to help these individuals with their psychological needs. Other psychological conditions that may be associated with impaired sleep, and should be considered for screening, are depression disorders (Riemann et al., 2001), psychotic disorders (Monti and Monti, 2004), and substance abuse disorders (McGregor et al., 2005, Angarita et al., 2014). Various tools are available to assess the risk for these psychological conditions; however, this is out of scope of this thesis.

A framework of the considerations discussed in this section: stakeholders, identification of individuals who may benefit, screening for OSA and underlying psychological conditions, and the sleep behaviour intervention, are depicted in **Figure 6.1**.

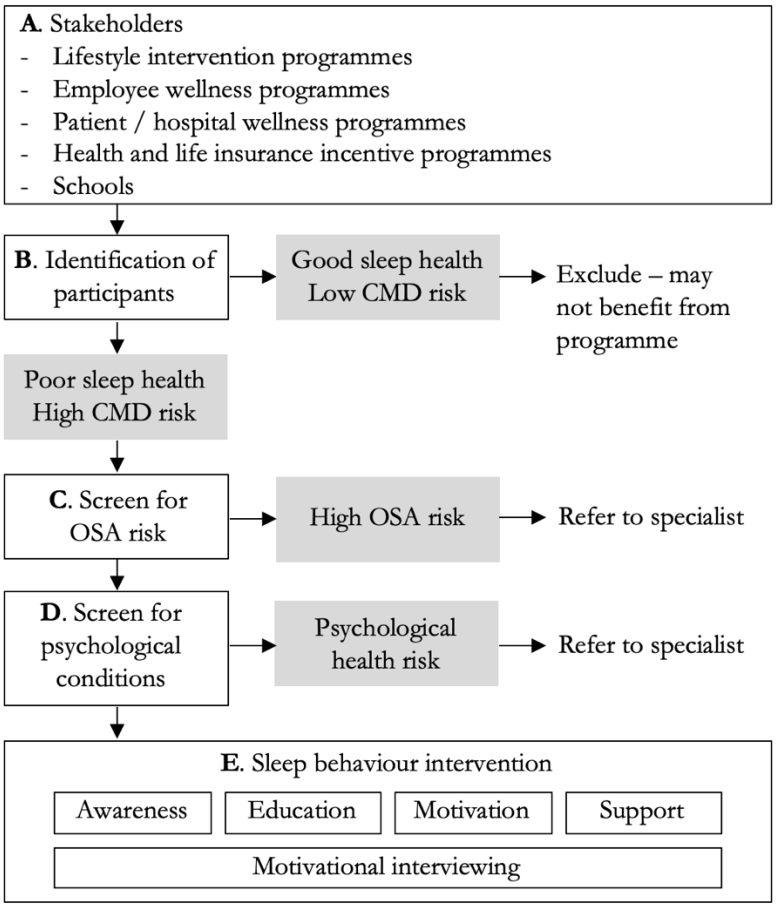

Figure 6.1. A framework for the implementation of sleep behaviour interventions. Participants, patients, students, employees, and clients of various stakeholders (**A**) may be identified to determine if a sleep behaviour intervention may be beneficial to the individual (**B**). Those identified may be screened for OSA risk (**C**), for underlying psychological conditions that may impair sleep (**D**), and referred to specialists if applicable. Identified individuals will participate in the sleep behaviour intervention on the basis of motivational interviewing (**E**). The four principles (awareness, education, motivation and support) of the sleep behaviour intervention are tailored to fit the participants' and stakeholders' needs. CMD: cardiometabolic disease; OSA: obstructive sleep apnoea.

6.1.5 Format of sleep behaviour interventions

The sleep behaviour intervention in the format used in **Chapter 5** may not be suitable for each of the stakeholders. For example, because of the personalised nature of the sleep behaviour intervention, a consultant can only attend to one individual per session. Thus, the sleep behaviour intervention of **Chapter 5** is demanding to the consultants, especially with large groups of participants. To make implementation of a sleep behaviour intervention for any of the stakeholders more feasible and affordable, the intervention format may be tailored to each stakeholder.

Cost of the programme and pressure on the sleep consultant(s) may be reduced if sleep behaviour interventions are provided in group settings. Group sessions for cognitive behavioural therapy for insomnia have already been applied, and have been shown to be successful (Koffel et al., 2015). Recognizing that sleep impairment is different to clinical insomnia, these findings are promising and warrant further exploration of the utilisation of sleep behaviour interventions in group sessions in individuals with poor cardiometabolic health.

Alternatively, parts of the sleep behaviour intervention, such as those that involve creating awareness, educating participants, and support to behaviour change, could be provided in group sessions, while the parts which require personal attention, such as intrinsic motivation, may be provided one-on-one. Furthermore, alternative modes-of-delivery for sleep behaviour interventions must also be explored, and may include online consultation sessions (e.g. chat, videocall) or online video courses.

6.1.6 Content of sleep behaviour interventions

Finally, like the intervention format, the content of the sleep behaviour intervention may also be tailored to the needs of the target group or stakeholders. Sleep behaviour intervention programmes for schools may be focused mainly on awareness and education, while intrinsic motivation and support to behaviour change were suggested to be important components too (Cain et al., 2011). Furthermore, where changes to sleep behaviour are desired in children and adolescents, educating teachers and parents about sleep health and cardiometabolic consequences may be an important part of the intervention programme.

Sleep behaviour intervention programmes for patients may be tailored for specific groups of patients. For example, Li et al. (2018) developed and tested a sleep education programme for patients with T2DM, and observed improvements in PSQI scores and HbA1c levels (Li et al., 2018). In that study, lectures about the importance of good sleep health for glycaemic control may have provided motivation for the participants to make behavioural changes for the betterment of their sleep. Furthermore, sleep behaviour interventions specifically tailored to the needs of patient groups may address sleep disturbances that are specifically common in those patients. Patients with T2DM, for instance, may benefit from sleep behaviour strategies to avoid thirst, hypoglycaemia, and frequent urination during night-time.

A sleep intervention programme tailored for clients of health and life insurers may have little or no face-to-face interaction with a consultant, but rather be entirely electronic, for scalability and cost reduction. Recently, a self-help web-based intervention for improving sleep in workers was

found to improve Insomnia Severity Index scores in 88 men and women (Behrendt et al., 2020). Participants had access to an online learning platform, with modules on sleep in general, sleep hygiene, sleep restriction and stimulus control, monitoring progress, and included elements to reduce work-related stress. Although developed for the workplace, health and life insurers may offer a similar self-help sleep behaviour intervention programme to their clients, for sleep improvement.

6.1.7 Example: the healthy weight programme

The lifestyle intervention programme named the '*Healthy Weight Programme*' that served as the setting of the studies in **Chapter 4** and **Chapter 5**, has since included sleep health as one of its pillars for weight-loss and healthy living. To reduce costs, the purpose of the sleep intervention in this context was to screen the participants for common sleep disorders and refer on if necessary, to educate about sleep in general, and to help with sleep hygiene-related behaviour change. This sleep intervention programme was thus not as individualised and labour-intensive as the one described in **Chapter 5**. In short, during the first week of the programme, the participants attend a lecture about the importance of sleep for (cardiometabolic) health, receive general sleep hygiene tips and receive information about OSA, because of the high prevalence of OSA among individuals with overweight and obesity. The participants also complete an online sleep questionnaire, where information about their sleep habits is captured and their risk for sleep problems can be assessed. Then, during a 20-min one-on-one consultation session, each participant and the sleep consultant (one of the sleep scientists at the University of Cape Town) go over the results from the questionnaire and discuss challenges the participant may have with their sleep. At the end of this session, recommendations are made by the sleep consultant, which the participant may implement at home over the following weeks. Half-way through the programme, participants are asked to keep a two-week sleep diary, of which the interpretation is discussed during a group workshop with the sleep consultant. This exercise helps the participants to become aware of their habitual sleep patterns and to identify unhealthy sleep habits. Over the course of the programme, the sleep consultants are available to answer sleep-related questions from the participants via phone or email. Participants with suspected sleep disorders (e.g. OSA, narcolepsy, chronic insomnia) are referred on for further investigation and appropriate treatment. Although no data are yet available on the efficacy of this sleep behaviour intervention format, it is an example of how the implementation may be realised.

6.2 Final remarks

6.2.1 Healthy nature of study participants

As mentioned in **Chapter 5**, despite changes in sleep timing, the sleep behaviour intervention did not have any effect on other aspects of sleep that have been associated with cardiometabolic health, and especially obesity. The generally good sleep health of the intervention participants was discussed in **Chapter 5** as one of the reasons why no change was observed in sleep duration and sleep fragmentation. The participants with overweight or obesity of the HWP group in **Chapter 4**, and the SBI and CON groups in **Chapter 5** took the initiative to sign up for a lifestyle intervention programme, but also agreed to participate in the research study. As such, they were presumably willing to make changes to their lifestyle and improve their cardiometabolic health (although the latter objective may be secondary to weight-loss). In one way or another, these participants may have been more motivated to change their lifestyle behaviour than individuals who did not sign-up to the lifestyle intervention programme or who chose not to participate in the present studies. Individuals with significant daytime sleepiness, which may be caused by sleep impairment or a sleep disorder, take less initiative and experience less intrinsic motivation, as assessed with the checklist individual strength (Worm-Smeitink et al., 2017), compared to individuals with no sleepiness symptoms (van der Werf et al., 2003). As such, the generally good sleep health of most participants of the present studies, may have been the result of a selection bias, and may not be translatable to the general overweight-obese population.

Furthermore, the participants of **Chapter 5** were overweight-obese, but were not otherwise cardiometabolically impaired, which may have contributed to the lack of improvement in cardiometabolic outcomes other than HbA1c and RMR. It must be noted that the participants of the lifestyle intervention programme may have been of higher socioeconomic status than individuals with overweight and obesity who did not participate in the programme, since a considerable fee had to be paid. The association between higher socioeconomic status and better cardiometabolic health, sometimes referred to as the 'social causation hypothesis', is well-known (Elovainio et al., 2011, Ogunsina et al., 2018). It must be explored if individuals with overweight and obesity who do not voluntarily sign-up to a lifestyle intervention programme have different cardiometabolic health profiles than those in the present study, and whether they may benefit from a sleep behaviour intervention differently.

6.2.2 On the association between sleep and cardiometabolic health

Current belief indicates that overweight and obesity are associated with poor sleep health (Rao et al., 2009, Cappuccio et al., 2008). While this association was confirmed in the men and women with overweight and obesity in **Chapter 3** of this thesis, the results also suggest that not all individuals with overweight or obesity had poor sleep health. In fact, the majority of participants in that group had (independently of the other sleep health indicators) sufficient sleep duration, minimal sleep fragmentation, normal sSRI, no social jet lag and did not suffer from EDS.

Other markers of poor cardiometabolic health, rather than obesity, may have a stronger association with poor sleep health. Based on the model by Lucassen et al. (2012), such markers may be that of inflammatory state, which may be identified with inflammatory markers such as interleukin (IL)-6, C-reactive protein (CRP) and tumour necrosis factor (TNF)-α, and physical stress, which may be identified by measures of increased sympathetic nervous system activation, such as cortisol and decreased heart rate variability. These markers may be more suitable to identify participants who may benefit from sleep behaviour interventions than the ones used in the present study, namely overweight and obesity. Future research should explore which cardiometabolic health markers may be appropriate for identifying individuals who benefit from sleep behaviour interventions, and what the effect of sleep behaviour interventions on the cardiometabolic health of these individuals may be.

The definition of indicators of poor sleep health in this thesis was based on recommendations and a consensus statement from the United States National Sleep Foundation (Hirshkowitz et al., 2015, Ohayon et al., 2017). However, these indicators do not define poor sleep health itself. While the indicators of poor sleep health used in this thesis may be used as a starting point, it must be explored whether these criteria may sufficiently stratify individuals based on their sleep health and consequences on overall health.

Furthermore, more research is needed to better understand the causative relationship between poor sleep health and cardiometabolic impairment or adiposity. For example, it is not known whether the individuals with poor sleep in the OBII group of **Chapter 3** had poor sleep before becoming overweight or obese, or whether these individuals had poor sleep because they had class II obesity. Likewise, it is not known whether those with poor sleep health in the OW-OBI are at risk for further weight gain and progression into class II obesity, or whether those with good sleep health in the OW-OBI group are protected against progression to class II obesity. By better understanding the causative relationship between cardiometabolic and sleep health, individuals

who may benefit from a sleep behaviour intervention may be identified at an earlier stage, before further deterioration of cardiometabolic or sleep health occurs.

6.3 Conclusion

In conclusion, preliminary evidence to suggest that a sleep behaviour intervention may improve cardiometabolic health in individuals who are at risk for CMD is available. Considerations for implementation of such interventions are 1) tailoring the format and content of the intervention for different target groups, 2) identifying individuals who may benefit from a sleep behaviour intervention, 3) screening for sleep disorders such as OSA, and 4) screening for psychological conditions that are precursors for poor sleep. Further research in this field is needed to determine how individuals who are at risk for CMD and who may benefit from a sleep behaviour intervention can be identified.

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