Towards an understanding of the relationship between sleep and cardiovascular disease risk in adults of African descent living in a low socioeconomic status community

Philippa Forshaw

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Supervisors:

A/Prof. Dale E. Rae *(Primary Supervisor - University of Cape Town)*

A/Prof. Laura C. Roden *(Co-Supervisor - Coventry University)*

Prof. Estelle V. Lambert *(Co-Supervisor - University of Cape Town)*

Author Declaration

I, Philippa Forshaw, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise). Neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university. I authorise the University to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

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Student Name: Philippa Forshaw Student Number: FRSPHI002

The tables and figures in this thesis have been edited to allow for consecutive numbering. Similarly, the referencing style has been updated to maintain consistency throughout the thesis and are presented collectively in a reference list at the end of the document.

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Table of Contents

Abbreviations

ABPM	Ambulatory Blood Pressure Monitoring
ANS	Autonomic Nervous System
BMI	Body Mass Index
BP	Blood Pressure
BQ	Berlin Questionnaire
CAD	Coronary Artery Disease
CI	Confidence Interval
CMD	Cardiometabolic Disease
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
EDS	Excessive Daytime Sleepiness
EEG	Electroencephalogram
EMG	Electromyogram
EOG	Electrooculogram
ESH	European Society of Hypertension
ESS	Epworth Sleepiness Scale
GPAQ	Global Physical Activity Questionnaire
HDL-C	High Density Lipoprotein Cholesterol
HR	Heart Rate
ISI	Insomnia Severity Index
JBI	Joanna Briggs Institute

MAP	Mean Arterial Pressure
METS	Modelling the Epidemiological Transition Study
MVPA	Moderate- to Vigorous-Intensity Physical Activity
NCD	Non-Communicable Disease
NREM	Non-Rapid Eye Movement
OR	Odds Ratio
OSA	Obstructive Sleep Apnoea
PNS	Parasympathetic Nervous System
PSG	Polysomnography
PSQI	Pittsburgh Sleep Quality Index
PTSD	Post Traumatic Stress Disorder
RAAS	Renin-Angiotensin-Aldosterone System
REM	Rapid Eye Movement
SBP	Systolic Blood Pressure
SCN	Suprachiasmatic Nucleus
SD	Standard Deviation
SE	Sleep Efficiency
SES	Socioeconomic Status
SFI	Sleep Fragmentation Index
SNS	Sympathetic Nervous System
SOL	Sleep Onset Latency
SRI	Sleep Regularity Index
SWS	Slow Wave Sleep

TIB	Time-in-Bed
TST	Total Sleep Time
USA	United States of America
WASO	Wake After Sleep Onset
WC	Waist Circumference

Terms

10-year CVD risk score	BMI-modified Framingham CVD risk score used to predict the 10-year risk of manifesting clinical CVD.
Ambulatory Blood Pressure Monitoring	Method used to measure BP throughout the day and night as a person engages in their regular activities. Regarded as being more accurate compared to office BP.
Autonomic Nervous System	Regulates involuntary physiological processes such as heart rate, blood pressure and respiration. Has two main arms: Sympathetic Nervous System (SNS) and Parasympathetic Nervous System (PNS).
Community clinical insomnia symptoms	Insomnia Severity Index score ≥10.
Circadian rhythm	"*Circa"*, meaning 'about', and "*diem"* meaning 'day'; endogenous 24h cycles that are part of the body's internal clock and influence many physiological and behavioural processes.
Circadian misalignment	Altered/inappropriate relationship between sleep and wakefulness relative to internal circadian timing.
Hypertension	High blood pressure.
Hypervigilance	Constant alertness; the elevated state of constantly assessing for potential threats.
RU-SATED	Defined as: "Are you" – Satisfaction, Alertness, Timing, Efficiency, Duration and used to assess overall Sleep Health.
Nocturnal blood pressure dipping	Natural and physiological decrease in nighttime BP (sleep) relative to daytime BP (wake).
Nocturnal hypertension	High blood pressure during nighttime (sleep). Specifically, nighttime SBP ≥120 mmHg and / or DBP ≥70 mmHg.
Parasympathetic Nervous System	Among other things, responsible for the body's relaxation response (e.g. decreasing the heart rate

	and dilating blood vessels). This response is also known as “rest and digest”.
Office blood pressure	Traditional, once-off BP measured by a healthcare professional in a clinical setting, such as a doctor's office or clinic.
Sleep Fragmentation Index	Index of restlessness during the sleep period expressed as a percentage.
Sleep Regularity Index	Probability of a person being in the same state (sleep of wake) at any two timepoint 24h apart.
Standard clinical insomnia symptoms	Insomnia Severity Index score ≥15.
Sex-specific	Differences (biological and physiological) between men and women.
Socioeconomic Status	The social standing or class of an individual or group involving education, income, financial security, living conditions and resources. Typically categorized into lower or higher SES.
Sympathetic Nervous System	Among other things, responsible for the body’s response to stress or dangerous situations (e.g. increasing heart rate, blood pressure and breathing rate). This response is also known as “fight or flight”.

Sleep-Specific Terms

Self-reported sleep terms:

Utilized in Chapters 2 and 4

Midsleep	Calculated as: self-reported wake-up time – (time-in-bed)/2
Sleep efficiency (SE)	Percentage of time spent in bed sleeping. For self-reported sleep data calculated as (TIB/ TST)*100
Time-in-bed (TIB)	Difference between self-reported bedtime and wake-up time (h)
Total sleep time (TST)	Self-reported total sleep time (h)

Actigraphy-derived sleep terms:

Utilized in Chapters 3, 4 and 5

Midsleep	Calculated as: sleep offset – (sleep duration)/2
Sleep duration	Defined by Phillips Actiware Software as: The time elapsed between start of the sleep interval and the end of the sleep interval
Sleep efficiency (SE)	Percentage of time spent in bed sleeping. For actigraphy-derived sleep data calculated as (Sleep duration/Sleep time)*100
Sleep time	Defined by Phillips Actiware Software as: The total number of epochs for the given interval scored as sleep multiplied by the epoch length in minutes (i.e. total sleep time)
Sleep onset	Defined by Phillips Actiware Software as: the time of the first epoch scored as sleep
Sleep offset	Defined by Phillips Actiware Software as: the time of the last epoch scored as sleep

Wake After Sleep Onset (WASO)	Defined by Phillips Actiware Software as: Total number of epochs between the sleep onset and the sleep offset scored as wake multiplied by the epoch length in minutes

Abstract

Background: Individuals of African descent, specifically African Americans and those from Sub-Saharan Africa, experience a higher burden of cardiovascular disease (CVD) and its associated risk factors (such as obesity, diabetes and hypertension) as well as shorter, poorer sleep quality, compared to Caucasian American individuals. Blood pressure (BP) non-dipping (i.e. the failure of BP to decrease at night during sleep) and nocturnal hypertension are important markers of CVD risk and are substantially more prevalent in African American, compared to Caucasian American, individuals. Two additional layers that need consideration are socioeconomic status (SES) and sex. In contrast to much of the research in the Global North predominantly demonstrating shorter objective and subjective sleep durations (around 6-7h per night) among African descended individuals living in low SES environments, South Africans of African descent living in low SES communities report much longer sleep durations, around 8-10h per night. Thus, while on one hand, lower SES has been associated with higher risk for CVD possibly through shorter sleep, the nature of the relationship between long sleep duration and CVD risk in the South African context is not well understood. Given the significant sex-specific differences in both CVD risk and sleep, there is a need for research focused on understanding sex-specific associations between CVD and sleep health. Thus, the purpose of this thesis was to investigate sex-specific relationships between CVD risk, nocturnal BP and sleep health in adults of African descent living in a low SES community in South Africa. This purpose was achieved through the following aims: i) to investigate sex-specific relationships between self-reported sleep characteristics and CVD risk among individuals of African descent living in a low SES community, ii) to investigate sex-specific relationships between actigraphy-derived sleep characteristics and CVD risk in these same individuals, iii) to systematically review the literature on sleep and BP dipping in apparently healthy individuals, iv) to explore sex-specific associations between actigraphy-derived sleep characteristics, nocturnal BP and CVD risk among adults of African descent living in a low SES community and v) to conduct qualitative interviews with these same individuals to explore how external (e.g. environmental barriers to and promoters of good sleep) and internal (e.g. individual knowledge, attitudes, beliefs and perceptions around sleep) factors might impact sleep health. This thesis explored the hypothesis that adverse environmental conditions associated with living in low SES communities are not conducive to healthy sleep, driving BP non-dipping, nocturnal hypertension and higher CVD risk.

Methods: For Chapters 2 and 3, individuals of African descent (56% women, 29-51y, 40% employed) living in Khayelitsha (an informal settlement in South Africa characterised by high rates of crime,

violence and poverty) were recruited and studied. Sleep characteristics were measured subjectively using self-reported questionnaires (Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), Insomnia Severity Index (ISI); n=412) and objectively with seven days of wrist-worn actigraphy (n=194). CVD risk was assessed using the body mass index (BMI)-modified Framingham 10-year CVD risk score and clinical measures (BMI, waist circumference, resting BP, fasting glucose). We then conducted a systematic review (Chapter 4) exploring associations between BP dipping and sleep in healthy individuals. In Chapter 5 we measured twenty-four hour ambulatory BP in a sub-set of individuals from the original cohort (n=59) to explore associations between BP dipping, nocturnal hypertension, sleep characteristics and CVD risk scores. Finally, we conducted one-on-one qualitative interviews (Chapter 6) in a further sub-set of participants (n=15) to explore possible external (e.g. environmental barriers to and promoters of good sleep) and internal (e.g. individual knowledge, attitudes, beliefs and perceptions around sleep) factors related to sleep health in this population.

Results: When we examined associations between subjectively measured sleep and CVD risk (Chapter 2), found that men (n=178) reporting poor sleep quality (PSQI>5, OR: 1.95, 95%CI: 1.07, 3.51, p=0.025) and earlier bedtimes (OR: 0.54, 95%CI: 0.39, 0.74, p<0.001) were more likely to have higher CVD risk scores. Women (n=234) reporting earlier bedtimes (OR: 0.72, 95%CI: 0.55, 0.95, p=0.020) and wake-up times (OR: 0.30, 95%CI: 0.13, 0.73, p=0.007), longer sleep onset latencies (OR: 1.47, 95%CI: 1.43, 1.88, p=0.003), shorter total sleep times (OR: 0.84, 95%CI: 0.72, 0.98, p=0.029), higher PSQI global scores (OR: 1.93, 95%CI: 1.29, 2.90, p=0.001) and more moderate to severe insomnia symptoms (ISI≥15, OR: 3.24, 95%CI: 1.04, 10.04, p=0.042) were more likely to have higher CVD risk scores. We confirm actigraphy-derived long (men: 9.4 ± 1.4h, women: 8.9 ± 1.2h) but disturbed sleep (low sleep efficiencies [men: 81.8 (76.8, 85.7)%), women: 79.9 (72.5, 84.6)%], high sleep fragmentation indices [men: 58.3 (52.5, 65.2)%, women: 63.4 (56.3, 68.2)%] and high wake after sleep onset (WASO) times [men: 103.1 (76.1, 127.0)min, women: 84.9 (68.8, 110.4)min]) in this population, for whom obesity (specifically among women: 60.3%) and hypertension (men: 48%, women: 44%) are prevalent. Associations between actigraphy-derived sleep measures and CVD risk (Chapter 3) found that among men (n=94), earlier midsleep time was associated with higher CVD risk scores (β =–0.17, 95%CI:–0.33, –0.02, p=0.030) while shorter sleep duration was associated with obesity (OR: 0.48, 95%CI: 0.25, 0.90, p=0.023). Among women (n=100), earlier wake-up times (β: –0.24, 95%CI: –0.41, –0.07, p=0.007) and midsleep times (β: –0.18, 95%CI: –0.39, 0.00, p=0.046) were associated with higher CVD risk scores. Women with earlier bedtimes (OR: 0.53, 95%CI: 0.33, 0.85, p=0.009) and midsleep times (OR: 0.47, 95%CI: 0.26, 0.83, p=0.010) were more likely to have

elevated BP, and those with earlier wake-up times (OR: 0.54, 95%CI: 0.35, 0.81, p=0.003) and midsleep times (OR: 0.46, 95%CI: 0.27, 0.77, p=0.003) were also more likely to be obese. Interaction effects revealed that among women, CVD risk scores were higher in those who had shorter sleep combined with later bedtimes or in those who had longer sleep combined with earlier bedtimes (β:–2.38, 95%CI: –0.35, –0.12, p<0.001). A weaker interaction effect was found for WASO such that CVD risk score was higher in women with longer sleep and more WASO or shorter sleep with less WASO (β: 0.004, 95%CI: 0.00, 0.00, p=0.014). The systematic review (Chapter 4) showed that BP non-dipping in apparently healthy individuals was associated with short sleep duration, more sleep fragmentation, less sleep depth and increased variability in sleep timing. Measuring 24h ambulatory BP (Chapter 5) found a high proportion of SBP non-dipping (men: 50%, women: 61%), with 48% of men and 72% of women also presenting with nocturnal hypertension. Among the women (n=36), shorter total sleep times (rho: 0.42, p=0.020) and worse sleep efficiencies (rho: 0.51, p=0.003) were correlated with smaller SBP dipping percentages. Similarly, shorter sleep durations (rho: 0.39, p=0.029), shorter total sleep times (rho: 0.44, p=0.014) and worse sleep efficiencies (rho: 0.37, p=0.037) were correlated with smaller DBP dipping percentages. Women with worse sleep efficiencies (rho: –0.39, p=0.016) has higher nocturnal SBP. Among the men (n=23), worse sleep efficiencies (SBP rho: –0.47, p=0.024; DBP rho: –0.50, p=0.015), greater WASO (SBP rho: 0.59, p=0.003; DBP rho: 0.50, p=0.014) and greater sleep fragmentation indices (SBP rho: 0.59, p=0.003; DBP rho: 0.59, p=0.003) were correlated with higher nocturnal SBP and DBP. Worse sleep duration regularity scores were correlated with lower SBP (rho: –0.48, p=0.025) and DBP (rho: –0.52, p=0.013) dipping percentages. Men with nocturnal hypertension had higher WASO (116.8 (88.8, 163.3)min vs. 88.1 (65.1, 98.3)min, p=0.031) and sleep fragmentation indices (36.4(33.4, 40.8)% vs. 29.6(25.8, 34.7)%, p=0.019) compared to those without nocturnal hypertension. Insights from the qualitative interviews (Chapter 6) revealed that external factors such as high-density living, noise, crime, violence and excessive alcohol use within the community primarily contributed to disturbing the sleep of participants.

Conclusions: This thesis provides new insights, from a Global South lens, to relationships between sleep and cardiovascular health as they relate to adults of African descent living in a low SES environment. Two main features of sleep emerge as important risk factors for CVD in these study participants: mistimed sleep and disturbed sleep, despite adequate sleep opportunities. By considering the lived experiences of individuals in this low SES community, we gained an understanding of the major role that the adverse conditions of the neighbourhood has on impairing sleep health in this population. We speculate that this earlier timed sleep observed predominantly in

women, but to some extent in men, might be a direct consequence of environment-related fear, prompting residents to seek refuge in bed at a time which may be too early, potentially contributing to circadian misalignment, which in turn may increase CVD risk. We further hypothesise that when faced with these adverse neighbourhood conditions, some residents may be in a state of hypervigilance at night, resulting in insufficient sympathetic nervous system (SNS) withdrawal, which in turn leads to disturbed sleep. Disturbed sleep may contribute to BP non-dipping or nocturnal hypertension, which may subsequently increase CVD risk, potentially through insufficient cardiovascular system recovery at night. Interestingly, we note that some participants appear to demonstrate resilience through attaining healthy sleep despite living in a challenging neighbourhood environment. Perhaps these are the individuals in whom appropriate SNS withdrawal takes place at night, improving their sleep health and reducing their CVD risk. Considering all the evidence generated though these studies, this thesis proposes the term Sleep Health Insecurity - a lack of regular access to healthy sleep (that which is of sufficient duration, regular, appropriately timed, consolidated, satisfying and refreshing), which is essential for optimal mental and physical health, emotional well-being and cognition. Although we propose that residents of Khayelitsha are experiencing Sleep Health Insecurity, which may increase their CVD risk, these residents likely represent not only a large sector of the South African population but also other similar low SES populations around the world, making this concept a fundamental global health issue.

Chapter 1

General Introduction

1.1 Background

Cardiovascular diseases (CVDs) are among the leading causes of death worldwide, accounting for around 18 million deaths annually[1]. Of these deaths, at least three quarters of them take place in low- and middle- income countries[1]. While many CVDs can be prevented by addressing lifestyle or behavioural risk factors (such as tobacco use, diet, and physical activity)[2], addressing one's sleep, a fundamental aspect of life, has only recently started to gain recognition and attention[3].

Social determinants of health (SDOH) can be defined as economic and social factors that influence health outcomes, including risk for CVD[4,5]. In fact that The American College of Cardiology/American Heart Association Joint Committee on Clinical Data Standards has defined various SDOH, which can be characterised at the individual level, the interpersonal level, and the community level[6]. For the scope of this thesis, we will be mainly focusing on the individual-level SDOH (specifically socioeconomic status (SES) which includes race, ethnicity, sex, educational attainment, income and employment). SES is a complex concept that can be defined as the societal position of an individual or group, which is determined by a combination of social and economic factors such as income, education, occupation, living conditions, overall financial security, resources, and opportunities afforded to individuals within the society[7,8]. Low SES environments are well known to adversely impact health outcomes including increasing the risk for developing CVDs[9]. Furthermore, people living in lower SES communities often have more disturbed and shorter sleep than those from higher SES levels[9].

Sleep is essential for overall physical health and well-being and, importantly for the scope of this thesis, plays a crucial role in maintaining cardiovascular health[10]. Sleep which is too short, too long or of poor quality has been linked to increased CVD mortality[11] as well as increased risk for CVD risk factors such as obesity, hypertension, insulin resistance and type 2 diabetes[12–14]. Biological sex plays a key role in CVD, with distinct differences observed between sexes in CVD pathophysiology, risk factors, clinical manifestation, management and treatment response[15]. These differences tend to converge in underlying differences in hormones (e.g. oestrogen), genetics (e.g. sex-determining genes) and physiology (e.g. cardiac tissue physiology) between sexes[15,16]. Additionally, sex also impacts sleep health. For example, women are more likely than men to experience sleep disruption, poor sleep quality and insomnia, throughout their lifespan[16]. Sex-specific differences in sleep health are largely attributed to differences in sex steroids (e.g. oestrogen and progesterone)[17], hormonal changes (e.g. menopause and ageing)[17] and as a side effect of mental health conditions (e.g. anxiety

and depression) that tend to be more prevalent among women[16]. For these reasons, sex is an essential consideration when investigating both sleep and cardiovascular health.

Finally, there is also evidence to suggest that individuals of African descent are at a higher risk of developing CVD[18,19], compared to their Caucasian counterparts, particularly since they present with a greater burden of CVD risk factors[19]. In addition to this, individuals of African descent present with poorer sleep, including shorter sleep duration, worse sleep efficiency, longer sleep onset latency, lower satisfaction with their sleep, less slow wave sleep and more wake after sleep onset time, compared to Caucasian Americans[20,21]. Thus, multiple factors may conspire to place individuals of African descent living in low SES environments in a vulnerable position when it comes to future CVD risk.

This introductory chapter will address the key concepts of i) CVD risk, as a global public health issue and as a specific concern for individuals of African descent, ii) sleep health, as a novel, modifiable risk factor for CVD and iii) the predicament of men and women of African descent living in low SES communities.

1.2 Cardiovascular disease

CVDs are a group of disorders of the heart and blood vessels that include coronary artery disease (CAD), heart failure, myocardial infarction and atrial fibrillation, to name a few. It is estimated that globally, 1 in 13 (620 million) people are living with a heart or circulatory disease[22]. Death rates from CVD vary worldwide but tend to be higher in Africa, Asia, Eastern Europe and South America compared to North America and Western Europe[23]. These disparities between countries may arise from differences in overall risk factors between populations such as smoking, obesity and alcohol consumption as well as poorer access to healthcare or a growing and aging population[23]. In Africa, CVDs are the largest contributor to the total non-communicable disease (NCD) burden, accounting for 38% of NCD deaths annually[24,25]. Within the last three decades, Africa has registered close to a 50% increase in the CVD burden[24]. Alarmingly, a pooled analysis of data from Sub-Saharan Africa revealed that of those with hypertension, only 27% of individuals knew their hypertensive status, 18% of individuals with hypertension were receiving treatment but only 7% had controlled blood pressure[26]. In conjunction with this, South Africa has one of the highest levels of overweight and obesity in the world; around two in three women (66%) and one in three men (33%) are overweight

or obese[27]. This makes individuals of African descent living in South Africa an extremely vulnerable population for future CVD.

1.2.1 CVD risk factors: modifiable and non-modifiable

CVD risk factors can be split into two categories: modifiable and non-modifiable. Non-modifiable CVD risk factors are those that cannot be changed and examples include age, sex, ethnicity, and family history. CVD is strongly age-dependent where CVD risk increases substantially with advancing age[28]. Men generally have higher CVD risk at younger ages compared to women, although the risk for women increases and often surpasses that of men after menopause[29]. Ethnicity has also shown strong relationships with CVD risk, with disproportionately higher CVD rates seen in racial and ethnic minority populations[30] and individuals of African descent[31]. Importantly for the scope of this thesis, individuals of African descent experience a higher burden of CVD risk factors, such as obesity, diabetes and hypertension, and are more than twice as likely to die of CVD, compared to Caucasian individuals[32].

Modifiable CVD risk factors are those that can be at least partially controlled through behaviour change, to reduce the overall risk of CVD. A large proportion (over 70%) of CVD cases and deaths can be attributed to modifiable risk factors[33]. The main modifiable risk factors for CVD are high cholesterol, hypertension, smoking, diabetes, obesity, physical inactivity and poor nutrition[2]. These modifiable risk factors also tend to cluster, for example, physical inactivity contributes to obesity, high blood glucose and hypertension[28]. Recently, healthy sleep has been recognised as a novel and modifiable CVD risk factor since poor sleep health has been associated with increased risk of all main modifiable CVD risk factors[10,12,14,34,35].

The individual CVD risk factors used in this study include body mass index (BMI), waist circumference, resting blood pressure (BP) and fasting glucose concentration. The defining cut-points for these clinical risk factors are presented in Table 1.1

Table 1.1 Defining criteria for individual clinical risk factors for cardiovascular disease.

Clinical risk factor	
Body mass index	Overweight: BMI >25 kg/m^2, Obese: BMI ≥30 kg/m^2
High waist circumference	≥102 cm (men), ≥88 cm (women)
Elevated blood pressure	≥130/85 mmHg, diagnosed hypertension or being treated with anti-hypertensive medication

Elevated blood glucose	≥5.6 mmol/L, diagnosed diabetes or being treated with diabetes medication

BMI: body mass index

1.2.2 BMI-modified Framingham 10-year CVD risk score

The criteria for identifying those at increased risk for CVD within this thesis are based on the BMI-modified Framingham 10-year CVD risk score developed by D'Agostino *et al.* (2008) as well as individual risk factors proposed by The Adult Treatment Panel III[36] (Table 1.1). The BMI-modified CVD risk score integrates seven risk factors (age, sex, measured systolic blood pressure (SBP), treatment of hypertension (yes or no), diagnosed diabetes (yes or no), measured BMI and smoking status (yes or no)) to create a multivariable, weighted, continuous risk prediction score, designed to estimate the 10-year absolute risk of developing CVDs[37]. This modified version of the Framingham 10-year CVD risk score substitutes laboratory values of measured total cholesterol and high-density lipoprotein cholesterol (HDL-C) with measured BMI. Previous studies have shown that there is strong agreement between the BMI-modified and laboratory-based Framingham CVD risk scores in African populations[38,39], allowing the non-laboratory risk score to be used in resource-limited settings[40,41].

1.2.3 Sex-specific differences in CVD

It must be noted that sex and gender carry distinct meanings: sex refers to *"the different biological and physiological characteristics of males and females, such as reproductive organs, chromosomes, hormones, etc."* while gender refers to "*the socially constructed characteristics of women and men – such as norms, roles and relationships of and between groups of women and men"*[42]. Throughout this thesis, the terms "sex" and "sex-specific" are used given their biological relevance and clinical context to CVD. While technically distinct, sex and gender are arguably linked and we acknowledge that there might be overlap between sex and gender in the population studied in this thesis, given the societal norms between men and women in the African culture. CVDs show significant sex-specific differences in prevalence, underlying mechanisms and risk factor profiles:

1.2.3.1 Differences in prevalence of CVD: Men generally experience CAD, hypertension and myocardial infarction earlier in life, while women have a higher prevalence of heart failure, hypertension and stroke later in life, particularly post-menopause[43]. Alarmingly, however, is that young adults (particularly women) are increasingly developing CVD at a younger age[44]. Myocardial infarction and hypertension incidence in women increases

significantly later in life, matching or even exceeding[45] men's absolute numbers living with and dying of CVD and stroke due to their longer life expectancy[43].

1.2.3.2 Differences in underlying mechanisms of CVD: Sex differences in the pathophysiology of CVDs depend on, amongst other factors, sex-specific hormones[43]. Hormonal differences, such as the protective role of oestrogen in women, influences vascular function and reduces the risk of atherogenesis, thereby reducing CAD development[43]. Additionally, sex differences in the sympathetic nervous system, renin-angiotensin-aldosterone system and endothelin system may contribute to sex differences in BP regulation[43].

1.2.3.3 Differences in risk factor profiles: Traditional risk factors such as smoking, alcohol consumption and high cholesterol are more common in men than women[43]. In contrast, more women have conditions such as autoimmune diseases and metabolic syndrome, including obesity and diabetes, which increase their CVD risk[43]. Physical stress is a common myocardial infarction trigger in men, while emotional stress, including depression, is more frequently reported in women[43].

1.2.4 Socioeconomic status disparities in CVD

Research has consistently shown a strong relationship between lower SES countries or communities and higher rates of CVD incidence, morbidity and mortality[9]. Specifically, four measures of SES have been repeatedly associated with CVD risk: income level, educational achievement, employment status and neighbourhood SES characteristics[9]. Another significant factor at play which contributes to this disparity is the limited access to healthcare or resources for disease prevention and management in low-income countries[9]. This increased burden of CVD in individuals living in low SES environments appears to be attributable to a combination of biological (e.g. hypertension), behavioural (e.g. greater alcohol consumption) and psychosocial (e.g. anxiety and depression or social cohesion) risk factors that are more prevalence in disadvantaged individuals[9,46]. There is now evidence to show that low SES environments might act as a separate CVD risk factor, conferring risk that is equivalent to that of the traditional risk factors[9].

1.3 Blood pressure

BP is a pivotal physiological parameter related to CVD and is described as the force exerted by blood against the walls of the arteries as the heart pumps blood throughout the body. BP follows a natural diurnal rhythm: increasing before awakening (morning surge in BP), highest during waking hours (specifically mid-morning), falling progressively throughout the day and lowest during sleep at night[47]. BP is characterized by two components: SBP and diastolic blood pressure (DBP). SBP

represents the force when the heart contracts, while DBP reflects the force when the heart is at rest between beats. In recent years, some experts have focused mainly on SBP as a major risk factor for CVD, however, many studies have highlighted the importance of both SBP and DBP as important markers and indicators of cardiovascular health[48,49]. As such, this thesis focuses on both SBP and DBP. Table 1.2 represent the current 2023 European Society of Hypertension (ESH) guidelines to classify office BP and hypertension[50]. Office BP is that which is measured by a healthcare professional in a clinical setting, such as a doctor's office or clinic[51]. Worldwide, hypertension remains the number one risk factor for CVD, responsible for almost 10 million deaths annually[52]. BP is a useful indicator of cardiovascular health since it is directly influenced by heart function and vascular condition. Elevated BP often signals increased resistance in the arteries due to narrowing or stiffness, which are strong markers of CVD. It also indicates the workload on the heart; a higher workload suggests the heart must pump harder to maintain blood flow, pointing to potential cardiovascular issues.

Table 1.2 Classification of office BP and definitions of hypertension[50].

	Systolic BP (mmHg)		**Diastolic BP** (mmHg)
Optimal	<120	and	<80
Normal	120-129	and	80-84
Elevated (or high-normal)	130-139	and/or	85-89
Grade 1 hypertension	140-159	and/or	90-99
Grade 2 hypertension	160-179	and/or	100-109
Grade 3 hypertension	≥180	and/or	≥110

BP: blood pressure

1.3.1 Ambulatory blood pressure monitoring

Ambulatory blood pressure monitoring (ABPM) is a method used to measure BP throughout the day and night as a person engages in their regular activities. Unlike traditional office BP measurements, ABPM involves wearing a portable device that automatically inflates and records BP at regular intervals, usually every 15 to 30 minutes during waking hours and every 30 minutes during sleep[53]. Current guidelines[54,55] unanimously recommend the use of 24h ABPM as the state-of-the-art technique for BP measurement. Since its development and application, many studies have shown its advantages over the traditional office measurement, including a higher reproducibility, lack of placebo and white coat effect, and most importantly, its superiority in predicting CVD[56–58]. In addition to providing information about BP during periods of sleep, a further advantage of ABPM is

that it provides an insight into the features of 24h BP variability. Table 1.3 represents conventional thresholds from the European Society of Hypertension (ESH) which are used in ABPM studies to define high BP over 24h hours.

Table 1.3 Definitions of ambulatory blood pressure measurement-derived hypertension[50].

	Systolic BP (mmHg)		**Diastolic BP** (mmHg)
24h mean	≥130	and/or	≥80
Daytime (awake)	≥135	and/or	≥85
Nighttime (asleep)	≥120	and/or	≥70

BP: blood pressure

1.3.2 Blood pressure dipping

BP dipping refers to a normal physiological phenomenon where there is a decrease or "dip" in BP during nighttime (i.e. sleep phase) compared to daytime (i.e. wake phase), commonly known as nocturnal BP dipping. In healthy individuals, nighttime BP should decrease or dip by about 10-20% compared to daytime levels. This has been represented graphically in Figure 1.1 below. This dipping profile is considered a crucial aspect of cardiovascular health and can act as an independent CVD risk factor. In some individuals, however, this nocturnal dipping may be blunted or absent, a condition known as BP non-dipping. BP non-dipping during sleep has been associated with an increased risk of cardiovascular events as well as target end organ damage[59]. Detailed descriptions of the four BP dipping profiles can be found in Section 1.3.3 below. While the underlying physiological mechanisms of BP non-dipping are not fully understood, several mechanisms for the non-dipping pattern have been proposed. These include high salt intake, high nighttime urinary sodium excretion, dysregulation of the autonomic nervous system (including decreased nighttime parasympathetic input), and poor sleep health (including sleep deprivation or presence of sleep disorders such as obstructive sleep apnoea)[60,61]. Comorbidities such diabetes, obesity, chronic kidney disease and sleep disorders have also been shown to affect nocturnal BP[62,63]. Relevant to this thesis, BP non-dipping and nocturnal hypertension (explained below) have never been explored in adults of African descent living in a low SES environment, such as is typical of many residents in South Africa. Finally, while the morning surge in blood pressure is recognized as another significant marker of cardiovascular health[64], it falls beyond the scope of this thesis.

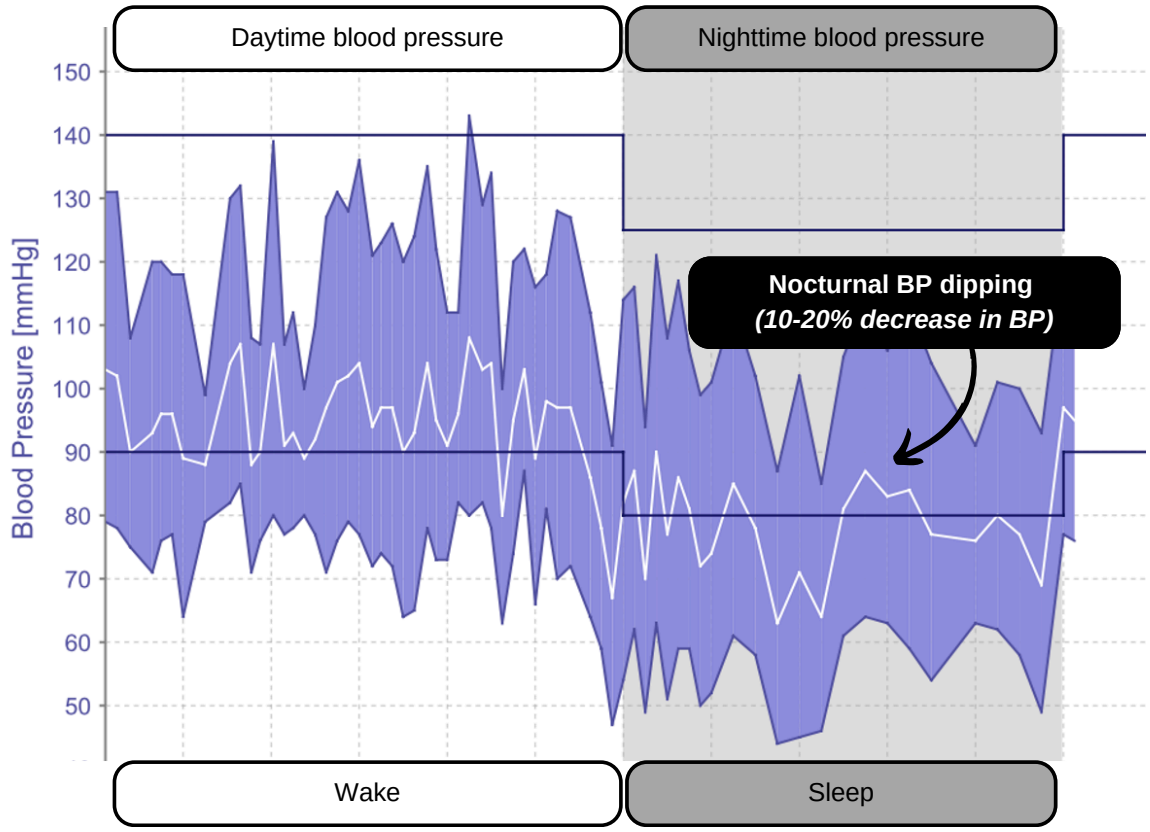
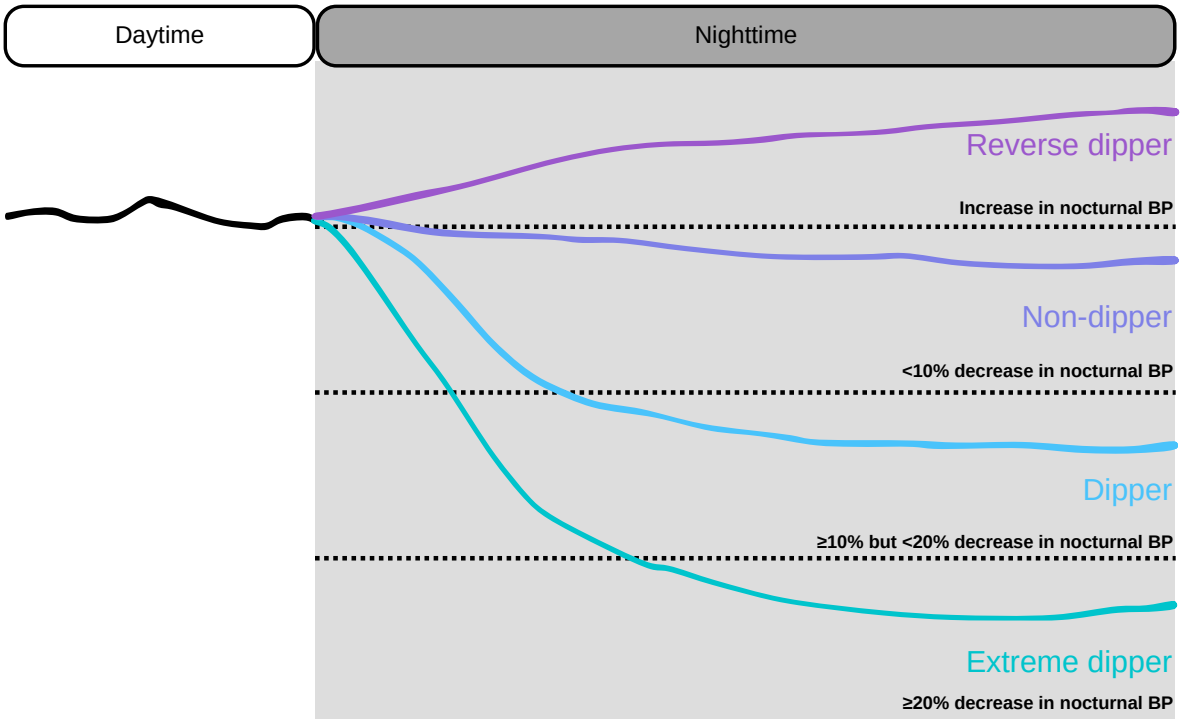


Figure 1.1 Graphical representation of nocturnal blood pressure dipping measured using 24h ambulatory blood pressure monitoring. *Figure adapted from IEM Mobil-O-Graph Hypertension Management Software (HMS).*Top horizontal line represents upper SBP limits for day and night, bottom horizontal line represents upper DBPs limit for day and night. Top trace represents SBP measurements over 24h, bottom trace represents DBP measurements over 24h, middle white line represents mean 24h BP.

Based on their BP dipping profiles, individuals can be categorized into one of four BP dipping groups: i) dippers, ii) non-dippers, iii) reverse dippers and iv) extreme dippers, which are summarized and presented in Figure 1.2 and Table 1.4 below. Dippers experience a normal nighttime reduction in BP, typically 10-20% compared to daytime levels, a phenomenon understood to contribute to better cardiovascular health[60]. Non-dippers, on the other hand, exhibit a blunted BP dipping pattern at night of less than 10%, indicative of a higher risk for future CVD events[60]. Reverse dippers

demonstrate an increase in BP during sleep which is strongly associated with worse cardiovascular health[65]. Extreme dippers have a >20% reduction in BP during sleep. There is a lack of conclusive evidence indicating that extreme dipping has an adverse impact on cardiovascular prognosis at the community level and in the general hypertensive population[66]. A recent study in 10 868 participants



by Palatini *et al.* (2020) showed that extreme dippers who were under 70 years of age showed no increase in cardiovascular event risk compared with dippers[67]. However, the authors showed hazard ratios among extreme dippers that were similar to those of reverse dippers for cardiovascular events in participants older than 70 years, suggesting that that relationship between extreme nocturnal dipping and CVD is age-dependent[67].

Figure 1.2 Simplified graphical representation of the four nocturnal blood pressure dipping profiles. *Figure adapted from Tang et al. (2024)*[61]. BP: blood pressure

Table 1.4 Blood pressure dipping profiles and their respective associations with CVD risk.

	Relative % decrease in BP	Association with CVD risk
Dippers	10 – 20	↓ CVD risk
Non-dippers	0 – 10	↑ CVD risk
Reverse dippers	<0	↑↑ CVD risk
Extreme dippers	≥20	Debated; likely ↓ CVD risk (or no change) when younger than 70 years old

BP: blood pressure, CVD: cardiovascular disease

1.3.3 Socioeconomic status disparities in blood pressure dipping

Similar to SES disparities in CVD, there are strong SES disparities in BP dipping[68] where lower SES individuals present with higher rates of BP non-dipping, even after accounting for known risk factors such as age, sex, BMI, health behaviours and hypertension status[69]. These SES-related health disparities are, however, often confounded by ethnic differences[68]. For example, some research has shown that SES mediates the relationship between ethnic differences and BP dipping, such that the effect of ethnicity on BP dipping decreased by 21% when education was added to the equation that also controlled for age, sex, BMI and 24h SBP[70]. Unfortunately, in many countries around the world, individuals of African descent often live in lower SES environments, which presumably compounds their risk for BP non-dipping and future CVD events.

1.3.4 Nocturnal hypertension

With the current use of ABPM, nocturnal hypertension has received increased attention. According to European Society of Hypertension (ESH) guidelines, nocturnal hypertension is defined as nighttime SBP ≥120 mmHg and/or DBP ≥70 mmHg[71]. While nocturnal hypertension represents a physiological feature distinct from BP non-dipping, these two phenomena are frequently interconnected[59], with BP non-dippers and reverse dippers often exhibiting nocturnal hypertension. Both nocturnal hypertension and BP non-dipping are associated with increased CVD risk[61], however, there is debate as to which is a better clinical and prognostic indicator of CVD outcomes[61]. A recent review by Tang *et al.* (2024) suggests that nocturnal hypertension might be favoured over BP non-dipping, when it comes to associations with adverse cardiovascular outcomes, largely due to the dependence of BP non-dipping on daytime BP measurements which are subject to significant fluctuations[61].

1.4 Sleep

Sleep is a biological necessity, vital for optimal well-being, physical and mental health[72]. While there are many definitions of sleep, it is widely acknowledged and accepted that it is an extremely complex process. A simplified definition of sleep is that it is a normal, reversible state of reduced consciousness and responsiveness to external stimuli that is characterized by behavioural quiescence and intricate changes in physiology such as brain wave activity, breathing, heart rate and body temperature[73]. Healthy sleep is understood to be that which is of sufficient duration, with minimal disruptions, appropriately timed with respect to the light dark cycle and a person's circadian

rhythms, and in which sufficient time is spent in each of the stages, to support optimal physical, cognitive and mental health.

1.4.1 Sleep health

In recent years, it has been recognised that sleep is a complex but multidimensional phenomenon in which individual dimensions are distinct but often interrelated[74]. Studying one single dimension of sleep likely provides an inaccurate or incomplete picture of the complex phenomena at play. The two most common approaches to investigating sleep are i) to study all sleep dimensions independently or ii) to combine the individual dimensions into a composite score, which has its own advantages and disadvantages. The concept of sleep health, proposed by Buysse *et al.* (2014), provides a composite view of sleep and includes dimensions of sleep such as regularity, satisfaction, alertness, timing, efficiency and duration (referred to as the RU-SATED model of sleep health)[74]. Since it's conception, the RU-SATED model has been widely adopted by many researchers in various formats. While some researchers classify individuals as having good or poor sleep health (scored as 0 or 1) in each of the six dimensions[75,76], others prefer a continuous or composite scoring approach[77,78]. One main disadvantage of the composite approach to sleep health is that combining or summing these dimensions into a single measure means potentially losing the resolution and nuance of important independent dimensions (See Chapter 7, Section 7.4 for further detail). Additionally, using a binary approach to create "good" or "poor" categories for each sleep dimension reduces the power of continuous variables and risks error through inaccurate binary categorisations. For this reason, in this thesis we have decided to focus on the individual dimensions of sleep.

1.4.2 Sleep duration

Sleep duration is by far the most well-researched dimension of sleep and refers to the total amount (i.e. hours) of sleep obtained per night. Adequate sleep duration is a fundamental aspect of sleep health and is crucial for maintaining optimal physical and mental health[79]. The National Sleep Foundation in the United States of America (USA) recommends that adults (18-64y) need 7-9h of sleep per night for optimal human health[80], although individual needs can vary based on age, lifestyle and genetic factors. Sleeping less than 6 hours or more than 10 hours per night has consistently been shown to increase mortality risk[81,82].

1.4.3 Sleep efficiency

Sleep efficiency is a measure of sleep quality and is calculated as the percentage time spent asleep relative to the total time spent in bed. Healthy sleep contains as few disturbances or disruptions as

possible. While some disturbances are normal, too many arousals or awakenings will fragment sleep, reducing overall total sleep time, interfering with sleep staging and impairing the restorative value of sleep. A high sleep efficiency (≥85%) generally indicates continuous, good sleep quality while a low sleep efficiency (<85%) can be indicative of fragmented or disturbed sleep or sleep disorders, such as insomnia[83]. The Sleep Fragmentation Index (SFI), used in Chapters 3 and 5 of this thesis, is an index of restlessness during the sleep period expressed as a percentage. Further detailed methodology of this sleep dimension can be found in Chapters 3 and 5.

1.4.4 Sleep timing

Human beings are diurnal, designed to be active during daylight hours and resting between sunset and sunrise. Sleep timing refers to the time at which an individual goes to sleep and wakes up and essentially speaks to the time-of-day at which the main sleep period takes place. It is influenced by both biological and social factors, including circadian rhythms, work schedules, and social obligations. The precise timing for each person is unique to their own circadian biology, however, it is understood that optimal sleep timing is that which aligns with one's natural circadian rhythm[84]. Misalignment of sleep timing, such as in cases of shift work, can lead to sleep disturbances and poor physical and mental health[84].

1.4.4.1 Circadian rhythms and chronotype

Circadian rhythms are endogenous oscillations with an approximate 24h period, that influence many physiological and behavioural processes, such as sleep-wake patterns, hormone release and metabolism[85]. The term circadian stems from the Latin words "*circa"*, meaning 'about', and "*diem"* meaning 'day'. The suprachiasmatic nucleus (SCN), located in the hypothalamus of the brain, is the pacemaker of the circadian timing system. In its free-running state, the circadian system oscillates with an innate period (termed *tau*) of slightly longer than 24h. The circadian system therefore needs to be synchronized or "entrained" to the light-dark cycle and 24h clock time of the environment via external cues, referred to as *zeitgebers* ("time givers"). Zeitgebers include mealtimes and exercise, however, light has the most notable effect[86]. Photoreceptive ganglion cells in the retina transmit light information to the SCN. This information then synchronises internal peripheral clocks with external cues, adjusting the body's internal clock to match the 24-hour day to ensure that biological activities are appropriately aligned with the external light-dark cycle[85].

One of the most well-known circadian rhythms is the sleep-wake cycle. As humans are diurnal, our consolidated period of sleep occurs during the night, the timing of which is regulated by the

circadian clock. As night falls, the SCN responds by signalling to the pineal gland to release melatonin, a hormone that promotes sleepiness and communicates the change from active to rest phase within the body. Conversely, as daylight approaches, melatonin production decreases, facilitating wakefulness[85]. This interplay between sleep-wake cycles and circadian rhythms ensures that our rest periods align with the natural day-night cycle, optimizing the quality and timing of sleep to support overall health and well-being. When circadian rhythms become desynchronised from the light-dark cycle (a process referred to as "circadian misalignment"), natural physiological processes that follow circadian rhythms, such as hormone secretion, metabolism and immune function are disrupted[87].

Chronotype can be described as a behavioural manifestation of an one's innate circadian rhythm. It typically refers to an individual's preferred sleep-wake timing and natural inclination towards being more "morning-orientated" or "evening-orientated". About half of an individual's chronotype is estimated to be genetic[88], however, other factors such as environment and age also play a role[88]. "Morning-types" tend to feel the most awake, alert and productive in the early hours of the day, but tend to go to sleep and wake up early[89]. "Evening-types" experience peak alertness and productivity later in the day or evening and tend to go to sleep and wake up later[89]. It is crucial to account for inter-individual differences in chronotypes when assessing sleep timing, as these variations significantly impact individuals' optimal sleep schedules and overall sleep quality.

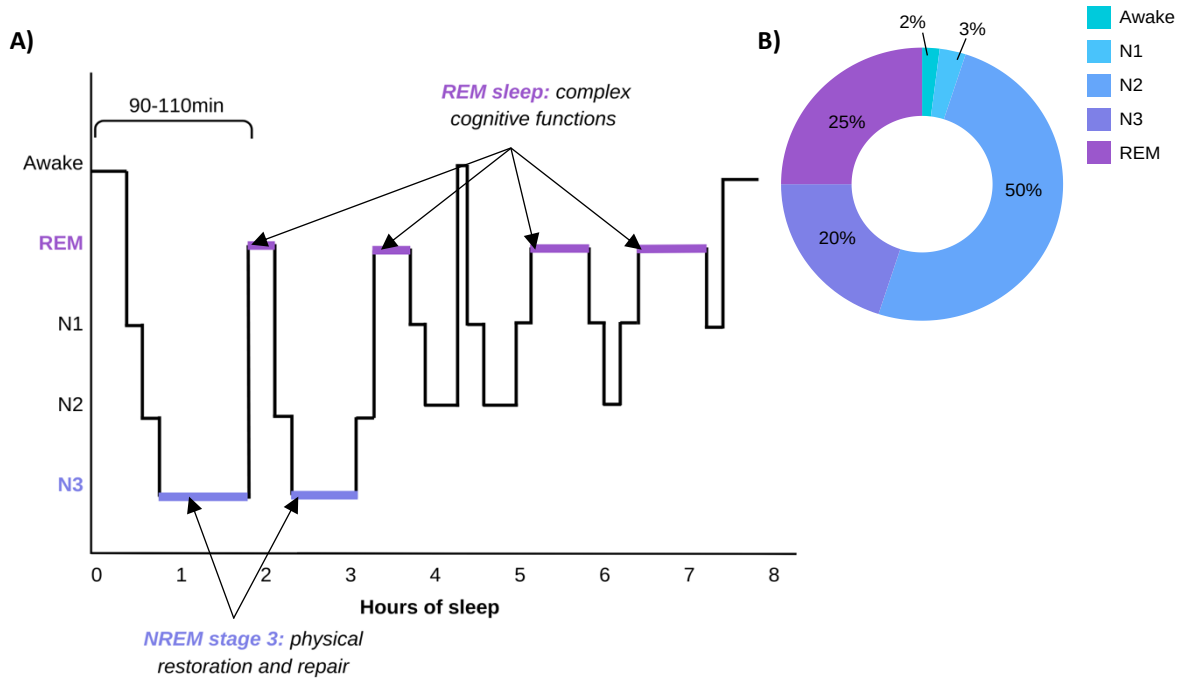
1.4.5 Sleep regularity

Sleep regularity refers to the day-to-day consistency of sleep-wake timing and duration, often measured by the variability in sleep-wake times over 24h. The Sleep Regularity Index (SRI) proposed by Phillips *et al.* (2017) is used in Chapter 3 and measures the similarity of an individual's sleep-wake timing from one day to the next. It calculates the percentage probability of an individual being in the same state (sleep vs. wake) at any two time points 24h apart[90]. Further detailed methodology of this sleep dimension can be found in Chapter 3.

1.4.6 Sleep architecture and staging

Sleep architecture refers to the structural organisation of sleep based on two main types of sleep: non-rapid eye movement sleep (NREM) and rapid eye movement sleep (REM), measured using a technique known as polysomnography (PSG). NREM sleep comprises three stages, each characterized by distinct brain activity, levels of consciousness and physiological changes in heart rate, breathing and muscle tone. These stages typically progress orderly from wakefulness to NREM

stage 1 (also called N1 or light sleep), NREM stage 2 (N2) and then NREM stage 3 (also called N3 or deep sleep)[91]. The NREM sleep stages are usually follow by a bout of REM sleep, typically occurring about 90 minutes after falling asleep. The cyclical alternating between NREM and REM sleep is referred to as a sleep cycle, which typically lasts ±90-110 minutes[91]. The first REM period is usually short and, as the night progresses, longer periods of time are spent in REM and less time is spent in NREM sleep[91] (Figure 1.3A). NREM stage 3 sleep is thought to be vital for physical restoration, promoting hormone release and facilitating tissue growth and repair[92]. During REM sleep the brain is highly active, accompanied by rapid eye movements and loss of muscle tone[92]. This stage is



associated with dreaming and supports complex cognitive functions such as emotion processing, information organization, memory consolidation, and long-term memory formation[92]. A graphical representation of sleep architecture expected in a healthy sleeper (represented as a hypnogram) and the proportion of time spent in each sleep stage is depicted in Figures 1.3A and 1.3B, respectively.

Figure 1.3 A) Hypnogram representing typical sleep architecture derived from polysomnography; B) Proportion of time spent in each sleep stage. NREM: non-rapid eye movement sleep, REM: rapid eye movement

1.4.7 Functions of sleep

One of the main ways that researchers have tried to understand sleep is through sleep deprivation models, to observe what happens when we don't sleep. From this, most researchers agree that

there is no single physiological function of sleep, rather, it is clear that sleep has many different biological roles[93]. These include physical, cognitive and psychological functions[94]. While it is beyond the scope of thesis to examine the specific functions of sleep in depth, the role that sleep plays in metabolic and cardiovascular health will be discussed as a means to contextualise why it is important to study sleep from a physical health perspective. During sleep, the body undergoes vital repair and restoration processes, including the regulation of hormones (such as leptin and ghrelin) that control appetite, metabolism and glucose control, thereby impacting weight and diabetes risk[94]. Sleep is also essential for cardiovascular health and helps to regulate and balance the autonomic nervous system[95]. During NREM sleep, parasympathetic tone dominates while sympathetic tone is reduced, allowing heart rate and blood pressure to decrease. This provides the cardiovascular system with a period of rest to promote recovery[11]. This balance of autonomic nervous system activity is crucial for maintaining cardiovascular health and preventing conditions such as hypertension[11].

1.4.8 Obstructive Sleep Apnoea and CVD risk

Obstructive sleep apnoea (OSA) is a sleep disorder characterized by repeated episodes of partial or complete upper airway obstruction during sleep[96]. These disruptions result in oxygen desaturation, frequent arousals from sleep, and fragmented sleep architecture[96]. While this complex sleep disorder falls outside of the scope of this thesis, it's important to note that OSA has been linked to various cardiovascular complications, including hypertension, stroke, metabolic syndrome, diabetes, and increased cardiovascular mortality[97]. Therefore, due to the relationship between OSA and CVD, we screened for sleep apnoea in this population using the Berlin Questionnaire[98], which is described in more detail in Table 1.5 below.

1.4.9 Sleep disorders vs disordered sleep

Sleep disorders and disordered sleep, while often used interchangeably, refer to distinct issues. Sleep disorders are clinically diagnosed conditions that disrupt normal sleep patterns, such as insomnia, OSA, restless legs syndrome, and narcolepsy. These disorders have specific diagnostic criteria and often require medical or therapeutic interventions for management. In contrast, disordered sleep refers to irregularities or disruptions in sleep patterns that may not meet the clinical criteria for a sleep disorder but still impact sleep quality and overall health. Examples of disordered sleep might include irregular sleep timing, frequent disturbances or difficulty staying asleep due to stress, caffeine or environmental factors. While disordered sleep can sometimes be resolved with lifestyle changes and improved sleep hygiene, sleep disorders typically necessitate a

more comprehensive approach involving healthcare professionals. Understanding the distinction between these terms is crucial for accurately addressing the sleep-related issue at hand.

1.4.10 Measuring sleep

There are a variety of methods that can be used to assess and measure sleep and a person's associated daytime function. These methods can be divided into objective measures (i.e. PSG and actigraphy) and subjective measures (i.e. self-reported questionnaires and sleep diaries). Each method has its own strengths and limitations that need to be considered when choosing which measure is appropriate for the specific research question and population.

1.4.10.1 Objective measures of sleep

PSG is the gold standard method for the measurement of sleep architecture and for the diagnosis of some sleep disorders, such as OSA. PSG is a comprehensive technique that simultaneously measures and records brain activity (electroencephalogram [EEG]), eye movements (electrooculogram [EOG]), muscle activity (electromyogram [EMG]), heart rate (electrocardiogram [ECG]) and breathing patterns through non-invasive electrode sensors attached to specific parts of the head, face and body[99]. Information from all of these channels is integrated to build a hypnogram (see Figure 1.3A) describing the architecture and associated sleep stages of a single night of sleep. While PSG is the gold standard method to measure sleep structure, it is costly, time-consuming, impractical in low-resourced settings, requires a trained sleep technician and does not provide information around habitual sleep characteristics[99]. It is for these reasons that actigraphy was chosen as the main method to objectively measure habitual home-based sleep in Chapters 3 and 5 of this thesis.

Actigraphy is a non-invasive method used to measure sleep-wake patterns by recording movement with a small device (typically worn on the wrist during the day and night) called an actigraph[100]. The primary function of the actigraph is to detect and record motion, however, it can also record light exposure. It uses an accelerometer to monitor movements during the day and night, which are in turn used to estimate whether the individual is asleep or awake within any given 30s epoch of time[100]. The sleep-wake activity scores are then translated to sleep-wake periods based on computerized scoring algorithms. Its major strength lies in its practicality and user-friendliness allowing for the continuous monitoring of sleep patterns in the home environment, over longer periods of time, without the need for specialized laboratory equipment or personnel[100]. The accuracy of actigraphy is improved when complemented with a sleep diary, enabling confirmation of

sleep and wake periods[100]. Additionally, actigraphy is more affordable and scalable, allowing for sleep monitoring of more individuals in a given timeframe compared to PSG. It is for this reason that actigraphy is often the preferred method of measuring sleep for large scale epidemiological studies[101].

Outcome variables of actigraphy and features of habitual sleep include: sleep onset, sleep offset, sleep duration (elapsed time between sleep onset and sleep offset), total sleep time (actual time spent asleep), arousals, sleep efficiency (%) and wake after sleep onset (WASO, min). A graphical representation of the main sleep period obtained using actigraphy is shown in Figure 1.4 below. Further detailed methodology of the additional outcome variables derived from actigraphy (e.g. SFI, SRI and sleep duration regularity) are described in Chapters 3 and 5.

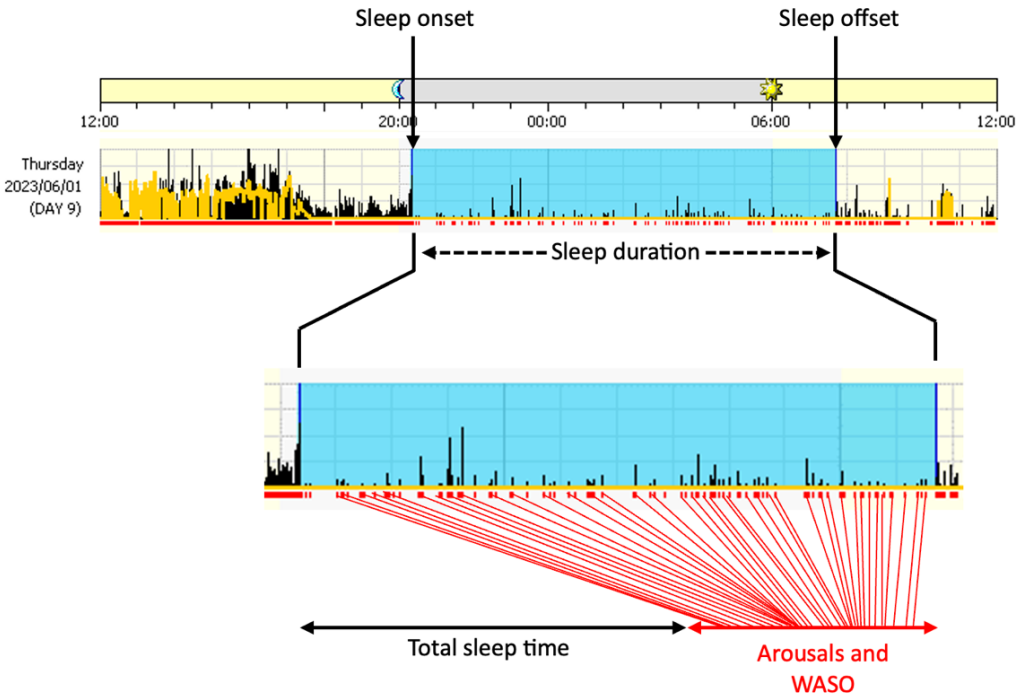


Figure 1.4 Graphical representation of one night of actigraphy recording. WASO: wake after sleep onset.

1.4.10.2 Subjective measures of sleep

Subjective measures of sleep relate to an individual's perception of their sleep health and associated daytime function. Subjective measures of sleep include perceived sleep quality, daytime sleepiness and alertness, overall daytime function and symptoms of a sleep disorder such as insomnia.

Perceived sleep quality is an all-inclusive term describing a person's overall sleep including ease of falling asleep and waking up, fragmentation, depth, timing, duration, satisfaction and restoration. Daytime sleepiness is a common symptom of poor sleep quality or insufficient sleep duration. It is characterized by a persistent feeling of drowsiness and an increased tendency to fall asleep during the day, even during activities that require attention. Daytime function refers to how a person's sleep impacts their ability to effectively perform daily activities, maintain cognitive and physical performance, and stay alert and focused throughout the day. Subjective symptoms of insomnia include difficulties falling asleep, staying asleep, or waking up too early. This results in feeling unrefreshed in the morning and leads to daytime impairments like irritability, mood disturbances, difficulty concentrating, and reduced daytime functioning.

Subjective measures of sleep are important since they can capture an individual's personal experience of sleep that may not be evident through objective data alone. Additionally, if sleep is of good quality and adequate duration, individuals should feel optimal levels of daytime functioning, mood and alertness. Poor sleep often manifests as impaired daytime functioning, fatigue, and reduced alertness, which can be effectively captured through subjective measures.

There are multiple tools are available for screening OSA, with the Berlin Questionnaire[102] and STOP-BANG Questionnaire[103] being the most commonly used. Since this thesis is part of a larger parent study (The Modelling the Epidemiologic Transition Study (METS)-Sleep) in which the Berlin Questionnaire was selected by the primary investigators, we have also used this tool in our study. Given that this study is an observational epidemiological investigation, a screening questionnaire was deemed appropriate. In epidemiological settings, such tools are widely accepted as they serve to identify individuals at risk rather than provide a clinical diagnosis. The Berlin Questionnaire offers a more comprehensive assessment of symptoms compared to STOP-BANG. However, it's main limitations include the omission of certain objective risk factors - such as neck circumference, age, and sex - which are known to enhance the reliability of OSA screening. Despite this, the Berlin Questionnaire has been validated in multiple populations and is widely adopted[104].

These self-reported measures are usually assessed using validated questionnaires and self-administered sleep diaries. Their major strength lies in their simplicity and ease of administration, allowing for quick and cost-effective data collection[105]. Their main limitations, however, are their susceptibility to biases, inaccuracies, and variations in interpretation or even appropriateness among

different populations[105]. The validated questionnaires that have been used throughout this thesis to describe the sleep health of the participants are summarized in Table 1.5.

Table 1.5 Summary of the subjective measures of sleep used in this thesis.

	Description	Score interpretation
Pittsburgh Sleep Quality Index (PSQI)[106]	Assesses perceived sleep quality during the previous month. Comprises 19 items across seven components: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction.	Sum of seven components yields a PSQI global score ranging from 0-21, with higher scores indicating poorer sleep quality. PSQI global scores of >5 are indicative of poor sleep quality.
Insomnia Severity Index (ISI)[107,108]	Assesses the perceived severity of insomnia symptoms over the past two weeks. Comprises seven items that evaluate the severity of sleep onset, sleep maintenance, early morning awakenings, sleep dissatisfaction, interference with daily functioning, noticeability of impairments attributed to sleep problems, and distress caused by the sleep difficulties.	Sum of seven components yields ISI scores ranging from 0-28, with higher scores indicating greater insomnia symptom severity. ISI scores can be categorised as clinically significant insomnia symptoms (moderate and severe) with ISI scores ≥15. Given that the population of interest in this thesis is not a clinical sample, and rather a community sample, the lower cut-point of ISI≥10 was also used. This aligns with suggestions that this lower cut-point might be more suitable for community samples[108].
Epworth Sleepiness Scale (ESS)[109]	Assesses daytime sleepiness in recent times. It consists of eight items that measure the likelihood of falling asleep unintentionally in different situations commonly encountered in daily life. Participants rate their likelihood of dozing off on a scale from 0 (would never doze) to 3 (high chance of dozing).	ESS scores range from 0-24, with higher scores indicating greater daytime sleepiness. Excessive daytime sleepiness (EDS) is defined as ESS scores >10.
Berlin Questionnaire (BQ)[98]	Screening tool used to identify individuals at risk for obstructive sleep apnoea (OSA). It comprises three categories: snoring behaviour and witnessed apnoea, daytime sleepiness, and hypertension/obesity. Each category consists of several questions related to symptoms and risk factors for OSA.	In category one, high risk is defined as the presence of symptoms in two or more questions related to snoring. In category two, high risk is defined as the presence of daytime sleepiness. In category three, high risk is defined as a history of hypertension or a BMI greater than 30 kg/m^2. Participants are classified as high-risk for OSA if they score high risk in at least two of the three categories.

1.4.11 Sex-specific differences in sleep

Sex also plays a significant role in sleep health. Research consistently shows that women are more likely than men to experience sleep disruptions, poor sleep quality, and insomnia across their lifespan[16]. These sex-specific differences are primarily linked to variations in sex steroids (such as oestrogen and progesterone)[17], hormonal changes associated with menopause and aging[17], and a higher prevalence of mental health conditions (such as anxiety and depression) among women which are comorbid with sleep difficulties (ref). On the other hand, at all ages, OSA is more common in men than women[110]. For these reasons, it is critical to consider sex when investigating sleep and its associations with health outcomes.

1.4.12 Socioeconomic status disparities in sleep

A systematic review by Sosso *et al.* (2021) examined relationships between SES and sleep characteristics and found that lower SES was associated with less total sleep time, longer sleep onset latency, greater sleep fragmentation and WASO[111]. Furthermore, more education and income were associated with better sleep efficiency and longer sleep duration[111]. While factors such as unemployment, less education and less income have all been associated with worse sleep health[112], poor environmental and neighbourhood factors associated with lower SES environments are also central to SES disparities in sleep. An individual's SES is often reflected in the neighbourhood in which they live, which is one of the multiple stressors affecting sleep[112]. Individuals of lower SES often live in neighbourhoods characterized by more noise, light and pollution and in inadequate housing, lacking adequate safety and ambient temperature control. In addition to this, individuals living in low SES neighbourhoods often report more fear or feelings of being unsafe due to more crime and violence[113]. Due to these environmental conditions, the majority of research investigating the impact of SES on sleep health in Global North populations has found that individuals with lower SES have poor sleep quality and shorter sleep durations[112]. However, in contrast to this, previous research has shown the low SES South Africans of African descent report long sleep durations[114–118], which requires further investigation. Additionally, the effect of the environment on sleep health, including both the external environment (i.e. neighbourhood context) and the sleep environment (i.e. type of housing or number of people) has never been assessed in a low-income South African population.

1.4.13 Sleep in the South African context

Khayelitsha, the neighbourhood in which the participants in this thesis reside, is the largest urban township in Cape Town (38.7km^2) with a population of 461,116 (11,915 people/km^2)[119]. Around 55% of residents live in informal dwellings which have no security and are usually lacking basic services. Khayelitsha is characterised by high rates of poverty, crime and violence[120]. It has the fifth highest number of contact crimes (i.e. murder or attempted murder, assault, common or aggravated robbery and sexual offences) nationwide and recorded the highest number of murders in the top 10 police precincts in Cape Town in 2021/2022[120]. Thus, inhabitants of Khayelitsha are particularly vulnerable, but also represent a significant proportion of the South African population, making them an important focus for research and intervention.

1.5 Sleep and CVD

For many years, the sleep dimension most strongly associated with CVD has been sleep duration, where both short and long sleep durations are strong predictors of worse cardiovascular outcomes and mortality[11,121,122]. Chronic insufficient sleep (<6h per night) has been clearly associated with CVD risk factors such as obesity, hypertension, insulin resistance, diabetes and CVD events[35,123]. Long sleep (>10h per night) on the other hand, while also associated with mortality[124], likely also points to an underlying physical (e.g. CVD presence)[124] or mental health (e.g. major depressive disorder)[124] condition. More recently, however, there is accumulating evidence associating other sleep health dimensions with increased CVD risk. For example, greater sleep disruption and fragmentation has been associated with increased risk for CVD and metabolic syndrome[125]. There has also been a significant paradigm shift in the literature, with a pronounced emphasis on investigating the effects of sleep regularity on health and mortality[126,127]. In fact, a recent study by Windred *et al.* (2024) indicated that sleep regularity may be a more important predictor of mortality than sleep duration[128]. The investigations of irregular sleep timing and CVD risk appear to centre around chronic circadian misalignment since irregular sleep-wake times can disrupt our circadian rhythms, as has been well-established in shift work models[129]. Chronic circadian misalignment is associated with a cascade of adverse physiological effects such as metabolic dysregulation and cardiovascular dysfunction[130]. A number of potential mechanisms explaining the association between poor sleep and increased CVD risk have been proposed, such as inflammation, autonomic nervous system imbalances, hormonal dysregulation, metabolic dysfunction or underlying sleep disorders[131]. A novel approach to improve our understanding of relationships between sleep and CVD risk, and elucidate

potential mechanisms underlying this relationship, is through investigating BP dipping during sleep. BP dipping is a well-known risk factor for CVD and a good predictor of future CVD events[65].

1.6 Summary and conclusions

Studies investigating the relationships between sleep and CVD have generally focused on individuals from the Global North[132,133], leaving cohorts from the Global South, and specifically adults of African descent, considerably unexplored. Furthermore, while research in North America has demonstrated that African Americans are more likely to report both extremes of sleep duration – both very short sleep and very long sleep[134] – short sleep duration (<6h[135] or <7h[136] per night) is far more commonly reported [20]. In contrast, a number of studies of South African individuals of African descent more commonly report longer sleep durations (8-10h per night)[114–118], with less evidence of short sleep duration as seen in the Global North. The nature of the relationship between long sleep duration and CVD risk is not well understood, not only in South Africa but globally. Studying long sleeping men and women of African descent living in a low SES African environment provides a unique opportunity to extend what is known about the sleep-CVD risk relationship to contexts relevant to the Global South.

1.7 Purpose and structure of the thesis

The overall purpose of this thesis was to investigate sex-specific relationships between CVD risk, nocturnal BP (i.e. nocturnal hypertension and BP dipping) and sleep health in adults of African descent living in a low SES community in South Africa. Figure 1.5 summarises chapter-specific aims related to the overall research purpose.

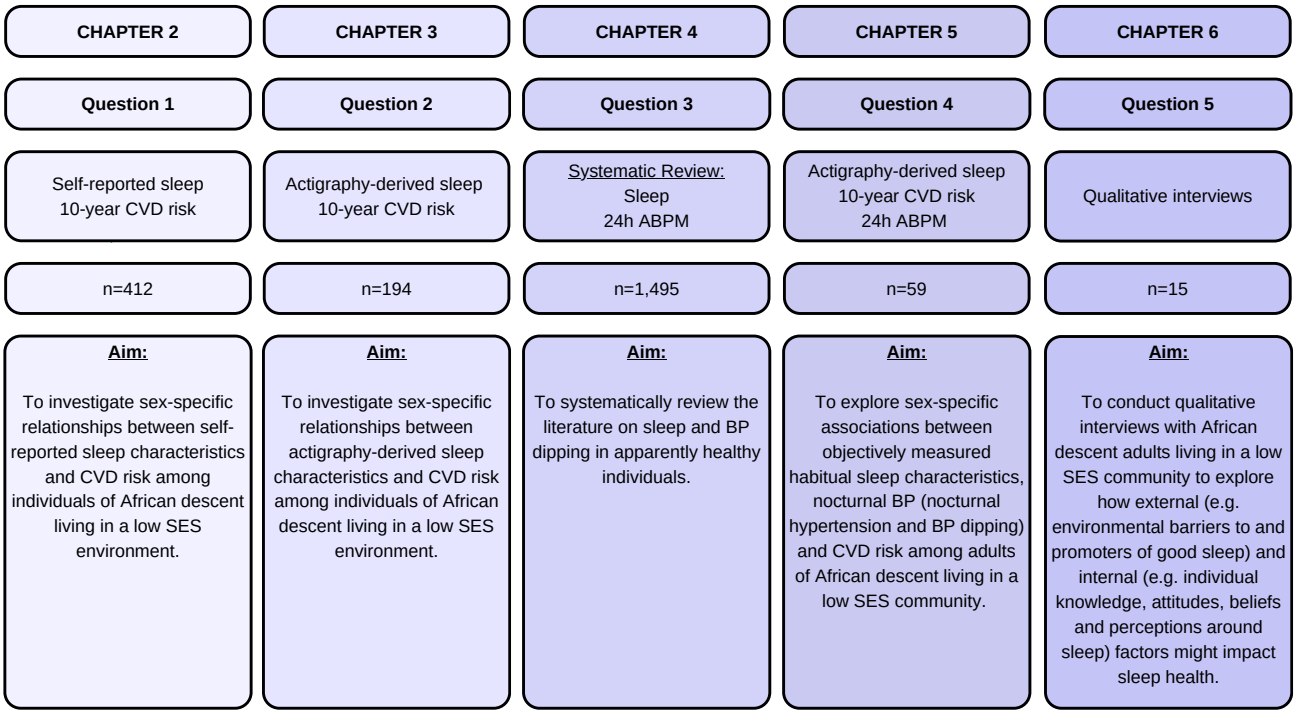


Figure 1.5 Overview of each experimental chapter of the thesis. ABPM: ambulatory blood pressure monitoring, BP: blood pressure, CVD: cardiovascular disease, SES: socioeconomic status

To address and support the overarching thesis purpose, this thesis asked five main questions:

1. **Are self-reported (subjective) habitual sleep characteristics related to CVD risk among individuals of African descent living in a low SES community and do these relationships differ between men and women?**

   Chapter 2 lays the groundwork for the thesis by describing the background of the population of interest and providing first insights into the relationships between sleep and CVD risk in 412 adults of African descent living in a low SES community, typical of where ±24% of the South African population lives[137]. Importantly, since the relationships were strongly sex-dependent, this provided a rationale to look at the men and women separately throughout the thesis. Given the limitations of self-report, a logical next step was to confirm the long sleep duration

reported by the study participants and whether the observed relationships held true with objectively measured sleep.

2. **Are actigraphy-derived (objective) habitual sleep characteristics related to CVD risk among men and women of African descent living in a low SES community?**
   Actigraphy-derived sleep characteristics were obtained from 194 of the 412 adults of African descent studied in Chapter 2. Acknowledging the complexity of the often interrelated dimensions of sleep, this chapter explored sex-specific associations between actigraphy-derived habitual sleep characteristics and CVD risk factors and used moderation analyses to explore interaction effects between sleep dimensions. To better understand this relationship mechanistically, we decided to focus next on a key marker of CVD health: BP dipping during sleep. Given that previous studies typically explored BP dipping during sleep in populations living with chronic disease and/or sleep disorders, we wished to first learn more about BP non-dipping and sleep parameters in apparently healthy individuals.

3. **Are any sleep characteristics associated with nocturnal BP dipping in apparently healthy individuals?**
   A systematic review (Chapter 4) was conducted to identify whether sleep characteristics might be associated with BP dipping during sleep in adults with no known diseases. Systematic literature searches were conducted in three electronic databases and only original peer-reviewed research studies reporting on relationships between sleep and BP dipping (derived from 24h ABPM) were included.

4. **What is the relationship between actigraphy-derived habitual sleep characteristics, nocturnal BP (i.e. BP dipping and nocturnal hypertension) and CVD risk variables among adults of African descent living in a low SES community?**
   Chapter 5 utilised objective (actigraphy) and subjective (questionnaires) measures of sleep, in combination with 24h ABPM in 59 participants studied in Chapter 3 to address this research question. Through choosing to measure sleep and BP dipping in the home environment, it become important to explore the potential influence of environmental factors on sleep in this cohort. We hypothesised that the environment might play a critical moderating role on the relationship between sleep, nocturnal BP and CVD risk. Thus, the final chapter (Chapter 6) aimed to qualitatively explore the potential influence of the environment on the sleep health of these individuals.

5. **What are the potential external (e.g. home and neighbourhood environment) and internal (e.g. knowledge, attitudes, beliefs and behaviours around sleep) factors influencing sleep in adults of African descent living in a low SES community?**

   Qualitative one-on-one interviews were conducted on a subset of individuals studied in the previous chapters (n=15). While some researchers have speculated that the long, poor quality sleep present in this population likely relates to adverse neighbourhood and physical sleep environments, this had never been investigated. Despite the cohort studied in this thesis having been investigated quantitatively for over a decade, there is a notable absence of qualitative work exploring participants perceptions around sleep, their health and their living circumstances, leaving a gap in understanding the holistic experience of this group. Chapter 6 is the first of its kind to investigate individuals' perceptions, thought and beliefs around their neighbourhood and physical sleep environment, and how it relates to their overall sleep health.

Chapter 2

Sex-specific associations between self-reported sleep characteristics and cardiovascular disease risk in men and women of African descent living in a low socioeconomic status environment

Philippa E. Forshaw, Arron T. L. Correia, Laura C. Roden, Estelle V. Lambert, Brian T. Layden, Sirimon Reutrakul, Stephanie J. Crowley, Amy Luke, Lara R. Dugas, Dale E. Rae

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2.1 Introduction

Globally, cardiovascular diseases (CVD) are the main contributors to non-communicable disease (NCD) mortality, accounting for 17.9 million deaths annually[138]. African populations are disproportionately affected by CVD with CVD-related deaths contributing to 38% of all NCD-related deaths in Africa[19]. In the United States of America (USA), African Americans have poorer overall cardiovascular health with higher CVD mortality[18] and significantly higher rates of hypertension compared to their Caucasian counterparts[18]. Of particular concern, compared to the global burden of CVD, Africans with CVD are typically younger, predominantly women, and mostly from disadvantaged communities[19].

It is well-established that both metabolic risk factors (i.e. elevated blood pressure, overweight/obesity, hyperglycemia and hyperlipidemia) and poor lifestyle choices and behaviours (i.e. smoking, physical inactivity and excess alcohol use) contribute to the development of NCDs and CVD[139]. Many of these lifestyle factors are considered sexed in that some are more relevant for women and others for men. For example, obesity is predominantly a risk factor for women but smoking still remains a more prominent risk factor for men[139].

Sleep has been identified as a key health behaviour that impacts numerous CVD risk factors[35]. The American Heart Association has recently added sleep as one of the eight essential metrics influencing cardiovascular risk[3]. Sleep Health has been defined by Buysse and colleagues as *"a multidimensional pattern of sleep-wake-fulness, adapted to individual, social, and environmental demands, that promotes physical and mental well-being. Good sleep health is characterized by subjective satisfaction, appropriate timing, adequate duration, high efficiency, and sustained alertness during waking hours"*[74]. When looking at overall sleep health and CVD risk, evidence supports the association of adverse health outcomes with both short and long sleep durations such as increased risk for obesity, hypertension, coronary heart disease and type 2 diabetes[81]. In terms of the other sleep health components, studies are now emerging to show that poor sleep quality is associated with higher risk of hypertension and CVD[140], later sleep timing is associated with increased BMI[141], CVD [142] and overweight/obesity[143], sleep disturbance or fragmentation is associated with CVD[144] and poor sleep regularity is associated with a higher risk for CVD[75,142] and diabetes[145].

Much of the research investigating associations between sleep and CVD has been conducted in European, Asian or American populations. Very little sleep-related research exists on African-origin

populations living outside of the USA or the UK. This is relevant since several studies suggest that there may be distinct differences in sleep parameters between European- and African-origin populations[20]. For example, African-Americans have been shown to have poorer sleep continuity and short sleep duration, less slow wave sleep and a greater proportion of non-rapid eye movement (REM) stage 2 sleep than other ethnic groups in the USA[20]. In addition, South African men and women living in low-income settings report much longer sleep durations (8-10h per night)[114–118] compared to American populations (6-8h per night)[115]. Thus, the association between sleep characteristics and CVD risk may well differ between socioeconomic contexts.

Given the well-established relationship between sleep duration and CVD risk, this study aims to investigate the relationship between CVD risk and other sleep characteristics, such as sleep timing, sleep onset latency, sleep quality, daytime sleepiness and insomnia symptom severity in adults of African descent living in a low SES community in South Africa. Furthermore, due to sex differences in CVD risk, the second aim is to determine whether these relationships differ between men and women.

2.2 Methods

2.2.1 *Study design and overview*

The Modelling the Epidemiologic Transition Study (METS) is a well-established prospective, five-country (Ghana, South Africa, Jamaica, Seychelles, USA, n=500 per site) cohort study[146]. We report on baseline data collected in the South African cohort of METS-Microbiome, a continuation of the original study, involving members of the original cohort, now investigating associations between gut microbiota and cardiometabolic disease risk[147]. A full description of the METS-Microbiome study protocol for field staff training, data collection, measurement and laboratory procedures has been published previously[148]. The South African cohort includes both men and women living in Khayelitsha. Data collection took place between July 2018 and November 2019. The protocols for the original METS cohort and the present study were approved by the Human Research Ethics Committee of the University of Cape Town, South Africa (Reference numbers: 696/2014 and 155/2020). All participants gave written informed consent and the study strictly adheres to the principles and protocols from the Declaration of Helsinki[149].

2.2.2 *Participants*

Four hundred and twelve adults of African descent (178 men [min-max age: 23-55y], 234 women [min-max age: 24-55y]) were recruited and enrolled into the METS-Microbiome study. Participants were excluded at initial enrolment if they were pregnant or lactating (women) or had a condition preventing them from engaging in normal physical activities (e.g. severe osteo- or rheumatoid-arthritis, or lower extremity disability). Two participants were shift workers and were excluded.

2.2.3 *Demographic and lifestyle questionnaires*

The study-specific questionnaires captured demographic information, medical history, medication and supplement use, tobacco and alcohol use, current employment status and highest level of education achieved, as previously described[146]. Participants were classified as current smokers, ex-smokers or non-smokers. They were also classified as alcohol users or non-users, with current number of drinks consumed per week reported for those using alcohol. Current employment status was assessed by the question "Did you do any type of work for pay in the last month?". Levels of moderate- to vigorous-intensity physical activity (MVPA) were calculated using the Global Physical Activity Questionnaire (GPAQ) analysis guide[150] and reported as minutes per day. The GPAQ is designed to capture physical activity performed in different behavioural domains, namely work, transport and recreation/leisure. Within the work and recreation/leisure domains, questions assess the frequency (i.e. days per week) and duration (i.e. minutes per day) of physical activity. Efforts to address information bias as a result of self-reported data collection included a robust protocol for the collection, measurement and interpretation of information as well as the use of standardized questionnaires and calibrated instruments to ensure consistency in data collection[148].

2.2.4 *Sleep characteristics*

Self-reported sleep characteristics were assessed using the Pittsburgh Sleep Quality Index (PSQI) questionnaire[106], the Epworth Sleepiness Scale (ESS)[109] and the Insomnia Severity Index (ISI)[107]. Habitual bedtimes (hh:mm), wake-up times (hh:mm), time-in-bed (difference between bedtime and wake-up time (h)), total sleep time (h), sleep onset latency (min) and sleep onset latency >30min[151] were all derived from the PSQI questionnaire. Midpoint of sleep (i.e. midsleep) was calculated as PSQI wake-up time – (PSQI time-in-bed)/2). The PSQI global score ranges from 0 to 21 with higher scores indicating poorer sleep quality. Individuals were classified as having poor sleep quality if their PSQI score was >5. We also report the PSQI sub-component score for sleep disturbances, which ranges from 0 to 3 (0 being "no disturbance" and 3 being "severe disturbance"), as this was the only sub-component significantly associated with CVD risk. The PSQI sub-component of sleep disturbance comprises various dimensions (namely, waking up in the middle of the night or early morning,

having to get up to use the bathroom, cannot breathe comfortable, cough or snore loudly, feel too cold, feel too hot, have bad dreams or have pain) which were individually investigated with CVD risk (Supplementary Table 2.1, Appendix 2). The PSQI questionnaire was administered such that participants reflected on their usual sleep habits during the past month only. Analyses for the other sub-components of the PSQI are presented in the supplementary material (Supplementary Table 2.2, Appendix 2). ESS scores range from 0 to 24 with higher scores indicating greater levels of daytime sleepiness. Participants were categorized as having excessive daytime sleepiness if their ESS scores were >10. ISI scores range from 0 to 28, with higher scores indicating a higher degree of insomnia symptom severity. Participants were classified as having clinical insomnia symptoms (moderate and severe) with ISI scores ≥15, since this is standard practice and enables comparison to existing literature[108]. Given that this population is not a clinical sample, and could rather be classified as a community sample, the lower cut-point of ISI≥10 was also used. This decision aligns with suggestions that this lower cut-point might be more suitable for community samples[108]. The ISI questionnaire was administered such that participants reflected on their usual sleep habits during the past two weeks only. Given that employment may play a key role in an individual's sleep timing, duration and quality, descriptive sleep characteristics between employed and unemployed men and women are presented in Supplementary Table 2.3 (Appendix 2).

2.2.5 *Anthropometry*

Weight (kg), height (cm), waist and hip circumferences (cm) were measured according to the previously reported METS standard procedures[148]. Body mass index (BMI) was calculated as weight/height^2 (kg/m^2). Participants were classified as normal weight (BMI: ≥18.5 but <25kg/m^2) overweight (BMI: ≥25kg/m^2 but <30kg/m^2), or obese (BMI: ≥30kg/m^2) and having a high waist circumference (≥102cm in men and ≥88cm in women).

2.2.6 *Clinical measurements*

Resting systolic (SBP) and diastolic (DBP) blood pressure were measured in triplicate on two separate occasions (Omron HEM-747Ic, Omron Healthcare, Bannockburn, IL, USA) as previously described[146]. Participants were classified as having elevated BP if either their measured SBP was ≥130mmHg, their DBP was ≥85mmHg, they reported being diagnosed with hypertension or they were on antihypertensive medication. Following an overnight fast, fasting capillary plasma glucose concentration was determined using the finger stick method (Accu-check Aviva, Roche, Indianapolis, USA). Participants were classified as having elevated fasting plasma glucose if their measured

glucose was ≥5.6mmol/L, they reported being diagnosed with diabetes or they were currently using medication to treat diabetes.

2.2.7 *BMI-modified Framingham CVD risk score*

CVD risk was assessed using the BMI-modified, sex-specific Framingham CVD risk score, which substitutes laboratory values of measured total cholesterol and high-density lipoprotein cholesterol (HDL-C) with measured BMI[37]. The seven risk factors include: age, sex, measured SBP, treatment of hypertension, diagnosed diabetes, measured BMI and smoking status. This modified score substitutes measured cholesterol and HDL-cholesterol with measured BMI and estimates the risk of developing CVD within the next 10 years. The decision to use the BMI-modified Framingham CVD risk score was based on the previously identified "triglyceride paradox" present in individuals of African descent[152]. This paradox describes how, even though insulin resistance, CVD and type 2 diabetes have been associated with hypertriglyceridemia in some populations, individuals of African descent with these conditions usually have normal triglyceride levels.

2.2.8 *Data and statistical analyses*

Data are presented as mean ± standard deviation, median (interquartile range), frequency counts (%), or odds ratios (OR) with 95% confidence intervals (CI). The Shapiro-Wilk test was used to test for normality. Between group comparisons were made using Mann-Whitney U or Kruskal-Wallis tests, Chi-Squared or Fisher's exact tests. Since the CVD risk score was not normally distributed and could not be transformed, the score was coded into quintiles (reference quintile 1). Ordered logistic regression analyses examined associations between self-reported sleep variables (independent) and CVD risk score quintiles (dependent). The continuous version of the independent variables (i.e. all sleep variables) were used.

We ensured that our ordered logistic regression models met all key assumptions, which includes meeting the proportional odds assumption. To confirm this, we utilized the Brant test, a statistical method specifically designed to assess the validity of the proportional odds assumption. We only present data for models which met the assumption. Covariates included in the fully adjusted model for CVD risk were alcohol consumption, MVPA and employment status. Age, sex, BMI and smoking status were not included as covariates as they are factors included in the CVD risk score. Data were analysed using Stata v15.1 (StataCorp, Texas, USA). Since only six participants (1.5%) reported any previous CVD events and only two participants (0.5%) reported being diagnosed with depression, these variables were not statistically modelled with CVD risk scores.

2.3 Results

2.3.1 *Participant characteristics*

The descriptive characteristics of the participants are presented in Table 2.1. Significantly more women than men were classified as being overweight (women: 81%, men: 21%, p<0.001) or obese (women: 60%, men: 6%, p<0.001) or having a high waist circumference (women: 75%, men: 6%, p<0.001). Women also had higher BMIs (women: 33 (27, 38)kg/m^2, men: 22 (19, 24)kg/m^2, p<0.001) and engaged in less MVPA (women: 19 (9, 43)min/day, men: 51 (23 ,99)min/day, p<0.001) than men. More men presented with higher SBP (women: 111 (103, 122)mmHg, men: 121 (110, 131)mmHg, p<0.001), fasting blood glucose levels (women: 4.7 (4.4, 5.2)mmol/L, men: 5.0 (4.5, 5.6)mmol/L, p<0.001) and CVD risk scores (women: 2.0 (1.0, 4.4)%, men: 3.9 (1.9, 6.9)% , p<0.001) compared to women. More men were smokers (women: 18%, men: 71%, p<0.001), consumed alcohol (women: 73%, men: 94%, p<0.001) and consumed more alcoholic units per week (women: 0 (0, 8)drinks per week, men: 16 (0, 36)drinks per week, p<0.001) than women. Employment was higher among men (women: 30%, men: 53%, p<0.001). No participants reported taking any sleep medication.

2.3.2 *Self-reported sleep characteristics*

Self-reported sleep characteristics for both men and woman are presented in Table 2.2. Among all participants, 28 (6.8%) reported a total sleep time of <7h per night, 245 (59.5%) reported 7-9h per night and 139 (33.7%) reported >9h per night. Sleep timing and duration were similar between the men and women, however, men reported taking longer to fall asleep compared to women (women: 20 (10, 30)min, men: 30 (15, 30)min, p=0.011) while women reported more moderate sleep disturbances than men (women: n=112, 47%, men: n=55, 31%, p=0.003). Differences in sleep characteristics between employed and unemployed men and women, respectively, can be found in Supplementary Table 2.3 (Appendix 2). Among the women, those who were unemployed (70%) had later wake-up times (employed: 06:00 (06:00, 07:00), unemployed: 07:00 (06:00, 08:00), p=0.017), longer time-in-bed (employed: 9.0 (8.0, 10.0)h, unemployed: 9.5 (8.5, 10.5)h, p=0.007) and longer total sleep time (employed: 8.3 (7.0, 9.5)h, unemployed: 9.0 (8.0, 10.0)h, p=0.013) compared to employed women (29%). Unemployed men (46%) had later wake-up times (employed: 07:00 (06:00, 07:30), unemployed: 07:05 (06:00, 08:00), p=0.028), longer time-in-bed (employed: 9.0 (8.0, 10.0)h, unemployed: 9.5 (8.3, 10.5)h, p=0.034) and later midsleep times (employed: 02:00 ± 00:49, unemployed: 02:30 ± 00:55, p=0.030) compared to employed men (54%).

2.3.3 *Sex-specific associations between self-reported sleep characteristics and CVD risk score quintiles*

Separate ordered logistic regression models for men and women testing associations between CVD risk score and self-reported sleep characteristics are also shown in Table 2.3. In the fully adjusted models, men who reported earlier bedtimes were more likely to belong to a higher CVD risk score quintile compared to those with later bedtimes (OR: 0.54, 95%CI: 0.39, 0.74, p<0.001). Men who were classified as having poor sleep quality were 1.95 times (95%CI: 1.07, 3.51, p=0.025) times more likely to belong to a higher CVD risk score quintile compared to those with good sleep quality. Although the overall PSQI sleep disturbance model was not significant, when investigating the PSQI sleep disturbance sub-component dimensions, men who reported having pain three or more times a week were 2.79 times (95%CI: 1.11, 7.03, p=0.029) more likely to belong to a higher CVD risk score quintile compared to those who reported no pain (Supplementary Table 2.1, Appendix 2).

Among the women, in the fully adjusted models (Table 2.3), those reporting earlier bedtimes (OR: 0.72, 95%CI: 0.55, 0.95, p=0.020) and wake-up times (OR: 0.30, 95%CI: 0.13, 0.72, p=0.007) were more likely to belong to a higher CVD risk score quintile than those reporting later bedtimes and wake-up times. Those women who reported a longer sleep onset latency were 1.47 times (95%CI: 1.43, 1.88, p=0.003) more likely to belong to a higher CVD risk score quintile than women who reported a short sleep onset latency. Those with shorter total sleep times (OR: 0.84, 95%CI: 0.72, 0.98, p=0.029) were more likely to belong to a higher CVD risk score quintile than those with longer total sleep times. Women with higher PSQI global scores were 1.93 times (95%CI: 1.29, 2.90, p=0.001) more likely to belong to a higher CVD risk score quintile. Women classified as having moderate to severe insomnia symptoms (ISI≥10 and ISI≥15) were 2.25 times (95%CI: 1.15, 4.37, p=0.016) and 3.24 times (95%CI: 1.04, 10.04, p=0.042), respectively, more likely to belong to a higher CVD risk score quintile. Although the overall PSQI sleep disturbance model was not significant, when investigating the PSQI sleep disturbance sub-component dimensions, women who reported waking up in the middle of the night or early morning once or twice a week or three or more times a week were 2.39 times (95%CI: 1.30, 4.37, p=0.005) and 2.73 times (95%CI: 1.38, 5.37, p=0.004), respectively, more likely to belong to a higher CVD risk score quintile compared to those who reported not waking up in the middle of the night. Similarly, women who reported their sleep being disturbed through feeling hot once or twice a week were 1.88 times (95%CI: 1.08, 3.28, p=0.027) more likely to belong to a higher CVD risk score quintile compared to those who reported no heat-related sleep disturbances (Supplementary Table 2.1, Appendix 2).

Table 2.1. Descriptive characteristics of participants stratified by sex.

	Women (n=234)	**Men (n=178)**	**p-value**
Age (y)	34 (29, 42)	36 (31, 42)	0.178
BMI (kg/m^2)	32.7 (26.7, 38.2)	21.5 (19.4, 24.3)	**<0.001**
Overweight (count, %)	190 (81.2)	37 (20.8)	**<0.001**
Obese (count, %)	141 (60.3)	10 (5.6)	**<0.001**
Waist circumference (cm)	98.1 (88.5, 112.0)	79.6 (73.8, 87.1)	**<0.001**
High waist circumference (count, %)	176 (75.2)	11 (6.2)	**<0.001**
SBP (mmHg)	111 (103, 122)	121 (110, 131)	**<0.001**
DBP (mmHg)	73 (66, 80)	74 (66, 82)	0.492
Elevated BP (count, %)	66 (28.2)	62 (34.8)	0.150
Fasting glucose concentration (mmol/L)	4.7 (4.4, 5.2)	5.0 (4.6, 5.6)	**<0.001**
Elevated blood glucose (count, %)	8 (3.4)	7 (3.9)	0.789
CVD risk score (%)	2.0 (1.0, 4.4)	3.9 (1.9, 6.9)	**<0.001**
Highest degree of formal education			0.238
None or Primary (count, %)	144 (61.6)	114 (64.1)	
Secondary (count, %)	75 (32.0)	47 (26.4)	
Tertiary (count, %)	14 (5.9)	16 (8.9)	
Employed (count, %)	69 (29.6)	95 (53.7)	**<0.001**
MVPA (min/day)	19 (9, 43)	5 (23, 99)	**<0.001**
Smoking status			**<0.001**
Smoker (count, %)	42 (17.9)**	126 (70.8)**	
Non-smoker (count, %)	188 (80.3)**	38 (21.3)**	
Ex-smoker (count, %)	5 (2.1)*	11 (6.2)*	
Alcohol user (count, %)	171 (73.1)	168 (94.4)	**<0.001**
Alcohol (no. drinks per week)	0.0 (0, 7)	16.0 (0, 36)	**<0.001**

Data are presented as median (interquartile range) or count (%). P-values represent differences between men and women determined using Mann-Whitney U or Chi-Squared tests. *p<0.050 and **p<0.001 represent significant post-hoc analyses using Fisher's exact tests.

BMI: body mass index; BP: blood pressure; CVD: cardiovascular disease; DBP: diastolic blood pressure; MVPA: moderate- to vigorous-intensity physical activity; SBP: systolic blood pressure.

Table 2.2. Self-reported sleep characteristics of participants stratified by sex.

	Women (n=234)	**Men (n=178)**	**p-value**
PSQI bedtime (hh:mm)	21:30 (21:00, 22:00)	22:00 (21:00, 22:00)	0.620
PSQI wake-up time (hh:mm)	07:00 (06:00, 08:00)	07:00 (06:00, 08:00)	0.875
PSQI time-in-bed (h)	9.30 ± 1.55	9.16 ± 1.65	0.338
PSQI total sleep time (h)	8.79 ± 1.53	8.55 ± 1.57	0.131
PSQI midsleep (hh:mm)	02:00 ± 00:55	02:25 ± 00:55	0.724
PSQI SOL (min)	20 (10, 30)	30 (15, 30)	**0.011**
PSQI SOL >30min (count, %)	40 (17.09)	41 (23.03)	0.131
PSQI global score	4 (3, 6)	4 (3, 6)	0.560
Poor sleep quality (PSQI>5) (count, %)	67 (28.6)	54 (30.3)	0.679
PSQI: Sleep disturbance (count, %)			**0.003**
None	8 (3.4)	5 (2.8)	
Mild	110 (47.0)	109 (61.2)	
Moderate	112 (46.9)**	55 (30.9)**	
Severe	4 (1.7)	8 (4.5)	
ESS score	7 (4, 11)	6 (3, 10)	0.129
Excessive daytime sleepiness (ESS>10) (count, %)	80 (34.3)	49 (27.5)	0.151
ISI score	3 (1, 6)	2 (1, 5)	0.089
Standard clinical insomnia symptoms (ISI≥15) (count, %)	10 (4.3)	7 (3.9)	0.531
Community clinical insomnia symptoms (ISI≥10) (count, %)	32 (13.7)	22 (12.4)	0.399

Data are presented as mean ± standard deviation, median (interquartile range) or count (%). P-values represent comparisons between men and women determined using Mann-Whitney U or Chi-Squared tests. *p<0.050 and **p<0.001 represent significant post-hoc analyses using Fisher's exact tests.

ESS: Epworth Sleepiness Scale; ISI: Insomnia Severity Index; PSQI: Pittsburgh Sleep Quality Index; SOL: sleep onset latency.

Table 2.3. Fully adjusted ordered logistic regression models exploring the associations between CVD risk score quintile (dependent variable) and self-reported sleep characteristics (independent variables) stratified by sex.

	Women		Men	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**
Bedtime	0.72 (0.55, 0.95)	**0.020**	0.54 (0.39, 0.74)	**<0.001**
Overall model	*n=233, LR chi²=11.76, p=0.016*		*n=177, LR chi²=22.04, p=0.002*	
Wake-up time	0.30 (0.13, 0.73)	**0.007**	0.45 (0.18, 1.14)	0.093
Overall model	*n=233, LR chi²=13.47, p=0.009*		*n=176, LR chi²=9.71, p=0.045*	
Time-in-bed	0.91 (0.78, 1.06)	0.216	1.05 (0.89, 1.23)	0.532
Overall model	*n=232, LR chi²=7.65, p=0.105*		*n=176, LR chi²=8.04, p=0.090*	
Total sleep time	0.84 (0.72, 0.98)	**0.029**	1.01 (0.85, 1.19)	0.927
Overall model	*n=233, LR chi²=11.18, p=0.025*		*n=176, LR chi²=6.89, p=0.141*	
SOL	1.47 (1.43, 1.88)	**0.003**	1.25 (0.93, 1.69)	0.139
Overall model	*n=233, LR chi²=15.55, p=0.004*		*n=176, LR chi²=9.11, p=0.058*	
SOL >30min (vs. SOL ≤30min)	1.27 (0.78, 2.07)	0.344	0.76 (0.42, 1.37)	0.366
Overall model	*n=232, LR chi²=7.26, p=0.122*		*n=176, LR chi²=7.98, p=0.092*	
PSQI global score	1.93 (1.29, 2.90)	**0.001**	1.45 (0.95, 2.22)	0.085
Overall model	*n=233, LR chi²=116.65, p=0.002*		*n=176, LR chi²=9.97, p=0.041*	
Poor sleep quality (PSQI>5) (vs. PSQI≤5)	1.41 (0.85, 2.35)	0.176	1.95 (1.07, 3.51)	**0.025**
Overall model	*n=233, LR chi²=8.08, p=0.088*		n=*176, LR chi²=12.00, p=0.017*	
PSQI disturbance				
Mild vs. None	3.89 (0.93, 16.16)	0.063	2.12 (0.43, 10.35)	0.353
Moderate vs. None	4.51 (1.08, 18.68)	0.038	3.80 (0.74, 19.45)	0.108
Severe vs. None	7.31 (0.61, 88.78)	0.117	1.78 (0.23, 13.77)	0.579
Overall model	*n=233, LR chi²=11.43, p=0.076*		*n=176, LR chi²=12.44, p=0.053*	
ESS	1.07 (0.86, 1.34)	0.523	0.89 (0.69, 1.15)	0.399
Overall model	*n=232, LR chi²=6.77, p=0.148*		*n=176, LR chi²=7.87, p=0.096*	
Excessive daytime sleepiness (ESS>10) (vs. ESS≤10)	1.26 (0.78, 2.07)	0.344	0.76 (0.43, 1.37)	0.366
Overall model	*n=232, LR chi²=7.26, p=0.123*		*n=176, LR chi²=7.98, p=0.092*	

ISI	1.05 (1.00, 1.11) **0.038**	1.00 (0.94, 1.07) 0.955
Overall model	*n=232, LR chi^2=10.66, p=0.031*	*n=176, LR chi^2=6.88, p=0.142*
Standard clinical insomnia symptoms (ISI≥15)	3.24 (1.04, 10.04) **0.042**	1.39 (0.41, 4.67) 0.591
Overall model	*n=232, LR chi^2=10.50, p=0.014*	*n=177, LR chi^2=7.17, p=0.013*
Community clinical insomnia symptoms (ISI≥10)	2.25 (1.15, 4.37) **0.016**	0.95 (0.43, 2.09) 0.900
Overall model	*n=232, LR chi^2=12.15, p=0.016*	*n=177, LR chi^2=6.90, p=0.141*

Models were determined using ordered logistic regressions and data are presented as odds ratios (OR) with 95% confidence intervals (CI). Models were adjusted for alcohol, MVPA and employment.

CVD: cardiovascular disease, SOL: sleep onset latency, PSQI: Pittsburg Sleep Quality Index, ESS: Epworth Sleepiness Scale, ISI: Insomnia Severity Index; MVPA: moderate- to vigorous-intensity physical activity.

2.4 Discussion

We confirm the long self-reported sleep duration (time-in-bed – men: 9.16 ± 1.65h, women: 9.30 ± 1.55h) observed in previous South African studies among individuals of African descent[115,153]. In the present study, among the men, earlier bedtimes and poorer sleep quality were associated with an increased CVD risk. Among the women, earlier bedtimes and wake-up times, taking longer to fall asleep, shorter total sleep time, poor sleep quality and greater severities of insomnia symptoms were all independently associated with an increased CVD risk. Three main factors could likely explain these findings: i) the participants' sleep environments, ii) the neighbourhood environment and iii) the poor overall health of this population.

Earlier bedtimes were associated with higher CVD risk score quintiles among the men and the women. Later bedtimes are commonly considered a negative sleep behaviour since later sleep timing is often associated with poorer cardiovascular health[154], however, we have found the opposite. We speculate that these participants are trying to fall asleep too early which might be out of phase with their endogenous circadian rhythms. It is well-established that disruption to our body's natural circadian rhythms can be detrimental to cardiovascular health[154]. Thus, whether early bedtimes are associated with circadian misalignment in this population should be assessed in future studies. In addition, it may be that the general physical health of this population is relatively poor, therefore they are going to bed earlier because they may feel unwell. One could speculate that this is similar to long sleep (i.e. sleep >10h) being associated with adverse health outcomes not because of the sleep itself, but because of underlying conditions that change sleep behaviour[124]. While this finding contrasts with findings from studies conducted largely in the Global North regarding later bedtimes and poorer overall health, it reinforces the need to examine questions concerning the relationship between sleep and CVD risk in more diverse populations to understand population-specific CVD risk factors.

Poor sleep quality was associated with higher CVD risk score quintiles among the men and women. Among women specifically, waking up in the middle of the night or waking too early in the morning, as well as feeling too hot were all associated with higher CVD risk score quintiles. These findings may be explained, in part, by the fact that many participants live in informal houses which are over-crowded, have poor ventilation, are often noisy and have poor safety or security. Typically, these temporary homes comprise only one or two rooms, with a housing density of 4 (range: 3-6) individuals per home (38-84m^4), leaving occupants with little privacy or quiet spaces for sleep. Many

of these factors have been previously associated with worse sleep quality[155] and worse CVD health[156]. Other possible explanations for these findings could be that sleep disturbances may interrupt the physiological recovery function of sleep, preventing the body from fully decreasing sympathetic nervous system (SNS) activity and resting[157]. Alternatively, poorer sleep quality may be leading to higher levels of inflammation[158] and subsequent poorer cardiovascular health in this population, especially among the women where the obesity rates are very high. Altogether, this finding strengthens the need to include sleep quality as an important indicator when assessing CVD risk among low-income populations such as this, especially in women.

Longer PSQI sleep onset latencies as well as presenting with more moderate to severe insomnia symptoms were also associated with higher CVD risk scores among the women. Stress-related psychological factors are central to the pathogenesis and maintenance of insomnia, mostly due to increased and inappropriate SNS activity during sleep[159]. Additionally, overactivity of the SNS has long been recognized to be a major mediator in the relationship between stress and CVD[160]. In addition to the poor sleep environment mentioned above, the crime and violence rates (specifically contact crimes such as murder, assault and sexual offences) in this township are well above the national average[161]. Given that women in this neighbourhood are often the victims of crime, it is entirely plausible that hyperarousal or overactivation of the SNS may play a key role in the difficulties falling asleep. Previous work by Mellman *et al.* (2018) in urban-residing African Americans reported associations between indicators of stressful environments and increased SNS activity (i.e. hyperarousal) during sleep[162]. It is also worth noting that in this particular study, greater effects were observed in women, particularly for those with a higher degree of exposure to violence [162]. Another study done in South African female survivors of sexual assault found that post-traumatic stress disorder (PTSD)-diagnosed individuals felt safer sleeping in the laboratory than in their home environments and experienced fewer sleep disruptions during a night of laboratory sleep than during sleep at home[163]. Neighbourhood environment aside, the prevalence of sleep disorders (specifically insomnia) and the risk of developing psychiatric problems (such as depression and anxiety[164] which often increase the risk of insomnia) are more common in women compared to men[164]. Qualitative studies using interviews to explore perceptions around sleep and the home or neighbourhood environment in this population are needed to assess how neighbourhood safety and stress might contribute to poor sleep quality.

Among the women, earlier wake-up times were associated with higher CVD risk score quintiles. This is similar to what has previously been shown in individuals of European descent in whom waking up

early was associated with an increased risk of mortality from CVD[165]. Two important cultural aspects of this society may help explain this finding. Firstly, women in the community are often the caregivers and the ones who need to get the children, grandchildren or extended family ready for school or work, meaning that their wake-up times may be earlier than preferred. One might hypothesize that those women who wake up earlier may subsequently have a shorter overall sleep opportunity. Secondly, due to the low socioeconomic circumstances of this population, individuals who are employed may have to wake up very early to catch public transport to get to work on time. Indeed, this is what we see when looking at the sleep characteristics of employed versus unemployed women; employed women wake up around one hour earlier and had a shorter time-in-bed and total sleep time, compared to those who were not employed. After adjusting for employment, no significant observations were seen between employment and CVD risk. Thus, we are confident that these associations between sleep and CVD risk persist independently of one's employment status.

Among the women, shorter total sleep times were associated with increased CVD risk. Intriguing is that even though the women are spending around 9h (±1.5h) in bed (i.e. the upper limit of the recommended guidelines of 7-9h[166]), the relationship between shorter sleep and higher CVD risk still exists. This relationship is not present in the men, but one could argue that it seems the women have poorer overall sleep health compared to the men. While it appears that their sleep duration is sufficient, they are potentially accumulating less sleep overall, as their sleep is more fragmented as described above. Given the limitation of self-report, however, future research that objectively measures sleep duration through actigraphy is needed to shed more light on this aspect of sleep. Finally, while the sleep health between sexes in this population may be different due to crime, employment/unemployment or cultural aspects of the society, for example, it may also be due to the drastically different primary CVD risk factors (i.e. smoking status and obesity) between men and women.

Our study is not without limitations, the main one being that sleep measured in this study is self-reported, as opposed to objectively measured, and limited in time to the past month or past two weeks for PSQI and ISI tools, respectively. It is possible that individuals may over- or under-estimate their sleep duration and quality. The presence of obstructive sleep apnoea or other sleep and mental health disorders was not assessed in this study, but may have influenced the nature of sleep in this population and thus the sleep-CVD risk relationships. This is something that needs to be included in future studies. Our data are cross-sectional, and we are therefore not able to speculate any cause

and effect relationships between self-reported sleep characteristics and CVD risk scores. Finally, we acknowledge that different dimensions of sleep are often interrelated, however, given the limitation of self-reported sleep data we have chosen a simplified approach for assessing relationships between sleep and CVD in this chapter.

2.5 Conclusion

Overall, we have shown that in addition to thinking about only short or long sleep duration as a risk factor for CVD we should also consider other components of sleep health such as sleep timing, sleep onset latency and sleep quality when assessing an individuals' CVD health. Although we have looked at these sleep factors individually in this chapter, we know that sleep is actually multifaceted with sleep variables being distinct but often interrelated. Future use of a multidimensional sleep health score or interactions between sleep health variables may be more important for better prevention and treatment of CVD. This will be addressed in Chapter 3. Furthermore, Chapter 3 will address the limitation of self-report by utilising objectively measured sleep variables.

Chapter 3

Unpacking the enigma of long sleep and cardiovascular disease risk in adults of African descent living in a low socioeconomic status environment

3.1 Introduction

Sleep is a fundamental physiological process that is essential for overall health and well-being and plays an essential role in maintaining cardiovascular health[3,125]. Sleep which is too short, too long or of poor quality has been linked to obesity, hypertension, cardiovascular disease (CVD), insulin resistance and type 2 diabetes[12–14]. In 2010, the American Heart Association created Life's Simple 7 which are guidelines to define ideal cardiovascular health according to seven modifiable risk factors[167]. These health factors include healthy diet, participation in physical activity, avoidance of nicotine, healthy weight, and healthy levels of blood lipids, blood glucose and blood pressure[167]. Sleep has recently been recognised as a novel and important modifiable CVD risk factor, having associations with each of the original seven components of cardiovascular health[12,35]. Healthy sleep has since been added as a new component of cardiovascular health, creating the now updated Life's Essential 8[3].

African Americans in the United States of America (USA) as well as individuals of African descent living in Sub-Saharan Africa experience a higher burden of CVD risk factors, such as obesity, diabetes and hypertension as well as CVD morbidity and mortality compared to Caucasian Americans and individuals of European descent[18,19,168]. In addition, a meta-analysis by Ruiter *et al.* (2011) showed that African Americans have poorer sleep (including shorter sleep duration, lower sleep efficiency, longer sleep onset latency, less slow wave sleep and more wake after sleep onset time[20]) compared to Caucasian Americans. In contrast to much of the research done in African Americans demonstrating shorter objective and subjective sleep durations compared to Caucasian Americans, South African individuals of African descent report much longer sleep durations (8-10h per night)[114–118]. The nature of the relationship between this long sleep duration and CVD risk is not well understood and might differ to that seen globally, where short sleep is often associated with higher CVD risk[81]. Notably, there is a scarcity of literature pertaining to objectively-measured sleep and CVD in any South African populations. The majority of research focuses on self-reported sleep data and/or cardiometabolic disease[114,169]. Furthermore, in South Africa, individuals of African descent often live in low socioeconomic status (SES) environments, which, in some studies have been shown to be an independent risk factor for CVD, equivalent to the traditional risk factors mentioned above[9], further amplifying CVD risk in these already vulnerable populations.

There is robust evidence showing heterogeneity in underlying mechanisms, manifestation and prognosis of CVD between sexes (specifically innate differences in physiology and lifestyle

factors)[170,171]. For example, lifestyle factors differ in that tobacco and alcohol use are generally more common in men than women, and the prevalence of obesity is typically higher in women than men[172]. Additionally, there are also differences in sleep health between men and women, with women usually reporting poorer sleep quality and having a higher risk for developing insomnia compared to men[16]. For this reason, sex-specific research of CVD and sleep health has received increasing recognition in recent years.

Therefore, the primary aim of this study was to explore sex-specific associations between objectively measured habitual sleep characteristics (namely sleep duration, quality, timing and regularity) and CVD risk factors among individuals African descent living in a low SES environment. We hypothesize that among these individuals, CVD risk may be exacerbated by long, poor-quality sleep. Since sleep is a multidimensional phenomenon, a secondary aim was to determine whether any other sleep variables (specifically sleep quality variables) moderated associations between sleep duration and CVD risk.

3.2 Methods

3.2.1 *Study design and overview*

The original five-country (Ghana, South Africa, Jamaica, Seychelles, USA) Modelling the Epidemiologic Transition Study (METS)[146] was extended to the METS-Microbiome (n=400 per site) and METS-Sleep (n=200 per site) studies[148]. The current cross-sectional observational study is a sub-analysis limited to the South African METS-Sleep participants. This cohort comprises 200 men and women living in Khayelitsha. Residents of this low SES community live in high-density temporary or semi-permanent houses and face high rates of unemployment and crime. Data collection took place between January and December 2021. It is a consideration that data collection occurred in the second year of the COVID-19 pandemic. In South Africa, all lock-down related restrictions had been removed by this stage, and only participants who were not currently ill were allowed to take part in the study. Since employment rate was similar for women (4% reduction) but lower for men (22% reduction) during this year of data collection (Table 3.1 below) compared to before COVID in 2019 (see Chapter 2, Table 2.1), we account for this in our analyses and note this as a limitation. The protocols for METS, METS-Sleep and the present study were all approved by the Human Research Ethics Committee of the University of Cape Town, South Africa (Reference numbers: 696/2014 and 155/2020). All participants gave written informed consent and the study strictly adheres to the principles and protocols from the Declaration of Helsinki[149]. Briefly, participants completed detailed

questionnaires and field staff measured anthropometric and clinical health parameters. Participants were then given wrist-worn actigraphy devices to measure seven consecutive days of habitual sleep.

3.2.2 *Participants*

Participants in the current analysis (n=194; 100 women, 94 men; median age 39 [33-46] years) were recruited and enrolled into METS-Sleep. Participants were excluded if they were pregnant or lactating, had a condition preventing them from engaging in normal physical activities (e.g. severe osteo- or rheumatoid-arthritis, or lower extremity disability), presented with COVID-symptoms or were shift workers. It is important to note that this is not an entirely random selection of participants. Volunteers were the first 200 of the 400 METS-Microbiome participants to specifically volunteer for METS-Sleep. Of the 200 participants, three were excluded as they were shift workers, two were breastfeeding and one had incomplete data.

3.2.3 *Questionnaires*

The METS-Sleep study-specific questionnaires captured participant demographics, medical history, medication and supplement use, tobacco and alcohol use, current employment status and years of education, as previously described and presented in Chapter 2[148,173]. Participants were classified as smokers or non-smokers with number of current tobacco products smoked per day being reported. They were also classified as alcohol users or non-users, with current number of drinks consumed per week reported. The Global Physical Activity Questionnaire (GPAQ)[150] was used to report usual time spent in moderate- to vigorous-intensity physical activity (MVPA, min per day). Asset index was based on possession of up to 19 items reflecting individual and household wealth[174].

The Berlin questionnaire (BQ) was used to screen for obstructive sleep apnoea (OSA)[98] and the Insomnia Severity Index (ISI) for symptoms of insomnia[107]. Self-reported sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI) questionnaire[106] and daytime sleepiness with the Epworth Sleepiness Scale (ESS)[109]. The BQ consists of 10 questions focused on three categories related to signs and symptoms of sleep apnoea: snoring, daytime sleepiness and obesity/high blood pressure. In category one, high risk was defined as presence of symptoms in two or more questions related to snoring. In category two, high risk was defined as presence of daytime sleepiness. In category three, high risk was defined as a history of hypertension or a body mass index (BMI) ≥30 kg/m^2. Participants were classified as high-risk for OSA if scored as high risk in at least two of the three categories. ISI scores range from 0 to 28, with higher scores indicating a higher degree of insomnia symptom severity. Participants were classified as having moderate and severe clinically

significant insomnia symptoms with ISI scores ≥15. Similarly to Chapter 2, since this population is not a clinical sample, and rather a community sample, we also used the lower threshold of ISI≥10[108]. The PSQI global score ranges from 0 to 21 with higher scores indicating poorer sleep quality. Individuals were classified as having poor sleep quality if their PSQI score was >5. ESS scores range from 0 to 24 with higher scores indicating greater levels of daytime sleepiness. Participants were categorized as having excessive daytime sleepiness if their ESS scores were >10.

3.2.4 *Anthropometry and clinical measurements*

Weight (kg), height (cm) and waist circumference (cm) were measured according to the METS standard procedures[146]. BMI was calculated as weight/height^2 (kg/m^2). Participants were classified as overweight (BMI: ≥25kg/m^2 but <30kg/m^2), obese (BMI: ≥30kg/m^2) or having a high waist circumference (≥102cm in men and ≥88cm in women). Resting blood pressure was measured in triplicate on two separate occasions (Omron HEM-747Ic, Omron Healthcare, Bannockburn, IL, USA) as previously described[148], with final values being the average of all six measures. Participants were classified as having elevated blood pressure if their measured systolic blood pressure (SBP) was ≥130mmHg[175], measured diastolic blood pressure (DBP) was ≥85mmHg[175], they reported being diagnosed with hypertension or they were currently using antihypertensive medication. Following an overnight fast, fasting capillary plasma glucose concentration was determined using the finger stick method (Accu-check Aviva, Roche, Indianapolis, USA). Participants were classified as having elevated fasting plasma glucose if their measured glucose was ≥5.6mmol/L, they reported being diagnosed with diabetes or they were currently using medication to treat diabetes.

3.2.5 *BMI-modified Framingham 10-year CVD risk score*

As described and presented in Chapter 2[173], CVD risk was assessed using the BMI-modified sex-specific Framingham 10-year CVD risk score, which estimates the risk of developing CVD within the next 10 years[37]. The seven risk factors include: age, sex, measured SBP, treatment of hypertension, diagnosed diabetes, measured BMI and smoking status.

3.2.6 *Actigraphy-derived sleep measures*

Participants were given a wrist-worn accelerometer (Actiwatch Spectrum Plus, Philips Respironics, Bend, OR, USA) to wear on their non-dominant wrist continuously for seven consecutive days while keeping a sleep diary. They were allowed to remove the device while bathing or showering and used an event marker button to indicate the beginning and end of nocturnal sleep periods. Actiwatches were programmed to collect activity and light data in 30s epochs. Only participants with five days of

valid actigraphy data were included in analyses. Data from the sleep diary were used to confirm sleep onset and offset manually based on published guidelines[176]. Five immobile minutes were used to define sleep onset, zero immobile minutes for sleep offset, and a wake threshold activity count of 40cpm was applied to generate sleep/wake status for each epoch. Data were processed using Philips Actiware software (v6.3, Philips Respironics, Bend, OR, USA). Outcome variables include sleep onset (mm:hh), sleep offset (mm:hh), sleep duration (elapsed time between sleep onset and sleep offset, h), total sleep time (actual time spent asleep, h), sleep efficiency (%), wake after sleep onset (WASO, min), midsleep (sleep offset–(sleep duration)/2) (hh:mm), sleep duration regularity, midsleep regularity and sleep fragmentation index (SFI, %). Sleep duration and midsleep regularity variables were calculated as the standard deviation of all daily variable values for each participant. Long sleep was defined as sleep duration >9h[80] and poor sleep efficiency was defined as sleep efficiency <85%[177]. Midsleep was calculated as (sleep onset + (sleep duration/2)). Since median midsleep was around 03:00 for both men and women, the midsleep variable was categorized into midsleep <03:00 and midsleep ≥03:00 and termed midsleep binary. Due to the current limited validity of actigraphy in estimating sleep onset latency, this dimension of sleep was not investigated[178].

The SFI, obtained from the Actiware software[179], is a measure of the degree to which sleep is interrupted by physical movement and is calculated as:

$$100 \times \frac{\text{\# of mobile epochs lasting four epochs + \# of immobile epochs <1 minute duration}}{\text{\# of immobile epochs >1 minute duration}}$$

The higher the SFI, the more disrupted the sleep period.

We also determined the Sleep Regularity Index (SRI, %), proposed by Phillips *et al.* (2017), which measures the similarity of an individual's sleep–wake patterns from one day to the next, based on binary sleep/wake state classifications. It calculates the percentage probability of an individual being in the same state (sleep vs. wake) at any two time points 24h apart, averaged across the study. The SRI ranges from 0 (random) to 100 (perfectly regular)[90]:

$$-100 + \frac{200}{M(N-1)} \sum_{j=1}^{M} \sum_{i=1}^{N-1} \delta(S_{i,j}, S_{i+1,j})$$

where M is the number of daily epochs, N is the number of days, $s_{i,j} = 0$ for sleep and $s_{i,j} = 1$ for wake, and $\delta(s_{i,j}, s_{i+1,j}) = 1$ if $s_{i,j} = s_{i+1,j}$ and 0 otherwise. This index is constructed based on the reasoning that changes in sleep schedules from one 24h interval to the next may cause circadian disruption and thus impact normal biological functioning and health[90].

3.2.7 *Data and statistical analyses*

Data are presented as mean ± standard deviation, median with the interquartile range, frequency counts (%) or beta coefficients or odds ratios (OR) with 95% confidence intervals (CI). The Shapiro-Wilk test was used to test for normality. Between-group comparisons were made using independent t-tests or Mann-Whitney U tests. Chi-Squared tests were used to compare frequency differences between groups. Significance was accepted at $p<0.050$ and data were analysed using Stata v15.1 (StataCorp, Texas, USA).

Since we observed relatively low CVD risk scores among men and women in Chapter 2[173], we decided to also consider a simplified approach of looking at binary risk factor variables (i.e. elevated BP and obesity) in this chapter. Therefore, to best describe the relationships between the CVD risk factors (CVD risk score, elevated BP and obesity) and multiple sleep variables (primary study aim), we followed a model building approach, constructing separate models for men and women.

In step 1, we performed three sets of regression analyses to test for candidate independent variables: i) simple linear regression analyses for each independent variable (sleep variables and potential covariates) with the CVD risk score (Supplementary Table 3.1, Appendix 3), ii) simple logistic regression analyses for each independent variable with elevated BP (Supplementary Table 3.2, Appendix 3) and iii) simple logistic regression analyses for each independent variable with obesity (Supplementary Table 3.3, Appendix 3).

We did not include the BQ (i.e. sleep apnoea risk) as a potential covariate, since both the BQ score and the CVD risk score used in this study include BMI and hypertension status, thus making them collinear with elevated BP and obesity. We constructed a binary chronic disease covariate to indicate the presence of any reported chronic disease; this covariate was modified to exclude CVD for the CVD risk score regression and hypertension for the elevated BP regression. Based on the simple linear/logistic regressions (step 1), independent variables with p-values <0.150 were carried forward for further analyses in step 2. Since asset index and years of education were collinear covariates in the women, we carried forward years of education to step 2 as it had a stronger association with CVD risk score. Employment status was carried through to step 2 *a priori* since sleep characteristics differed significantly between employed and unemployed women (Supplementary Table 3.13, Appendix 3).

In step 2, we built multivariable models for each of the three outcome variables (CVD risk score, elevated BP and obesity). Using a backward stepwise selection approach, we started with models

including each candidate sleep variable and all covariates identified in step 1, removing the weakest covariates one at a time until only significant ($p<0.050$) covariates remained in the final model, which always retained the sleep variable of interest (Supplementary Tables 3.4 – 3.9, Appendix 3). To explore potential moderating effects of other sleep variables on the sleep duration-CVD risk relationship (secondary study aim), step 3 consisted of two sub-steps: (i) first, we performed simple linear regressions between sleep duration and all other sleep variables to identify candidate moderators (Supplementary Table 3.10, Appendix 3) and (ii) we then built models (Supplementary Tables 3.11 and 3.12, Appendix 3) which included interaction terms of sleep duration and candidate sleep variables identified in the first sub-step, and were adjusted for potential covariates identified in step 1 (Supplementary Tables 3.1 – 3.3, Appendix 3). We also included SFI as a potential moderator for men due to the disrupted nature of this cohort's sleep. While beyond the aims and scope of this study, the same interaction relationships were explored for elevated BP and obesity, however, no significant relationships were found (data not shown).

3.3 Results

3.3.1 *Participant characteristics*

The descriptive characteristics of the participants are presented in Table 3.1. Disproportionately more women than men were classified as being overweight (women: 86%, men: 23%, $p<0.001$) or obese (women: 63%, men: 5%, $p<0.001$) or having a high waist circumference (women: 48%, men: 6%, $p<0.001$). Women also had higher BMIs (women: 33 (27, 39)kg/m^2, men: 21 (20, 25)kg/m^2, $p<0.001$) and engaged in less MVPA (women: 29 (15, 51)min/day, men: 51 (29, 90)min/day, $p<0.001$) compared to men. Men presented with higher SBP (women: 117 (108, 129)mmHg, men: 124 (117, 135)mmHg, $p=0.003$) and higher CVD risk scores (women: 3.1 (1.3, 6.1)%, men: 6.4 (3.4, 11.6)% , $p<0.001$). More men were smokers (women: 27%, men: 66%, $p<0.001$) and they consumed more alcoholic drinks per week (women: 0 (0, 8)drinks per week, men: 12 (0, 24)drinks per week, $p<0.001$) than women.

3.3.2 *Sleep characteristics*

Actigraphy-derived and self-reported sleep characteristics for men and woman are presented in Table 3.2. Men had longer sleep duration compared to women (women: 8.9 ± 1.2h, men: 9.1 ± 1.4h, $p=0.009$). Men presented with more WASO time (women: 85 (77, 86)min, men: 103 (76, 127)min, $p=0.005$) and higher SFI scores (women: 28 (23, 34)%, men: 34 (27, 41)%, $p<0.001$) compared to women. Women presented with higher ESS scores (women: 5 (1, 9), men: 3 (1, 8), $p=0.011$), higher

risk for sleep apnoea (women: 23%, men: 11%, p=0.018) and more moderate to severe symptoms of insomnia (ISI≥10) compared to men (women: 16%, men: 6%, p=0.027). Differences in sleep characteristics between employed and unemployed men and women, respectively, can be found in Supplementary Table 3.13, Appendix 3. There were no differences in sleep characteristics between employed (22%) and unemployed (78%) men. Among the women, those who were unemployed (74%) had later sleep offsets (employed: 07:00 (06:36, 07:36), unemployed: 07:46 (06:44, 08:37), p=0.004), later midsleep times (employed: 02:48 (02:12, 03:00), unemployed: 03:06 (02:37,03:53), p=0.013), poorer sleep efficiencies (employed: 84.6 (82.0, 87.1)%, unemployed: 80.38 (74.3, 85.3)%, p=0.005), more WASO (employed: 74.0 (60.9, 90.5)min, unemployed: 94.9 (70.4, 112.8) p=0.007), higher sleep fragmentation indices (employed: 25.8 (21.8, 29.6)%, unemployed: 29.7 (24.0, 35.1)%, p=0.027) and lower sleep regularity indices (employed: 67.5 (61.1, 72.1), unemployed: 62.9 (54.0, 64.8), p=0.026) than those who were employed (26%).

3.3.3 *Sex-specific associations between sleep variables and the CVD risk score*

Simple linear regression analyses found that in the women, earlier sleep offset (β=–0.24, 95%CI: –0.41, –0.07, p=0.007), earlier midsleep (β=–0.29, 95%CI: –0.51, –0.07, p=0.008) and having a midsleep time before 03:00 (β=–0.48, 95%CI: –0.86, –0.01, p=0.014) were associated with higher CVD risk scores (Supplementary Table 3.1, Appendix 3). Among the covariates, fewer years of education (β=–0.32, 95%CI: –0.41, 0.22, p<0.001), a lower asset index (β=–1.93, 95%CI: –3.67, –0.19, p=0.029) and having a chronic disease (β=0.86, 95%CI: 0.39, 1.33, p<0.001) were all associated with higher CVD risk scores (Supplementary Table 3.1, Appendix 3). Of the five candidate sleep variables identified in step 1 (sleep onset, sleep offset, midsleep, midsleep after 03:00 and SRI), a higher CVD risk score was only weakly associated with earlier midsleep (β=0.18, 95%CI: –0.04, –0.00, p=0.046, R^2=0.390) in the adjusted model (Figure 3.1A, Supplementary Table 3.4, Appendix 3).

Among the men, simple linear regression analyses found that only earlier midsleep (β =–0.17, 95%CI:–0.33, –0.02, p=0.030) was associated with higher CVD risk scores (Supplementary Table 3.1, Appendix 3). Of the covariates, a lower asset index (β=–1.82, 95%CI: –2.86, –0.76, p=0.001) and having a chronic disease (β=0.42, 95%CI: 0.02, 0.83, p=0.039) were associated with a higher CVD risk score (Supplementary Table 3.1, Appendix 3). No associations were found between CVD risk score and any of the five candidate sleep variables identified in step 1 (sleep onset, sleep offset, midsleep, midsleep regularity and sleep duration regularity) in the adjusted models in the men (Figure 3.1B, Supplementary Table 3.5, Appendix 3).

3.3.4 *Sex-specific associations between sleep variables and elevated BP*

Among the women, none of the sleep variables were associated with elevated BP in the simple logistic regression analyses (Supplementary Table 3.2, Appendix 3). Women who consumed more alcohol (OR: 1.05, 95%CI: 1.00, 1.11, p=0.047), reported less MVPA (OR: 0.99, 95%CI: 0.97, 0.99, p=0.044), were older (OR: 1.08, 95%CI: 1.02, 1.13, p=0.005) or who had chronic diseases other than hypertension (OR: 4.15, 95%CI: 1.59, 10.84, p=0.004), however, were more likely to have elevated BP (Supplementary Table 3.2, Appendix 3). Of the four candidate sleep variables identified in step 1 (sleep onset, midsleep, midsleep after 03:00 and midsleep regularity), adjusted models found that women with earlier sleep onsets, earlier sleep midpoints and sleep midpoints before 03:00 were 1.8 (OR: 0.53, 95%CI: 0.33, 0.85, p=0.009), 2.1 (OR: 0.47, 95%CI: 0.26, 0.83, p=0.010) and 3.1 (OR: 0.32, 95%CI: 0.12, 0.81, p=0.017) times more likely, respectively, to have elevated BP (Figure 3.1C, Supplementary Table 3.6, Appendix 3).

For the men, simple logistic regression analyses found no associations between elevated BP and the sleep variables (Supplementary Table 3.2, Appendix 3). Older men, however, were more likely to have elevated BP than younger men (OR: 1.11, 95%CI: 1.04, 1.18, p=0.001). Of the two candidate variables identified in step 1 (sleep onset and midsleep after 03:00), neither were significantly associated with elevated BP in the adjusted models (Figure 3.1D, Supplementary Table 3.7, Appendix 3).

3.3.5 *Sex-specific associations between sleep variables and obesity*

Simple logistic regression analyses indicated that among the women, those with an earlier sleep offset (OR: 0.54, 95%CI: 0.35, 0.81, p=0.003), midsleep time (OR: 0.46, 95%CI: 0.27, 0.77, p=0.003) or sleep midpoint before 03:00 (OR: 0.41, 95%CI: 0.17, 0.94, p=0.035) were 1.9, 2.2 and 2.0 times, respectively, more likely to be obese (Supplementary Table 3.3, Appendix 3). In addition, women who consumed less alcohol per week (OR: 0.94, 95%CI: 0.89, 0.99, p=0.020) or were older (OR: 1.07, 95%CI: 1.01, 1.12, p=0.011) were more likely to be obese (Supplementary Table 3.3, Appendix 3). Six candidate sleep variables for women (sleep onset, sleep offset, midsleep, midsleep after 03:00, sleep duration >9h and SFI) identified in step 1 were explored in adjusted logistic regression models in step 2. In step 2, only the sleep offset and midsleep models remained significant, however, none of the potential covariates identified in step 1 contributed significantly to either of the models. Thus, earlier sleep offset and midsleep in the women appeared to be independently associated with obesity (Figure 3.1E, Supplementary Table 3.8, Appendix 3).

Men with a shorter sleep duration were 2.1 times more likely to be obese (OR: 0.48, 95%CI: 0.25, 0.90, p=0.023, Supplementary Table 3.3, Appendix 3). When the five candidate sleep variables (sleep onset, sleep duration, sleep duration >9h, total sleep time and SRI) identified in step 1 were explored in adjusted logistic regression models in step 2, only the sleep duration association remained significant. None of the potential covariates contributed significantly to the model (Figure 3.1F, Supplementary Table 3.9, Appendix 3).

3.3.6 *Sex-specific relationships between sleep duration and other sleep variables*

We assessed relationships between sleep duration and other sleep variables to identify candidate moderator variables for the relationship between sleep duration and CVD risk (Supplementary Table 3.10, Appendix 3). Simple linear regressions showed that women with longer sleep durations had earlier sleep onsets (β: –0.59, 95%CI: –0.79, –0.39 p<0.001), later sleep offsets (β: 0.66, 95%CI: 0.49, 0.83, p<0.001), more WASO (β: 0.01, 95%CI: 0.01, 0.02, p<0.001), higher SFIs (β: 0.03, 95%CI: 0.00, 0.59, p=0.043), more irregular sleep midpoints (β: –0.88, 95%CI: –1.34, –0.41, p<0.001) and more irregular sleep durations (β: –0.36, 95%CI: –0.64, –0.07, p=0.014). Among the men, simple linear regressions showed that men with longer sleep durations also had earlier sleep onsets (β: –0.70, 95%CI: –0.89, –0.51, p<0.001), later sleep offsets (β: 0.68, 95%CI: 0.47, 0.88, p<0.001), more WASO (β: 0.01, 95%CI: 0.00, 0.15, p=0.001) and worse SRI scores (β: –0.05, 95%CI: –0.08, –0.02, p<0.001) (Supplementary Table 3.10, Appendix 3).

3.3.7 *Sex-specific interactions between sleep variables and associations with the CVD risk score*

Among the women, sleep onset time moderated the relationship between sleep duration and CVD risk score (β:–2.38, 95%CI: –0.35, –0.12, p<0.001, Figure 3.2A, Supplementary Table 3.11, Appendix 3) such that for women who went to bed later, shorter sleep was associated with higher CVD risk scores, while for those who went to bed earlier, longer sleep was associated with higher CVD risk scores. A weaker relationship was found whereby WASO moderated the relationship between sleep duration and CVD risk score (β: 0.004, 95%CI: 0.00, 0.00, p=0.014, Figure 3.2B, Supplementary Table 3.11, Appendix 3). In women with less WASO, shorter sleep was associated with higher CVD risk scores, while among women with more WASO, longer sleep was associated with higher CVD risk scores. Both of these models adjusted for education and presence of chronic disease and both covariates contributed significantly to the models.

No significant interactions were found among the men in adjusted models. One interaction, however, was trending towards significance: SFI appeared to moderate the relationship between longer sleep duration and CVD risk scores such that among the men with greater fragmentation,

longer sleep was associated with higher CVD risk scores, while for the men with less fragmentation, shorter sleep was associated with higher CVD risk scores (β: 0.014, 95%CI: 0.00, 0.02, p=0.050, Supplementary Table 3.12, Appendix 3).

Table 3.1. Descriptive characteristics of the men and women.

	Women (n=100)	**Men (n=94)**	**p-value**
Age (y)	39 (32, 47)	39 (34, 46)	0.667
BMI (kg/m^2)	33.3 (26.6, 39.3)	21.3 (19.5, 24.7)	**<0.001**
Overweight (count, %)	86 (86.0)	22 (23.4)	**<0.001**
Overweight and Obese (count, %)	63 (63.0)	5 (5.3)	**<0.001**
Waist circumference (cm)	100.4 (85.7, 111.6)	80.9 (76.1, 87.7)	**<0.001**
High waist circumference (count, %)	48 (48.0)	6 (6.4)	**<0.001**
SBP (mmHg)	117 (108, 129)	124 (117, 135)	**0.003**
DBP (mmHg)	78 (72, 86)	77 (72, 85)	0.906
Elevated BP (count, %)	44 (44.0)	45 (47.9)	0.346
Hypertension medication (count, %)	18 (18.0)	10 (10.6)	0.105
Any chronic diseases (count, %)	35 (35.0)	24 (25.5)	0.101
Fasting glucose concentration (mmol/L)	4.8 (4.5, 5.3)	4.8 (4.4, 5.4)	0.928
Elevated blood glucose (count, %)	15 (15.0)	16 (17.0)	0.462
CVD risk score (%)	3.1 (1.3, 6.1)	6.4 (3.4, 11.6)	**<0.001**
MVPA (min/day)	29 (15, 51)	51 (29, 90)	**<0.001**
Smoker (count, %)	27 (27.0)	62 (65.9)	**<0.001**
Alcohol use (no. drinks per week)	0 (0, 8)	12 (0, 24)	**<0.001**
Employed (count, %)	26 (26.0)	21 (22.3)	0.335
Education (y)	11 (10, 12)	11 (10, 12)	0.054
Asset index	0.47 (0.21, 0.53)	0.47 (0.41, 0.53)	0.383

Data are presented as median (interquartile range) or count (%). P-values represent differences between men and women determined using Mann-Whitney U or Chi-Squared tests.

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; BP: blood pressure; CVD: cardiovascular disease; MVPA: moderate- to vigorous-intensity physical activity.

Table 3.2. Actigraphy-derived and self-reported sleep characteristics for men and women.

	Women (n=100)	Men (n=94)	p-value
Sleep onset time (hh:mm)	22:34 (21:56, 23:11)	22:24 (21:36, 22:47)	0.089
Sleep offset time (hh:mm)	07:36 (06:44, 08:18)	07:48 (07:04, 08:17)	0.103
Midsleep (hh:mm)	03:00 (02:28, 04:43)	03:02 (02:36, 03:31)	0.867
Sleep duration (h)	8.9 ± 1.2	9.4 ± 1.4	**0.009**
Duration >9h (count, %)	49 (49.0)	62 (65.9)	**0.017**
Total sleep time (h)	7.4 ± 1.1	7.6 ± 1.3	0.267
Sleep efficiency (%)	81.8 (76.8, 85.7)	79.9 (72.5, 84.6)	0.085
Sleep efficiency <85% (count, %)	69 (69.0)	72 (76.5)	0.235
WASO (min)	84.9 (68.8, 110.4)	103.1 (76.1, 127.0)	**0.005**
Sleep Fragmentation Index (%)	28.3 (23.3, 34.3)	34.2 (27.4, 40.9)	**<0.001**
Sleep Regularity Index (%)	63.4 (56.3, 68.2)	58.3 (52.5, 65.2)	0.065
Midsleep regularity (h)	0.8 (0.5, 1.1)	0.9 (0.6, 1.2)	0.111
Sleep duration regularity (h)	1.5 (1.1, 2.1)	1.8 (1.2, 2.4)	0.139
High OSA risk (count, %)	22 (22.5)	10 (11.2)	**0.018**
ISI score	1 (0, 6)	2 (0, 5)	0.678
Standard clinical insomnia symptoms (ISI≥15) (count, %)	3 (3.1)	4 (4.4)	0.637
Community clinical insomnia symptoms (ISI≥10) (count, %)	15 (15.5)	5 (5.5)	**0.027**
ESS score	5 (1, 9)	3 (1, 8)	**0.011**
Excessive daytime sleepiness (ESS>10) (count, %)	21 (21.2)	16 (17.8)	0.552
PSQI score	4 (3, 6)	4 (3, 5)	0.162
Poor sleep quality (PSQI>5) (count, %)	29 (29.3)	16 (17.4)	0.061

Data are presented as mean ± standard deviation, median (interquartile range) or count (%). P-values represent differences between men and women determined using independent t-tests, Mann-Whitney U or Chi-Squared tests.

WASO: Wake after sleep onset; OSA: Obstructive sleep apnoea; ISI: Insomnia Severity Index; ESS: Epworth Sleepiness Scale; PSQI: Pittsburgh Sleep Quality Index.

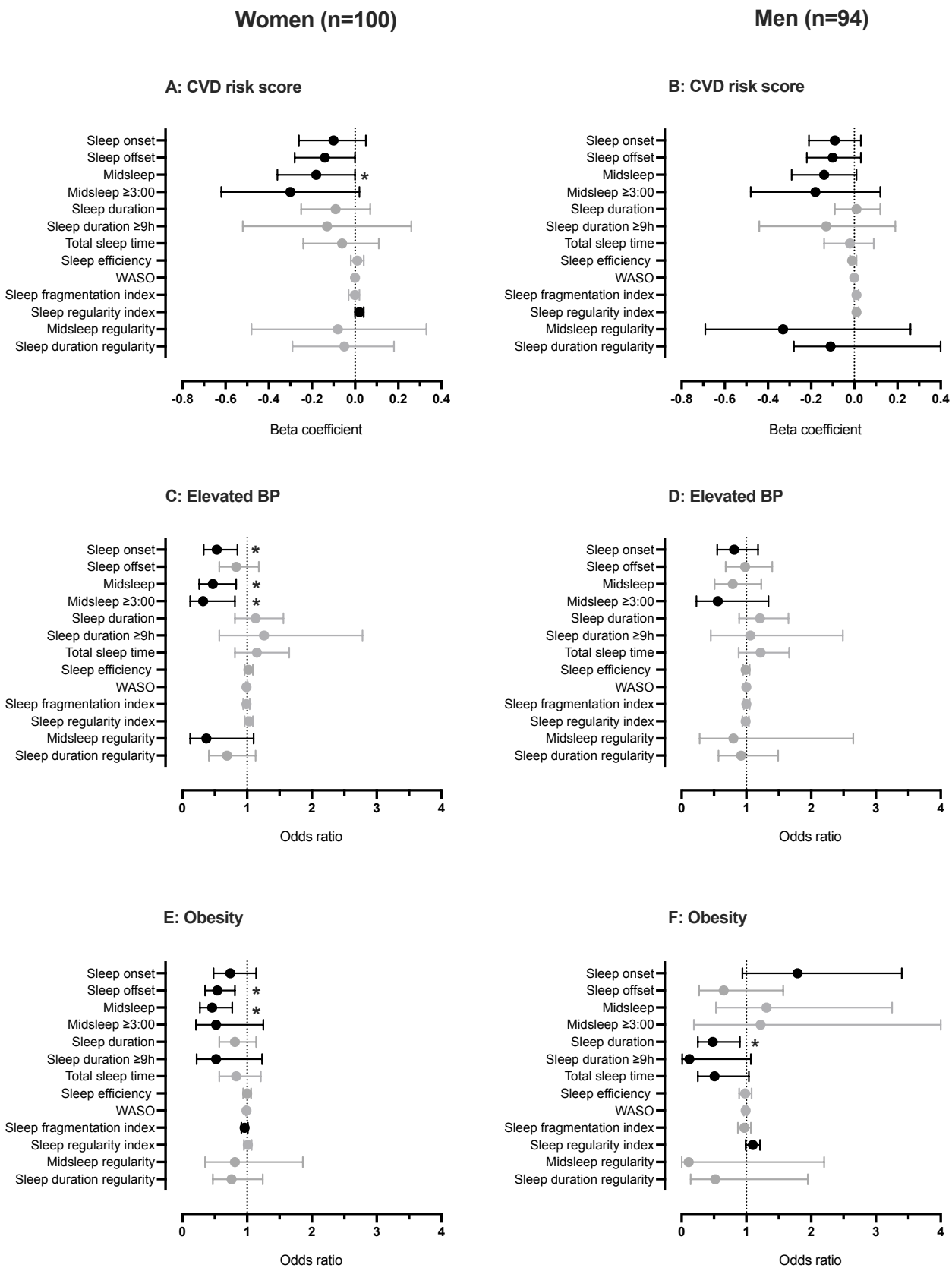

Figure 3.1. Associations between sleep variables and CVD risk score (A and B), elevated BP (C and D) and obesity (E and F) in women (n=100, left panel) and men (n=94, right panel). Grey symbols represent sleep variables from the step 1 simple regressions that did not qualify for step 2 but are shown for interest and remain unadjusted (Supplementary Tables 3.1 – 3.3, Appendix 3). Black symbols represent sleep variables explored in step 2 multivariable models, adjusted only for significant covariates in respective models (See Supplementary Tables 3.4 – 3.9, Appendix 3). Data are presented as beta coefficients or odds ratios with 95% confidence intervals. CVD: cardiovascular disease, BP: blood pressure, WASO: wake after sleep onset. **p<0.050.*

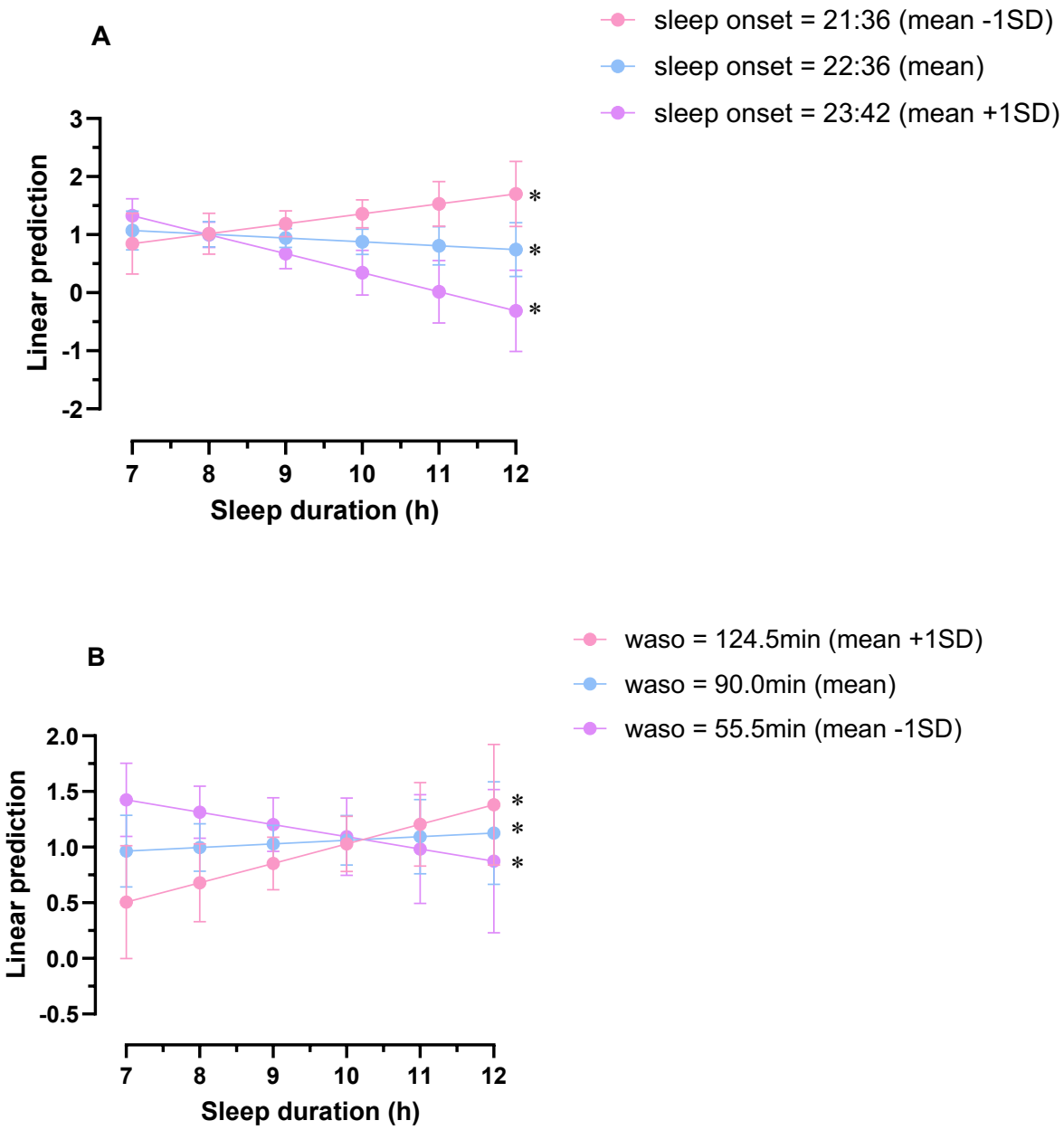

Figure 3.2. Interaction effects of sleep duration and sleep onset (A) and sleep duration and WASO (B) on CVD risk scores in women (n=100). Associations were explored using multivariable linear regression models adjusted for education and non-CVD chronic disease. To visualise these models we divided the candidate sleep variable into three groups (mean, mean +1SD, mean -1SD) and plotted sleep duration (X-axis) vs. CVD risk (beta coefficient, Y-axis) for each group. CVD: cardiovascular disease, SD: standard deviation, WASO: wake after sleep onset.

3.4 Discussion

Among low SES South African adults of African descent, we confirm objectively-measured long, but poor quality and disturbed sleep. Half of the women and two thirds of the men have sleep durations of nine or more hours per night, which is longer than the 6-8h per night[180,181] reported in many other populations. Interestingly, we found none of the expected associations between sleep duration (long or short) and CVD risk scores or elevated BP[34,124] in either the men or the women, although men with shorter sleep were more likely to be obese than those with longer sleep. In part this may be attributed to the fact that so few of these participants are short sleepers, or perhaps because so many of the women are obese.

Before discussing the key findings of this study, it is essential to contextualize the poor-quality sleep of these individuals against normative standards. In this study, men and women present with average SFI scores of 34.2 (27.4, 40.9)% and 28.3 (23.3, 34.3)%, respectively. Previous studies in healthy, community-dwelling populations have found lower SFI scores of 16.4 ± 0.9%[182] and 24.7 ± 0.5%[183]. Another study in healthy, middle-aged adults found SFI scores to be 6.1 ± 2.1%[184]. In this study, poor sleep efficiency (SE) (<85%) was found in 76% and 69% of men and women, respectively. In two previous studies who classified poor sleep efficiency at SE ≤80%, the first found that 57% of men and 43% of women presented with poor sleep efficiencies[185], while the second (in older community-dwelling individuals) found that, 21% of men and 33% of women presented with poor sleep efficiencies[186]. Finally, in this study, men and women present with average SRI scores of 63.4 (56.3, 68.2) and 58.3 (52.5, 65.2), respectively. To the best of our knowledge, these are some of the lowest SRI scores reported in the literature, with the next closest SRI scores being reported as 70.3 ± 12.6 in individuals with alcohol use disorder[187] and 71.6 ± 14.5 among healthy older adults in the Multi-Ethnic Study of Atherosclerosis[188]. Together, these strongly highlight the poor sleep quality experienced by participants in this cohort.

Among the women, all analyses suggest a relationship between sleep timing and CVD risk. Women with earlier timed sleep were more likely to have higher CVD risk scores, elevated BP and be obese compared to those who had later sleep timing. This is similar to findings in Chapter 2[173]. We hypothesize two main reasons as to why these women may be going to bed so early. The first is due to safety concerns, where women might choose to go to bed early to avoid being outside during nighttime hours when the neighbourhood is less safe[189]. Khayelitsha, the site of the study where these participants reside, is an urban township in South Africa. The township is characterized by high

rates of poverty and crime[120] during the day and night, where at night, specifically, there is poor street lighting and limited police presence. Feelings of not being safe at night might therefore be a significant factor influencing the sleep behaviours of some of these women[189]. As suggested in Chapter 2, the second reason relates to family responsibility, where women often bear a significant burden of parenting, childcare and elder care[190], which might curtail their sleep opportunity earlier than they would like, as they have to be up to get children ready for school, for example. These tasks might therefore prompt women to go to bed earlier as wish to ensure they are well-rested to manage these responsibilities the next day.

When interactions and associations between sleep variables were investigated, the complex relationship between sleep and CVD in this population started to unfold. Notably, the relationship between longer sleep and higher CVD risk scores in women who go to sleep earlier suggests a possible role for circadian misalignment as a result of mistimed sleep in the development of CVD among women in this population[191,192]. Since we did not observe a linear relationship between longer sleep and higher CVD risk, we speculate that these longer sleeping women with earlier sleep onsets are perhaps sleeping out of phase in relation to their endogenous circadian rhythms. Perhaps it is circadian disruption rather than longer sleep, *per se,* that is increasing their risk for CVD as it is well-established that disruption to our body's natural circadian rhythms can be detrimental to cardiovascular health[154].

The second interaction-related finding was that longer sleep was associated with higher CVD risk scores among women with more WASO. Similarly, among the men, while the interaction between sleep duration and fragmentation only trended towards significance, it is starting to show a similar picture whereby longer sleep that is more fragmented may be associated with greater CVD risk. A proposed mechanism by which sleep disturbance and fragmentation might increase CVD risk could be through overactivation of the sympathetic nervous system (SNS). Sleep fragmentation caused by noise has been shown to produce sympathetic overactivity during sleep[193]. A study by Chouchou *et al.* (2013) showed that repetitive sympathetic arousals during sleep are associated with elevated SBP and higher risk of hypertension[194]. One of the primary challenges that individuals living in Khayelitsha face is the overcrowded informal settlement. In such close quarters, noise and disruptions from neighbouring households are inevitable, creating an environment that may not be conducive to healthy sleep[195]. It is entirely plausible to suggest that fragmented sleep results from prolonged overactivity of the SNS owing to noise-related disturbances or even hypervigilance relating to fears around safety at night, and subsequently elevated BP and heart rate[157], potentially

increasing CVD risk. The direction of this relationship (i.e. fragmented sleep contributing to heightened CVD risk) is likely bidirectional (i.e. individuals with worse cardiovascular health may have higher sleep fragmentation) and requires further investigation.

While sleep duration and sleep onset did not differ between employed and unemployed women, the latter had later sleep offsets and midsleep times with overall poorer quality sleep (poorer sleep efficiency, greater sleep fragmentation and poorer sleep regularity). When adjusting for employment, however, we observed no significant effect of employment on CVD risk, elevated BP or obesity. Thus, we are confident that the associations between sleep and CVD risk persist independently of one's employment status.

The finding that shorter sleep was associated with higher CVD risk scores among the women who either went to bed later or had less WASO likely points to the fact that, while these women appear to have better quality sleep (likely due to higher sleep pressure[86]), their sleep duration is possibly too short for their need. This is in line with a significant body of research that shows adults with insufficient sleep are at greater risk for CVD[34]. It is also well known that later timed sleep is associated with a higher risk for CVD, specifically in those who are evening-types[154]. It is challenging, however, to classify this cohort as evening-types given that the median sleep onset time was 22:30 and no one had a median sleep onset time after midnight. It also appears that, regardless of sleep onset timing, the shorter sleepers (i.e. those around 7h) are at a similar CVD risk to the longer sleepers.

Apart from the sleep variables, the covariates of education and chronic disease (non-CVD) for women, and asset index for men, showed independent and expected associations with CVD risk, where fewer years of education and presence of chronic disease other than CVD were associated with greater CVD risk. Both of these findings are well-established in the literature with lower education having been shown to be independently associated with an increased risk of all-cause and CVD mortality[196] and other chronic diseases being comorbid with CVD[197]. In the men, higher asset index was associated with lower CVD risk. Similarly to education, asset index, as a social determinant of health, signals the association between SES and the development of CVD risk factors as well as CVD morbidity and mortality[5]. Sleep variables aside, we cannot underestimate the role of these factors in overall CVD risk in this population.

The observed sex differences in the relationship between sleep and CVD risk is likely multifactorial. It can be argued, however, that similarly to Chapter 2[173], one key factor at play is the starkly different primary CVD risk factors between men and women in this study (e.g. higher smoking, alcohol use and SBP among the men versus higher rates of obesity among the women), which likely contribute to distinct sleep and CVD health profiles[170]. These lifestyle factors not only impact sleep directly but may also influence other cardiovascular risk factors such as elevated blood glucose or blood lipids.

We acknowledge several limitations to the current study. The cross-sectional nature of the data precluded the causal relationship assumption, warranting future studies utilising longitudinal or even intervention research designs. Additionally, there may be other factors which were not investigated in this study, such as mental health or psychiatric disorders including depression, stress, anxiety and post-traumatic stress disorder which may influence the associations between sleep health and CVD risk. Napping behaviour was not investigated in this Chapter since we focused solely on nocturnal sleep. Future studies need to investigate the role of napping in CVD risk in this cohort. Finally, since the Berlin Questionnaire could not be included as a covariate due to collinearity, the potential contribution of sleep apnoea to CVD risk is a limitation. We do, however, feel that this study adds immense value to the current body of literature as it has becoming increasingly evident that cultural context and socioeconomic determinants likely play a major role in both sleep and cardiovascular health.

3.5 Conclusion

In conclusion, we have found that the typical relationships between sleep duration and CVD risk are not present, other than to note that obese men do have a higher risk for CVD. Rather, the moderation analyses suggest that sleep timing and disturbances appear to be important factors to consider when interpreting associations between sleep duration and risk for CVD. These results reinforce current thinking in the field which suggests that rather than focussing on isolated sleep variables, interactions between variables or composite sleep variables should be considered when examining relationships between sleep and health outcomes. Future studies should focus on mechanisms and causes of circadian disruption among women and sleep disruptions among men, and should also take sex into account when assessing relationships about sleep health in relation to CVD. Since Chapters 2 and 3 have given us a better understanding of the overall relationships between sleep and CVD in this cohort, Chapter 4 will delve into an important marker of CVD health – BP dipping.

Chapter 4

Sleep characteristics associated with nocturnal blood pressure non-dipping in healthy individuals: a systematic review

Philippa E. Forshaw, Arron T. L. Correia, Laura C. Roden, Estelle V. Lambert, Dale E. Rae

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4.1 Introduction

Blood pressure (BP) displays circadian rhythmicity with the 24h sleep-wake cycle representing the most important and consistent source of circadian variation. In most healthy, normotensive persons, BP declines during sleep by 10-20% from mean waking values, a process known as nocturnal BP dipping. In fact, this phenomenon has emerged as a BP-related biomarker of healthy sleep physiology[198]. Nocturnal BP non-dipping[65,199–201], defined as a difference between sleep and wake BP of <10%, and nocturnal hypertension[200,202–206] have been associated with an increased risk for several cardiovascular diseases (CVD) and should be regarded as abnormal[207]. A recent review[199] highlighted the fact that, while many studies have emphasised the importance of ambulatory BP monitoring, the importance of BP monitoring during sleep has yet to be fully appreciated.

There is rapidly accumulating evidence suggesting that poor sleep, including insufficient sleep duration, poor sleep quality and sleep disruption, is associated with both short- and long-term poor health outcomes[79,125,208], such as an increased risk for the development of CVD[202,209,210]. Depriving healthy participants of sleep has been shown to acutely increase BP, especially in the elderly[211]. Individuals with sleep disorders such as insomnia and obstructive sleep apnea (OSA) have also been shown to have a higher prevalence of hypertension[212–214]. It is thought that prolonged periods of short sleep lead to hypertension through extended exposure to elevated average 24h BP and increased synthesis of catecholamines due to heightened sympathetic nervous system (SNS) activity[215].

Several studies have shown that aspects of sleep are associated with nocturnal BP non-dipping in clinical populations, such as hypertensives[198] or individuals with OSA[216], insomnia[217] or narcolepsy[218]. For example, the degree of 24h BP variation in hypertensive populations has been related to sleep quality[198], with the general consensus being that hypertensive persons with nocturnal BP non-dipping have more disturbed sleep (as determined by electroencephalogram [EEG]) compared to those who do experience dipping[219]. Similarly, individuals with narcolepsy who exhibit nocturnal BP non-dipping have increased sleep fragmentation and a higher arousal index compared to healthy controls[218,220] which suggests that changes in nocturnal BP in patients with narcolepsy may be the result of, not only hypocretinergic deficiency, but also the altered sleep-wake regulation characterising narcolepsy. Insomnia has been shown to be related to hypertension and nocturnal BP non-dipping, where the association becomes stronger with more frequent insomnia symptoms and shorter objective sleep duration[217]. In contrast, despite the high prevalence of non-dipping in individuals with OSA[221] and the fact that non-dipping may be regarded as a marker of OSA[216], several

studies have found no evidence for an association between sleep quality and nocturnal BP non-dipping[221] or sleep quality, habitual sleep duration and sleep efficiency on nocturnal hypertension and BP non-dipping[222]. However, it has been shown that sleep timing (specifically midpoint of sleep or midsleep) is associated with systolic blood pressure (SBP) non-dipping in OSA patients[222].

Since the exact mechanisms responsible for BP non-dipping are unclear, and the majority of studies have focused on clinical populations, we aim to build on these findings by investigating BP non-dipping in healthy individuals to better understand the underlying causes. Many studies have indeed shown that these disease states and disorders (hypertension, OSA, insomnia and narcolepsy) are confounding factors on nocturnal BP dipping. Since both non-dipping and poor sleep are associated with an increased CVD risk one might speculate that good sleep health, defined by Buysse *et al.* (2014) as *"subjective satisfaction, appropriate timing, adequate duration, high efficiency, and sustained alertness during waking hours"*[74] may play a crucial role in normal nocturnal BP dipping.

Therefore, the primary aim of this study is to systematically review the current literature to determine whether BP non-dipping during nocturnal sleep is a phenomenon observed in apparently healthy individuals. The secondary aim was to identify specific sleep characteristics (i.e. total sleep time, sleep onset latency, wake after sleep onset (WASO), sleep depth, quality and efficiency) that are associated with nocturnal BP non-dipping in apparently healthy individuals. It is anticipated that an improved understanding of the aspects of sleep that contribute to nocturnal BP dipping may inform future sleep-related behavioural interventions aimed at improving nocturnal BP dipping and ultimately reducing the burden of CVD. To the best of our knowledge, this is the first systematic review to address the relationship between sleep and BP dipping in apparently healthy individuals.

4.2 Methods

4.2.1 *Literature search*

Peer-reviewed original studies where sleep and nocturnal BP dipping or non-dipping were measured as outcomes, were assessed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[223]. Systematic literature searches were conducted in three databases: PubMed, Scopus and Web of Science. The electronic search strategy included the following terms: "sleep" or "insomnia" and "blood pressure dip*" or "BP dip*" or "blood pressure nondip*" or "blood pressure non-dip*". The term "insomnia" was used in the literature search to ensure that all possible papers related to sleep were captured. As per the exclusion criteria below, such papers were only

included if they reported separately on a control group of apparently healthy (i.e. without insomnia) participants. The final search terms for PubMed, Scopus and Web of Science are presented in Supplementary Table 4.1. As is the case with all reviews, there was a potential for bias, such as search, inclusion criteria and selector bias. Numerous strategies were employed to minimize these biases, such as utilizing broad search terms to capture all studies and having objective inclusion and exclusion criteria, established prior to screening to further limit bias.

4.2.2 *Inclusion and exclusion criteria*

The following inclusion criteria were applied: (i) original articles published from inception until Feb 2022 in English, (ii) study designs including randomized controlled trials, cross-sectional, case-control and cohort studies, (iii) adult participants (≥18y of age) and (iv) reported sleep characteristics (derived from self-report, actigraphy or polysomnography [PSG]) and nocturnal BP dipping derived from ambulatory blood pressure monitors. Studies were excluded if (i) they were reviews, commentaries, letters, editorials, conference proceedings, case reports, conference abstracts or non-peer reviewed articles, (ii) participants had any pre-existing mental health disorders including but not limited to generalized anxiety disorder, major depressive disorder, bipolar disorder or post-traumatic stress disorder (in order to avoid possible confounding effects of these diseases or associated medications on sleep health), (iii) participants had any known sleep disorders or the study did not include apparently healthy participants (non-clinical population), (iv) participants had any diagnosed medical conditions (e.g. hypertension, cardiovascular disease and diabetes) and (v) participants were >64y, since sleep and cardiovascular health typically show age-related changes from 65y onwards. In cases where studies examined participants with the above-mentioned exclusion criteria, the study was retained for review if they also reported separately on control participants, free from the excluded disorders. Apparently healthy participants were therefore defined as individuals with no reported medical or sleep condition or disease.

4.2.3 *Nocturnal BP dipping*

Nocturnal BP dipping is measured by collecting multiple BP measurements over a 24h period using an ambulatory BP monitor. The percent difference between mean BP measured during wakefulness and mean BP measured during sleep is used to calculate the extent to which BP dips during sleep as follows: [(awake BP – sleep BP) / awake BP] X 100. A reduction in mean BP from wake to sleep of ≥10% is classified as nocturnal BP dipping, while a reduction of <10% is classified as non-dipping. Currently, there are no guidelines on which specific measure of BP [(i.e. SBP, diastolic blood pressure (DBP), a combination of SBP and DBP, or mean arterial blood pressure (MAP)] should be used to

classify a particular individual as having a dipping or non-dipping profile[48]. As such, we report the nocturnal BP dipping results specific to each included study (i.e. SBP dipping, DBP dipping, a combination of SBP and DBP dipping or MAP dipping).

4.2.4 *Data extraction*

The original search strategy was devised and agreed upon by PEF, DER and AC. In the first round, articles were screened on the basis of titles and abstracts by PEF. The second round involved assessing the eligibility criteria. PEF and AC independently screened the titles and abstracts and tested the eligibility criteria. Discrepancies were resolved through discussion between PEF, AC and DER, where DER served as the arbitrator. The item in question was then included or excluded accordingly. PEF assessed the quality and risk of bias of included studies using the Joanna Briggs Institute (JBI) Critical Appraisal Tools for analytical cross-sectional studies, randomized controlled trials and case-control studies[224–226] (Supplementary Tables 4.2 and 4.3, Appendix 4). These tools assist in assessing the methodological quality of a study and the extent to which a study has addressed the potential for bias in its design, conduct and analysis.

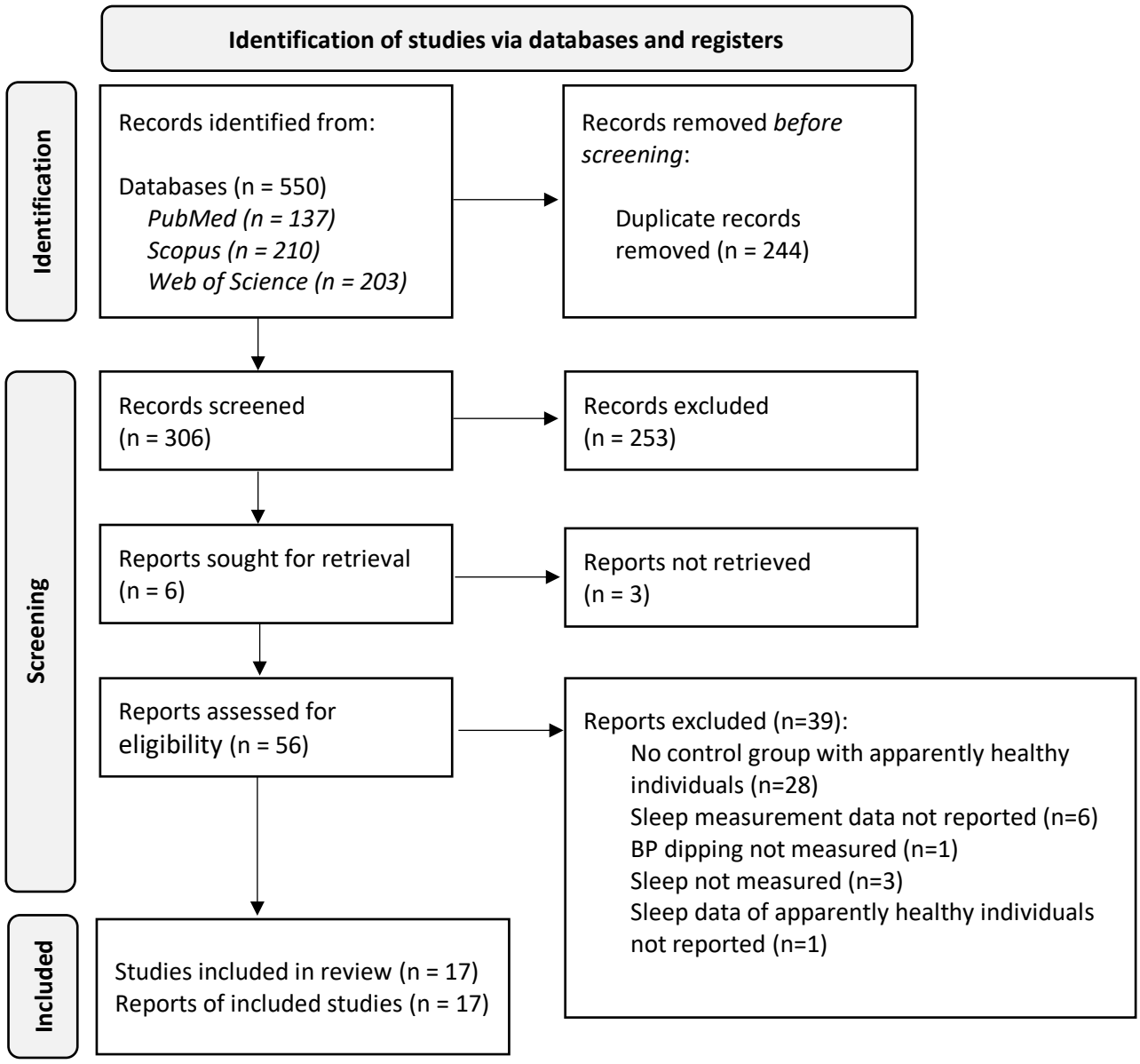

Figure 4.1 PRISMA flow diagram used to outline the literature search procedure and article selection.

4.3 Results

4.3.1 *Search results*

The initial search identified a total of 550 studies using the criteria described above. After 244 duplicates were removed, the titles and abstracts of the remaining 306 studies were screened. Of these, 253 studies were excluded and 6 studies were retrieved. Finally, 56 studies were tested for eligibility and 39 were excluded for reasons mentioned in Figure 4.1, such that 17 studies fully met

the inclusion criteria for the review. The reference lists in these studies were also subjected to screening and eligibility testing.

4.3.2 *Study characteristics*

Table 4.1 reports the main features and characteristics of the included studies. Fourteen studies were cross-sectional, two were randomized control trials and one was a non-randomized control trial. Twelve studies completely fulfilled the JBI checklist criteria, however all studies were considered to be of sufficiently good quality (see Supplementary Tables 4.2 and 4.3, Appendix 4). In the 5 studies that did not fully meet the criteria, a lack of confounding factors identified was with the main factor contributing to their lower appraisal. Seven studies assessed sleep using PSG[227–233], six used wrist actigraphy[229,230,233–236], six used only self-report methods (e.g. sleep diaries and questionnaires)[237–242] and one used an EEG headband[243]. Nocturnal BP dipping was mostly assessed using 24h ambulatory BP monitoring (ABPM) (n=13), two studies used 48h ABPM, one study used 96h ABPM and one study used overnight ABPM. For all studies, nocturnal BP dipping was defined as a reduction in mean BP from wake to sleep of ≥10%, while non-dipping was defined as a reduction of <10%.

4.3.3 *Sleep deprivation*

Kamperis *et al.* (2010) examined the effects of acute complete sleep deprivation on MAP and nocturnal urine production in young adults. Nocturia (i.e. awakening at night to void) is a recognized, but understudied, symptom of uncontrolled hypertension[244] and the most common cause of disturbed sleep, with repeated arousals further increasing nocturnal BP and nocturia[245]. During the complete sleep deprivation nights, participants retired to their beds at bedtime but were not allowed to sleep or be ambulatory unless for voiding, resulting in complete sleep deprivation. Both men and women displayed blunted MAP dipping ($p<0.05$) on the complete sleep deprivation nights compared to the baseline nights.

Sayk *et al.* (2010) specifically deprived participants of slow wave sleep (SWS) using a single-blinded design in which participants had one undisturbed sleep period (control) and one SWS-deprived sleep period. To achieve the latter, a 440Hz sound was applied from a loudspeaker placed next to the participant's head as soon as two subsequent 30s epochs of SWS were detected until the delta waves disappeared from the EEG trace, and sleep shifted back to non-rapid eye movement (NREM) sleep stages 1 or 2 or microarousal. Although BP dipping still evolved in the absence of SWS, mean nocturnal BP was significantly lower during undisturbed sleep compared with the SWS-deprivation

condition (p=0.048). In addition, SWS-deprivation lead to significantly attenuated mean BP dipping during the first half of the night (p=0.017), but not during the rapid eye movement (REM)-dominated second half of the night (p=0.17).

Yang *et. al.* (2017) used a model of chronic, partial sleep deprivation by randomly assigning 43 participants to either an experimental group involving four blocks of sleep restriction or to an 8h/night sleep control group. In the sleep restriction group, participants slept 4h/night for three consecutive nights, and then were permitted a night of 8h recovery sleep. This pattern was repeated four times. Nocturnal BP dipping during all four blocks of sleep restriction was significantly less compared to the control nights (p=0.002). Furthermore, after repetitive exposure to shortened sleep, SBP was significantly increased for the whole day during block one of sleep restriction, while daytime DBP was significantly increased in the first, second and fourth blocks (all p<0.01).

4.3.4 *Sleep fragmentation or disturbance*

Loredo *et al.* (2004) associated sleep quality and stages measured using PSG with nocturnal BP dipping. They observed that nearly 18% of 62 otherwise healthy participants were non-dippers. Participants with more awakenings throughout the night had less DBP dipping (r=–0.360, p=0.004). Similarly, Matthews *et al.* (2008) used actigraphy and showed that greater sleep fragmentation index scores (measure of movement during sleep inferred to be a measure of sleep disruption) were associated with blunted nocturnal SBP and DBP dipping (SBP: r=0.27, p<0.01 and DBP: r=0.28, p<0.01). In the same study, participants who had blunted nocturnal SBP dipping had a longer sleep onset latency (SOL, r=0.18, p<0.05 unadjusted) and a greater number of arousals (r=0.18, p<0.05 adjusted). Participants who had blunted nocturnal DBP dipping spent less time in REM sleep (r=–0.16, p<0.05 adjusted) and had a greater number of arousals (r=0.18, p<0.05 adjusted). Likewise, Mellman *et al.* (2015) showed that in a predominantly African American sample, 38.2% of participants displayed nocturnal BP non-dipping and that non-dipping was associated with higher WASO (r=–0.18, p<0.05). Three studies found no significant differences in any self-reported sleep characteristics relating to sleep fragmentation or disturbance between adults classified as dippers and non-dippers[227,238,240]. Possible reasons for these findings are discussed later.

4.3.5 *Sleep depth*

In addition to the findings above by Loredo *et al.* (2004), the authors also found that those who spent more time in PSG-derived stage NREM stage 3 sleep (i.e. deep sleep) exhibited a larger degree of DBP and MAP dipping (r=0.410 and r=0.378, respectively, p≤0.002). Similarly, Matthews *et al.*

(2008) showed that participants who had less nocturnal SBP dipping also spent more time in PSG-derived NREM stage 1 sleep (i.e. light sleep) (r=0.20, p<0.01, adjusted) and less time in REM sleep (r=–0.17, p<0.05, adjusted).

It is well known that alcohol consumption disturbs sleep architecture in adults[246,247]. Payseur *et al.* (2020) measured the effects of alcohol consumption on sleep architecture including nocturnal BP dipping in young adults. Following consumption of 2ml alcohol/kg of body, participants had a longer total sleep time (p<0.05) and shorter SOL (p<0.05) but spent more time in light sleep (219.5 ± 0.1min vs. 186.9 ± 1.0min, p<0.05; as measured by the Zeo™ sleep monitoring headband) compared to baseline. Nocturnal SBP increased following alcohol consumption (134.2 ± 6.9mmHg vs. 120.8 ± 3.5mmHg, p<0.05) which attenuated nocturnal BP dipping.

4.3.6 *Sleep timing and shift work*

Chin *et al.* (2022) aimed to test whether sleep characteristics (specifically duration, regularity and continuity) helped to explain the association between social integration (determined using a social role diversity score: sum of the number of different type of roles than an individual had participated in at least once every two weeks) and BP dipping. They recruited 359 healthy adults who wore an ambulatory BP monitor for four days, obtaining hourly BP measurements, and a wrist actigraphy for seven days. The participants had an average sleep duration of 7.0 ± 0.9h, an average WASO of 0.8 ± 0.3h and an average midsleep of 3.1 ± 1.3h. Greater average sleep duration (β=–0.15, 95%CI not reported, p=0.006), less WASO (β=0.17, 95%CI not reported, p=0.001) and lower variability in sleep timing (β=0.25, 95%CI not reported, p<0.001) were associated with more MAP dipping[236].

McHill *et al.* (2022) aimed to determine whether transitioning from regular daytime shifts into shiftwork (and vice versa) changes an individuals' nocturnal BP dipping pattern. Furthermore, they aimed to identify the potential mechanisms for any such changes. Participants were studied in a 90-day protocol where measurements were repeated after ±30 and 90 days after transitioning. During the one-week sleep diary at baseline, participants reported an average bedtime and wake-up time occurring at 21:53 (95%CI: 21:22, 22:25) and 05:39 (95%CI: 05:25, 05:53), respectively, resulting in an average sleep duration of 7.1h (95%CI: 6.7, 7.5h). Newly transitioned shift workers displayed dramatic changes in overnight blood pressure, with 62% converting from a healthy BP dipping pattern to the non-dipping pattern, resulting in 93% of shift workers displaying a non-dipping pattern at 90 days. In contrast, 50% of shift workers who transitioned back to regular daytime shifts had a non-dipping pattern at baseline which decreased to 0% non-dippers at 90 days. When

examining the magnitude of BP dipping in relation to sleep timing variability, they found that a higher variability in bedtime timing was associated with less BP dipping (r^2=–0.53, p=0.03)

Carev *et al.* (2011) measured anesthesiologists during a 24h on-call workday, where they obtained about 3h less sleep compared to their normal workdays. Fewer staff displayed nocturnal DBP dipping when on-call vs. normal workday nights (p=0.036).

Patterson *et al.* (2021) studied emergency medical service nightshift workers during their scheduled nightshift and their non-workday. They found that, during the scheduled nightshift (>18h work), 49.1% of participants experienced blunted nocturnal dipping of SBP or DBP during periods of sleep (<6h sleep). This was significantly more than the number of participants who experienced blunted nocturnal SBP (25%) and DBP (3.9%) dipping during the non-workday sleep (SBP: p=0.029, DBP: p=0.001). Most participants (92.5%) napped during nightshifts with blunted nighttime BP dipping (i.e. blunted dipping during wake while on shift) being observed in all participants who did not nap during the nightshift, while <15% of participants who did nap (specifically for >60min) experienced blunted BP dipping during wake while on shift (p<0.05).

4.3.7 *Other associations*

Ulu *et al.* (2013) recruited equal numbers of otherwise healthy adults classified as dippers and non-dippers into their study. More of the non-dippers (62%) reported poorer PSQI-derived sleep quality compared to dippers (40%, p=0.002). The non-dipper group had worse overall PSQI scores and scores for all the PSQI sub-components (sleep duration, sleep onset latency, sleep efficiency, use of sleep medication, sleep disturbance, sleep quality, and daytime dysfunction) compared to the dipper group (all p<0.05).

Hughes *et al.* (2007) examined the contribution of sleep to ethnic differences in nocturnal BP dipping observed in healthy African American and Caucasian men and women. Among other results, African American men and women were more likely to be classified as non-dippers than Caucasian men and women (59% vs. 29%, p=0.01), spend less time-in-bed (p=0.03) and have a shorter sleep duration (p=0.007) and lower sleep efficiency (p=0.005). Collectively, blunted nocturnal DBP dipping was associated with longer SOL (r=0.28, p<0.05) and a lower sleep efficiency (r=–0.26, p<0.05).

Sherwood *et al.* (2001) evaluated the effects of natural menopause on nocturnal BP dipping in otherwise healthy African American and Caucasian women. Hypertension is considered a major risk

factor for cardiovascular morbidity and mortality in postmenopausal women[248]. Compared to premenopausal women, postmenopausal women exhibited blunted nocturnal SBP ($p<0.01$) and DBP ($p<0.02$) dipping.

Troxel *et al.* (2017) examined the association between marital conflict and nocturnal BP dipping in military couples, given that veterans are a population known to be at high risk for sleep disturbances. The authors aimed to determine whether self-reported sleep disturbances mediated associations between marital conflict and BP dipping. Greater marital conflict was associated with blunted nocturnal BP dipping ($\beta=0.27$, $p=0.03$) with the effects being stronger in women compared to men ($p<0.05$). It should be noted, however, that all the participants exhibited BP dipping in the normal range.

Table 4.1. Summary of the studies addressing the relationship between sleep and blood pressure (BP) non-dipping.

Citation Study design	Sample (size, age, M/W)	Measurement		Primary outcome variables		
		Sleep	BP dipping	Sleep		BP dipping [#]
Carev *et al.,* (2011) CS	• 12 shift workers • 45.5 (33, 61)y • 8/4	Sleep diaries	24h ABPM	<u>On-call</u>*:* TIB (h): 5 (2, 7)	<u>Normal day</u>*:* TIB (h): 8 (7, 9)	<u>On-call</u>*:* 33.3% dippers* <u>Normal day</u>*:* 83.3% dippers*
Chin *et al.,* (2022) CS	• 359 healthy adults • 52.6 ± 7.1y • 140/219	Wrist actigraphy	96h ABPM	TST (h): 7.0 ± 0.9 WASO (h): 0.8 ± 0.3 Midsleep (h): 3.1 ± 1.3		<u>Mean BP dipping ratio</u>: 0.84 ± 0.08 <u>Mean nocturnal SBP (mmHg):</u> 118.6 ± 12.1 <u>Mean nocturnal DBP (mmHg):</u> 66.8 ± 10.3
Fallo *et al.,* (2002) CS	• 173 healthy adults • 49.8 ± 13.6y	Self-reported sleep disturbance	24h ABPM	<u>Dippers:</u> Sleep disturbance score from the Psychosocial Index: 1.66 ± 1.57	<u>Non-dippers:</u> Sleep disturbance score from the Psychosocial Index: 1.51 ± 1.70	42.2% dippers 57.8% non-dippers
Hughes *et al.,* (2007) CS	• 89 healthy adults • 19.7y • 46/43	Wrist actigraphy, sleep diaries	24h ABPM	<u>AA men:</u> TIB (min): 380.9 ± 100.1 TST (min): 340.1 ± 98.0 SOL (min): 29.0 ± 30.1 SE (%): 77.6 ± 9.8* <u>AA women:</u> TIB (min): 392.0 ± 99.3* TST (min): 342.0 ± 103.7* SOL (min): 30.6 ± 33.1 SE (%): 74.9 ± 11.4*	<u>Caucasian men:</u> TIB (min):422.1 ± 112.2 TST (min): 393.9 ± 117.8 SOL (min): 15.7 ± 20.9 SE (%): 84.4 ± 7.6* <u>Caucasian women:</u> TIB (min): 464.4 ± 120.6* TST (min): 437.7 ± 121.7* SOL (min): 18.2 ± 16.6 SE (%): 83.3 ± 6.2*	<u>AA:</u> 44% dippers* <u>Caucasian:</u> 71% dippers*
Ishikawa *et al.,* (2008)	• 52 healthy adults • 64y • 29/23	PSG	24h ABPM	<u>Dippers:</u> Daytime sleepiness symptoms (%): 14.3	<u>Non-dippers:</u> Daytime sleepiness symptoms (%): 16.7	53.8% dippers 46.2% non-dippers

CS				SE (%): 64 ± 17 Arousal index (h^{-1}): 29.0 ± 13	SE (%): 63 ± 13 Arousal index (h^{-1}): 27.4 ± 9.5	
Kamperis *et al.,* (2010) CS	• 20 healthy adults • 25 ± 1.5y • 10/10	Sleep diary	24h ABPM	Complete sleep deprivation (10h time in bed with no sleep allowed)		<u>Men:</u> Baseline night MAP (mmHg): 81.6 ± 2.8 Sleep deprivation MAP (mmHg): 85.3 ± 1.3* <u>Women:</u> Baseline night MAP (mmHg): 74.1 ± 1.9 Sleep deprivation MAP (mmHg): 82.3 ± 2.2*
Loredo *et al.,* (2004) CS	• 62 healthy adults • 36.0 ± 7.9y • 29/33	PSG	24h ABPM	<u>Dippers:</u> TST (min): 408 ± 65 SOL (min): 18.2 ± 27.3 WASO (%): 8.5 ± 7.2 N1 (%): 7.4 ± 3.9 N2 (%): 62.8 ± 8.2 N3&4 (%): 10.2 ± 5.0 REM (%): 19.6 ± 5.3	<u>Non-dippers:</u> TST (min): 411 ± 78 SOL (min): 15.2 ± 14.3 WASO (%): 9.8 ± 8.0 N1 (%): 7.0 ± 3.4 N2 (%): 63.1 ± 8.0 N3&4 (%): 7.9 ± 4.0 REM (%): 22.0 ± 6.3	82.3% dippers 17.7% non-dippers
Matthews *et al.,* (2008) CS	• 186 healthy adults • 59.6 ± 7.19y • 98/88	Wrist actigraphy, PSG, sleep diary	24h ABPM	<u>Correlations between SBP sleep/awake ratios and sleep:</u> Fragmentation index: 0.28** SOL: 0.13 SE (%): –0.11 N1 (%): 0.20** N3&4 (%): –0.02 REM (%): –0.17* Arousals (per h): 0.18*	<u>Correlations between DBP sleep/awake ratios and sleep:</u> Fragmentation index: 0.24** SOL: 0.11 SE (%): –0.06 N1 (%): 0.10 N3&4 (%): –0.06 REM (%): –0.16* Arousals (per h): 0.18*	48.9% SBP dippers 31.2% DBP dippers
McHill *et al*., (2022) CS	• 20 healthy adults • 36.3 ± 7.1y • 12/8	Sleep diary	48h ABPM	<u>Baseline</u>: TST (h): 7.1 (6.7, 7.1) <u>Change to early-morning shift work:</u> No significant difference from baseline, data not reported		<u>Baseline</u>: 31% non-dippers <u>Change to early-morning shift work</u>: 93% non-dippers**

Mellman *et al.,* (2015) CS	• 136 healthy adults • 23.1 ± 4.7y • 62/74	PSG, ISI, wrist actigraphy, sleep diaries	24h ABPM	ISI: 9.8 ± 6.5 Diary TST (min): 380.7 ± 103.0 Diary WASO (min): 28.2 ± 37.5* Actigraphy TST (min): 345.4 ± 90.4 Actigraphy WASO (min): 70.2 ± 53.1		38% dippers
Patterson *et al.,* (2021) CS	• 53 shift workers • 26.5 ± 7.5y • 23/30	Wrist actigraphy, PSQI, ESS	24h ABPM	PSQI: 6.0 ± 3.5 PSQI>5 (%): 47 ESS: 8.3 ± 4.7 Nap length (h): 2.5 ± 1.6		<u>Workday</u>: 50.9% dippers <u>Workday night shift:</u> 16.1% dippers <u>Non-workday</u>: 75% dippers
Payseur *et al.,* (2020) NRCT	• 17 healthy adults • 21.67 ± 0.05y • 17/0	EEG headband	ABPM	<u>Pre-alcohol:</u> TST (min): 333.9 ± 14.7* SOL (min): 32.5 ± 6.8* REM (min): 85.1 ± 0.1* Light sleep (min): 186.9 ± 1.0*	<u>Post-alcohol:</u> TST (min): 394.9 ± 18.6* SOL (min): 16.1 ± 3.2* REM (min): 108.4 ± 0.1* Light sleep (min): 219.5 ± 0.1*	<u>Nocturnal SBP (mmHg) without alcohol:</u> 120.8 ± 3.5 <u>Nocturnal SBP (mmHg) with alcohol</u>: 134.2 ± 6.9
Sayk *et al.,* (2010) RCT	• 11 healthy adults • 24.5 ± 1.6y • 5/6	PSG	24h ABPM	<u>Control Sleep:</u> TST (min): 408.8 ± 4.8* WASO (%): 0.8 ± 0.3* N1 (%): 6.9 ± 1.4* N2 (%): 46.0 ± 2.8* N3&4 (%): 23.7 ± 3.1* REM (%): 20.3 ± 1.3	<u>SWS-deprived sleep:</u> TST (min): 379.5 ± 9.3* WASO (%): 6.9 ± 1.9* N1 (%): 17.4 ± 2.6* N2 (%): 53.4 ± 3.1* N3&4 (%): 3.0 ± 0.9* REM (%): 16.6 ± 2.0	<u>Control sleep:</u> Mean nocturnal BP (mmHg): 76.5 ± 2.4* <u>SWS-deprived sleep:</u> Mean nocturnal BP (mmHg): 79.5 ± 2.4*
Sherwood *et al.,* (2001) CS	• 62 premenopausal, 50 postmenopausal • 50.3y • 0/112	Sleep diaries	24h ABPM	<u>Premenopausal:</u> TST (h): 6.6 ± 1.4	<u>Postmenopausal:</u> TST (h): 6.6 ± 1.4	<u>Premenopausal:</u> SBP dip (mmHg): 18.9 ± 7.7** DBP dip (mmHg): 14.5 ± 6.6* <u>Postmenopausal:</u> SBP dip (mmHg): 14.7 ± 8.2** DBP dip (mmHg): 12.3 ± 5.9*
Troxel *et al.,* (2017)	• 50 healthy adults • 31.03y	PSG	48h ABPM	<u>Men:</u> SE (%): 89.4 ± 5.6	<u>Women:</u> SE (%): 88.0 ± 4.0	<u>Men:</u> BP dipping ratio: 0.86 ± 0.06

CS	• 25/25			TST (h): 7.17 ± 61.0 N3 (%): 20.0 ± 8.7 REM (%): 23.8 ± 5.4	TST (h): 7.08 ± 60.0 N3 (%): 15.3 ± 7.2 REM (%): 24.9 ± 4.3	<u>Women:</u> BP dipping ratio: 0.85 ± 0.04
Ulu *et al.,* (2013) CS	• 100 healthy adults • 51.4y • 46/54	PSQI	24h ABPM	<u>Dippers:</u> PSQI: 4.24 ± 2.83** PSQI good sleep (count): 30* PSQI poor sleep (count): 20 PSQI sleep quality: 0.74 ± 0.77** PSQI sleep latency: 1.06 ± 0.76* PSQI sleep duration: 0.64 ± 0.74** PSQI SE: 0.32±0.62* PSQI sleep disturbance: 0.88 ± 0.47* Medication use: 0.06 ± 0.23* Daytime dysfunction: 0.57 ± 0.81*	<u>Non-dippers:</u> PSQI: 7.36 ± 4.03** PSQI good sleep (count): 19* PSQI poor sleep (count): 31 PSQI sleep quality: 1.36 ± 0.74** PSQI sleep latency: 1.58 ± 0.94* PSQI sleep duration: 1.34 ± 1.13** PSQI SE: 0.86 ± 1.14* PSQI sleep disturbance: 1.10 ± 0.54* Medication use: 0.38 ± 0.80* Daytime dysfunction: 1.02 ± 1.02*	<u>Dippers:</u> Nighttime SBP (mmHg): 103.20 ± 5.60** Nighttime DBP (mmHg): 70.70 ± 4.63** <u>Non-dippers:</u> Nighttime SBP (mmHg): 109.70 ± 8.12** Nighttime DBP (mmHg): 76.50 ± 4.19**
Yang *et al.,* (2017) RCT	• 43 healthy adults • 31.0 ± 21.0y • 21/22	PSG, wrist actigraphy, sleep diaries, daytime sleepiness	24h ABPM	<u>PSG:</u> TST ↓ during partial sleep restriction** SE ↑ during partial sleep restriction* No change in SWS despite restriction but ↓ N1, N2 and REM.		↓ SBP dip on 1st night of restriction compared to controls.* ↓ DBP dip on all nights of restriction compared to controls.*

Data are represented at mean ± SD, median (IQR) or correlation coefficient. * $p<0.05$, ** $p<0.001$ for comparison between groups.

Where possible, BP dipping represents the percentage of participants who were dippers or non-dippers. Otherwise, BP dipping results are presented the way the original study indicated.

AA: African Americans; ABPM: ambulatory blood pressure; CS: cross-sectional study; DBP: diastolic blood pressure; ESS: Epworth Sleepiness Scale; ISI: Insomnia Severity Index; M: men; MAP: mean arterial pressure; N1–4: non-rapid eye movement sleep stages 1–4; NRTC: non-randomized control trial; PSG: polysomnography; PSQI: Pittsburgh Sleep Quality Index; REM: rapid-eye movement; RCT: randomized control trial; SBP: systolic blood pressure; SE: sleep efficiency; SOL: sleep onset latency; SWS: slow wave sleep; TIB: time in bed; TST: total sleep time; WASO: wake after sleep onset; W: women

4.4 Discussion

Nocturnal BP dipping is an important physiological phenomenon that occurs during sleep. Regardless of its aetiology, which remains largely unknown, a blunted or failure of this response has been shown to be associated with CVD morbidity and mortality in both normotensive and hypertensive persons[200,203–205]. We build on what is known about the relationship between sleep and nocturnal BP non-dipping in clinical populations[198,216–218] by reviewing this association in apparently healthy individuals.

Given the heterogeneity of the studies no definitive conclusions can be made, however, the accumulated evidence suggests that sleep duration (specifically short sleep)[231,233,239], sleep fragmentation (frequent awakenings)[228,229,249], a lack of sleep depth (low NREM stage 3 time)[228,229,243] and increased variability in sleep timing (irregular sleep timing)[235–237,242] may be associated with nocturnal BP non-dipping in otherwise healthy individuals. The direction of this relationship, however, is unclear. These observations are similar to those found in individuals with hypertension[198], OSA[216], insomnia[217] and narcolepsy[218]. In addition to these sleep characteristics, however, individuals with hypertension who exhibit nocturnal BP non-dipping also have low sleep quality[198]; individuals with insomnia also have low sleep efficiency, decreased REM and increased arousals[217] and individuals with narcolepsy show distinct changes in sleep architecture associated with BP non-dipping[218] compared to otherwise healthy individuals.

Collectively, this might suggest that while some of the sleep characteristics overlap between individuals living with chronic disease and otherwise healthy individuals, individuals living with chronic disease seem to have additional sleep characteristics associated with nocturnal BP non-dipping. This might represent the progression of each condition from otherwise healthy to diseased. The presence of BP non-dipping in healthy individuals is, therefore, not only a risk factor for future CVD but also an important warning sign of future CVD risk. There is some evidence that sleep quality and sleep efficiency may be associated with nocturnal BP non-dipping in otherwise healthy individuals, however, the studies reporting on this were limited and further studies are required[234,235,241].

Sleep deprivation

The three studies that reported on nocturnal BP dipping in participants exposed to acute and chronic partial sleep deprivation provide evidence for a possible association between short sleep, or

insufficient sleep, and blunted BP dipping during sleep[231,233,239]. One might hypothesise that one of the main reasons why individuals experience BP non-dipping during sleep deprivation, or insufficient sleep, is due to increased SNS activity[250]. This is because the SNS has been shown to have a large effect on circadian BP variation[251]. It is well known that sleep deprivation acts as a major stressor on the body and increases SNS activity[252,253] while researchers have shown that BP non-dippers have increased SNS activity during sleep[254]. Previous studies have suggested that nocturnal BP non-dipping in narcolepsy patients and individuals with OSA is a result of SNS overactivity[220,255,256]. Therefore, one might hypothesise that chronic sleep loss could lead to sustained SNS overdrive in healthy individuals, manifesting as nocturnal BP non-dipping, thereby priming the future development of CVD. Alternatively, a person who displays nocturnal BP non-dipping may experience sleep deprivation, possibly through increased SNS activity at night which increases awakenings and arousals.

Additionally, it is also known that sleep deprivation disturbs the normal 24h variation in the renin-angiotensin-aldosterone system (RAAS)[239]. Sleep deprivation is characterized by natriuresis, osmotic diuresis, an increase in urine output and a dysregulated RAAS[239]. Therefore, one might speculate that sleep deprivation could be dysregulating the RAAS, with nocturnal BP non-dipping being a net effect[239]. Finally, habitually short sleep may increase nocturnal BP non-dipping and hypertension risk through circadian misalignment[14]. Chronically restricted sleep is associated with prolonged exposure to physical and psychological stressors including engaging in eating and activity at unconventional circadian times leading to a desynchrony between the master clock in the brain and the peripheral clocks in the organs[13,14]. Collectively, this may disrupt circadian rhythmicity with which physiological processes occur, including circadian variation of BP[13,257]. Continuous short sleep could therefore lead to hypertension through extended exposure to blunted nocturnal BP dipping, elevated sympathetic nervous system activity, RAAS dysregulation and circadian misalignment[215].

Sleep fragmentation and disturbance

Nocturnal BP non-dipping has been associated with sleep fragmentation in individuals with hypertension[198], OSA[216] and narcolepsy[218]. Evidence from this review supports the concept that fragmented or disturbed sleep is also associated with nocturnal BP non-dipping in otherwise healthy individuals[228,229,241,243,249]. Specifically, participants with more fragmented sleep (increased awakenings) had less nocturnal BP dipping[228,229]. Intuitively, researchers have presumed that the better the sleep quality (i.e. less disrupted sleep), the greater the BP dipping during sleep[228]. One might speculate that the reason why BP dipping is blunted during fragmented sleep is because BP

rises each time an arousal occurs, supported by findings that arousals result in higher nocturnal BP[258,259]. This implies that fragmented sleep consistently results in small increases in BP, preventing normal BP dipping during sleep. Sleep fragmentation is a hallmark of sleep disorders, because microarousals are consistently associated with sympathetic surges[194]. However, it has also been shown that repetitive sympathetic arousals during sleep of healthy individuals are associated with elevated daytime SBP and higher risk of hypertension[194]. Therefore, similar to the mechanism for short sleep, it has been proposed that SNS overactivity may be one of the underlying mechanisms responsible for BP non-dipping during fragmented sleep. One might argue that laboratory studies which measure 24h BP may observe higher sleep fragmentation owing to the hourly BP measurements being disruptive to sleep, however, several studies have shown that ABPM during the sleep period does not affect circadian BP profiles[260–262]. In addition, Tomitani *et al*. (2021) recently published a commentary which highlights several approach's to further reduce sleep disturbances caused by ABPM, should they arise[263]. As discussed above, a person who displays nocturnal BP non-dipping and the associated SNS overactivity during sleep may contribute to sleep fragmentation and disturbance.

Sleep depth

Spending more time in stage NREM stage 3 (deep or slow wave) sleep is associated with greater nocturnal BP dipping. Participants who were specifically SWS-deprived exhibited blunted BP dipping during the first half of sleep, which is dominated by SWS sleep, but not during the second half of the night, which is dominated by REM sleep[231]. As mentioned previously, one might hypothesise that this blunted BP dipping may be due to over-activation of the SNS during sleep. Sleep-related BP dipping is associated with the downregulation of SNS activity to the muscle vascular bed throughout the progressively deepening stages of NREM sleep[264,265]. It is therefore possible that those individuals who do not reach deeper sleep stages will not experience the subsequent decrease in SNS activity and, thus, exhibit blunted nocturnal BP dipping. Alternatively, a person who displays nocturnal BP non-dipping, secondary to SNS overactivity during sleep, may not be able to achieve and sustain NREM stage 3 sleep.

Sleep timing and shift work

As previously discussed, the implications of circadian misalignment between the biological clock and the sleep-wake cycle are well known[266] and it is well recognized that shift work has a negative impact on health, specifically that shift workers are already at a higher risk of developing hypertension[266–268]. Of the three studies reporting on shift workers[235,237,242] all showed that shift

workers displayed BP non-dipping during sleep on non-shift days. One might speculate that the fact that shift workers display BP non-dipping during sleep on non-shift days may, at least in part, be related to chronic circadian misalignment.

Shift workers typically undergo a large shift in the timing of behavioural and environmental cycles (e.g. sleep/wake, light/dark, fasting/feeding) and the resultant misalignment could be hypothesized to have a key role in their blunted nocturnal BP dipping. Of interest is the suggestion by Patterson *et al.* (2021), that nocturnal naps of longer duration (>60min) may help mitigate the impact of nightshift work on cardiovascular health in emergency medical shift workers, as those workers who napped for >60min at night on their scheduled nightshift exhibited normal nighttime BP dipping (i.e. BP dipping even while awake on shift). This finding is of great importance for shift workers as it points to the idea that when sufficient nocturnal sleep is not achievable, owing to the nature of their occupation, longer naps during nightshifts might restore nocturnal BP dipping in healthy individuals and possibly mitigate or minimise the impact of shift work on the cardiovascular system. However, as Patterson *et al.* (2021) pointed out, individuals need to weigh up the pros and cons of longer naps during shifts as long naps can increase risk of sleep inertia and reduced alertness immediately after waking[269]. Although beyond the scope of this review, the strategy of napping during shifts to protect the cardiovascular health of shift workers may be contentious, since they are supposed to be working, and would need to be taken up at the level of employers, stakeholders and policy makers in order to ensure an informed and unanimous understanding of such a proposed countermeasure. The drastic changes observed by McHill *et al.* (2022) in nocturnal BP dipping when workers transitioned to shift work may help to explain the increased risk for CVD observed in shift workers. BP non-dipping may, therefore, serve as an early warning sign of future CVD risk among shift workers.

Chin *et al.* (2022) found evidence for an association between more consistent sleep regularity and increased nocturnal BP dipping. As suggested by the authors, one possible future direction for this research is to test whether improving sleep regularity subsequently improves nocturnal BP dipping. On average, the participants were meeting the recommended guidelines for sleep duration (i.e. 7–9h[166]), had low-moderate WASO scores and were classified as dippers. One might speculate, therefore, that the healthy dipping profile seen in these participants might be due to their healthy sleep habits (i.e. they are obtaining sufficient sleep each night which is not drastically disturbed or fragmented).

Other associations

Three studies[227,232,238] found no significant differences in sleep characteristics between nocturnal BP dippers and non-dippers. In the case of Fallo *et al.* (2002), this could be because they measured sleep disturbances through a psychosocial assessment tool, the Psychosocial Index. This tool consists of 55 items, of which four sleep measures (difficulties falling asleep, restless sleep, early morning awakening and feeling tired on waking up) are scored with a Likert scale from 0 to 3 ('not at all' to 'a great deal'). One might speculate that a tool such as this is not sufficiently sensitive to capture key information about sleep. While Ishikawa *et al.* (2008) and Troxel *et al.* (2017) evaluated sleep using PSG, the current gold-standard method to measure sleep architecture, they found no association between any of the measured sleep characteristics and nocturnal BP dipping. One might speculate that the reason why Ishikawa *et al*. (2008) found no associations may be because the participants were not given a PSG familiarization night. Given the established first night effect of PSG[270,271] one might argue that this single night of PSG is not representative of participants' typical sleep. It must also be noted that Ishikawa *et al.* (2008) only reported on sleep efficiency and did not report on sleep staging or other sleep characteristics available from PSG, which may have been associated with BP dipping during sleep. While Troxel *et al.* (2017) used home-based PSG over two nights, their participants were not necessarily representative of the general population (being military recruits) and only specific PSG measures previously found to be associated with marital functioning and/or BP dipping were analysed. Thus, one might speculate that associations between nocturnal BP dipping and other PSG measures, such as WASO and arousals, might have been missed.

The mechanisms responsible for ethnic differences in nocturnal BP dipping remain poorly understood. Cohorts of African American individuals have disproportionately high overall cardiovascular risk[30], with BP non-dipping considered to be a major risk factor contributing to this phenomenon. It has recently been proposed that disturbed sleep may be a mechanism of ethnic differences in nocturnal BP non-dipping[272]. The studies we have reviewed demonstrate that shorter sleep duration, greater sleep fragmentation and less slow wave sleep are each associated with nocturnal BP non-dipping. These sleep disturbances, in turn, are more common in African Americans compared with Caucasian individuals[20] and thus it seems likely that poor sleep health may be contributing to blunted nocturnal BP dipping in African Americans. Definitive conclusions, however, are premature given the currently available literature in this area.

The finding that nocturnal BP dipping is blunted in postmenopausal women, is also important as it suggests an association between the menopausal decline in female reproductive hormones, in particular oestrogen, and nocturnal BP dipping[240]. Oral or transdermal oestrogen treatment, with or without the addition of progesterone, has been found to increase BP dipping in postmenopausal women[273,274].

It is well know that alcohol affects sleep architecture and that that the effects of alcohol on sleep vary between the first and second halves of nocturnal sleep[243,275]. During the first half of sleep when alcohol is at a peak concentration in the blood, more time is spent in deep sleep and less in light and REM stages. In the second half of sleep during alcohol metabolism, a "REM rebound" occurs resulting in lengthened REM sleep. Therefore, one might speculate that one of the mechanisms whereby alcohol results in BP non-dipping may be through disruption to sleep architecture.

Overall, these findings have a number of important implications. First, they are consistent with observations in other populations with pre-existing medical conditions in that nocturnal BP non-dipping appears to be associated with fragmented or disturbed sleep, and sleep with less time spent in stage NREM stage 3. It should be noted that we have presented the relationships between sleep deprivation, sleep fragmentation, sleep depth, sleep timing and BP non-dipping separately for simplicity. In reality, however, individual factors such as sleep fragmentation and sleep depth likely coexist. Thus, these characteristics may individually and collectively contribute to nocturnal BP non-dipping. Since the direction of these relationships is not clear, prospective studies could help improve our understanding of these associations and clarify whether the phenomenon of nocturnal BP non-dipping in otherwise healthy individuals may serve as an indication of future CVD risk. Second, our findings help address other associations between sleep and BP non-dipping (specifically short sleep duration and variability in sleep timing) in individuals with no diagnosed diseases or conditions, to the extent that obtaining adequate sleep duration and more consistent sleep timing may augment nocturnal BP dipping, thus lowering CVD risk in otherwise healthy individuals. Third, while there is no evidence-based approach for the treatment of nocturnal BP non-dipping, it seems promising that addressing one's sleep health may be an important starting point to reduce the prevalence of BP non-dipping and perhaps the progression to CVD.

Limitations

We acknowledge several limitations present in this review in addition to the limitations present in the included studies themselves. As with other clinical health markers, it is a valid concern that an

individual's BP dipping status may vary from night to night; however, this acute reproducibility has been shown to be moderate[276], and importantly, related to night-to-night changes in sleep quality[277]. A variety of methods were used to record and measure the different sleep characteristics, with the majority of the studies being cross-sectional, therefore no causal interpretations can be made. Lastly, only papers published in the English language were included.

4.5 Conclusion

Evidence from this systematic review, summarised in Figure 4.2, indicates that short sleep duration, more sleep fragmentation, less sleep depth and more variability in sleep timing may play a role in nocturnal BP non-dipping in otherwise healthy individuals. Therefore, interventions designed to improve sleep health in people with no known diseases or conditions may reduce the prevalence of BP non-dipping and perhaps the progression to hypertension, thus providing a non-pharmaceutical intervention to manage hypertension and associated cardiovascular consequences. Additional interventional studies are required to confirm if, through sleep-related interventions, BP non-dipping can be a reversible risk factor for CVD. As observed in this chapter, many dimensions of sleep are associated with BP non-dipping, however, the vast majority of these associations have been observed in Global North populations. This will be addressed in the subsequent experimental chapter (Chapter 5) by exploring associations between sleep characteristics, CVD risk and BP non-dipping in adults of African descent living in a low socioeconomic status community in South Africa.

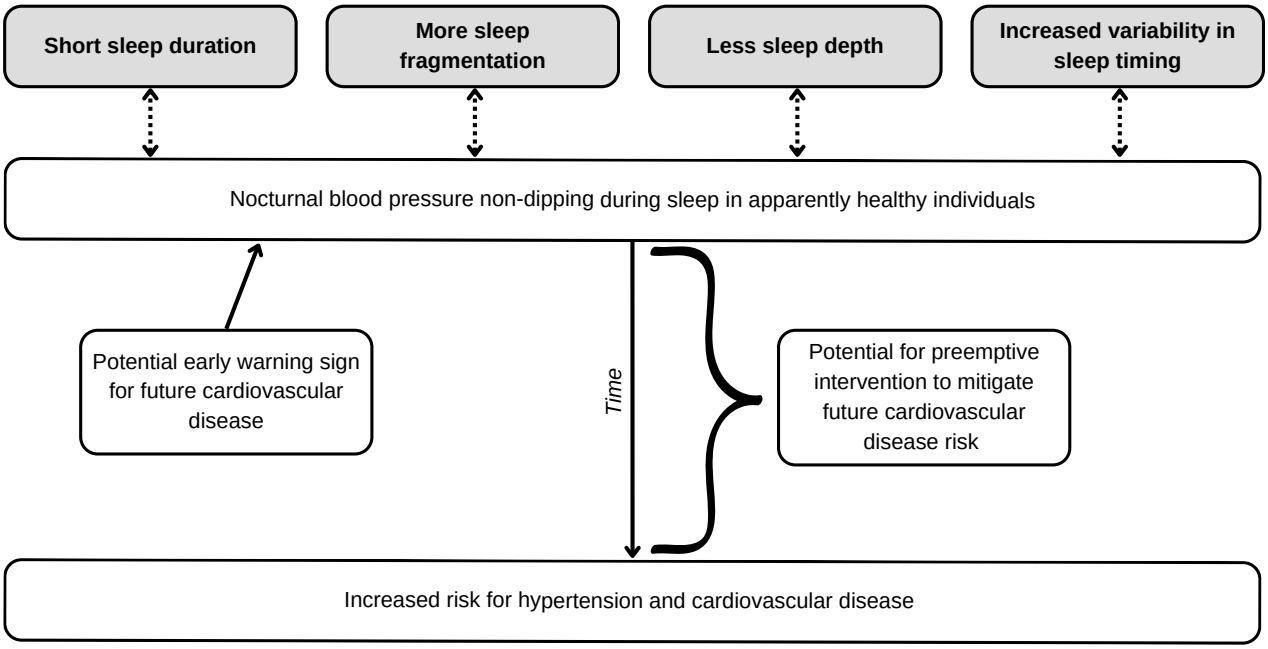

Figure 4.2. **Summary of the findings from this review**. Dotted arrows indicate the possible bidirectional relationships.

Chapter 5

Sleep, nocturnal blood pressure and cardiovascular disease risk in adults of African descent living in a low socioeconomic status environment

5.1 Introduction

An important prognostic marker of future CVD risk and CVD events is a phenomenon called blood pressure (BP) dipping. BP exhibits strong diurnal variations and normally decreases by 10% during the night, a process known as nocturnal BP dipping. The "dip" is defined as the difference between daytime mean BP and nighttime mean BP expressed as a percentage of the daytime value[278]. An absence of dipping, referred to as non-dipping, is currently regarded as a major risk factor for cardiovascular events and target organ damage[216,279–283]. In addition to BP dipping, the phenomenon of nocturnal hypertension has been shown to double CVD risk[284]. Nocturnal hypertension refers to abnormally elevated BP levels during sleep (≥120/70 mmHg) even when daytime BP is within the normal range[71]. The underlying mechanisms linking BP non-dipping and nocturnal hypertension to increased CVD risk are not fully understood, however, proposed mechanisms include SNS overactivity, water and sodium regulation imbalances, circadian misalignment and other pathologies associated with BP non-dipping such as chronic kidney disease[60,61].

To better understand the pathophysiological mechanisms linking BP non-dipping and nocturnal hypertension to increased CVD risk, previous research has investigated the potential role of sleep, since both these phenomena occur during the nocturnal sleep period[14,199]. Chapter 4 found that sleep characterized by short duration, more fragmentation, alterations in architecture with less time spent in deeper stages of sleep, and more variability in timing appear to be associated with BP non-dipping[285]. Less research has focused on the relationship between nocturnal hypertension and sleep characteristics. Some evidence, however, points to a relationship between short sleep duration (specifically sleep restriction) and increased nocturnal blood pressure, especially amongst women[286]. Since there is currently no specific guidance available for the management of nocturnal hypertension[287], investigating the relationship between sleep and nocturnal hypertension is a promising avenue to explore in the context of managing this CVD risk factor.

When investigating cardiovascular and sleep health, there are some important population factors to consider such as ethnicity, sex and socioeconomic status (SES). Compared to Caucasian individuals, those of African descent experience a higher burden of CVD risk factors, such as obesity, diabetes and hypertension[32] and BP non-dipping is nearly double in African American individuals[288]. Furthermore, individuals of African descent have been shown to have poorer sleep health (including shorter sleep duration, lower sleep efficiency, longer sleep onset latency, less slow wave sleep and more wake after sleep onset) compared to Caucasian individuals[20,289]. Consequently, individuals of African descent may experience synergistic negative effects of high CVD risk factors and poor sleep.

Biological sex differences influence CVD mortality, with men often exhibiting higher rates of CVD earlier in life[290] compared to women. CVD risk factors are also different between sexes. For example, tobacco and alcohol use is generally more common in men than women, while the prevalence of obesity is typically higher in women[172]. Many studies have therefore highlighted the necessity to take sex into account when determining cardiovascular health. Additionally, sex differences influence sleep health, with women reporting poorer sleep quality and having a higher risk for developing insomnia compared to men[16]. There is also evidence to suggest that CVD mortality and risk is higher among individuals of low SES[291,292]. Similarly, some studies have observed shorter, poorer quality sleep among people living in low SES communities[112,289]. The nature of the relationship between sleep characteristics, BP dipping and nocturnal hypertension in African descent adults living in low SES areas is not well understood.

Studying South African men and women of African descent living in a low SES community provides the opportunity to account for these important sleep and CVD risk factors. This is particularly relevant since not only is this cohort representative of the majority of the South African population, but CVD is the third leading cause of death in South Africa[293]. We hypothesise that the low SES environment in which these individuals live (e.g. high crime and violence and neighbourhood disorder)[294], will not be conducive to good sleep quality[295], and that one of the consequences of this will be BP non-dipping and nocturnal hypertension, which in turn will contribute to increased risk for CVD. We further hypothesise that these pathways will be more pronounced among women. Therefore, the aim of this study was to explore sex-specific relationships between sleep, nocturnal BP (i.e. nocturnal hypertension and BP dipping) and CVD risk among South African adults of African descent living in a low SES community.

5.2 Methods

5.2.1 Study setting, design and overview

Participants for this cross-sectional observational study were drawn from the South African arm of the Modelling the Epidemiologic Transition Study (METS)-Sleep cohort[148]. The protocol for METS-Sleep and the present study were both approved by the Human Research Ethics Committee of the University of Cape Town (Reference numbers: 696/2014 and 155/2020). All participants gave written informed consent and the studies strictly adhered to the principles and protocols from the Declaration of Helsinki[149]. Briefly, data collection took place between January 2021 and November 2023, during which participants completed detailed questionnaires and field staff measured

anthropometric and clinical health parameters. Participants were given a wrist-worn accelerometer to measure their habitual sleep characteristics for seven consecutive days and, specific to this study, were fitted with an ambulatory BP monitor to wear for 24h to measure nocturnal BP dipping and hypertension.

5.2.2 Participants

We recruited 74 participants (44 women, 30 men) who were enrolled in METS-Sleep. Participants who were shift workers or women who were pregnant or lactating were not eligible for this study. All participants were of African descent and lived in Khayelitsha a low SES, informal settlement in South Africa. Twenty-one and fifteen participants were excluded from the nocturnal BP dipping and hypertension analyses, respectively, as their 24h BP datasets were not valid (criteria described below). Thus, 53 and 59 participants were retained for the nocturnal BP dipping and hypertension analyses, respectively.

5.2.3 Questionnaires

The METS-Sleep study-specific questionnaires captured participant demographic, medical history, medication and supplement use, smoking status and alcohol use, current employment status and years of education information, as previously described[146]. The Global Physical Activity Questionnaire (GPAQ)[150] was used to describe participants habitual levels of moderate- to vigorous-intensity physical activity (MVPA, min/day). The Berlin questionnaire (BQ) was used to screen for obstructive sleep apnoea (OSA) risk[98]. Self-reported sleep characteristics were assessed using the Pittsburgh Sleep Quality Index (PSQI) questionnaire[106], the Epworth Sleepiness Scale (ESS)[109] and the Insomnia Severity Index (ISI)[107] as previously described in Chapters 2 and 3.

5.2.4 Anthropometry and clinical measurements

Weight (kg), height (cm) and waist circumference (cm) were measured according to the METS standard procedures[148]. Body mass index (BMI) was calculated as weight/height^2 (kg/m^2). Participants were classified as overweight (BMI: ≥25kg/m^2 but <30kg/m^2), obese (BMI: ≥30kg/m^2) or having a high waist circumference (waist circumference ≥102cm in men and ≥88cm in women). Resting BP was measured as previously described in Chapters 2 and 3, according to METS standard procedures[148]. Participants were classified as having elevated BP if their measured systolic blood pressure (SBP) was ≥130mmHg[175], diastolic blood pressure (DBP) was ≥85mmHg[175], they reported being diagnosed with hypertension or they were currently using antihypertensive medication. Following an overnight fast, fasting capillary plasma glucose concentration was determined using the

finger stick method (Accu-check Aviva, Roche, Indianapolis, United States of America (USA)). Participants were classified as having elevated fasting plasma glucose if their measured glucose was ≥5.6mmol/L, they reported being diagnosed with diabetes or they were currently using medication to treat diabetes.

5.2.5 BMI-modified Framingham 10-year CVD risk score

CVD risk was assessed using the BMI-modified sex-specific Framingham 10-year CVD risk score[37] as presented described in Chapters 2 and 3. The seven risk factors include: age, sex, measured SBP, treatment of hypertension, diagnosed diabetes, measured BMI and smoking status.

5.2.6 Cardiometabolic disease (CMD) risk score

A continuous CMD risk score was used to estimate an individual's global CMD risk. It was calculated using the sums of standardized scores for fasting plasma glucose (Glu), BMI, waist circumference (WC), SBP and DBP using a modified version of a previously reported formula[296], with higher scores signifying greater CMD risk.

$$\text{CMD } \textit{Risk Score} = zGlu + (zBMI + zWC)/2 + (zSBP + zDBP)/2$$

5.2.7 24h ambulatory blood pressure monitoring (ABPM)

Participants were asked to wear an ambulatory BP monitor (IEM Mobil-O-Graph, IEM GmbH, Stolberg, Germany) continuously for 24h, except during exercise and when showering or bathing. The device was programmed to take SBP and DBP readings every 30 minutes using an appropriately sized cuff. Participants were permitted to continue with their normal daytime activities during this 24h period, but were asked to be as sedentary as possible when the measurements were being taken. While there are currently no gold standard criteria to define a valid dataset obtained from ABPM[297], we have used the guidelines presented by the European Society of Hypertension (ESH)[50] to ensure consistency with this society's recommendations around BP throughout the thesis[298]. Therefore, in this study a 24h ambulatory BP measurement was considered valid if it included SBP and DBP readings for *at least* two-thirds of the hours of both daytime and nighttime periods[298]. For example, if a monitoring period lasts for 24 hours, with 16h representing daytime and 8h representing the nocturnal period, a minimum of 11 and 5 BP readings during the daytime and nocturnal periods, respectively, are required for the measurement to be considered valid. Nocturnal periods were determined for each participant using their actigraphy-derived sleep onset and sleep offset times, such that only BP values which fell in the sleep period were included in the nocturnal

BP period. Thus, in this study, nocturnal periods corresponded to sleep and daytime periods corresponded to wake.

The 24h BP measurements were used to calculate average daytime (i.e. wake) and nocturnal (i.e. sleep) period values for SBP and DBP, from which BP dipping was calculated. Dipping profiles for SBP and DBP were computed using HMS-Client Server Hypertension Management Software (v5.1, IEM GmbH, Stolberg, Germany) using the following formula:

$$SBP\ dipping\ (\%) = 100 \times \frac{average\ daytime\ SBP - average\ nighttime\ SBP}{average\ daytime\ SBP}$$

$$DBP\ dipping\ (\%) = 100 \times \frac{average\ daytime\ DBP - average\ nighttime\ DBP}{average\ daytime\ DBP}$$

Participants were classified as dippers if SBP or DBP dipping values were ≥10%. Note that the dipping group includes extreme dippers (≥20% reduction in nocturnal SBP or DBP) and the non-dipping group includes reverse dippers (nocturnal SBP or DBP higher than daytime values, non-favourable condition). The rationale behind including extreme dipping in the dipping group (favourable condition) lies in the current lack of conclusive evidence indicating that extreme dipping has an adverse impact on cardiovascular prognosis at the community level and in the general hypertensive population[66]. As described in the Chapter 1, extreme dippers younger than 70y appear to show no increase in cardiovascular event risk compared to dippers of the same age. Since the median age of our cohort was 41 (25, 48)y, we feel comfortable with including extreme dipping in the favourable condition. Finally, 24h mean hypertension was defined as an average 24h BP ≥130/80 mmHg[53] and nocturnal hypertension was defined as an average BP ≥120/70 mmHg[53] during the nocturnal sleep period.

5.2.8 Actigraphy-derived sleep measures

As per the methodology outlined in Chapter 3, participants were given a wrist-worn accelerometer (Actiwatch Spectrum Plus, Philips Respironics, Bend, OR, USA) to wear on their non-dominant wrist continuously for seven consecutive days while keeping a sleep diary. Timing of sleep periods were established manually based on published guidelines[176]. Data were processed using Philips Actiware software (v.6.3, Philips Respironics, Bend, OR, USA). Outcome variables include sleep onset (mm:hh), sleep offset (mm:hh), midsleep (mm:hh), sleep duration (elapsed time between sleep onset and sleep offset, h), total sleep time (actual time spent asleep, h), sleep efficiency (%), wake after sleep onset (WASO, min), sleep fragmentation index (SFI, %), sleep duration regularity and midsleep regularity as described in Chapter 3. As in Chapter 3, long sleep was defined as sleep duration >9h[80]

and poor sleep efficiency was defined as sleep efficiency <85%[177]. Maintaining consistency with Chapters 2 and 3, descriptive sleep characteristics between employed and unemployed men and women are presented in Supplementary Table 5.1 (Appendix 5).

5.2.9 Data and statistical analyses

Data are presented as median with the interquartile range or frequency counts (%). The Shapiro-Wilk test was used to test for normality. Between-group comparisons were made using Mann-Whitney U tests and Fisher's exact tests. Given the small sample size for each of the two sex groups, limiting power, we chose a conservative analytical approach and used sex-stratified Spearman's correlations to explore associations between sleep, nocturnal BP and CVD/CMD risk factor variables (see Figure 5.1 for the three analyses). We acknowledge as a limitation that we are unable to adjust for potential covariates using this approach but note that the CVD risk score at least accounts for age and BMI.

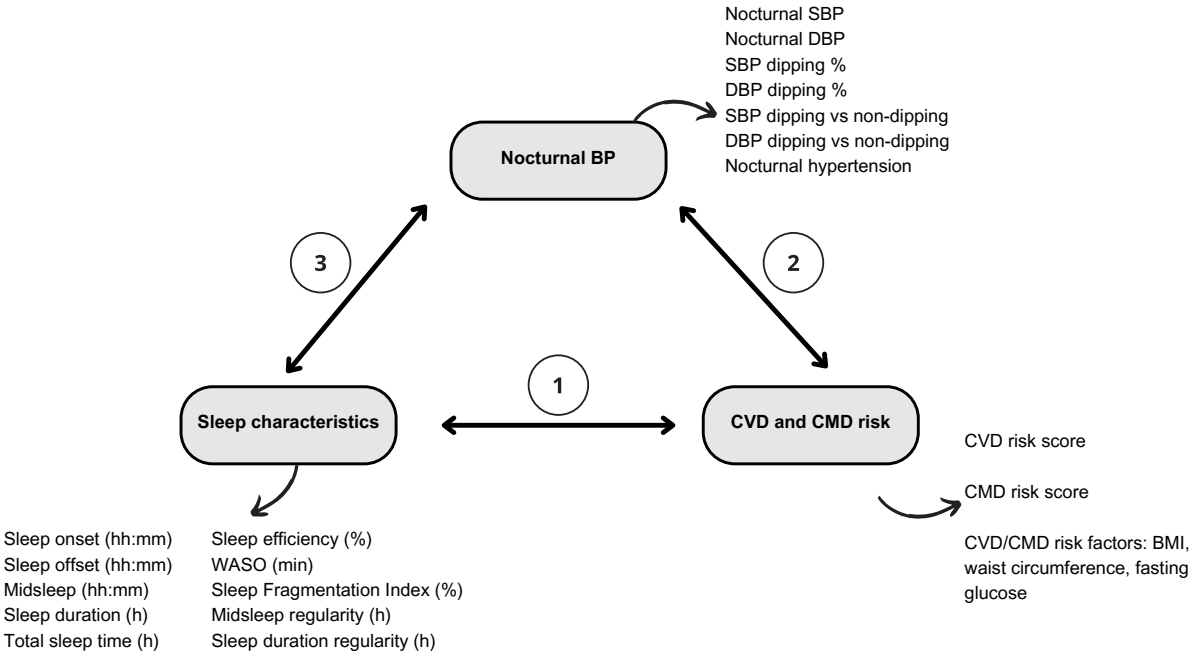

Figure 5.1. Three exploratory analyses performed to describe the relationships between sleep, nocturnal BP and CVD risk variables. BMI: body mass index, BP: blood pressure, CMD: cardiometabolic disease, CVD: cardiovascular disease, DBP: diastolic blood pressure, SBP: systolic blood pressure WASO: wake after sleep onset.

5.3 Results

5.3.1 Participant characteristics

The descriptive characteristics of the participants are presented in Table 5.1. Women had higher BMIs (women: 30 (25, 36)kg/m^2, men: 22 (19, 24)kg/m^2, p<0.001), higher waist circumferences (women: 97 (85, 103)cm, men: 82 (73, 85)cm, p<0.001), more obesity (women: 49%, men: 4%,

p<0.001), greater proportion reporting chronic diseases (women: 57%, men: 22%, p=0.008) and engaged in less MVPA (women: 20 (20, 52)min/day, men: 60 (34, 94)min/day, p=0.003) compared to men. Men had higher CVD risk scores (women: 3.7 (2.5, 6.1)%, men: 7.6 (4.6, 6.9)%, p=0.005), greater proportion of smokers (women: 78%, men: 32%, p=0.004) and consumed more alcoholic drinks per week (women: 0 (0, 11)drinks per week, men: 16 (0, 30)drinks per week, p=0.018) than women.

5.3.2 24h ambulatory BP monitoring

Compliance was moderate such that the men and women in this study wore the ambulatory BP monitor for an average of 21.9 (range: 20.5, 24.3)h and 21.5 (range: 20.5, 23.0)h, respectively, in the 24h period. BP variables derived from 24h ABPM are shown in Table 5.2. Almost half of the women (48.4%) and 27.3% of the men presented with 24h hypertension. The majority of women (72.2%) and almost half of the men (47.8%) presented with nocturnal hypertension. SBP non-dipping was a notable phenomenon, with a similar occurrence between men (50%) and women (61%). The occurrence of DBP non-dipping was also similar between men (23%) and women (39%). Trending towards significance, more women (72%) than men (48%) presented with nocturnal hypertension (p=0.054).

5.3.3 Sleep characteristic differences between men and women

The actigraphy-derived and self-reported sleep characteristics of the participants are presented in Table 5.3. Overall, both men and women present with long sleep (women: 43.2% >9h, men: 52.2% >9h) that is of poor quality (sleep efficiency <85%: women: 75.0%, men: 91.3%). Men presented with higher SFI scores compared to women (women: 29 (24, 33)%, men: 33 (27, 38)%, p=0.028) while women reported higher ESS scores than the men (women: 5 (2, 9), men: 2 (0, 5), p=0.037). Differences in sleep characteristics between employed and unemployed men and women, respectively, can be found in Supplementary Table 5.1, Appendix 5. There were no differences in sleep characteristics between employed (14%) and unemployed (86%) women. Among the men, those who were employed (22%) had better midsleep regularity compared to unemployed (78%) men (employed: 0.7 (0.5, 0.9)h, unemployed: 0.9 (0.8, 1.4)h, p=0.037).

5.3.4 Analysis 1: Associations between sleep characteristics and CVD/CMD risk variables

Correlation tables for the associations between sleep characteristics and CVD/CMD risk variables are presented in Supplementary Tables 5.2a (Women) and 5.2b (Men) (Appendix 5). Significant correlations are summarized in Figures 5.2 (Women) and 5.3 (Men). Among the women, earlier sleep offset times (rho: –0.39, p=0.014) and earlier midsleep times (rho: –0.42, p=0.009) were

correlated with higher CVD risk scores. Women with earlier sleep offset times also had higher fasting glucose concentrations (rho: –0.39, p=0.021). Men with better midsleep regularity had worse CVD risk scores (rho: –0.45, p=0.031) and larger waist circumferences (rho: –0.44, p=0.033). Men with higher SFI scores had worse CMD risk scores (rho: 0.43, p=0.043).

5.3.5 Analysis 2: Associations between nocturnal BP and CVD/CMD risk variables

Correlation tables for the associations between nocturnal BP variables and CVD/CMD risk factors are presented in Supplementary Table 5.3a (Women) and 5.3b (Men) (Appendix 5). Significant correlations are summarized in Figures 5.2 (Women) and 5.3 (Men). Among the men, higher nocturnal SBP (rho: 0.66, p=0.007) and DBP (rho: 0.65, p<0.001) were correlated with higher CMD risk scores. Higher nocturnal SBP was also correlated with higher BMI's (rho: 0.44, p=0.037), waist circumferences (rho: 0.57, p=0.004) and fasting glucose concentrations (rho: 0.42, p=0.047). Higher nocturnal DBP was correlated with larger waist circumferences (rho: 0.42, p=0.046).

5.3.6 Analysis 3: Associations between sleep characteristics and nocturnal BP

Correlation tables for the associations between sleep characteristics and nocturnal BP variables are presented in Supplementary Tables 5.4a (Women) and 5.4b (Men) (Appendix 5). Significant correlations are summarized in Figures 5.2 (Women) and 5.3 (Men). Among the women, lower sleep efficiencies (rho: –0.39, p=0.016) were correlated with higher nocturnal SBP. Shorter total sleep times (rho: 0.42, p=0.020) and worse sleep efficiencies (rho: 0.51, p=0.003) were correlated with smaller SBP dipping percentages. In addition, shorter sleep durations (rho: 0.39, p=0.029), shorter total sleep times (rho: 0.44, p=0.014) and worse sleep efficiencies (rho: 0.37, p=0.037) were correlated with smaller DBP dipping percentages. Among the men, worse sleep efficiencies (rho: –0.47, p=0.024), greater WASO (rho: 0.59, p=0.003) and greater SFI scores (rho: 0.59, p=0.003) were correlated with higher nocturnal SBP. Similarly, worse sleep efficiencies (rho: –0.50, p=0.015), greater WASO (rho: 0.50, p=0.014) and greater SFI scores (rho: 0.59, p=0.003) were also all correlated with higher nocturnal DBP. Worse sleep duration regularity scores were correlated with lower SBP (rho: –0.48, p=0.025) and DBP (rho: –0.52, p=0.013) dipping percentages.

5.3.7 Comparison of BP dippers to non-dippers and participants with and without nocturnal hypertension

There was a tendency for women classified as DBP non-dippers to have higher fasting glucose concentrations compared to non-dippers (p=0.054) (Figure 5.2 and Supplementary Table 5.5a, Appendix 5). SBP non-dippers (n=12) had shorter total sleep times (SBP non-dippers: 6.8 (6.3, 7.5)h,

SBP dippers: 7.5 (7.2, 8.2)h, p=0.038) and lower sleep efficiencies (SBP non-dippers: 79.9 (73.8, 83.2)%, SBP dippers: 83.4 (80.3, 86.1)%, p=0.047) (Figure 5.2 and Supplementary Table 5.6a, Appendix 5). Women classified as DBP non-dippers (n=12) had shorter sleep durations (DBP non-dippers: 7.8 (6.6, 8.6)h, DBP dippers: 8.7 (8.3, 9.6)h, p=0.018), total sleep times (DBP non-dippers: 6.5 (5.6, 7.3)h, DBP dippers: 7.5 (7.2, 8.0)h, p=0.013) and lower sleep efficiencies (DBP non-dippers: 79.4 (70.2, 85.7)%, DBP dippers: 82.5 (79.3, 86.5)%, p=0.046) compared to DBP dippers (Figure 5.2a, Supplementary Table 5.6a, Appendix 5). There were no sleep-related differences between women classified as having nocturnal hypertension (n=26) compared to those without (n=10) (Supplementary Table 5.7, Appendix 5).

There were no demographic or CVD risk parameter differences between men classified as dippers or non-dippers (Supplementary Table 5.5b, Appendix 5). However, both SBP and DBP non-dippers had worse sleep duration regularity than dippers (DBP non-dippers: 2.2 (1.9, 2.4)h, DBP dippers: 1.8 (1.2, 2.1)h, p=0.038; SBP non-dippers: 2.1 (1.9, 2.4)h, SBP dippers: 1.4 (1.2, 2.0)h, p=0.016) (Figure 5.3, Supplementary Table 5.6b, Appendix 5). DBP non-dippers had lower sleep efficiencies (DBP non-dippers: 71.5 (68.2, 75.6)%, DBP dippers: 81.1 (78.5, 82.9)%, p=0.017) and more were classified as at high risk for OSA (DBP non-dippers: 40%, DBP dippers: 0%, p=0.043) than DBP dippers (Figure 5.3, Supplementary Table 5.6b, Appendix 5). Finally, men with nocturnal hypertension (n=11) had higher WASO (116.8 (88.75, 163.25)min vs. 88.1 (65.08, 98.3)min, p=0.031) and greater SFI scores (36.4(33.4, 40.8)% vs. 29.6(25.8, 34.7)%, p=0.019) compared to those without nocturnal hypertension (n=12) (Figure 5.3, Supplementary Table 5.7, Appendix 5).

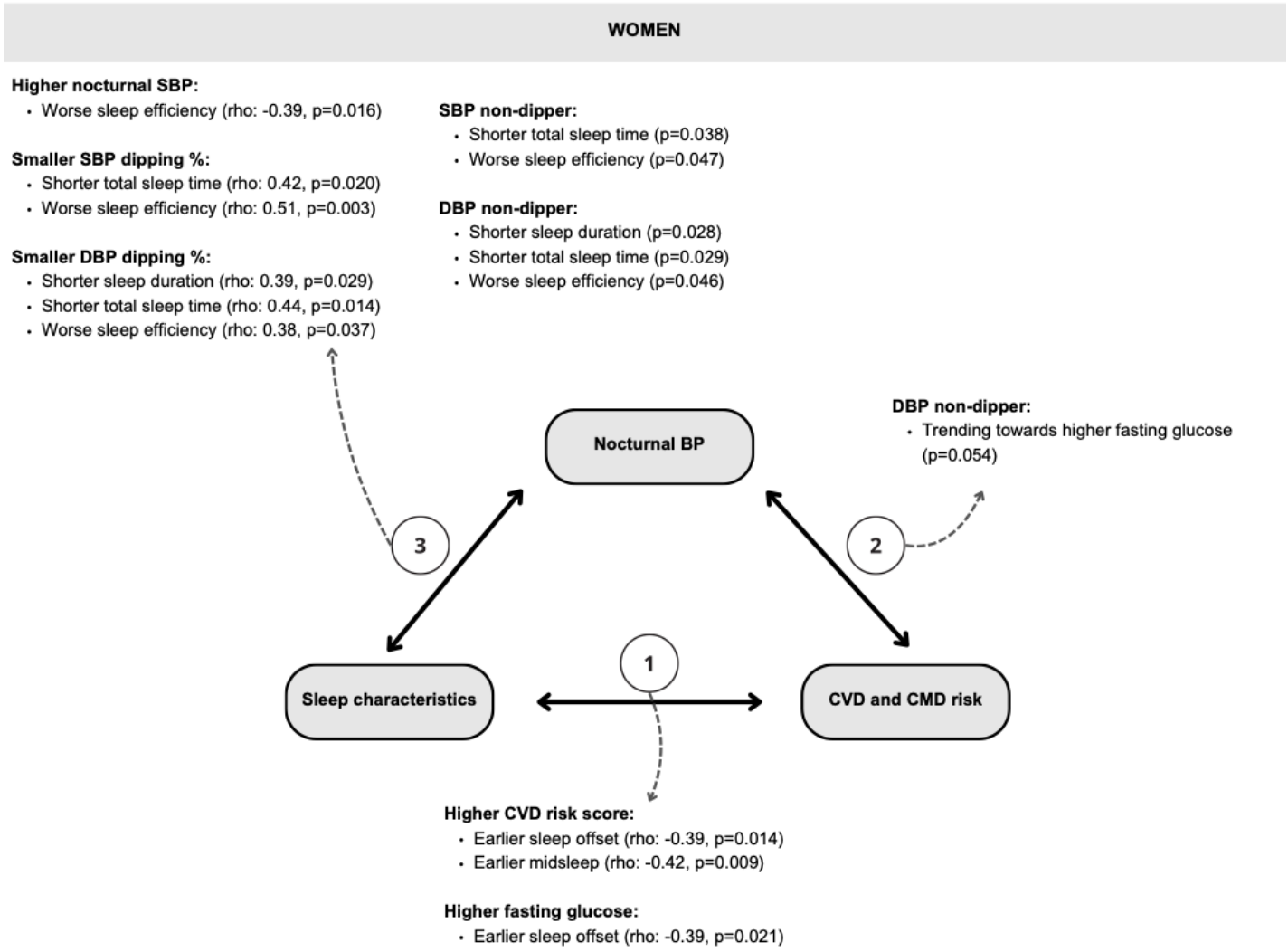

Figure 5.2. Summary of key relationships between the sleep, nocturnal BP and CVD risk factor variables in the women. BP: blood pressure, CMD: cardiometabolic disease, CVD: cardiovascular disease, DBP: diastolic blood pressure, SBP: systolic blood pressure, WASO: wake after sleep onset. Relationships were explored using Spearman's correlation and Mann-Whitney U tests.

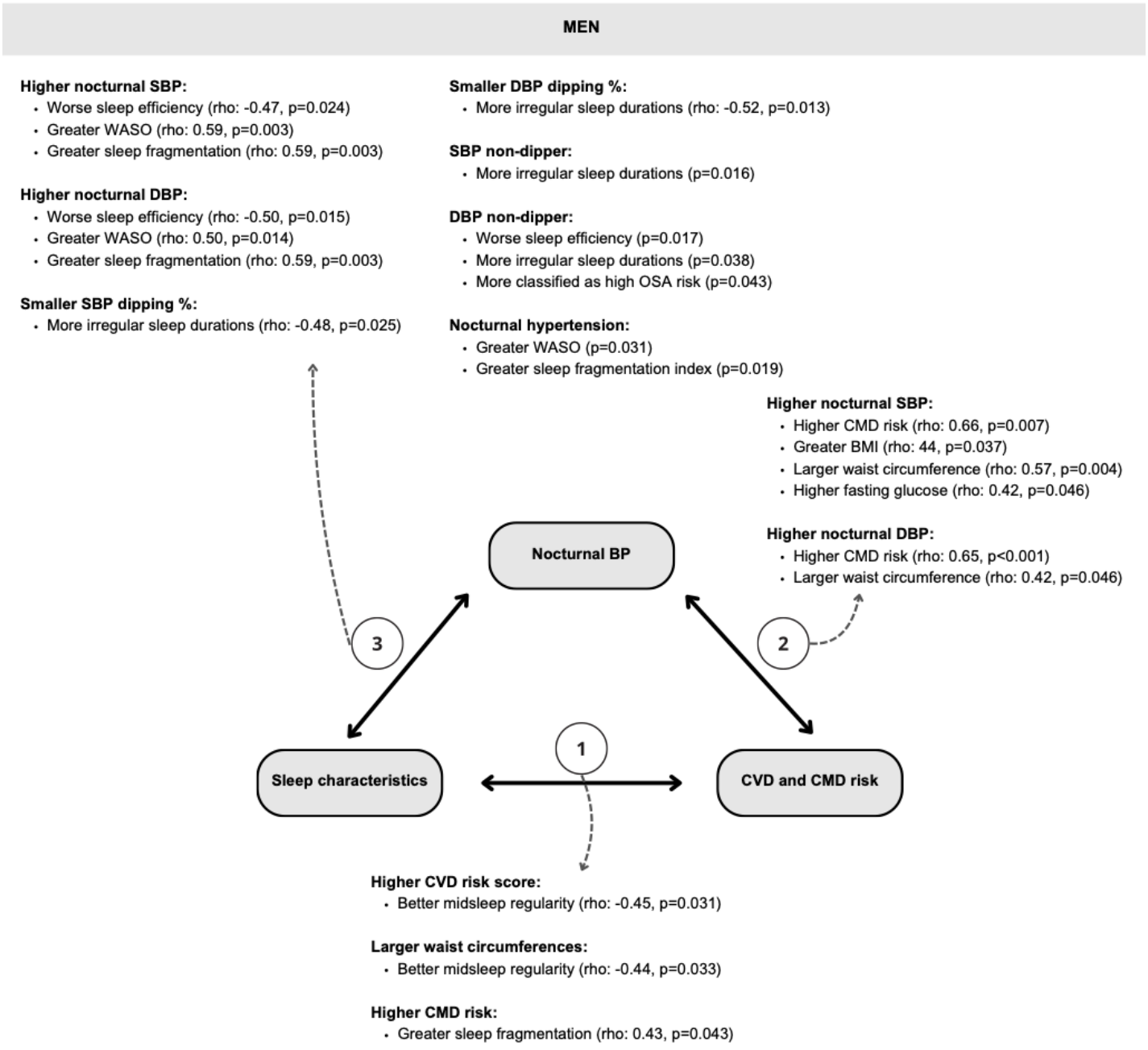

Figure 5.3. Summary of key relationships between the sleep, nocturnal BP and CVD risk factor variables in the men. BP: blood pressure, DBP: diastolic blood pressure, SBP: systolic blood pressure, WASO: wake after sleep onset. Relationships were explored using Spearman's correlation and Mann-Whitney U tests.

Table 5.1. Descriptive characteristics of participants.

	Women (n=37)	Men (n=23)	p-value
Age (y)	43 (36, 50)	39 (34, 43)	0.110
BMI (kg/m^2)	29.7 (25.4, 35.9)	21.9 (19.3, 24.1)	**<0.001**
Obese (count, %)	18 (48.6)	1 (4.4)	**<0.001**
Waist circumference (cm)	96.5 (84.5, 103.1)	82.0 (73.0, 85.0)	**<0.001**
Clinic SBP (mmHg)	122 (113, 133)	130 (119, 139)	0.267
Clinic DBP (mmHg)	79 (74, 87)	82 (73, 93)	0.319
Elevated BP (count, %)	19 (51.4)	15 (65.2)	0.292
Hypertension medication (count, %)	8 (21.6)	1 (4.3)	0.068
Chronic diseases (count, %)	21 (56.8)	5 (21.7)	**0.008**
Fasting glucose concentration (mmol/L)	4.6 (4.2, 5.4)	5.1 (4.6, 5.4)	0.172
Elevated blood glucose (count, %)	5 (14.7)	5 (21.7)	0.493
CVD risk score (%)	3.7 (2.5, 6.1)	7.6 (4.6, 9.6)	**0.005**
CMD risk score	0.1 (–0.7, 0.9)	–0.5 (–1.3, 0.0)	0.085
MVPA (min/day)	30 (20, 52)	60 (34, 94)	**0.003**
Smoker (count, %)	12 (32.4)	18 (78.3)	**0.004**
Alcohol use (no. drinks / week)	0 (0, 11)	16 (0, 30)	**0.018**
Employed (count, %)	5 (13.5)	5 (21.7)	0.406
Education (y)	11 (9, 11)	11 (10, 12)	0.678

Data are presented as median (interquartile range) or count (%). P-values represent differences between men and women determined using Mann-Whitney U or Fisher's exact tests.

BMI: body mass index, BP: blood pressure, CMD: cardiometabolic disease, CVD: cardiovascular disease, DBP: diastolic blood pressure, MVPA: moderate- to vigorous-intensity physical activity, SBP: systolic blood pressure.

Table 5.2. Blood pressure characteristics of participants derived from 24h ambulatory BP monitoring.

	Women (n=31)	Men (n=22)	p-value
Daytime SBP (mmHg)	125 (116, 132)	125 (118, 132)	0.956
Daytime DBP (mmHg)	80 (76, 88)	83 (75, 89)	0.906
Nocturnal SBP (mmHg)	115 (106, 129) *(n=36)*	116 (106, 127) *(n=23)*	0.652
Nocturnal DBP (mmHg)	72 (67, 84) *(n=36)*	69 (63, 76) *(n=23)*	0.263
SBP dipping (%)	8.3 (4.1, 13.0)	9.8 (7.3, 12.5)	0.362
DBP dipping (%)	12.8 (7.2, 18.3)	15.6 (10.4, 22.1)	0.187
SBP non-dipper (count, %)	19 (61.3)	11 (50.0)	0.296
DBP non-dipper (count, %)	12 (38.7)	5 (22.7)	0.177
24h hypertension (count, %)	15 (48.4)	6 (27.3)	0.121
Nocturnal hypertension (count, %)	26 (72.2) *(n=36)*	11 (47.8) *(n=23)*	0.054*

Data are presented as median (interquartile range) or count (%). P-values represent differences between men and women determined using Mann-Whitney U or Fisher's exact tests. * indicates difference trending towards significance.

DBP: diastolic blood pressure, SBP: systolic blood pressure.

Table 5.3. Actigraphy-derived and self-reported sleep characteristics of participants.

	Women (n=37)	Men (n=23)	p-value
Sleep onset time (hh:mm)	22:23 (21:40, 23:13)	22:22 (21:50, 22:44)	0.632
Sleep offset time (hh:mm)	06:58 (06:14, 08:00)	07:21 (06:39, 08:04)	0.442
Midsleep (hh:mm)	02:42 (02:07, 03:19)	02:50 (02:23, 03:13)	0.648
Sleep duration (h)	8.7 (7.7, 9.6)	9.1 (7.7, 9.9)	0.498
Duration >9h (count, %)	16 (43.2)	12 (52.2)	0.454
Total sleep time (h)	7.4 (6.5, 7.9)	7.5 (6.2, 7.9)	0.885
Sleep efficiency (%)	80.6 (77.7, 84.4)	79.2 (75.6, 82.4)	0.290
Sleep efficiency <85% (count, %)	27 (75.0)	21 (91.3)	0.117
WASO (min)	74.6 (68.2, 107.2)	92.9 (75.0, 118.8)	0.063
Sleep Fragmentation Index (%)	28.9 (23.8, 33.1)	33.4 (27.3, 37.6)	**0.028**
Midsleep regularity (h)	0.7 (0.5, 1.1)	0.9 (0.7, 1.3)	0.232
Sleep duration regularity (h)	1.3 (1.0, 1.9)	1.9 (1.5, 2.3)	0.090
High OSA risk (count, %)	8 (21.6)	2 (9.1)	0.215
ISI score	2 (0, 4)	1 (0, 2)	0.053
Community clinical insomnia symptoms (ISI≥10) (count, %)	2 (5.4)	1 (4.3)	0.675
Standard clinical insomnia symptoms (ISI≥15) (count, %)	6 (16.2)	1 (4.3)	0.165
ESS score	5 (2, 9)	2 (0, 5)	**0.037**
Excessive daytime sleepiness (ESS>10) (count, %)	8 (21.6)	1 (4.3)	0.068
PSQI score	4 (2, 6)	3 (2, 4)	0.126
Poor sleep quality (PSQI>5) (count, %)	9 (24.3)	4 (17.4)	0.492

Data are presented as median (interquartile range) or count (%). P-values represent differences between men and women determined using Mann-Whitney U or Fisher's exact tests.

ESS: Epworth Sleepiness Scale, ISI: Insomnia Severity Index, OSA: Obstructive sleep apnoea, PSQI: Pittsburgh Sleep Quality Index, WASO: Wake after sleep onset.

5.4 Discussion

Similarly to Chapter 3, we confirm objectively-measured long, poor quality, disturbed sleep among African descent adults residing in a low SES community. Overweight, obesity and chronic diseases are prevalent among the women and more than half of all participants had elevated BP. Half of the men and almost two out of three (61%) women were SBP non-dippers, while around 38% of women and 23% of men were DBP non-dippers. Alarmingly, most of the women (72%) and almost half of the man (48%) presented with nocturnal hypertension. These results are similar to other studies in South African populations which show a high proportion of BP non-dipping, between 46–78%[299–301]. Notably, this is one of the few studies that has investigated nocturnal hypertension in South African adults.

Analysis 1: Associations between sleep characteristics and CVD/CMD risk variables

Women with earlier midsleep and sleep offset (wake-up) times had higher CVD risk scores while those with earlier sleep offset times also had higher fasting glucose concentrations. This relationship between earlier sleep timing and greater CVD or CMD risk is consistent with observations in both Chapters 2 and 3 but in contrast to what is generally shown in the Global North – in which later sleep timing is usually considered a risk factor for CMD[302]. Perhaps higher CVD risk scores in women with earlier sleep timing suggests a role for circadian misalignment in the development of CVD or CMD. As suggested in Chapters 2 and 3, we speculate that these women are perhaps sleeping out of phase with their endogenous circadian rhythms, which is a well-known CVD risk factor[125,267]. This may be due to women assuming greater childcare responsibilities, necessitating the need to be up earlier to get children ready for school (which typically start early, between 07h30 and 08h00 in South Africa), for example. Earlier wake-up times may also result in shorter sleep durations due to a shortened sleep opportunities. Since shorter sleep duration was associated with smaller SBP and DBP dipping percentages during sleep and indeed, non-dippers (SBP and DBP) accumulated less sleep than dippers, the earlier sleep offset times in women in this population may be indirectly contributing to blunted nocturnal BP dipping through less sleep.

Among the men, those with better midsleep regularity had higher CVD risk scores and greater waist circumferences. At first glance this seems counterintuitive, since more regular sleep timing is typically associated with lower CVD risk[142]. However, it highlights the importance of interpretating data in context so that a complete picture and understanding of the complex relationships at play is considered. We speculated that perhaps men who have a more structured or fixed routine might be

employed, and thus might have better sleep timing regularity. When investigating this further we indeed found that men who were employed had better midsleep regularity. The heightened CVD risk they present with appears to be related to and partly driven by higher waist circumferences, but is likely also influenced by other unmeasured factors such as work-related stress[303] and commuting times to work, for example. Being employed, these men might have more income at their disposal, which may translate to increased spending on food, potentially contributing to larger waist circumferences. Alternatively, perhaps when men adjust their bedtime earlier and wake up later, their midpoint of sleep remains constant, compared to when they go to bed later and wake up earlier. This consistent midpoint creates the perception of regular midsleep timing, despite the actual irregular durations of sleep. Indeed, associations between sleep duration regularity and nocturnal BP were found and are discussed below.

Men with greater sleep fragmentation presented with greater CMD risk, which is in line with extensive research in other populations of African descent[304]. The men in the present study live in adverse conditions since Khayelitsha is a densely populated township in South Africa characterised by extreme poverty, violence and crime. Poor quality, fragmented sleep potentially resulting from a noisy neighbourhood, or one perceived not to be safe at night, may elevate sympathetic nervous system (SNS) activity and stress hormones such as cortisol during sleep[305]. Chronically elevated cortisol as well as poor-quality fragmented sleep, have both been associated with impaired glucose metabolism, insulin resistance and inflammation[12,305], all of which are risk factors for CMD.

Analysis 2: Associations between nocturnal BP and CVD/CMD risk variables

Among the men, those with higher nocturnal SBP had greater BMI's and waist circumferences, higher fasting glucose concentrations and CMD risk scores. Similarly, men with higher nocturnal DBP also had larger waist circumferences and higher CMD risk scores. This is consistent with previous literature showing that individuals with higher BMI's and obesity present with higher nocturnal BP compared to their non-obese counterparts[306,307]. Similarly, a study by Hermida *et al.* (2016) found that during a 5.9-year median follow up where 190 patients developed type 2 diabetes, mean nocturnal SBP was the most significant predictor of new-onset diabetes in a cox proportional-hazard model after adjusting for age, waist circumference, glucose, chronic kidney disease and hypertension treatment[308]. Some proposed mechanisms for the relationship between obesity and higher nocturnal BP include inflammation, SNS overactivity, insulin resistance, salt sensitivity and higher renin-angiotensin-aldosterone system (RAAS) activity[309,310]. What remains unclear is whether obesity and diabetes (and their associated conditions such as inflammation) drive higher nocturnal

BP, or if higher nocturnal BP drives conditions such as inflammation which increases the risk of obesity and diabetes, and consequently higher CVD risk.

Among the women, no significant relationships were found but it appears that BP non-dipping might play a role in fasting glucose concentrations. While this trend is in line with previous research in the field showing worse glucose control among BP non-dippers[311], more research is required in this population. The absence of associations between nocturnal BP and CVD risk in this study is intriguing, but could be explained by two main factors. Firstly, the small sample size in this study may have restricted any strength of associations between nocturnal BP and CVD risk. Secondly, since the majority of CVD risk algorithms rely on coefficients and weightings derived from analyses in European and American populations[312], such risk scores may not be entirely applicable to this population. The 10-year BMI-modified Framingham CVD risk score utilized in this study uses a binary of "yes" or "no" for diagnosed diabetes. Perhaps, in this population, a continuous variable of fasting glucose concentration will offer more important insights into future CVD risk. Additionally, the weighting of BMI in the current Framingham CVD risk score may not be representative of an African-specific population, whose obesity rates are some of the highest worldwide, especially amongst women[313]. Taken together, these findings re-iterate the need to derive population and context-specific CVD risk algorithms to allow for correct risk stratification and, ultimately, CVD treatment and management[312].

Analysis 3: Associations between sleep characteristics and nocturnal BP

Among both the men and women, markers of sleep disturbance (especially WASO, sleep efficiency and sleep fragmentation) was found to be an important factor related to nocturnal BP, where more disturbed sleep was associated with higher nocturnal SBP and DBP, smaller SBP and DBP dipping percentages and indeed, both SBP and DBP non-dippers had worse sleep efficiencies. Among men, those with nocturnal hypertension also had more WASO and sleep fragmentation compared to those without nocturnal hypertension. This is similar to previous research which shows that deeper and less fragmented sleep is associated with more BP dipping in healthy individuals[228,285]. The extremely disturbed sleep observed in the participants of this study may, in part, be explained by the poor neighbourhood and home environment of Khayelitsha residents. Additionally, since crime and violence are rampant in Khayelitsha, it is unsurprising that these individuals have difficulty sleeping, as sleep is a behaviour of extreme vulnerability. A smaller reduction in SNS activity during the night has been proposed as one explanation for the non-dipping profile as this may reflect a state of hypervigilance during sleep where the sympathetic arm of the ANS dominates[63,254]. Specific to the

men and women in our study, we hypothesise that adverse neighbourhood environments increase SNS activity at night which drives poor sleep health (including poor-quality, irregular sleep), and subsequent BP non-dipping, nocturnal hypertension and heightened CVD risk. This relationship likely originates from and, is underpinned by, the adverse neighbourhood conditions that these individuals live in, which are not conducive to good quality sleep[294] but also independently increase SNS activity at night[162] and CVD risk[314].

While we have proposed that this cycle is underpinned by the adverse neighbourhood environment that all individuals are exposed to, we do note that some individuals do not appear to be as affected by, or as vulnerable to, the neighbourhood environment as others. Some individuals have lower CVD risk scores or are BP dippers. Unfortunately, we do not have any measured variables in this study which might help explain these differences in vulnerability. We speculate, however, that vulnerability may be, in part, related to some individuals being more resilient than others. Resilience has been documented in many other low SES communities to the extent that a "shift-and-persist" model has been described which aims to help explain why some individuals from low SES environments maintain good physical health, despite the recurring adversities in life[315,316]. The "shift-and-persist" model describes how low SES individuals appear to develop an approach to life that prioritizes "*shifting"* (i.e. accepting stress for what it is and adapting oneself to it) in combination with "*persisting"* (i.e. enduring life challenges by holding onto meaning and optimism)[315,316]. Future studies in this population should investigate the applicability of this model and the concept of resilience.

In addition to the relationships between sleep quality and BP during sleep, we also observed that among the women, shorter sleep durations and total sleep times were associated with smaller SBP and DBP dipping percentages. The non-dipper women were also shorter sleepers compared to the women who demonstrated normal BP dipping during sleep. This is in line with previous work showing that short sleep durations are associated with blunted BP dipping[285]. One reason for this finding might relate to the autonomic nervous system. Since we have proposed that these individuals are in state of hypervigilance during sleep, we speculate that SNS overactivity due to hypervigilance exacerbates poor sleep quality, consequently leading to a shorter overall total sleep times. This is further supported by the fact that both dippers and non-dippers have adequate sleep opportunities, yet these are often converted into shorter total sleep times due to fragmentation and disruption.

Among the men, being a non-dipper or dipping less at night was associated with worse sleep duration regularity. A study by Huang *et al.* (2020) showed that greater variability in sleep duration in an American population was associated with worse CVD risk[142] and suggested that irregular sleep duration might be a novel and independent risk factor for CVD. While the underlying mechanisms remain unclear, many have speculated that irregular sleep timing likely contributes to circadian misalignment[90,142,317]. Since almost every major cardiovascular function is regulated by the circadian clock[318], individuals with more erratic sleep timing may be at a higher CVD risk due to disrupted circadian functions specifically related to the cardiovascular system[142,208].

Limitations and future research

The limited sample size, inability to adjust for potential covariates (specifically presence of chronic diseases and risk of OSA) and cross-sectional design of this study restrict the generalizability of the results. Mental health conditions such as depression and anxiety, which are comorbid with sleep, were not measured in this study. We are addressing this limitation in a current parallel study in this same cohort. Finally, napping behaviour was not investigate in this Chapter. Future studies should investigate the role of napping in BP non-dipping CVD risk. Future studies should investigate the perceptions of the neighbourhood environment in relation to sleep health in this population.

5.5 Conclusion

This study found a high proportion of BP non-dipping among men and women of African descent living in a low SES environment. While sleep quality, specifically disturbed sleep, appears to be associated with BP non-dipping in men and women, sex-specific relationships found that irregular sleep among men and short sleep among women are associated with BP non-dipping. We speculate that in this low SES, high-crime environment, overactivation of the SNS, due to hypervigilance during sleep, may underpin these BP non-dipping and nocturnal hypertension profiles. A key piece of this complex sleep and CVD risk relationship is therefore the lived experience of participants in Khayelitsha. This will be addressed in Chapter 6 using qualitative methods to better understand the nuanced interplay between external and internal factors that have the potential to impact sleep quality, and ultimately cardiovascular health.

Chapter 6

Towards an understanding of external and internal sleep health factors in adults of African descent living in a low socioeconomic community: a qualitative study

6.1 Introduction

Since we spend a significant portion of our lives asleep, the physical and neighbourhood environment in which we sleep holds immense importance in shaping the quality of our rest[319]. Poorer sleep quality, shorter sleep duration and worse insomnia symptoms have all been associated with living in neighbourhoods characterized by disadvantage, low social cohesion and high crime[294,319,320]. In addition to this, ambient environmental factors such as noise, light and temperature can also impact sleep[321]. Beyond the neighbourhood environment, the physical home – such as housing structure, household size, sleeping spaces and bed-sharing – has also been shown to impact sleep quality and quantity[322,323]. Given the critical role of sleep for maintain physical health and well-being[121], these factors pose a significant threat, not only to sleep, but also to overall health outcomes.

In recent years, there has been growing recognition of the need to understand sleep within diverse cultural and socioeconomic contexts, as these factors can significantly shape individuals' sleep[324,325]. Low socioeconomic status (SES) environments have been shown to adversely impact health outcomes[295] including an increased risk for CVD[9]. Previous research suggests that this association may in part be because low SES environments undermine sleep quality[320,326] as sleep has been shown to be a key mediator between perceived neighbourhood quality and health[320]. Importantly, ambient environmental factors (e.g. noise, light and temperature) often mirror SES, such that the homes of lower SES individuals are more likely to be more noisy or hot, or have more artificial light at night or even more pollution,[319] all of which have been shown to impair sleep quality[321].

In the previous chapters, we have shown that South African adults of African descent who live in a low SES community have long and disturbed sleep[173]. This is in contrast to much of the research done in low SES African Americans who typically demonstrate shorter, poor quality sleep[20]. Given this intriguing difference, it would be valuable to learn about perceptions of how the environment might impact overall sleep health in these long-sleeping South Africans. This is particularly relevant since this cohort likely represents a large proportion of the South African population. Therefore, this qualitative study will explore whether i) external (e.g. environmental barriers to and promoters of good sleep) and ii) internal (e.g. individual knowledge, attitudes, beliefs and perceptions around sleep) factors might impact the sleep health of African descent adults living in a low SES community. It is anticipated that by gaining insight into the possible external and internal factors influencing sleep, we may better understand the reasons behind the long, poor-quality sleep observed in this population.

6.2 Methods

6.2.1 Study setting and design

Participants for this study were recruited from the South African arm of the prospective, five-country (Ghana, South Africa, Jamaica, Seychelles, United States of America (USA)) cohort study called Modelling the Epidemiologic Transition Study (METS)-Sleep[148]. This cohort was chosen as participants live in Khayelitsha, a low SES, high-density, high-crime, informal settlement in Cape Town, South Africa. These urban settlements are home to many impoverished South Africans, desperately seeking employment and a way out of the poverty cycle.

While the METS participants have been followed longitudinally for over a decade, resulting in a wealth of quantitative data, there is an absence of qualitative data pertaining to them. A qualitative research design offers a promising avenue to provide insights to factors that may affect sleep in this particular group of long, but poor quality sleepers living in Khayelitsha. Semi-structured, one-on-one interviews were used to collect data for the present study and a parallel study entitled "'*I am always on my guard': a qualitative study towards understanding sleep-related fears in a low-income, high crime community*". Only emergent themes relevant to the present study are reported on. The protocols for METS-Sleep and the present study were approved by the Human Research Ethics Committee of the University of Cape Town, South Africa (Reference numbers: 696/2014 and 155/2020).

6.2.2 Participant recruitment

A convenience sampling strategy was used to invite participants from the METS-Sleep cohort to take part in this qualitative study. Fifteen adults of African descent living in Khayelitsha were recruited on a first come first served basis. There were no exclusion criteria. The decision to include 15 participants in this study was based primarily on data saturation (where no new information or themes are identified from additional interviews), which was reached at 15 participants. Written informed consent was obtained from all participants prior to the interview. Descriptive demographic data were captured through questionnaires administered by trained field workers when participants attended their annual METS-Sleep study visit. Specifically, 53% of the participants were women, their median age was 43 (38, 47)y, 73% were unemployed, and their median sleep duration was 8.6 (8.6, 9.7)h, with a median sleep efficiency of 79.7 (72.6, 83.3)%. This sub-group of individuals is therefore representative of the larger group of participants studied in Chapters 2, 3 and 5 from a sleep and demographic perspective. Participants were reimbursed for their transport to the interview location (Sleep Science Lab, University of Cape Town) and their time.

6.2.3 Interview procedure

Semi-structured, one-on-one qualitative interviews were conducted between April and June 2023 by a researcher trained in qualitative interview techniques (referred to as the "research interviewer" from here on). Participants were free to express themselves in the language they felt most comfortable in, which for all participants was isiXhosa, one of the 12 official languages of South Africa. This was also the home language of the research interviewer. Participant confidentiality and anonymity was maintained by assigning unique numerical participant identifiers (PID) to each volunteer and their transcripts. Interviews took place at the Sleep Science Lab, rather than in the participants' homes, due to the sensitive nature of the topics discussed and concerns related to personal safety.

Before the start of the interview, participants were briefed about the study's overall goal and purpose. The interview comprised 27 open-ended questions, with follow-up probes for each question. The full semi-structured interview guide can be found in Supplementary Table 6.1 (Appendix 6), with questions relevant to this study presented in blue text. Overall, the interview guide was designed to query greater neighbourhood environment, physical sleep environment and individual sleep-related factors that might explain poor sleep. The interview started with simple demographic questions such as *"How long have you lived in Khayelitsha for?",* designed to make participants feel at ease. Major topic areas that were then covered included: safety and the neighbourhood environment, participants' physical sleep environment and personal attitudes and understandings about sleep. Examples of questions include: *"Is there anything about your community or neighbourhood, or what's happening in the neighbourhood at night, that impacts your sleep?"* and *"How important is sleep to you and why?"*. The questions were designed based on expert consultation with members of the METS-Sleep field work team, who live in Khayelitsha themselves, to ensure the questionnaire was culturally sensitive and would capture the correct information required to achieve the study aim. Two pilot interviews were conducted with field workers to refine question clarity, relevance and flow. Each interview lasted between 20 and 60 minutes and was conducted in a quiet and private room by the research interviewer. The research interviewer had no prior relationship with the participants to minimize bias and ensure the confidentiality of responses. All interviews were audio-recorded, with permission from the participants.

6.2.4 Analysis

Translation and transcription of the interviews was completed by the trained researcher interviewer, who listened to the audio-recordings, mentally translated the scripts from isiXhosa to English and then transcribed the interviews into English. Transcripts were analysed using thematic analysis as proposed by Braun and Clarke (2006)[327,328] with NVivo v14.23.2 (Lumivero, Denver, Colorado, USA). The analysis started with familiarisation with the interviews through multiple readings of the transcripts by PEF, who also consulted with ATC and the research interviewer to clarify any unclear responses. Next, transcripts were coded primarily using an inductive approach (i.e. codes were derived from the information in the transcripts). Some information was coded deductively when responses related directly to the study's aim (e.g. promoters of good sleep). Codes were then used to identify themes and sub-themes. Analysis of the interviews was an iterative process, which involved continuously reviewing and refining themes. Direct quotations from participants, identified only through their unique PID, were included in the analysis to illustrate and support key findings. Given the sex-specific differences between men and women identified in the previous chapters, participants' quotes are labelled with their PID and either (M) or (F) to denote male or female sex, respectively.

6.2.5 Trustworthiness

The transcripts were initially coded by PEF. Subsequently, ATL independently coded the same transcripts to verify reliability and consistent coding. Finally, three random transcripts were coded by DER to enhance rigour. Reflexivity was maintained by all researchers through continuously reflecting on their positionality, preconceived ideas of what living in Khayelitsha might be like and interactions with participants, considering how these factors may shape their perspectives and decisions. Following each interview, PEF and ATL had discussions with the research interviewer to share insights and challenges encountered during the interview, contributing to transparency and rigour in an effort to minimise bias. The use of the quotations also supports credibility and trustworthiness.

6.3 Results

The analysis found three main themes and nine sub-themes represented in Table 6.1 below. Figure 6.1 shows their different layers of influence on sleep health, which are independent but interconnected.

Table 6.1. Themes and sub-themes identified through thematic analysis.

Theme 1: Neighbourhood environment	Theme 2: Physical sleep environment	Theme 3: Individual sleep-related factors
Sub-themes:	Sub-themes:	Sub-themes:
1. Neighbourhood characteristics	1. Home and bedroom characteristics	1. Knowledge, attitudes and beliefs around sleep
2. Neighbourhood barriers to good sleep	2. Ideal sleep space	2. Perceptions of the impact of sleep on overall health
3. Neighbourhood promoters of good sleep		3. Sleep-related behaviours
		4. Acceptance of situation

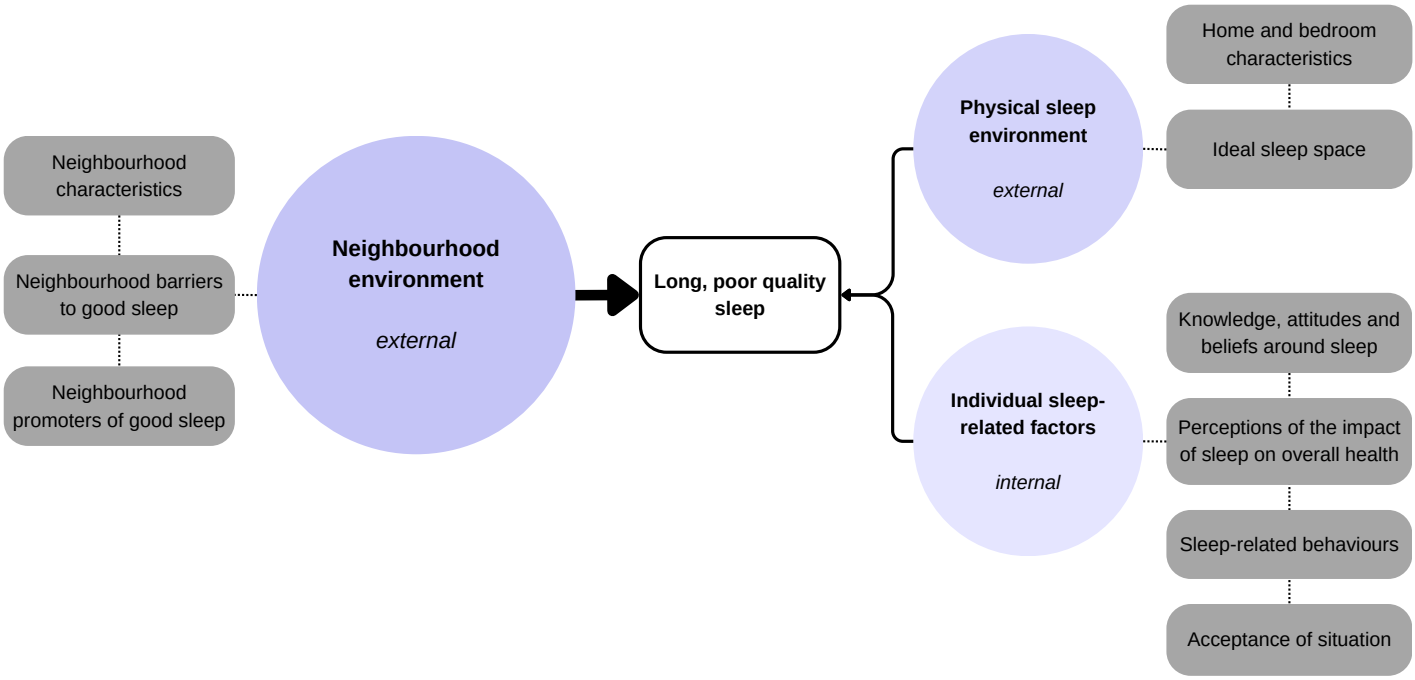

Figure 6.1. Overview of the sleep-related external (neighbourhood environment & physical sleep environment) and internal (individual) themes with their respective sub-themes.

6.3.1 Theme 1: Neighbourhood environment

Neighbourhood characteristics

Several neighbourhood characteristics were identified that allowed for contextualization of the participants' environment that might relate to sleep. They can be classified into five main factors: noise, crime and violence, safety, darkness, and alcohol and drugs. Noise was described as almost exclusively arising from neighbours who were partying or having loud gatherings and drinking alcohol, signing while drunk, coming home from taverns or fighting verbally and physically. Crime and violence encompassed perceptions of criminal activities that occurred within the neighbourhood, including incidents of theft, assault, gunshots, or gang-related violence. Safety involved perceptions and feelings of overall safety within the neighbourhood at night. A more

detailed analysis into the aspects of safety, fear and mental health are being extensively studied in a parallel study in this population, "'*I am always on my guard': a qualitative study towards understanding sleep-related fears in a low-income, high crime community*". As such, these topics will be touched on but not described in detail in the present study. In this context, the term darkness described the level of visibility within the neighbourhood environment, including concerns related to poorly lit areas or inadequate lighting during the evenings, which contributed to feelings of being unsafe due to the risk of crime and violence. Alcohol and drugs factors refer to the presence and prevalence of substance use and related behaviours within the neighbourhood, including concerns about drug dealing and increased crime and violence during periods of increased alcohol consumption.

All participants reported that excess noise was problematic in their neighbourhood. Since alcohol consumption in the community increases drastically on the weekend days and nights (Friday, Saturday and Sunday) compared to the weekdays, it was identified as being the largest contributor to disruptive noise.

> *"I think Friday, Saturday and Sunday are the most disruptive and unsafe days…There is too much drinking and partying taking place..." – PID 2030 (F)*
>
> *"Yes because there is a next door neighbour who has a tavern and there is always a loud music playing throughout … They sometimes get drunk and even bang the walls of my shack... There is always noise that is unbearable… Friday and Saturday are the worse days…" – PID 2455 (M)*
>
> *"It is days like Friday and Saturday are the busy days each and every week because there is too much noise as they drink a lot in those days." – PID 2263 (F)*

Linked closely to the increase in alcohol consumption on the weekends, most of the participants expressed that crime and violence were often worse on the weekends too. This suggests an association between alcohol-related behaviour and incidents of crime and violence within the neighbourhood. One interpretation could be that increased alcohol consumption on the weekends contributes to increased aggression or risk behaviour, potentially exacerbating levels of crime and violence.

> *"Yes Friday, Saturday and Sunday we are more cautious of any other days because most incidents happen during then. So we are more fearful when it comes to these days." – PID 2210 (F)*

"There is too much drinking and partying taking place and even the rate of crime goes up… There is always a shooting each weekend." – PID 2030 (F)

Participants unanimously expressed that crime and violence were rampant throughout their neighbourhood. While some participants reported that the weekends were worse compared to the weekdays, others noted that the crime and violence was not localised to the weekends, but it happened during the week too. This divergence in perspective might indicate that crime and violence persists across all days of the week, but perhaps some areas of the community being worse than others. In addition to crime and violence during periods of increased alcohol consumption, many participants reported that gang-related shooting and fights were also characteristic of their neighbourhood.

"It's Thursday and Monday there is always fights between gangster groups. Another group coming from a different area to attack the ones inside our area. There is always gunshots to be expected in our area during these days…." – PID 2224 (M)

Participants also reported that crime and violence exacerbated feelings of being unsafe, specifically during the darker winter months or when night falls, as many of the robberies and muggings happened when it got darker. Some participants explained that crime is particularly prevalent around public transport stop areas, where individuals are frequently targeted for muggings as they leave taxis and make their way home on foot.

"The area is not safe at all because there are no streetlights and its usually a bit dark and it makes it really unsafe." – PID 2222 (M)

"The area is very dangerous especially in winter because it gets dark sooner and there is these vacant shacks that these boys use to store things they rob out of people." – PID 2020 (F)

Overall, crime and violence in the neighbourhood were seen as a concern for all participants. Notably, participants expressed concerns about their safety when letting family members into their homes at night, fearing that unknown individuals might have followed them. Similarly, they were equally apprehensive about returning home to their families, fearing the possibility of being followed.

"People are brutal murdered. It's just a traumatic experience to live in that area. They steal people's cars and there's hijackings as well" – PID 2206 (F)

"…because sometimes I'd think what if there are people who are following me that when she opens for me they also enter to come and rob the house." – PID 2669 (M)

"I also don't feel safe because I don't know if she is alone and there aren't any people following her who might cause harm when I open for her." – PID 2222 (M)

Apart from the alcohol consumption, some participants expressed that their neighbourhood was also characterised by drugs and drug dealers. This often made these participants feel unsafe in their homes and wider neighbourhood largely due to the fact that that drug-related behaviour increased criminal activities within the neighbourhood. One participant even noted that, while community leaders were aware of the crime and violence in the neighbourhood, they too were involved in selling drugs, meaning that the community members had very few people who they could trust or rely on.

"There are these boys who are smoking drugs who are always on the lookout for people who are coming back from work. So it's not safe at all." – PID 2534 (M)

"There is someone who sells drugs next to my house and these people who smoke do not sleep so there's always constant knocks…" – PID 2654 (M)

"I don't feel safe at all because of the guys who smoke drugs and the house breaks ins they do." – PID 2715 (F)

A few participants shared that noise and crime and violence in the neighbourhood is much worse now compared to what it used to be a few decades ago. This seems to be driven by the younger members of the community who are consuming alcohol on the weekends and engaging in criminal activities. Unrelenting poverty, unemployment or lack of educational opportunities over the decades may be contributing to the increased risk-taking behaviours among younger individuals. Perhaps this reflects a shift in the community dynamics and social norms over time, indicative of frustration at the lack of progress when it comes to improvements in quality of life of these impoverished South Africans.

"When I arrived in Cape Town during 1987 things were different and there were no safety issues so sleeping was never a problem but a change that drastically changed lives of many started around early 90s. You could go where you want with no fear and at any time of the day prior that and we were happy mostly." – PID 2455 (M)

"No it's not the same because in the past there wasn't much of these noise we are now used to, because back in the days drinking and the use of alcohol was for old people and they

wouldn't be gallivanting after drinking, compared to the young ones who are now drinking." – PID 2222 (M)

Lastly, many participants highlighted a concerning trend. When community meetings are held to discuss neighbourhood concerns, it's typically the parents of the children who are involved in drug use, alcohol consumption, and criminal behaviour who protect them and shield them from consequences. This could reflect two things: i) a normalisation or acceptance of deviant behaviours within the community or ii) the protective instinct of parents, coupled with fears of stigma or being cast out from the community, which may motivate them to shield their children from accountability or consequences for their actions.

"…have been cases of house breaks and a meeting will be called for the whole area and you discover that most parents cover their children, even though somehow it is known who did what or it was witnessed by neighbours at the time of incident but people are not able to come out and say it was who because they are scared for their lives." – PID 2455 (M)

Barriers to good sleep

The main barriers to obtaining good sleep were mostly driven by the characteristics of the neighbourhood and less by the physical bedroom environment or individuals' attitudes and beliefs towards sleep. Noise and safety, mostly associated with crime and violence but also concerns around fires, were the main barriers identified. All participants expressed that noise was a significant disruptor to their sleep at night, specifically on the weekends.

"My sleep gets affected highly because in one of these houses that are next to where we live there's always people who are drinking, especially during weekends, and after they drunk they would sing and starting chanting and dancing banging walls and making it extremely difficult to sleep..." – PID 2224 (M)

"Nothing is as hectic as the noise that makes me to be unable to sleep" – PID 2455 (M)

"Sometimes I don't sleep at all because the noise is unbearable and my bed direction is facing the shack behind me and that is where the noise comes from." – PID 2263 (F)

Safety was identified as the second major barrier to good sleep. Many participants described themselves as "always being on their guard" and "alert" for potential intruders. These feelings of hypervigilance at night were closely linked to crime and violence, specifically hearing gunshots and people fighting. Most participants expressed an inability to achieve good sleep, both struggling to fall asleep and stay asleep, due to the crime and violence in the area as well as feeling hypervigilant.

"Yes because you are always on your guard that anything might happen so you aren't at ease and you end up having anxiety and failing to rest peacefully." – PID 2534 (M)

"I keep on waking up in the middle of the night, I don't sleep entirely peaceful because I have fears of criminals breaking in the window because it is so close to the gate and now since the bed is also close to the window I continuously worry that something might happen." – PID 2715 (F)

"…once I hear feet sounds and people talking then I sit up and listen attentively to the voices." – PID 2669 (M)

"A very little sound of anything makes me paranoid and I am always on my guard, so a person who does that cannot sleep well at all." – PID 2206 (F)

Several participants also voiced that concerns of fires starting in the neighbourhood at night disrupts their sleep. These concerns were driven by worries about children stealing electrical cables, leading to short-circuiting and fires, as well as load shedding (a controlled rotation of blackouts around South Africa to control energy usage and reduce power demand) causing fires when power surged back on.

"Because of the boys who goes around stealing electricity cables. So in the process of cutting them I sometimes fear that when they do that might also cause fire and which might affect our shack then it gives me sleepless nights and I become restless." – PID 2224 (M)

Promoters of good sleep

While this study intended to identify promoters of good sleep, very few promoters emerged. They generally centered around behaviours that increased feelings of safety, such as locking doors, windows and gates before bed. This suggests that improving safety may alleviate some of these participants' fears that interfere with sleep. Finally, a couple of participants noted that they only sleep "well" when they are drunk. This raises concern around potential reliance on alcohol as a coping mechanism for sleep difficulties and, by implication, the impact of excessive alcohol consumption on one's physical health.

"Sometimes I feel safe because my gate has a lock and my door also gets locked so when I go to sleep I then go to sleep peacefully." – PID 2020 (F)

"for an example I drink a lot so I automatically sleep because I am drunk…. at that time [when he drank] I use to sleep like a baby" – PID 2654 (M)

In summary, the theme of neighbourhood environment highlighted the interconnectedness and interplay between neighbourhood characteristics, barriers to and promoters of good sleep. Factors such as noise, crime, safety and substance abuse (all characteristic of the neighbourhood) directly impact sleep quality, particularly on the weekend when noise, alcohol consumption and crime rates surge. Individuals' fear of crime exacerbate feelings of insecurity, leading to hypervigilance and poor sleep quality. Safety precautions, like securing doors and windows, offer minor reprieve, yet the systemic issues of crime, noise and safety still persist.

6.3.2 Theme 2: Physical sleep environment

Home and bedroom characteristics

More than half of the participants reported that they live in shacks, mostly made from zinc sheets, wood or other temporary materials. Visual examples of housing structures can be found in Supplementary Table 6.2 (Appendix 6). The shacks are generally divided into two rooms: one kitchen or living area and one bedroom. The remaining participants live in houses, some of which are constructed from brick, ranging in size from one room (with no division or separation between spaces) to six rooms.

> *"I stay in a 2 room shack and I use 1 room as a bedroom then the other room as a lounge and a kitchen." – PID 2030 (F)*

> *"I live in a formal brick house and it's a house that has 3 bedrooms" – PID 2556 (F)*

The participants primarily expressed their concern that because their homes are made of zinc sheets, wood or other temporary materials, bullets can easily penetrate the walls and hurt those inside the home. This related to the sub-theme of "ideal sleep space" below, where participants described wanting to make their homes safer from stray bullets. This suggests that interventions aimed at improving structural housing issues may alleviate some concern.

> *"These random shooting that's usually happen outside can also be harmful to us because what if you are caught in a crossfire of the bullet penetrates through your walls since we using temporary materials." – PID 2030 (F)*

> *"For instance in our area there is a lot of shooting that haphazardly takes place…because it might also penetrate inside the house, even though it wasn't coming to you, because we live and our houses are made with temporary structure or build with zinc." – PID 2020 (F)*

Many participants explained that because their homes are very close together, with narrow pathways between them, it makes the home noisy (as people are always using those pathways, creating a thoroughfare) and unsafe (as criminals often hide in the dark in the pathways). Participants who live close to the main roads also expressed feeling unsafe as they felt living near main roads increased their risk for traffic hazards, specifically accidents or traffic-related incidents such as cars skidding off the road and crashing into their homes. Participants also perceived living near the road as increasing their vulnerability to crime, suggesting that it provides convenient access and escape routes for criminals.

> *"Our houses are close to each other so much that it is impossible not to hear any form of noise that comes from the neighbours." – PID 2210 (F)*

> *"I don't feel safe at all because I stay in a shack, and it is a corner house that is nearby the road so I don't feel safe in any way." – PID 2263 (F)*

> *"…and my shack has a yard only in front then people walking through the passage at the back then it's easy for them to bump in my shack as well and sometimes I hear people being mugged and robbed and there's nothing I can do." – PID 2669 (M)*

When it comes to the physical sleep environment and bedroom characteristics, most participants were comfortable and happy with their bedroom and sleep environment. Most participants slept in a double bed with one other person or they slept alone. Three participants slept in a double bed with two other people (making three persons in the bed), one participant slept in a queen bed with her three children (making four persons in the bed) while one participant reported sleeping on a foam mattress on the floor since her daughter and new-born baby needed the double bed. While participants express contentment (or perhaps another form of acceptance as described below) with their current sleep arrangements, their sleep environment highlights limited space and resources.

> *"I just sleep with my 3 children and it is a queen base with a mattress. I have a 21 year old firstborn daughter and two 8 year old twins." – PID 2206 (F)*

> *"I am sleeping in a double bed and I happen to share the bed with my partner and my 2 year old child." – PID 2587 (M)*

Many participants report using more than one duvet (or duvets and blankets) to keep warm and feel comfortable, even those participants who are sleeping alone. This suggests that participants use multiple duvets or blankets not only for warmth but also to enhance their sense of psychological comfort and perhaps safety or security while sleeping.

"I use 3 duvets to cover myself to be able to feel comfortable." – PID 2556 (F)

"I sleep in a three quarter bed and I use about 3 blankets for me to feel okay." – PID 2222 (M)

Finally, there were mixed responses as to how the temperature of participants' homes impacted their sleep. More participants reported that their shack was too cold, specifically entering into winter months. It is important to note that these interviews were conducted during autumn and winter months in South Africa, a period known for its colder temperatures. Therefore, it is unsurprising that participants mentioned feeling cold. Some participants did report that their shacks were very warm, but they were comfortable with the heat.

"I always put on a heater to ensure that the room is warm before we go to bed because the shack is not really warm" – PID 2030 (F)

"…we don't feel like the room is warm enough or even the blankets since we are now approaching winter it will be worse." – PID 2455 (M)

"My shack is very warm and I am comfortable with the heat is just okay." – PID 2587 (M)

Ideal sleep space

When asked what changes they would make, if they could, to improve their sleep environment many of the answers centered around privacy, both for themselves and their family members. They would ideally like to build separate rooms for themselves or their teenage children and make their homes bigger. Participants also expressed that they would like to build brick houses that were impenetrable to the rain and were safer. One participant noted that they would like to replace their bed as it is no longer comfortable and is causing them pain. This suggests that most participants desire more privacy and personal space as well as infrastructure that is more protective against crime and the elements.

"I would probably build a separate room for myself so that I may also have privacy because I need it both my sons are old, they also need their privacy now." – PID 2020 (F)

"I would rebuild my house into a brick and safer house...Especially there isn't any burglar gate at the door." – PID 2030 (F)

"I'd change my bed where it is situated at the moment because there is an opening on the roof so when it rains then there are rain drops that comes through the zinc roof." – PID 2654 (M)

Finally, some participants commented that they would rather relocate and stay somewhere else entirely. This indicates significant dissatisfaction with their current community (likely due to safety, noise, crime and violence or other concerns) or it may reflect a longing for a fresh start where they feel that a different neighbourhood or living arrangement would offer better opportunities and quality of life.

> *"If there is anything I'd change is to relocate and stay somewhere else other than Site B." – PID 2210 (F)*

> *"I would probably relocate so that I can stay in a quiet and conducive space." – PID 2455 (M)*

In summary, the theme of physical sleep environment found that the majority of participants live in shacks made of temporary materials, expressing concerns about safety due to vulnerability to stray bullets and crime. Noisy and unsafe surroundings, inextricably linked to the high density of the neighbourhood and resultant narrow pathways between the homes, contributed to poor sleep quality. Interestingly, none of the participants commented on the privacy of their homes in relation to other homes, but did comment on the lack of privacy of the individuals living within the home, since most of the homes had little division between rooms or bedrooms. The majority of individuals were comfortable with their bed, bedding and mattress arrangements. The use of multiple duvets and blankets may suggest a desire for psychological comfort and safety. Participants express a longing for improved houses that were more safe and secure from the neighbourhood and the natural environment, with some considering relocation for a fresh start and better quality of life.

6.3.3 Theme 3: Individual sleep-related factors

Knowledge, attitudes, and beliefs around sleep

Overall, participants displayed an understanding about the importance of sleep with the majority acknowledging that sleep is critical for health and well-being. Many participants expressed that sleep was very important to them, specifically allowing their body, brain and mind to rest. More women than men described healthy sleep as inclusive of dimensions of duration and quality, i.e. they thought healthy sleep was that without disturbances or disruptions and was about 8 hours per night. Men generally described healthy sleep as being sufficient in duration only. A few participants also expressed that healthy sleep was about sleep timing, specifically going to bed between 18h00 and 20h00 in the evening to allow the body to rest.

"Yes I think it is very important because that is my time to give my body rest. If I were not to sleep my brain wouldn't function properly." – PID 2587 (M)

"I think it's talking about sleeping enough hours that being 8 hours and also peacefully without any disturbances." – PID 2020 (F)

"I think it speaks about the importance of sleeping during night time at around 6pm. I think sleeping in time so that the body can receive rest." – PID 2587 (M)

When asked about their feelings regarding their own sleep health, the majority of participants expressed that their sleep was not good, and they were not happy with their sleep. The main reason for this related to being disturbed by noise or issues of safety during sleep. Overall, the poor sleep health expressed by these participants does not appear to be a result of a lack of effort or intentional actions on their part to achieve better sleep. Instead, it seems that their sleep difficulties are primarily attributed to environmental factors that exacerbate sleep disturbances.

"It is not up to standard at all and in fact it's very poor." – PID 2455 (M)

"I keep on waking up in the middle of the night, I don't sleep entirely peaceful." – PID 2715 (F)

"I get to sleep fewer hours than I would love." – PID 2222 (M)

"… I don't sleep in a well standard manner to an extent that if I sleep right through until morning without waking up in between I panic and get scared of what if something could have happened." – PID 2263 (F)

Perceptions of the impact of sleep on overall health

Almost all of the participants expressed that sleep has a significant impact on their overall physical health. Participants felt that if they didn't sleep or struggled with their sleep, they would suffer from fatigue or bodily pain. They specifically described that they would get headaches or migraines from poor sleep and acknowledged that poor sleep could contribute to getting sick (i.e. influenza).

"Yes you might get sick if you don't sleep well." – PID 2645 (F)

"Yes because now I am constantly tired compared to how I was before I experienced this [poor sleep] and I always have these constant headaches and migraines." – PID 2030 (F)

Only two participants felt that their poor sleep health was related to their current chronic disease (i.e. hypertension). These two participants, however, appear to be drawing erroneous associations

between the two factors. For example, one participant attributed their high blood pressure to a belief that 'blood needs to cool down during sleep', and since they aren't sleeping well, their blood is always hot. The other participant noted that their body was impacted by their sleep because they believe that their blood doesn't flow thoroughly when they are not resting well.

> *" So it is always high and I understand that it is affected by the way which I am currently sleeping because the blood needs to cool down, so this thing of not resting causes my blood to be hot." – PID 2263 (F)*

Most participants linked a lack of sleep to poor cognition (specifically poor decision making, concentration, focus and motivation) and emotional instability (specifically moodiness, irritability and anger) the next day. They typically described that if they did not sleep well, they would struggle to do their daily tasks the next day (such as hanging the washing) since they were lacking the motivation and would rather procrastinate.

> *"I am always filled with anger and moody. I even lose concentration that I even lash at children for small things." – PID 2020 (F)*

> *"If I don't sleep I struggle to concentrate and if I can't concentrate then lose focus and that leads to not being able to do anything or be productive in anything I have to do." – PID 2020 (F)*

Sleep-related behaviours

The sleep-related behaviours sub-theme can be divided into daytime napping behaviours, week vs. weekend sleep and sleep hygiene, the latter of which relates to behaviours and habits during the day that can either promote better sleep or adversely affect sleep. None of the participants reported diagnosed sleep disorders (e.g. insomnia or obstructive sleep apnoea) or used any sleeping medication. Overall, there was a very polarized view on napping. Individuals either loved napping and felt they could not go a day without it, or they felt that napping was not necessary at all. Over half of the participants reported napping during the day. The main reason given for napping was related to not sleeping well at night or feeling safer when sleeping during the day than at night. Some reported that they had just always been a napper, while others napped as they didn't have anything else to do during the day. Among those who do not nap, it appears that the connotation of napping is partly cultural, where they have been brought up to believe that napping was only meant for individuals who were sick.

"No mostly I'd just feel tired because I am not sleeping well at night and I would wake up and go lay in bed just to give myself time to rest." – PID 2030 (F)

"Most of these times I have nothing better to do so I would just take a nap or sometimes I am just tired or avoid gallivanting the streets." – PID 2587 (M)

"Yes I've always been a person who loves sleeping or taking naps during the day." – PID 2210 (F)

"No, if I am sleeping then you must know that I am sick or I am drunk." – PID 2654 (F)

Many participants noted that their sleep duration was shorter on the weekends compared to the weekdays. A finding that contrasts with current literature where weekend sleep duration is often longer than weekday. For some, this was attributed to staying out later and going to bed later, while for others, it was due to increased neighbourhood noise and activity on the weekends.

"I don't sleep much on weekends because I'd go to bed around 11 -12 midnight then wake up again around 7:00 so I spend less hours than during the week in bed" – 2534 (M)

"I think its longer during the week and its less on weekend because on weekends I don't sleep at all, sometimes I would be awake until the morning because of the many activities happening and it's difficult to fall asleep" – 2206 (F)

Some participants described common behaviours relating to sleep hygiene. Between sunset and bedtime, one third of participants reported screen time, either from their cell phones or televisions. Two participants also reported going on their cell phones when they were woken up in the middle of the night.

"I enter bed and just scroll through my phone for roughly 10 minutes then I doze off." – PID 2715 (F)

"I am watching TV until I doze off." – PID 2534 (M)

"I normally wake up and be on my phone nothing much, fiddle with it until fall asleep again." – PID 2669 (M)

Two participants described that they smoke cigarettes when they are woken in the middle of the night and are trying to fall back to sleep. One participant expressed that they use alcohol to help them sleep. Therefore, alongside challenging environmental conditions, some of these participants

are vulnerable to the well-described exacerbators of poor such as screen use before bedtime and during the sleep period, and the use of stimulants (such as tobacco) or alcohol.

> *"It doesn't take me long so I go out and then come back smoke a cigarette then go back to sleep." – PID 2654 (M)*

> *"For an example I drink a lot so I automatically sleep because I am drunk….But you see, if today or tomorrow I attempt to sleep and I am sober I haven't touched alcohol, I am not going to sleep, it would be until morning dawn still struggling to sleep…" – PID 2654 (M)*

Acceptance of situation

Many participants described an acceptance of their situation, embracing both their favourable and unfavourable circumstances. While the interviewees recognised that they were living in challenging situations (specifically with regards to high crime and violence in the neighbourhood), they seemed to accept it for what it is and choose not to make too much of a fuss about it. They also appear to refrain from speaking out in their community as they fear their own safety might be compromised if they are too vocal about their concerns and worries. This "acceptance" may highlight the remarkable resilience demonstrated by these South Africans; despite the extreme adversity they face daily.

> *"No there are fears that I have but there is nothing I can do about them so it is what it is." – PID 2222 (M)*

> *"Yes because when you understand your situation you tend to accept it and eventually see nothing wrong with it." – PID 2206 (F)*

> *"…What I am trying to show you is that it's even difficult to complain about these certain acts at times, you just have to let things be for the sake of your peace and safety too." – PID 2210 (F)*

> *"And I am not a person who likes to talk much so I just let things be." – PID 2455 (M)*

6.4 Discussion

This qualitative study is the first-of-its-kind to shed light on the impact that external and internal factors have on sleep health among adults of African descent living in a low SES community in South Africa. The most prominent finding relates to the challenging environmental conditions, over which these individuals have little control. Specifically, noise, crime, violence and alcohol use were all identified as barriers to good sleep by both men and women, which likely explains much of this

cohort's disturbed sleep. This fits well with the recently defined term "sleep deserts": neighbourhoods that are not conducive to adequate sleep health[329] and are a major cause of health inequity[330]. An intriguing sub-theme of acceptance was identified, encapsulated by the sentiment of "it is what it is." A significant portion of men and women recognize the challenges inherent in their circumstances, yet express a remarkable level of acceptance with their situation, almost as if they have embraced their living conditions as the norm. On one hand, this finding might highlight the resilient nature of these individuals, capable of adapting to even the most adverse of environments. This sentiment is similar to the "shift-and-persist" model described in Chapter 5 among other low SES populations[315]. On the other hand, it's possible that this acceptance represents a sobering acknowledgment among participants that they are trapped in their circumstances and poverty cycle, feeling unable to break free and thus, almost accepting defeat.

Considering the views expressed by the participants in this study, it is clear that external factors related to the community were the major drivers of poor sleep quality. Environmental noise is a well-known contributor to sleep disturbances and overall sleep quality[331], having been shown to fragment sleep, and as a consequence, disrupt sleep architecture, typically increasing wake and non-rapid eye movement (NREM) stage 1 sleep and decreasing NREM stage 3 sleep and REM sleep[332]. One possible intervention to alleviate the effects of noise on sleep could be through insulating the homes against noise. A study by Amundsen *et al.* (2013) insulated 2500 dwellings against traffic noise and found that one and two years later, the proportion of individuals reporting sleep disturbances due to traffic noise was halved[333].

Previous work in this cohort has also shown that participants who report fears related to safety during sleep were more likely to report poor sleep quality[334]. Since both the men and women in this study echoed these concerns around crime-related safety and identified lack of safety and security as a major barrier to sleep, it is reasonable to suppose these individuals are in a state of hypervigilance at night through constantly scanning the environment for potential threats, which only worsens sleep quality[335]. While there is no immediate way to resolve safety in this community, one potential solution to improve the sense of security in the home at night might be through weighted blankets[336]. This was inadvertently suggested by one of the participants who noted that they need multiple blankets for them to "feel okay". While this participant was primarily responding to the question of warmth, it suggests that the psychological aspect of using weighted blankets might be valuable for these individuals. Previous research has shown that weighted blankets are beneficial in reducing insomnia severity[337], sleep difficulties[337] and anxiety[338] in adults. Weighted

blankets inadvertently improve sleep and anxiety by calming the nervous system through deep pressure touch[336]. Deep pressure has been defined as the "sensation produced when an individual is hugged, squeezed, stroked, or held"[339] and is a sensory input that provides proprioceptive input to the whole body that relaxes the nervous system[336].

When considering the influence of alcohol on sleep, one tends to think of its direct effects on the sleep of the consumer, such as its disruption to sleep architecture and overall sleep quality[340]. In this study, however, we have found strong indirect effects of alcohol use on the sleep of non-users, raising a potentially lesser-discussed aspect of sleep and alcohol. Individuals who do not partake in drinking themselves find their sleep disrupted by the noise, commotion and crime that accompanies excess alcohol use. This is an example of alcohol-related collateral damage in a community plagued by high levels of binge drinking. Previous chapters in this thesis have found that around 95% of men 70% of women consume alcohol, with men consuming significantly more alcohol per week compared to women (men: 16 (0, 36) drinks per week, women: 0 (0, 11) drinks per week). Although not reported in this thesis, patterns of alcohol consumption among the METS participants indicate excessive drinking on Thursdays – Sundays, with abstinence from Mondays to Wednesdays. Interestingly, despite men being heavier drinkers compared to women in this cohort, both sexes reported being disturbed by, and feeling unsafe when, others drink. There is therefore an urgent need to address the alcohol consumption culture in these disadvantaged communities.

Participants noted that their homes are closely packed together with narrow pathways between them, leading to constant noise from people passing through. Overcrowding, as a result of rapid urbanization and population growth, is characteristic of low SES neighbourhoods and is particularly severe in developing countries[341]. This problem of inadequate town planning is one of two issues identified in this study that is largely out of these individuals' control. The second issue relates to their home structure. When it came to the physical home environment, we found that both men and women were primarily concerned around the vulnerability of their homes to crime, consistently mentioning their worries about stray bullets. Being shot by stray bullets is quite common in these communities. Statistics from the 2022-2023 South African Police Services annual crime report found that, nationwide, 11,300 people were killed with a firearm, of which almost 10% of those deaths were gang related and victims were shot by stray bullets[342]. Implementing home safety improvements, such as using more bullet-resistant materials, can be done but requires financial resources that many community members currently lack.

Within the home, both men and women commented on the need for more privacy in their bedroom, specifically allowing their children to have their own bedroom since, currently, most families share one bedroom. Creating more privacy, however, requires financial resources, demonstrating that the consequences of poverty impact both internal (bedroom) and external (neighbourhood) factors relating to sleep. A previous survey-based study by Dincer *et al.* (2024) in an Australian population investigated use of bedrooms, focusing on user preferences and bedroom needs[343]. The authors found that, while privacy did emerge as a significant factor impacting respondents' bedroom experience, 70% of respondents stated that they would like to make changes to their bedrooms for physical, functional, comfort-based and aesthetic reasons[343]. This likely represents the differing priorities of various socioeconomic groups, where higher SES populations desire more aesthetic and functional changes, while lower SES population desire privacy and safety.

Interestingly, none of the participants in this study commented on the influence of light-at-night in their homes or neighbourhood on sleep. Given that light is widely recognized as a significant factor influencing sleep quality[344], the absence of this topic was unexpected. Internal home lighting is limited in our participants homes, presumably owing to home size and the cost of electricity, and screen time after sunset did not appear to be particularly prevalent. The consequence of neighbourhood light-at-night on sleep, however, was expected as the city council has installed large floodlights in informal settlements in lieu of traditional street lights to improve safety at night. Despite this, the participants in this study were more concerned about a lack of lighting at night. We speculate that perhaps, in low SES communities such as this where safety concerns are prevalent, individuals may rely on light as a primary means of protection during the night. In such contexts, the presence of light may act as a deterrent to crime or provide a sense of security such that people may not perceive light as a negative factor affecting their sleep. Instead, they may view it as essential for safety and may prioritize its presence over potential sleep disruptions. Even though most homes in Khayelitsha have access to electricity[345], issues such as loadshedding (rolling blackouts) or cable theft often leave many areas in darkness for long periods of time. This was brought up several times by participants who expressed concerns regarding darkness and lack of lighting, particularly with its association to safety and crime. This is similar to findings in other studies done in Khayelitsha, highlighting the lack of reliable lighting at night, and particularly street lighting[346]. In a similar vein, one would expect that temperature, specifically being too cold since these interviews were conducted during winter in Cape Town, would be a significant factor relating to sleep[321] in these non-insulated homes. This did not appear to be a sleep-related concern among these participants, who seem to adapt to cold homes by using more duvets and blankets to stay comfortable.

Despite almost all participants in this study expressing dissatisfaction with their sleep quality, they also showed a clear understanding of the significance of sleep for both mental and physical well-being. Similar findings were shown by Johnson *et al.* (2023) among an ethnically diverse sample of overweight/obese American adults, in which participants believed that sleep was essential to their health[347]. Interestingly, only African American participants in that study framed improvement in sleep health as a long-term health promotion strategy[347]. In the present study, more women described healthy sleep as including dimensions of quality and duration, while men commented mostly on sleep duration. This suggests that women in this community might have a broader understanding of what constitutes healthy sleep, but this requires further research. While the source of participants' understanding of sleep health is not known, it may relate to their decade-long involvement in the METS study, and more recently METS-Sleep..

It is concerning that for the majority of these individuals, poor sleep health is unlikely to be due to an inadequate understanding of, or attitude towards, sleep; rather, it appears to be predominantly attributable to environmental factors. Contrasting findings were reported Ruggiero *et al.* (2019), who found that among a mixed ethnicity group of adults (Caucasian, African American, Asian, Hispanic and Native American) living in the USA, those with lower perceived SES had less favourable sleep attitudes[348]. The authors suggested that this might be due to these individuals perceiving less control of their ability to get good quality sleep due to their "uncontrollable" environments[348]. While the current study also identifies the environment as a key uncontrollable factor impacting sleep, it found that low SES individuals had positive attitudes towards sleep. This difference could be explained by methodological differences since Ruggiero *et al.* (2019) used an anonymous survey and series of online questionnaires to collect data[348]. Furthermore, as suggested in Chapter 5 and above, perhaps participants in this study and in South Africa are more resilient to their challenging environment, allowing them to adopt more favourable sleep attitudes despite their circumstances.

Methodological considerations

A limitation of the study lies in the process of conducting interviews in isiXhosa, the native language of the participants, and subsequently translating them into English. While this approach facilitates communication with participants and ensures their comfort and understanding during interviews, it introduces the risk of losing nuance or subtle meanings in the translation process. Another limitation of this study is the exclusion of the research interviewer as an author on the manuscript. Their direct involvement in data collection could offer valuable insight into findings, however, being a member

of the Khayelitsha community themselves, it underscores the commitment to impartiality and objectivity in data interpretation in this study. A strength of this study is the fact that the same researcher conducted both the interviews and subsequent translation and transcription processes, both ensuring a consistent contextual understanding and mitigating potential loss of meaning. Other strengths of the study include the fact that the interviews were done in real time (i.e. in-person interviews) and in the participants home language. This made it possible to collect richer, more comprehensive information and context to responses, compared to gathering information through surveys or questionnaires.

6.5 Conclusion

In qualitatively addressing the question of *"Why do adults of African descent living in a low SES environment experience poor-quality sleep"*, one key answer emerged from this study. The poor sleep quality measured in our participants in the previous chapters of this thesis likely stems from the challenging environmental conditions prevalent in these communities, such as high levels of noise, crime and alcohol consumption. Environmental noise fragments sleep, while safety concerns due to crime and violence contribute to hypervigilance, exacerbating sleep disturbances, and potentially limiting time spent in the deeper stages of sleep. Collectively, these contribute to less restorative sleep which in turn might impact daytime function, as well as physical and mental health. In a community that is already vulnerable from a SES perspective, the impact of chronically disturbed sleep, which stems from the "sleep desert" nature of this neighbourhood, is a major determinant of sleep and health inequity in this population and is a serious public health concern. There is a clear need for urgent, targeted interventions to address these environmental challenges, which are largely beyond the control of the residents of low-income communities. Finally, in contrast to previous chapters in this thesis which observed key sex-specific differences in relationships between sleep health and CVD risk, no such clear distinctions are seen here. Instead, it appears that both the men and women are significantly and similarly affected by the adverse neighbourhood conditions.

Chapter 7

General Discussion

The purpose of this thesis was to investigate sex-specific relationships between cardiovascular disease (CVD) risk, nocturnal blood pressure (BP dipping and nocturnal hypertension) and sleep health in adults of African descent living in a low socioeconomic status (SES) community in South Africa. We chose to study this cohort as we wished to understand the unusually long nocturnal sleep durations previously reported in low SES South Africans of African descent[114,116,118,153,173]. The young to middle-aged men (39 (34, 46)y) and women (39 (32, 47)y) studied in this thesis are considered vulnerable from both social and health perspectives, owing to their high rates of unemployment (men: 78%, women: 74%), hypertension (men: 48%, women: 44%), and excessive obesity (women: 60.3%). Not only did the overwhelming majority report disturbed sleep (men: 97.2%, women: 96.6%), but actigraphy-derived measures confirmed that they uniquely present with long (men: 9.4 ± 1.4h, women: 8.9 ± 1.2h), poor quality sleep. Specifically their sleep is unacceptably disturbed as evidenced by low sleep efficiencies (men: 81.8 (76.8, 85.7)%), women: 79.9 (72.5, 84.6)%), high sleep fragmentation indices (men: 58.3 (52.5, 65.2)%, women: 63.4 (56.3, 68.2)%) and high wake after sleep onset (WASO) times (men: 103.1 (76.1, 127.0)min, women: 84.9 (68.8, 110.4)min).

7.1 Summary of main findings

The main findings from this thesis are presented visually in Figure 7.1.

7.1.1 Chapter 2

To the best of our knowledge, this study was the first to unveil a novel association between earlier self-reported sleep timing and higher CVD risk. We showed that men reporting earlier bedtimes and poorer sleep quality presented with higher CVD risk scores[173]. In contrast, women reporting earlier bedtimes, earlier wake-up times, longer sleep onset latencies, shorter total sleep times, poorer sleep quality, more disturbed sleep, and moderate to severe insomnia symptoms presented with higher CVD risk scores[173]. This suggest that timing, duration and continuity are all critical components of sleep health for these women. While this relationship between earlier sleep timing and CVD risk differs to what is observed in the Global North, where later sleep timing is usually associated with higher CVD risk[154], it underscores why we need to examine questions around sleep and CVD risk in more diverse settings to understand population-specific and context-specific CVD risk factors. The finding that CVD risk scores were higher among men and women with poor sleep quality was expected as this relationship has been well-described in the literature in other populations[12].

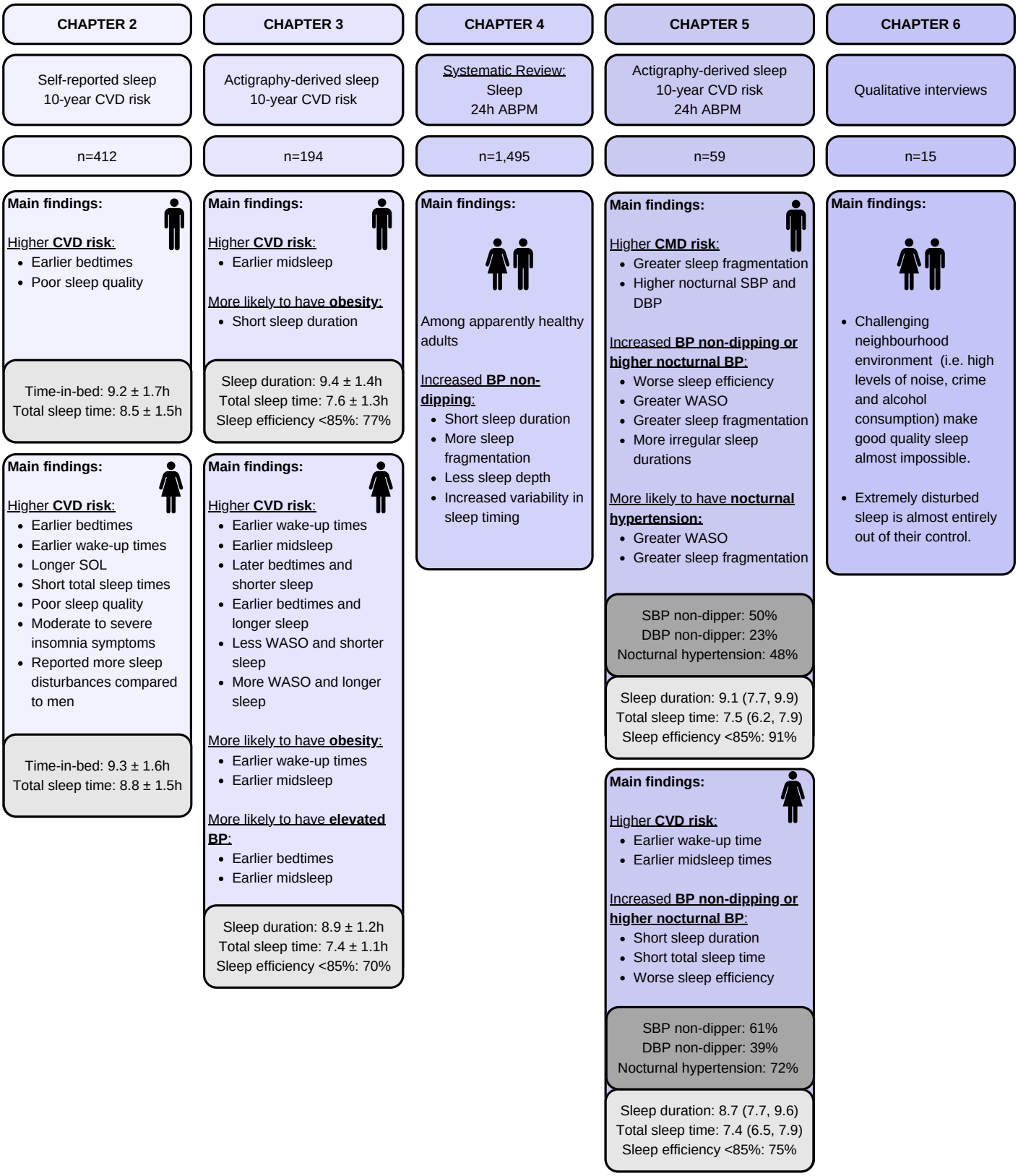

Figure 7.1 Visual summary of the main findings of the thesis. Data are presented as mean ± standard deviation, median (interquartile range) or frequency (%). ABPM: ambulatory blood pressure monitoring, BP: blood pressure, CVD: cardiovascular disease, DBP: diastolic blood pressure, SBP: systolic blood pressure, SOL: sleep onset latency, WASO: wake after sleep onset.

7.1.2 Chapter 3

Overall, this chapter highlights the complexity of the role that sleep plays in the context of physical health. We confirmed objectively-measured long (men: 9.4 ± 1.4h, women: 8.9 ± 1.2h), but very disturbed (sleep efficiency <85% – men: 77%, women: 69%) sleep in this population. These durations are significantly longer than the 6–8h per night[180,181] reported in many other populations, and half of the women and two thirds of the men have sleep durations longer than the 9h upper limit recommended for optimal health[80]. Since we initially found none of the expected associations between long sleep duration and CVD risk scores[34,124], it would be tempting to speculate that perhaps long sleep is protective of health in this population. This seems like an especially promising line of thought since a relationship between longer sleep and lower CVD risk has recently been shown in individuals of Iranian Arab descent[349] and we did observe the typical relationship between shorter sleep duration and obesity among the men[350].

Considering interactions between sleep variables, however, produced a key finding in this thesis and prompts a shift in thinking when interpreting the relationship between sleep habits and CVD risk. Among the women, shorter sleep was only associated with higher CVD risk scores in those who went to bed later. This aligns with current global messaging that curtailing sleep through delayed or later bedtimes is associated with worse health outcomes[351,352]. Given that this cohort comprised predominantly long sleepers, it was interesting to note that longer sleep was associated with higher CVD risk scores in women who went to bed earlier. This fits with the global sentiment that longer sleep may be detrimental to health, specifically cardiovascular health and CVD mortality[124]. We speculate that perhaps these participants are trying to initiate sleep at a time which might be out of phase with their endogenous circadian rhythms, since it is well-established that disruption to our body's natural circadian rhythms can be detrimental to cardiovascular health[154].

Indeed, the relationship between earlier sleep timing and CVD risk came through even more strongly in this chapter with objectively-measured sleep. Among the women, earlier wake-up times and midsleep times were associated with higher CVD risk scores and more obesity, while among the men, earlier midsleep times were associated with higher CVD risk scores. After adjusting for covariates (alcohol per week and presence of chronic diseases), women with earlier bedtimes and midsleep times were more likely to have elevated daytime blood pressure. Overall, this suggests a role for circadian misalignment in the pathway to CVD in this population, which should be assessed in future studies.

7.1.3 Chapter 4

To better understand the complex relationship between sleep and CVD mechanistically, we decided to focus on a key marker of CVD health: BP dipping during sleep. Given that previous studies typically explored BP dipping during sleep in individuals living with chronic disease (i.e. individuals with hypertension[198], obstructive sleep apnoea (OSA)[216], insomnia[217] or narcolepsy[218]), in **Chapter 4** we systematically reviewed the literature on sleep and BP dipping in apparently healthy individuals. The rationale for this was that since the exact mechanisms responsible for BP non-dipping are unclear, it might be useful to investigate BP non-dipping in healthy individuals (with no confounding factors such as presence of disease) to better understand potential underlying causes. **Chapter 4** found that short sleep duration, more sleep fragmentation, less sleep depth and increased variability in sleep timing were all associated with BP non-dipping in healthy individuals. Overall, while there is no evidence-based approach for the treatment of nocturnal BP non-dipping, it seems promising that addressing one's sleep health may be an important starting point to reduce the prevalence of BP non-dipping and perhaps the progression to cardiovascular disease. Importantly, for the scope of this thesis and the next chapter, BP dipping and nocturnal hypertension had never been assessed in South African individuals of African descent specifically living in a low SES environment.

7.1.4 Chapter 5

Poor sleep[11], nocturnal BP non-dipping[353] and nocturnal hypertension[61] are well-established risk factors for CVD, all of which are more prevalent among individuals of African descent. This chapter used the novel approach of assessing 24h BP in our participants to explore sex-specific associations between sleep health characteristics (sleep duration, quality, regularity, continuity and timing), nocturnal BP (i.e. BP dipping and nocturnal hypertension) and both cardiovascular and cardiometabolic disease risk. While we observed that more than half of our participants were classified as BP non-dippers or had nocturnal hypertension, of great concern was that three quarters of the women presented with nocturnal hypertension. Poor sleep appears to contribute to these suboptimal nocturnal cardiovascular profiles, although the picture emerging differed slightly between the men and women. Among the men, disturbed and irregular sleep was associated with BP non-dipping and higher nocturnal BP. In contrast, having less efficient sleep and consequently attaining less sleep in total was associated with BP non-dipping and higher nocturnal BP among the women. Collectively, these observations are similar to those found in **Chapter 4** and in other studies investigating sleep and nocturnal hypertension[354]. Furthermore, we found evidence to suggest that not only does more fragmented sleep (men) or earlier timed sleep (women) increase risk for CMD and CVD, but elevated BP during sleep increases risk for metabolic disease among the men. Thus,

disturbed sleep in these men may contribute to future CVD risk through compromised cardiovascular system recovery at night. One potential explanation relating to the lack of any similar observation among the women may relate to the limited heterogeneity among the women with regards to daytime and nocturnal hypertension and obesity.

7.1.5 Chapter 6

Given the observations of disturbed sleep and elevated nocturnal BP measured during home-based sleep in the previous chapters, the final study in this thesis used a qualitative approach to explore the potential influence of the participants home and neighbourhood environments on their sleep. **Chapter 6** is a first-of-its-kind study in South Africa, investigating individuals' perceptions around how external (e.g. environmental barriers to and promoters of good sleep) and internal (e.g. individual knowledge, attitudes and beliefs around sleep) factors might impact sleep health. Key findings were that adverse aspects of the neighbourhood environment (i.e. noise and high rates of crime, violence, alcohol consumption and drug use) almost exclusively contribute to poor sleep quality in this population. Individuals' knowledge, attitudes and beliefs around the importance of sleep as well as their physical sleep environment (e.g. number of bedrooms and type of bed) pale in comparison to the systemic issues prevalent in this deprived community. In comparison to other higher-income populations, where improving sleep health could be as simple as focusing on specific sleep hygiene habits (e.g. limiting caffeine intake, avoiding screens before bedtime or participating in regular physical activity), addressing these same suggestions in this low SES community will likely prove inadequate due to the underlying societal factors at play which conspire to make the neighbourhood unconducive to restorative sleep in many of the residents.

In summary, two main features of sleep emerge as important risk factors for CVD in these study participants: mistimed sleep and disturbed sleep. We speculate that the earlier timed sleep observed in **Chapters 2, 3 and 5** predominantly in women, but also in men, might reflect a behavioural response to needing to retreat to a safer place at night to escape the adverse conditions of their neighbourhood. Unfortunately, this behaviour, which may be a direct consequence of the environment, may contribute to circadian misalignment and consequently higher CVD risk. Our primary hypothesis to explain the disturbed sleep observed in **Chapters 2, 3 and 5** and the high proportion of BP non-dippers and nocturnal hypertension in **Chapter 5** relates to activity of the sympathetic nervous system (SNS) during sleep. We hypothesise that adverse environmental conditions experienced in a low-income neighbourhood at night places some individuals in a state of hypervigilance (i.e. constantly scanning their environment for threats), resulting in insufficient SNS

withdrawal, which in turn leads to disturbed sleep. Poor sleep quality then manifests as BP non-dipping or nocturnal hypertension, with subsequent increased CVD risk. As observed in **Chapter 5**, however, some individuals appear to demonstrate resilience to the adverse neighbourhood environment. Perhaps these are the individuals in whom appropriate SNS withdrawal takes place at night, reducing their risk of disturbed sleep, nocturnal hypertension, BP non-dipping, and CVD. An overview of these hypotheses has been visually depicted in Figure 7.2.

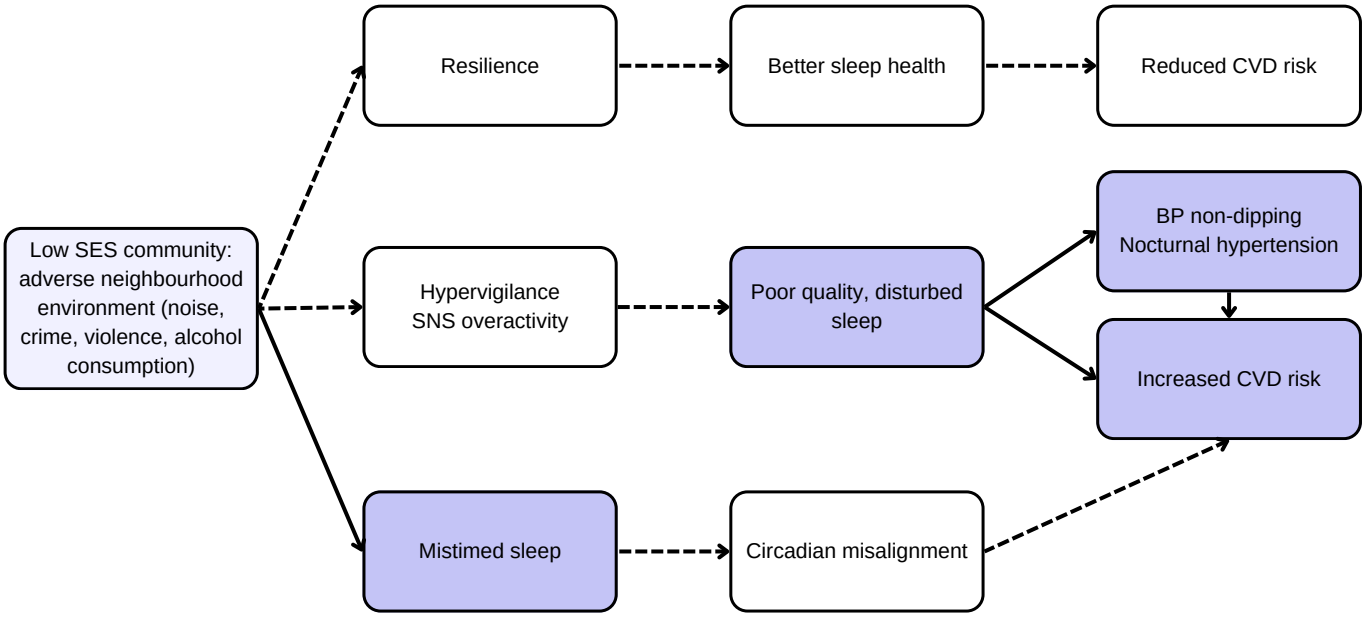

Figure 7.2 Hypothetical model to explain the relationship between an adverse neighbourhood environment, poor sleep and CVD risk. BP: blood pressure, CVD: cardiovascular disease, SES: socioeconomic status, SNS: sympathetic nervous system. *The light purple block represents adverse aspects of a low SES community, such as noise, crime, violence and alcohol use, described by participants in the qualitative interviews. Dark purple blocks represent variables that were directly measured in thesis. White blocks represents variables not measured in this thesis but which are hypothetical pathways through which adverse neighbourhood conditions may drive disturbed, mistimed sleep and subsequently increase risk for CVD. Solid lines represent pathways directly measured in this thesis, while dotted lines represent hypothetical pathways requiring further investigation.*

7.2 Sleep Health Insecurity

This thesis has measured significantly disturbed sleep in residents of a low SES community, with clear links to CVD risk, potentially through insufficient recovery of the cardiovascular and even

metabolic systems at night. Given that participants almost unanimously attribute their disturbed sleep to adverse neighbourhood conditions, social injustice may well be the crux of the poor sleep–CVD risk challenge faced by these community members. Since attaining healthy sleep is likely entirely out of participants control, we propose that this population is experiencing **Sleep Health Insecurity**. Similar to the term "food insecurity" (defined as a lack of regular access to safe and nutritious food for normal growth and development to lead an active and healthy lifestyle[355]), we propose that **Sleep Health Insecurity** is a "lack of regular access to healthy sleep (that which is of sufficient duration, regular, appropriately timed, consolidated, satisfying and refreshing), which is essential for optimal mental and physical health, emotional well-being and cognition". This expands on what Dunietz *et al.* (2022) proposed and termed "*Sleep Insecurity*"[356] ("*limited or uncertain availability of adequate sleep*") since the word "adequate" implies sufficient duration, which is only one of the many dimensions of sleep health.

Like *Sleep Insecurity*, **Sleep Health Insecurity** coexists with *Sleep Deserts*[329], defined by Attarian *et al.* (2022), as neighbourhoods which are often disadvantaged and not conducive to good sleep health[329]. Low-income communities like Khayelitsha, are home to a significant proportion of citizens in South Africa. If these communities are viewed as *Sleep Deserts*, driving the **Sleep Health Insecurity** of the residents, the vulnerability of the numerous community members to not only CVD risk as demonstrated in this thesis, but also to poor mental health and even access to education and employment through insufficient cognitive recovery at night or consequent daytime dysfunction, is a public health matter demanding immediate attention. To address **Sleep Health Insecurity** in this context, it is imperative to address its fundamental contributor – the adverse neighbourhood conditions associated with low-income communities. Alternatively, considering the massive societal undertaking required to positively change the neighbourhood environment, one could explore what it is about the individuals who are able to attain sleep health security, despite living in such *Sleep Deserts*. By learning about factors related to resilience in the face of adversity, we might gain insights into interventions targeted at individuals that could be implemented in the shorter term to promote sleep health security. Finally, since sex-specific differences in sleep and CVD risk were observed throughout this thesis, these differences may relate to sex-specific differences in **Sleep Health Insecurity.** Perhaps men and women may face unique challenges in their access to healthy sleep and thus, may experience **Sleep Health Insecurity** differently.

7.3 Methodological considerations and limitations

It is important to note that we do not have a non-African descent comparator group in this thesis. As such, it remains unclear how much our observations are influenced by the participants' SES or high rates of obesity and hypertension, for example, rather than being inherently related to their ethnic background.

The cross-sectional study design of **Chapters 2, 3 and 5**, and that they were specific to a unique population, namely low SES individuals, means that a causal relationship could not be determined and the findings cannot be generalized to the broader population. Despite this, there is very little research to date related to the sleep health of individuals of African descent from the Global South, and even less when it relates to their sleep health relative to nocturnal BP and CVD risk. These chapters therefore contribute to the current paucity in sleep health literature for this group of individuals.

In **Chapter 2**, self-reported data were used to describe sleep parameters, which has the inherent limitation of recall bias. While making use of self-reported data does allow for a larger sample size, this limitation was addressed through using objective measurement of sleep in **Chapters 3 and 5**, albeit with reduced sample sizes. Similarly, the potential for recall bias is also noted for the self-reported lifestyle factors and demographics data used for **Chapters 3 and 5**. Despite this, for **Chapters 2, 3 and 5** all participants were from the same community sample with similar demographics and backgrounds. As mentioned in previous chapters, we acknowledge the possibility of OSA as an additional sleep factor that increases risk for CVD. Together, these chapters provide subjective and objective measures of sleep, coupled with standardized routine data collection procedures, increasing the internal validity of the present results.

The relatively small sample size for **Chapter 5** warrants future studies with a larger group of individuals and more evenly distributed men and women. This limitation was unexpected for **Chapter 5**, stemming largely from the disruption caused by the COVID-19 pandemic, which interrupted and delayed the recruitment and data collection process. Furthermore, while data collection actively took place over three years, significant compliance difficulties with 24h ambulatory BP monitoring were encountered.

The insights obtained from the qualitative interviews in **Chapter 6** describe the perspectives and experiences of men and women living in a low SES environment solely in South Africa. Although

some findings likely only apply within a South African context, themes pertaining to crime and violence, safety and noise within a low SES setting, are relevant to comparable settings worldwide.

Lastly, a recurring theme throughout this thesis is the cultural sensitivity of the ISI tool. While we consistently found that poor sleep quality and disturbances were linked to increased CVD risk, ISI scores remained notably low, with few participants reporting clinically significant insomnia symptoms and no clear associations between ISI scores and CVD risk. This raises important questions about the tool's cultural relevance, translation, and practicality in a low-SES South African population, warranting further investigation.

7.4 Recommendations for future research

- The development of a composite sleep health score (SHS) was one of the key focuses of this thesis. Our methodology and thought process behind the score can be found in Appendix 7 and Supplementary table 7.1. However, when implementing the SHS, we found no statistically significant relationships between the SHS and CVD risk factors. We speculate that this may be due to low variability in overall sleep health, as most participants have long but poor-quality sleep, with few exhibiting characteristics of healthy sleep. It is also possible that a composite score blunts the effects of individual sleep dimensions, since combining or summing these dimensions into a single measure means potentially losing the resolution and nuance of important independent dimensions. Future research is required to develop, refine and test a composite sleep health score in this population. Especially since cut-offs and composite scores have been created based on European and American populations, which do not necessarily apply to this cohort of African descent individuals living in a low SES environment.
- Future research should investigate associations between chronotype (measured through questionnaires), circadian phase (measured through dim light melatonin onset experiments) and CVD risk which may yield important insights into the relationships between sleep timing or circadian misalignment and CVD risk among this population.
- Experimental studies designed to investigate the role that the autonomic nervous system (ANS) (specific SNS overactivity and hypervigilance during sleep) might play in the relationship between neighbourhood environment, poor sleep health and CVD risk, to see if an imbalanced ANS mediates the relationship between neighbourhood environment and poor sleep health or between poor sleep health and increased CVD risk, are warranted. Common methodologies which can be used as a proxy to measure ANS function during

sleep, include heart rate variability (HRV) derived from electrocardiogram (ECG), pulse wave amplitude (PWA) derived from single-finger plethysmography and urinary cortisol from a urine sample collected in the morning[357].

- Since we note that not all participants' sleep was affected by their adverse neighbourhood circumstances, studies investigating coping strategies or resilience would be interesting.
- While this thesis focused specifically on nocturnal sleep, there is evidence of a daytime napping culture in this community, which was specifically mentioned in the interviews in Chapter 6. Daytime napping may well be one of the coping mechanisms for poor quality, disturbed nocturnal sleep at night and requires further investigation into its associations with mental and physical health.
- Future studies should repeat **Chapter 5** (i.e. investigations between sleep, nocturnal BP and CVD risk) among women with more heterogeneity with respect to obesity, hypertension and other chronic diseases.
- Finally, there is a need for larger longitudinal studies, given the limited sample size and cross-sectional nature of the presented work.

7.5 Recommendations for intervention

Sustained improvements in sleep health in individuals living in communities like Khayelitsha necessitate long-term governmental action to address the neighbourhood environment. Thus, ultimately recommendations need to centre around governmental policymakers. **Chapter 6** has specifically shown strong evidence for the impact that the neighbourhood environment has on sleep and CVD among those living in a low SES neighbourhood. The following section provides recommendations for consideration at the individual, neighbourhood and government levels:

7.5.1 Individual Level

- Interventions to tackle the multifaceted issue of the environment on sleep health might include noise reduction or dampening interventions. This may involve soundproofing homes or windows. To offset the costs associated with soundproofing, the government could offer subsidies, making soundproofing more accessible and affordable. While earplugs seem like the most logical solution, we fear that earplugs would only make these individuals feel more vulnerable to their unsafe environment, only making their sleep quality worse.

7.5.2 Neighbourhood Level

- Promoting community safety initiatives, such as neighbourhood watch programmes, might be beneficial for sleep as they may promote a sense of safety among the community. Crucial

to note, however, is that such initiatives might work in some communities but not in all of them, since many of the participants in the qualitative study noted that they were afraid to "stand up" in case they became targets. Systematic reviews assessing the efficacy of neighbourhood watch programmes find mixed results. On the whole, however, it appears that these programmes are at least 56% effective at reducing crime, or at least show no increase in crime, compared to areas with no such programmes[358]. Neighbourhood watch programmes that appear to be the most successful are those that include property marking (i.e. a simple way to protect valuables by marking them with a permanent marker or by engraving them thus making them far less attractive to thieves) and security surveys (i.e. a site inspection designed to identify security weaknesses and make recommendations for strengthening security that will deter burglary)[358].

- Peer counselling or training community members as counsellors may also be a starting point to provide support and guidance to those struggling with sleep difficulties. Fostering a sense of community and mutual support can empower individuals to proactively take steps towards better sleep health.
- Since many of the participants in the qualitative study commented on how a lack of lighting made them feel more unsafe, increased street lighting in the neighbourhood might alleviate some concerns around safety or hopefully crime – especially among "hotspot" areas.

7.5.3 Government Level

It's essential to recognize that while interventions aimed at individuals and the neighbourhood may have a meaningful impact on sleep quality, addressing the broader societal factors contributing to sleep health insecurity is paramount for sustainable improvements in overall well-being. Unfortunately, a significant number of the sleep challenges experienced by these individuals relate to systemic issues of poverty and crime, necessitating policy changes at the governmental level to effect meaningful solutions.

- Government needs to prioritize crime prevention efforts in these communities. We acknowledge, however, that crime prevention and policing is complex and multifaceted. A study by Siegelaar *et al.* (2023) argues that the prevention of violent crime in South Africa is ineffective due to an overreliance on policing agencies and law enforcement, who cannot deal with the high levels of crime on their own. To address the high crime rates effectively, crime prevention efforts need to be supplemented with additional strategies, such as Community Policing Forums. These strategies have, however, also shown limited effectiveness[359] and thus further crime prevention strategies are required.

- Government should start by addressing the root causes of crime in low SES communities like Khayelitsha. Similar to the findings from **Chapter 6** in this thesis, a study by Manaliyo *et al.* (2014) found that i) poverty and high unemployment, ii) alcohol consumption and drug use, iii) lack of proper parental guidance, iv) ineffective criminal justice systems and v) bad social role models were the root causes of crime in Khayeltisha[360]. Addressing these five root causes of crime could therefore be a starting point to improve safety in the long term.
- Since participants in **Chapter 6** noted that it was often the youth who were engaged in criminal activities, government needs to prioritize education and stable employment opportunities for the youth. Investing in education ensures that young people have the skills and knowledge needed to secure stable jobs in the future, thereby reducing financial instability that can contribute to increased crime. By improving access to education, governments can also empower the youth to break the cycle of poverty.

7.6 Conclusion

Overall, this thesis provides new insights, from a Global South lens, to relationships between sleep and cardiovascular health as they relate to adults of African descent living in a low SES environment. The findings from this thesis suggest the need to consider all dimensions of sleep health - specifically sleep quality, timing, regularity, and continuity - in addition to thinking about sleep duration as a risk factor for CVD. By considering the lived experiences of individuals in this low SES community, we gained an understanding of the major role that the adverse neighbourhood environment has on sleep health in this population. Two main features of sleep emerge as important risk factors for CVD in these study participants: mistimed sleep and disturbed sleep. We speculate that this earlier timed sleep observed predominantly in women, but also in men, might be a direct consequence of the environment and may contribute to circadian misalignment and consequently higher CVD risk. We further hypothesise that due to the adverse neighbourhood environment, individuals are in a state of hypervigilance (i.e. constantly scanning their environment for threats) at night, resulting in insufficient SNS withdrawal, which in turn leads to disturbed sleep. Poor sleep quality then manifests as BP non-dipping or nocturnal hypertension, with subsequent increased CVD risk. Alternatively, we note that some individuals appear to demonstrate resilience to the adverse neighbourhood environment and perhaps these are the individuals in whom appropriate SNS withdrawal takes place at night, improving their sleep health and reducing their CVD risk. Finally, this thesis proposes the term Sleep Health Insecurity - a situation in which inequitable access to healthy sleep, a basic human need, impairs physical health and increases CVD risk.

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Appendices

Appendix 1: Published Chapters

Supplementary Table 2.1. Fully adjusted ordered logistic regression models exploring the associations between CVD risk score quintile (dependent variable) and the PSQI sleep disturbance dimensions (independent variables) stratified by sex.

	Women		Men	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**
Waking up in the middle of the night				
<1 time a week vs. None	1.22 (0.55, 2.70)	0.625	0.92 (0.32, 2.45)	0.864
1-2 times a week vs. None	2.39 (1.30, 4.37)*	**0.005**	1.29 (0.67, 2.47)	0.439
≥3 times a week vs. None	2.73 (1.38, 5.37)*	**0.004**	1.37 (0.65, 2.89)	0.406
Overall model	*n=233, LR chi^2=18.55, p=0.005*		*n=177, LR chi^2=8.11, p=0.229*	
Getting up for the bathroom				
<1 time a week vs. None	0.57 (0.14, 2.19)	0.415	0.46 (0.11, 1.88)	0.282
1-2 times a week vs. None	1.07 (0.56, 2.04)	0.829	1.07 (0.55, 2.07)	0.844
≥3 times a week vs. None	0.92 (0.49, 1.69)	0.782	1.65 (0.84, 3.32)	0.142
Overall model	*n=233, LR chi^2=7.52, p=0.010*		*n=177, LR chi^2=11.45, p=0.021*	
Cannot breathe comfortably				
<1 time a week vs. None	*0.89 (0.29, 2.70)*	*0.845*	1.32 (0.45, 3.82)	0.606
1-2 times a week vs. None	*0.83 (0.35, 1.96)*	*0.680*	1.52 (0.65, 3.53)	0.335
≥3 times a week vs. None	*3.24 (0.86, 12.21)*	*0.082*	0.44 (0.0, 2.16)	0.315
Overall model	*n=233, LR chi^2=9.59, p=0.013*		*n=177, LR chi^2=9.02, p=0.016*	
Cough or snore loudly				
<1 time a week vs. None	1.15 (0.38, 3.41)	0.797	0.84 (0.17, 4.01)	0.826
1-2 times a week vs. None	1.47 (0.77, 2.82)	0.239	1.20 (0.62, 2.72)	0.479
≥3 times a week vs. None	1.06 (0.58, 1.93)	0.845	1.11 (0.46, 2.66)	0.818
Overall model	*n=233, LR chi^2=8.02, p=0.011*		*n=177, LR chi^2=7.47, p=0.014*	
Feel too hot				
<1 time a week vs. None	1.02 (0.46, 2.22)	0.958	1.36 (0.58, 3.19)	0.469
1-2 times a week vs. None	1.88 (1.08, 3.28)*	**0.027**	1.33 (0.71, 2.49)	0.372
≥3 times a week vs. None	1.24 (0.58, 2.62)	0.572	1.90 (0.76, 4.71)	0.166
Overall model	*n=233, LR chi^2=11.32, p=0.016*		*n=177, LR chi^2=9.26, p=0.159*	
Feel too cold				
<1 time a week vs. None	0.78 (0.36, 1.69)	0.530	1.92 (0.66, 5.60)	0.230
1-2 times a week vs. None	1.43 (0.84, 2.48)	0.201	1.32 (0.67, 2.58)	0.418

≥3 times a week vs. None	1.52 (0.73, 3.15)	0.258	0.62 (0.23, 1.65)	0.345
Overall model	*n=232, LR chi^2=9.41, p=0.012*		*n=175, LR chi^2=10.92, p=0.091*	
Have bad dreams				
<1 time a week vs. None	0.86 (0.43, 1.72)	0.664	1.21 (0.54, 2.70)	0.639
1-2 times a week vs. None	1.03 (0.59, 1.080)	0.897	1.04 (0.56, 1.95)	0.895
≥3 times a week vs. None	1.03 (0.50, 2.11)	0.935	1.91 (0.70, 5.17)	0.204
Overall model	*n=230, LR chi^2=6.37, p=0.383*		*n=175, LR chi^2=9.06, p=0.017*	
Have pain				
<1 time a week vs. None	0.98 (0.47, 2.05)	0.963	1.63 (0.69, 3.81)	0.262
1-2 times a week vs. None	1.67 (0.96, 2.92)	0.069	1.40 (0.72, 2.72)	0.321
≥3 times a week vs. None	1.17 (0.55, 2.49)	0.683	2.79 (1.11, 7.03)*	**0.029**
Overall model	*n=233, LR chi^2=9.83, p=0.013*		*n=177, LR chi^2=12.52, p=0.023*	

Models were determined using ordered logistic regressions and data are presented as odds ratios (OR) with 95% confidence intervals (CI). Models were adjusted for alcohol, MVPA and employment. **p<0.05.* "None" refers to not during the past month.
CVD: cardiovascular disease, PSQI: Pittsburg Sleep Quality Index, MVPA: moderate- to vigorous-intensity physical activity.

Supplementary Table 2.2. Fully adjusted ordered logistic regression models exploring the associations between CVD risk score quintile (dependent variable) and self-reported PSQI sleep variables (independent variables) stratified by sex.

	Women		Men	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**
PSQI sleep efficiency	1.47 (0.88, 2.44)	0.135	1.32 (0.58, 2.16)	0.708
Overall model	*n=233, LR chi^2=6.34, p=0.175*		*n=175, LR chi^2=9.36, p=0.052*	
PSQI sleep medication	1.25 (0.78, 2.00)	0.347	0.87 (0.44, 1.69)	0.679
Overall model	*n=233, LR chi^2=4.87, p=0.301*		*n=176, LR chi^2=11.23, p=0.024*	
PSQI daytime dysfunction	1.18 (0.89, 1.57)	0.236	1.03 (0.75, 1.43)	0.839
Overall model	*n=233, LR chi^2=5.40, p=0.249*		*n=175, LR chi^2=9.26, p=0.055*	

Models were determined using ordered logistic regressions and data are presented as odds ratios (OR) with 95% confidence intervals (CI). Models were adjusted for alcohol, MVPA and employment.

CVD: cardiovascular disease; PSQI: Pittsburgh Sleep Quality Index

Supplementary Table 2.3. Self-reported sleep characteristics between employed and unemployed men and women.

	Women (n=233)			Men (n=177)		
	Employed (n=69)	**Unemployed (n=164)**	**p-value**	**Employed (n=82)**	**Unemployed (n=95)**	**p-value**
PSQI Bedtime (hh:mm)	21:30 (21:00, 22:00)	21:30 (21:00, 22:00)	0.479	22:00 (21:00, 22:00)	22:00 (21:00, 22:00	0.748
PSQI Wake-up time (hh:mm)	06:00 (06:00, 07:00)	07:00 (06:00, 08:00)	**0.017**	07:00 (06:00, 07:30)	07:00 (06:00, 08:00)	**0.028**
PSQI Time-in-bed (h)	9.0 (8.0, 10.0)	9.5 (8.5, 10.5)	**0.007**	9.0 (8.0, 10.0)	9.5 (8.3, 10.5)	**0.034**
PSQI Total sleep time (h)	8.3 (7.0, 9.5)	9.0 (8.0, 10.0)	**0.013**	8.5 (7.5, 9.5)	9.0 (7.8, 9.8)	0.056
PSQI Midsleep (hh:mm)	02:00 ± 00:50	02:09 ± 00:57	0.198	02:00 ± 00:49	02:30 ± 00:55	**0.030**
PSQI SOL (min)	15 (10, 30)	20 (10, 30)	0.390	20 (15, 30)	30 (15, 30)	0.316

Data are presented as mean ± standard deviation or median (interquartile range).
PSQI: Pittsburgh Sleep Quality Index; SOL: sleep onset latency.

Supplementary Table 3.1. Simple linear regressions exploring potential associations between candidate independent variables (sleep variables + covariates) and CVD risk score.

	Women (n=100)		Men (n=94)	
	β (95% CI)	**p-value**	**β (95% CI)**	**p-value**
Sleep variables				
Sleep onset (hh:mm)	–0.16 (–0.34, 0.03)	**0.108**	–0.12 (–0.24, 0.00)	**0.061**
Sleep offset (hh:mm)	–0.24 (–0.41, –0.07)	**0.007**	–0.11 (–0.24, 0.02)	**0.103**
Midsleep (hh:mm)	–0.29 (–0.51, –0.07)	**0.008**	–0.17 (–0.33, –0.02)	**0.030**
Midsleep binary				
<03:00	*Ref*	*Ref*	*Ref*	*Ref*
≥03:00	–0.48 (–0.86, –0.01)	**0.014**	–0.18 (–0.48, 0.12)	0.238
Sleep duration (h)	–0.09 (–0.25, 0.07)	0.262	0.01 (–0.09, 0.12)	0.791
Sleep duration category				
≤9h	*Ref*	*Ref*	*Ref*	*Ref*
>9h	–0.13 (–0.52, 0.26)	0.516	–0.13 (–0.44, 0.19)	0.433
Total sleep time (h)	–0.06 (–0.24, 0.11)	0.485	–0.02 (–0.14, 0.09)	0.672
Sleep efficiency (%)	0.01 (–0.02, 0.04)	0.494	–0.01 (–0.02, 0.01)	0.573
WASO (min)	–0.00 (–0.00, 0.00)	0.290	0.00 (–0.00, 0.00)	0.219
Sleep Fragmentation Index (%)	–0.00 (–0.03, 0.02)	0.686	0.01 (–0.00, 0.02)	0.369
Sleep Regularity Index	0.02 (–0.00, 0.05)	**0.126**	0.01 (–0.00, 0.02)	0.420
Midsleep regularity (h)	–0.08 (–0.48, 0.33)	0.701	–0.36 (–0.72, 0.05)	**0.083**
Sleep duration regularity (h)	–0.05 (–0.29, 0.18)	0.652	–0.15 (–0.32, 0.02)	**0.091**
Covariates				
Alcohol (no. per week)	–0.01 (–0.03, 0.02)	0.710	–0.01 (–0.01, 0.01)	0.361
Employed				
No	*Ref*	*Ref*	*Ref*	*Ref*
Yes	0.09 (–0.36, 0.54)	0.694	–0.21 (–0.56, 0.15)	0.250
MVPA (min/day)	–0.00 (–0.01, 0.00)	0.864	–0.00 (–0.00, 0.00)	0.765
Education (y)	–0.32 (–0.42, 0.22)	**<0.001**	–0.05 (–0.14, 0.04)	0.262
Asset index	–1.93 (–3.67, –0.19)	**0.029**	–1.82 (–2.86, –0.76)	**0.001**
Chronic diseases (non-CVD)				
No	*Ref*	*Ref*	*Ref*	*Ref*

Yes	0.86 (0.39, 1.33)	**<0.001**	0.42 (0.02, 0.83)	**0.039**

Data are presented as beta-coefficients with 95% confidence intervals (CI). Bold P-values indicate independent variables with p-values <0.15 selected for further analyses in Step 2.
CVD: cardiovascular disease, WASO: wake after sleep onset, MVPA: moderate- to vigorous-intensity physical activity.

Supplementary Table 3.2. Simple logistic regressions exploring potential associations between candidate independent variables (sleep variables + covariates) and elevated BP.

	Women (n=100)		Men (n=94)	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**
Sleep variables				
Sleep onset (hh:mm)	0.67 (0.44, 1.00)	**0.053**	0.75 (0.52, 1.08)	**0.129**
Sleep offset (hh:mm)	0.83 (0.57, 1.18)	0.300	0.98 (0.68, 1.40)	0.916
Midsleep (hh:mm)	0.66 (0.41, 1.05)	**0.078**	0.79 (0.51, 1.23)	0.303
Midsleep binary				
<03:00	*Ref*	*Ref*	*Ref*	*Ref*
≥03:00	0.48 (0.22, 1.08)	**0.075**	0.51 (0.22, 1.16)	**0.108**
Sleep duration (h)	1.13 (0.81, 1.56)	0.477	1.21 (0.89, 1.65)	0.214
Sleep duration category				
≤9h	*Ref*	*Ref*	*Ref*	*Ref*
>9h	1.26 (0.57, 2.78)	0.562	1.06 (0.45, 2.49)	0.889
Total sleep time (h)	1.15 (0.81, 1.65)	0.434	1.22 (0.88, 1.66)	0.222
Sleep efficiency (%)	1.02 (0.96, 1.09)	0.468	0.99 (0.95, 1.05)	0.995
WASO (min)	0.99 (0.98, 1.01)	0.978	1.00 (0.99, 1.00)	0.861
Sleep Fragmentation Index (%)	0.99 (0.94, 1.04)	0.704	1.00 (0.96, 1.05)	0.865
Sleep Regularity Index	1.03 (0.96, 1.09)	0.400	0.99 (0.94, 1.04)	0.693
Midsleep regularity (h)	0.47 (0.19, 1.14)	**0.097**	0.80 (0.28, 2.65)	0.676
Sleep duration regularity (h)	0.69 (0.41, 1.13)	0.144	0.92 (0.57, 1.49)	0.743
Covariates				
Alcohol (no. per week)	1.05 (1.00, 1.11)	**0.047**	0.99 (0.97, 1.02)	0.942
Employed				
No	*Ref*	*Ref*	*Ref*	*Ref*
Yes	0.59 (0.23, 1.49)	0.265	0.77 (0.29, 2.05)	0.602
MVPA (min/day)	0.99 (0.97, 0.99)	**0.044**	1.00 (0.99, 1.00)	0.472
Age (y)	1.08 (1.02, 1.13)	**0.005**	1.11 (1.04, 1.18)	**0.001**
Education (y)	0.80 (0.62, 1.03)	**0.080**	0.92 (0.71, 1.18)	0.524
Asset index	0.45 (0.01, 15.2)	0.656	0.30 (0.02, 6.12)	0.435
Chronic diseases (non-hypertension)				
No	*Ref*	*Ref*	*Ref*	*Ref*
Yes	4.15 (1.59, 10.84)	**0.004**	2.68 (0.91, 7.93)	**0.073**

Data are presented as odds ratios (OR) with 95% confidence intervals (CI). Bold P-values indicate independent variables with p-values <0.15 selected for further analyses in Step 2.
BP: blood pressure; WASO: wake after sleep onset, MVPA: moderate- to vigorous-intensity physical activity.

Supplementary Table 3.3. Simple logistic regressions exploring potential associations between candidate independent variables (sleep variables + covariates) and obesity.

	Women (n=100)		Men (n=94)	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**
Sleep Variables				
Sleep onset (hh:mm)	0.67 (0.44, 1.00)	**0.053**	1.79 (0.94, 3.40)	**0.075**
Sleep offset (hh:mm)	0.54 (0.35, 0.81)	**0.003**	0.65 (0.27, 1.57)	0.336
Midsleep (hh:mm)	0.46 (0.27, 0.77)	**0.003**	1.31 (0.53, 3.25)	0.557
Midsleep binary				
<03:00	*Ref*	*Ref*	*Ref*	*Ref*
≥03:00	0.41 (0.17, 0.94)	**0.035**	1.22 (0.19, 4.00)	0.829
Sleep duration (h)	0.81 (0.57, 1.14)	0.229	0.48 (0.25, 0.90)	**0.023**
Sleep duration category				
≤9h	*Ref*	*Ref*	*Ref*	*Ref*
>9h	0.51 (0.22, 1.16)	**0.111**	0.12 (0.01, 1.07)	**0.058**
Total sleep time (h)	0.83 (0.57, 1.21)	0.340	0.51 (0.25, 1.04)	**0.065**
Sleep efficiency (%)	1.00 (0.94, 1.06)	0.996	0.98 (0.89, 1.08)	0.727
WASO (min)	0.99 (0.98, 1.00)	0.403	0.99 (0.96, 1.01)	0.354
Sleep Fragmentation Index (%)	0.96 (0.91, 1.01)	**0.134**	0.97 (0.87, 1.07)	0.504
Sleep Regularity Index	1.01 (0.95, 1.07)	0.714	1.10 (0.99, 1.21)	**0.075**
Midsleep regularity (h)	0.81 (0.35, 1.86)	0.624	0.11 (0.00, 2.20)	0.150
Sleep duration regularity (h)	0.76 (0.47, 1.24)	0.277	0.52 (0.14, 1.95)	0.329
Covariates				
Alcohol week (no. per week)	0.94 (0.89, 0.99)	**0.020**	0.95 (0.86, 1.04)	0.262
Employed				
No	*Ref*	*Ref*	*Ref*	*Ref*
Yes	2.40 (0.86, 6.68)	**0.093**	0.86 (0.09, 8.15)	0.897
MVPA (min/day)	0.99 (0.98, 1.00)	0.334	1.00 (0.99, 1.01)	0.729
Age (y)	1.07 (1.01, 1.12)	**0.011**	1.08 (0.95, 1.24)	0.249
Education (y)	0.89 (0.69, 1.15)	0.394	1.08 (0.57, 2.03)	0.807
Asset index	10.41 (0.26, 410.19)	0.211	12.86 (0.00, 17346.2)	0.487
Any chronic diseases				
No	*Ref*	*Ref*	*Ref*	*Ref*
Yes	2.19 (0.88, 5.39)	**0.090**	0.71 (0.07, 6.65)	0.761

Data are presented as odds ratios (OR) with 95% confidence intervals (CI). Bold P-values indicate independent variables with p-values <0.15 selected for further analyses in Step 2.
WASO: wake after sleep onset, MVPA: moderate- to vigorous-intensity physical activity.

Supplementary Table 3.4. Multivariable linear regression analyses exploring associations between candidate independent variables (sleep variables + covariates) identified in step 1 and CVD risk score among the women.

	Model 1: Sleep onset		Model 2: Sleep offset		Model 3: Midsleep		Model 4: Midsleep ≥03:00		Model 5: Sleep regularity index	
	β (95% CI)	**p-value**	**β (95% CI)**	**p-value**	**β (95% CI)**	**p-value**	**β (95% CI)**	**p-value**	**β (95% CI)**	**p-value**
Sleep variable	–0.10 (–0.26, 0.05)	0.188	–0.14 (–0.28, 0.00)	0.052	–0.18 (–0.36, 0.00)	**0.046**	–0.30 (–0.62, 0.02)	0.070	0.02 (–0.00, 0.04)	0.061
Education (y)	–0.29 (–0.38, –0.19)	**<0.001**	–0.28 (–0.37, –0.18)	**<0.001**	–0.28 (–0.28, –0.02)	**<0.001**	–0.28 (–0.37, –0.18)	**<0.001**	–0.37 (–0.49, –0.25)	**<0.001**
Employment	–	–	–	–	–	–	–	–	–	–
Chronic disease (non-CVD)	0.54 (0.11, 0.97)	**0.015**	0.51 (0.08, 0.94)	**0.020**	0.52 (0.09, 0.94)	**0.019**	0.57 (0.13, 0.99)	**0.010**	–	–
Model Statistics	*n=95; R^2=0.375; P<0.001*		*n=95; R^2=0.388; P<0.001*		*n=95; R^2=0.390; P<0.001*		*n=95; R^2=0.385; P<0.001*		*n=95; R^2=0.470; P<0.001*	

Data are presented as beta-coefficients with 95% confidence intervals (CI). – indicates that the covariate did not contribute significantly to the model and was removed.
CVD: cardiovascular disease.

Supplementary Table 3.5. Multivariable linear regression analyses exploring associations between candidate independent variables (sleep variables + covariates) identified in step 1 and CVD risk score among the men.

	Model 1: Sleep onset		Model 2: Sleep offset		Model 3: Midsleep		Model 4: Midsleep regularity		Model 5: Sleep duration regularity	
	β (95% CI)	**p-value**	**β (95% CI)**	**p-value**	**β (95% CI)**	**p-value**	**β (95% CI)**	**p-value**	**β (95% CI)**	**p-value**
Sleep variable	–0.09 (–0.21, 0.03)	0.153	–0.10 (–0.22, 0.03)	0.128	–0.14 (–0.29, 0.01)	0.067	–0.33 (–0.69, 0.26)	0.069	–0.11 (–0.28, 0.40)	0.193
Asset index	–1.69 (–2.75, –0.62)	**0.002**	–1.76 (–2.81, –0.72)	**0.001**	–1.67 (–2.7, 0.63)	**0.002**	–1.83 (–2.88, –0.78)	**0.001**	–1.70 (–2.76, –0.64)	**0.002**
Chronic disease (non-CVD)	–	–	–	–	–	–	–	–	–	–
Model Statistics	*n=93; R^2=0.134; P=0.002*		*n=93; R^2=0.137; P=0.001*		*n=93; R^2=0.147; P<0.001*		*n=93; R^2=0.150; P<0.001*		*n=93; R^2=0.141; P=0.001*	

Data are presented as beta-coefficients with 95% confidence intervals (CI). – indicates that the covariate did not contribute significantly to the model and was removed.
CVD: cardiovascular disease.

Supplementary Table 3.6. Multivariable logistic regression analyses exploring associations between candidate independent variables (sleep variables + covariates) identified in step 1 and elevated BP among the women.

	Model 1: Sleep onset		Model 2: Midsleep		Model 3: Midsleep ≥03:00		Model 4: Midsleep regularity	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Sleep variable	0.53 (0.33, 0.85)	**0.009**	0.47 (0.26, 0.83)	**0.010**	0.32 (0.12, 0.81)	**0.017**	0.37 (0.12, 1.10)	0.074
Alcohol (no. per week)	1.10 (1.03, 1.17)	**0.004**	1.11 (1.04, 1.19)	**0.003**	1.10 (1.02, 1.16)	**0.005**	1.10 (1.03, 1.17)	**0.003**
Employment	–	–	–	–	–	–	–	–
MVPA (min/day)	–	–	–	–	–	–	–	–
Age (y)	–	–	–	–	–	–	1.10 (1.04, 1.16)	**0.001**
Education (y)	–	–	–	–	–	–	–	–
Chronic disease (non-hypertension)	6.72 (2.22, 20.29)	**0.001**	5.47 (1.95, 16.85)	**0.001**	5.94 (2.04, 17.26)	**0.001**	–	–
Model Statistics	*n=99; LR chi^2=23.54; P<0.001*		*n=99; LR chi^2=23.25; P<0.001*		*n=99; LR chi^2=21.91; P<0.001*		*n=99; LR chi^2=21.35; P<0.001*	

Data are presented as odds ratios (OR) with 95% confidence intervals (CI). – indicates that the covariate did not contribute significantly to the model and was removed.
BP: blood pressure. MVPA: moderate- to vigorous-intensity physical activity.

Supplementary Table 3.7. Multivariable logistic regression analyses exploring associations between candidate independent variables (sleep variables + covariates) identified in step 1 and elevated BP among the men.

	Model 1: Sleep onset		Model 2: Midsleep ≥03:00	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**
Sleep variable	0.81 (0.55, 1.18)	0.283	0.56 (0.23, 1.34)	0.194
Age (y)	1.10 (1.03, 1.18)	**0.002**	1.11 (1.04, 1.18)	**0.002**
Alcohol (no. per week)	–	–	–	–
Chronic disease (non-hypertension)	–	–	–	–
Model Statistics	*n=94; LR chi^2=13.18; P=0.001*		*n=94; LR chi^2=13.68; P=0.001*	

Data are presented as odds ratios (OR) with 95% confidence intervals (CI). – indicates that the covariate did not contribute significantly to the model and was removed.
BP: blood pressure

Supplementary Table 3.8. Multivariable logistic regression analyses exploring associations between candidate independent variables (sleep variables + covariates) identified in step 1 and obesity among the women.

	Model 1: Sleep onset		Model 2: Sleep offset		Model 3: Midsleep		Model 4: Midsleep ≥03:00		Model 5: Sleep duration >9h		Model 5: Sleep fragmentation index	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Sleep variable	0.74 (0.48, 1.14)	0.182	0.54 (0.35, 0.81)	**0.003**	0.46 (0.27, 0.77)	**0.003**	0.52 (0.21, 1.25)	0.144	0.53 (0.22, 1.23)	0.140	0.96 (0.91, 1.01)	0.167
Age (y)	1.06 (1.00, 1.12)	**0.029**	–	–	–	–	1.06 (1.00, 1.12)	**0.034**	1.07 (1.01, 1.13)	**0.013**	1.07 (1.01, 1.12)	**0.012**
Alcohol (no. per week)	–	–	–	–	–	–	–	–	–	–	–	–
Employment	–	–	–	–	–	–	–	–	–	–	–	–
Any chronic diseases	–	–	–	–	–	–	–	–	–	–	–	–
Model Statistics	*n=99; LR chi^2=9.03; P=0.011*		*n=100; LR chi^2=9.97; P=0.002*		*n=100; LR chi^2=9.86; P=0.002*		*n=100; LR chi^2=9.37; P=0.009*		*n=100; LR chi^2=9.42; P=0.009*		*n=100; LR chi^2=9.16; P=0.010*	

Data are presented as odds ratios (OR) with 95% confidence intervals (CI). – indicates that the covariate did not contribute significantly to the model and was removed.

Supplementary Table 3.9. Multivariable logistic regression analyses exploring associations between candidate independent variables (sleep variables + covariates) identified in step 1 and obesity among the men.

	Model 1: Sleep onset		Model 2: Sleep duration		Model 3: Sleep duration >9h		Model 3: Total sleep time		Model 4: Sleep regularity index	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Sleep variable	1.79 (0.94, 3.40)	0.075	0.48 (0.25, 0.90)	**0.023**	0.12 (0.01, 1.07)	0.058	0.51 (0.25, 1.04)	0.065	1.10 (0.99, 1.21)	0.075
Age (y)	–	–	–	–	–	–	–	–	–	–
Alcohol (no. per week)	–	–	–	–	–	–	–	–	–	–
Work	–	–	–	–	–	–	–	–	–	–
Any chronic diseases	–	–	–	–	–	–	–	–	–	–
Model Statistics	*n=99; LR chi^2=2.95; P=0.085*		*n=94; LR chi^2=5.35; P=0.021*		*n=94; LR chi^2=4.72; P=0.029*		*n=94; LR chi^2=3.62 P=0.057*		*n=75; LR chi^2=3.56; P=0.059*	

Data are presented as odds ratios (OR) with 95% confidence intervals (CI). – indicates that the covariate did not contribute significantly to the model and was removed.

Supplementary Table 3.10. Simple linear regressions exploring potential associations between sleep timing and quality variables (independent variables) and sleep duration (dependent variable).

	Women (n=100)		Men (n=94)	
	β (95% CI)	**p-value**	**β (95% CI)**	**p-value**
Sleep onset (hh:mm)	–0.59 (–0.79, –0.39)	**<0.001**	–0.70 (–0.89, –0.51)	**<0.001**
Sleep offset (hh:mm)	0.66 (0.49, 0.83)	**<0.001**	0.68 (0.47, 0.88)	**<0.001**
Midsleep (hh:mm)	0.13 (–0.14, 0.40)	0.344	–0.06 (–0.36, 0.23)	0.685
Sleep efficiency (%)	0.00 (–0.03, 0.03)	0.967	0.01 (–0.02, 0.03)	0.696
WASO (min)	0.01 (0.01, 0.02)	**<0.001**	0.01 (0.00, 0.15)	**0.001**
Sleep Fragmentation Index (%)	0.03 (0.00, 0.59)	**0.043**	0.01 (–0.02, 0.04)	0.376
Sleep Regularity Index (%)	–0.02 (–0.06, 0.13)	0.212	–0.05 (–0.08, –0.02)	**<0.001**
Midsleep regularity (h)	–0.88 (–1.34, –0.41)	**<0.001**	0.17 (–0.53, 0.86)	0.633
Sleep duration regularity (h)	–0.36 (–0.64, –0.07)	**0.014**	0.16 (–0.17, 0.49)	0.366

Data are presented as beta-coefficients with 95% confidence intervals (CI). Bold P-values indicate independent variables with p-values <0.15 selected for further analyses in the moderation models.
WASO: wake after sleep onset.

Supplementary Table 3.11. Exploring interactions between sleep duration and other sleep variables in multivariable linear regression models for CVD risk score in the women.

Model		β (95% CI)	p-value	*Model statistics*
1	**Sleep duration** (h)	5.31 (2.68, 7.29)	**<0.001**	
	Sleep onset time (hh:mm)	1.89 (0.88, 2.90)	**<0.001**	
	Duration*Sleep onset	–2.38 (–0.35, –0.12)	**<0.001**	*n=95*
	Education (y)	–0.30 (–0.38, –0.21)	**<0.001**	*R^2=0.489*
	Chronic disease (non-CVD)	0.51 (0.12, 0.91)	**0.012**	*P<0.001*
	Employment	–	–	
2	**Sleep duration** (h)	0.18 (–0.61, 0.97)	0.648	
	Sleep offset time (hh:mm)	–0.03 (–0.98, 0.92)	0.953	
	Duration*Sleep offset	–0.02 (–0.12, 0.08)	0.748	*n=95*
	Education (y)	–0.28 (–0.37, –0.18)	**<0.001**	*R^2=0.392*
	Chronic disease (non-CVD)	0.52 (0.08, 0.96)	**0.020**	*P<0.001*
	Employment	–	–	
3	**Sleep duration** (h)	–0.34 (–0.65, –0.03)	**0.032**	
	WASO (min)	–0.04 (–0.07, –0.01)	**0.006**	
	Duration*WASO	0.004 (0.00, 0.00)	**0.014**	*n=95*
	Education (y)	–0.31 (–0.40, –0.21)	**<0.001**	*R^2=0.430*
	Chronic disease (non-CVD)	0.44 (0.14, 0.86)	**0.043**	*P<0.001*
	Employment	–	–	
4	**Sleep duration** (h)	–0.48 (–0.87, 0.00)	0.051	
	Sleep fragmentation index (%)	–0.15 (–0.28, –0.01)	0.031	
	Duration*Sleep fragmentation index	0.02 (–0.00, 0.03)	0.052	*n=95*
	Education (y)	–0.31 (–0.40, –0.21)	**<0.001**	*R^2=0.408*
	Chronic disease (non-CVD)	0.52 (0.86, 0.94)	**0.019**	*P<0.001*
	Employment	–	–	
5	**Sleep duration** (h)	0.16 (–0.14, 0.46)	0.293	
	Midsleep regularity (h)	2.26 (–0.64, 5.17)	0.125	
	Duration* Midsleep regularity	–0.28 (–0.62, 0.06)	0.103	*n=95*
	Education (y)	–0.30 (–0.39, –0.20)	**<0.001**	*R^2=0.387*
	Chronic disease (non-CVD)	0.47 (0.03, 0.91)	**0.039**	*P<0.001*
	Employment	–	–	
6	**Sleep duration** (h)	0.04 (–0.29, 0.36)	0.826	*n=95*
	Sleep duration regularity (h)	0.41 (–1.13, 1.94)	0.601	*R^2=0.370*

Duration*Sleep duration regularity	–0.05 (–0.22, 1.22)	0.554	*P<0.001*
Education (y)	–0.29 (–0.38, –0.19)	**<0.001**	
Chronic disease (non-CVD)	0.51 (0.06, 0.96)	**0.024**	
Employment	–	–	

Data are presented as beta coefficients with 95% confidence intervals (CI). * indicates interaction term. – indicates that the covariate did not contribute significantly to the model and was removed.
CVD: cardiovascular disease, WASO: wake after sleep onset.

Supplementary Table 3.12. Exploring interactions between sleep duration and other sleep variables in multivariable linear regression models for CVD risk score in the men.

Model		β (95% CI)	p-value	*Model statistics*
1	**Sleep duration** (h)	0.70 (–0.56, 1.95)	0.274	
	Sleep onset time (hh:mm)	0.16 (–0.35, 0.67)	0.536	*n=93*
	Duration*Sleep onset	–0.03 (–0.09, 0.21)	0.223	*R^2=0.162*
	Asset index	–	–	*P=0.003*
	Chronic disease (non-CVD)	–	–	
2	**Sleep duration** (h)	0.08 (–0.64, 0.80)	0.823	
	Sleep offset time (hh:mm)	–0.12 (–1.02, 0.77)	0.787	*n=93*
	Duration*Sleep offset	–0.01 (–0.09, 0.09)	0.965	*R^2=0.146*
	Asset index	–1.68 (–2.74, –0.61)	**0.002**	*P=0.006*
	Chronic disease (non-CVD)	–	–	
3	**Sleep duration** (h)	–0.22 (–0.49, 0.06)	0.118	
	WASO (min)	–0.02 (–0.04, 0.00)	0.203	*n=92*
	Duration*WASO	0.00 (–0.00, 0.00)	0.139	*R^2=0.155*
	Asset index	–	–	*P=0.012*
	Chronic disease (non-CVD)	–	–	
4	**Sleep duration** (h)	–0.47 (–0.95, 0.00)	0.053	
	Sleep fragmentation index (%)	–0.13 (–0.25, 0.00)	0.059	*n=93*
	Duration*Sleep fragmentation index	0.01 (0.00, 0.02)	0.050†	*R^2=0.155*
	Asset index	–1.57 (–2.65, –0.50)	**0.005**	*P=0.004*
	Chronic disease (non-CVD)	–	–	
5	**Sleep duration** (h)	0.53 (–0.25, 1.30)	0.179	
	Sleep regularity index (%)	0.09 (–0.03, 0.22)	0.144	*n=74*
	Duration*Sleep regularity index	–0.01 (–0.02, 0.00)	0.178	*R^2=0.162*
	Asset index	–2.04 (–3.27, –0.81)	**0.002**	*P=0.015*
	Chronic disease (non-CVD)	–	–	

Data are presented as beta coefficients with 95% confidence intervals (CI). * indicates interaction term. – indicates that the covariate was not contributing significantly to the model and was removed. † indicates trending towards significance.

CVD: cardiovascular disease risk, WASO: wake after sleep onset.

Supplementary Table 3.13 Sleep characteristics of employed and unemployed men and women.

	Women (n=100)			Men (n=94)		
	Employed (n=26)	**Unemployed (n=74)**	**p-value**	**Employed (n=21)**	**Unemployed (n=73)**	**p-value**
Sleep onset (hh:mm)	22:12 (21:54, 23:06)	22:41 (22:06, 23:20)	0.115	22:18 (21:30, 22:36)	22:30 (21:36, 23:06)	0.303
Sleep offset (hh:mm)	07:00 (06:36, 07:36)	07:46 (06:44, 08:37)	**0.004**	07:30 (06:48, 08:12)	07:54 (07:12, 08:18)	0.140
Midsleep (hh:mm)	02:48 (02:12, 03:00)	03:06 (02:37,03:53)	**0.013**	02:54 (02:12, 03:18)	03:06 (02:42, 03:36)	0.129
Sleep duration (h)	8.6 ± 1.1	8.9 ± 1.2	0.171	9.2 ± 1.5	9.4 ± 1.3	0.546
Sleep duration category			0.069			0.579
≤9h (count, %)	17 (33.3)	34 (66.7)		7 (21.9)	25 (78.1)	
>9h (count, %)	9 (18.4)	40 (81.6)		14 (22.6)	48 (77.4)	
Total sleep time (h)	7.3 ± 1.1	7.4 ± 1.1	0.887	7.5 ± 1.4	7.6 ± 1.3	0.659
Sleep efficiency (%)	84.6 (82.0, 87.1)	80.38 (74.3, 85.3)	**0.005**	81.0 (76.2, 84.4)	78.6 (72.5, 85.1)	0.993
WASO (min)	74.0 (60.9. 90.5)	94.9 (70.4, 112.8)	**0.007**	99.3 (67.0, 120.4)	103.9 (81.5, 128.1)	0.595
Sleep Fragmentation Index (%)	25.8 (21.8, 29.6)	29.7 (24.0, 35.1)	**0.027**	34.1 (29.6, 38.3)	34.1 (27.4, 40.9)	0.845
Sleep Regularity Index (%)	67.5 (61.1, 72.1)	62.9 (54.0, 64.8)	**0.026**	56.9 (51.6, 63.2)	58.5 (52.5, 65.4)	0.639
Midsleep regularity (h)	0.7 (0.5, 1.0)	0.9 (0.6, 1.1)	0.620	0.9 (0.6, 1.2)	0.9 (0.6, 1.2)	0.973
Sleep duration regularity (h)	1.5 (1.1, 1.9)	1.5 (1.0, 2.1)	0.712	1.8 (1.2, 2.3)	1.8 (1.2, 2.4)	0.827

Data are presented as mean ± standard deviation, median (interquartile range) or count (%).P-values represent differences between the employed and unemployed groups determined using independent t-tests, Mann-Whitney U or Chi-Squared tests.
WASO: Wake after sleep onset.

Appendix 4: Supplementary data Chapter 4

Supplementary Table 4.1 Final search terms used to search the PubMed, Scopus and Web of Science databases.

Database	Search Terms
PubMed	((Sleep [MeSH] OR Sleep [tiab]) AND ("blood pressure dip*" OR "BP dip*" OR "blood pressure nondip*" OR "blood pressure non-dip*")
Scopus	TITLE-ABS-KEY (sleep) AND TITLE-ABS-KEY (“blood pressure dip*” OR “BP dip*” OR “blood pressure nondip*” or “blood pressure non-dip*”)
Web of Science	TS=(sleep) AND TS=(“blood pressure dip*” OR “BP dip*” OR “blood pressure nondip*” OR “blood pressure non-dip*”)

Supplementary Table 4.2 JBI Critical Appraisal Checklist for Analytical Cross-Sectional studies (n=16).

	Carev *et al.* (2011)	Chin *et al.* (2022)	Fallo *et al.* (2002)	McHill *et al.* (2022)	Hughes *et al.* (2007)	Ishikawa *et al.* (2008)	Kamperis *et al.* (2010)	Loredo *et al.* (2004)	Matthews *et al.* (2008)	Mellman *et al.* (2015)	Patterson *et al.* (2021)	Payseur *et al.* (2020)	Sayk *et al.* (2010)	Sherwood *et al.* (2001)	Troxel *et al.* (2017)	Ulu *et al.* (2013)
1. Were the criteria for inclusion in the sample clearly defined?	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Were the study subjects and the setting described in detail?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Was the exposure measured in a valid and reliable way?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4. Were objective, standard criteria used for measurement of the condition?	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5. Were confounding factors identified?	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
6. Were strategies to deal with confounding factors stated?	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
7. Were the outcomes measured in a valid and reliable way?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
8. Was appropriate statistical analysis used?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Overall appraisal:	**Include**	**Include**	**Include**	**Include**	**Include**	**Include**	**Include**	**Include**	**Include**	**Include**	**Include**	**Include**	**Include**	**Include**	**Include**	**Include**

Supplementary Table 4.3. JBI Critical Appraisal Checklist for Analytical Randomized Control Trials (n=1).

	Yang *et al.* (2017)
1. Was true randomization used for assignment of participants to treatment groups?	Yes
2. Was allocation to treatment groups concealed?	Yes
3. Were treatment groups similar at the baseline?	Yes
4. Were participants blind to treatment assignment?	No
5. Were those delivering treatment blind to treatment assignment?	No
6. Were outcomes assessors blind to treatment assignment?	No
7. Were treatment groups treated identically other than the intervention of interest?	Yes
8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?	Yes
9. Were participants analysed in the groups to which they were randomized?	Yes
10. Were outcomes measured in the same way for treatment groups?	Yes
11. Were outcomes measured in a reliable way?	Yes
12. Was appropriate statistical analysis used?	Yes
13. Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?	Yes
Overall appraisal:	**Include**

Supplementary Table 5.1 Sleep characteristics of employed and unemployed men and women.

	Women (n=37)			Men (n=23)		
	Employed (n=5)	**Unemployed (n=32)**	**p-value**	**Employed (n=5)**	**Unemployed (n=18)**	**p-value**
Sleep onset (hh:mm)	23:05 (21:56, 23:52)	22:19 (21:34, 23:01)	0.248	22.73 (22.41, 22.98)	22:09 (21.84, 22.68)	0.263
Sleep offset (hh:mm)	07:25 (06:08, 07:52)	06:57 (06:14, 07:52)	0.929	6.68 (6.65, 7.52)	7.40 (6.90, 8.22)	0.332
Midsleep (hh:mm)	02:54 (02:41, 03:15)	02:41 (02:07, 03:17)	0.505	26.83 (26.43, 27.02)	26.88 (26.39, 27.29)	0.709
Sleep duration (h)	8.4 (7.7, 8.6)	8.7 (7.85, 9.62)	0.266	7.7 (7.4, 9.2)	9.3 (7.8, 9.9)	0.296
Total sleep time (h)	7.2 (6.8, 7.5)	7.4 (6.7, 8.0)	0.477	6.4 (6.2, 7.8)	7.5 (6.4, 7.9)	0.551
Sleep efficiency (%)	85.8 (80.0, 88.3)	80.5 (77.7, 84.2)	0.155	83.6 (71.4, 83.8)	79.0 (78.1, 81.4)	0.456
WASO (min)	69.5 (31.4, 93.4)	75.6 (68.6, 99.3)	0.328	85.1 (69.6, 91.1)	100.3 (83.4, 118.8)	0.205
Sleep Fragmentation Index (%)	27.9 (13.1, 32.1)	29.2 (24.1, 33.2)	0.505	27.3 (25.9, 28.7)	34.8 (30.5, 38.3)	0.074
Midsleep regularity (h)	0.9 (0.7, 0.9)	0.7 (0.5, 1.1)	0.689	0.7 (0.5, 0.9)	0.9 (0.8, 1.4)	**0.037**
Sleep duration regularity (h)	2.1 (1.8, 2.5)	1.2 (1.0, 1.9)	0.100	1.9 (1.6, 2.1)	1.9 (1.5, 2.4)	0.709

Data are presented as median (interquartile range). P-values represent differences between the employed and unemployed groups determined using independent t-tests, Mann-Whitney U or Chi-Squared tests.
WASO: Wake after sleep onset.

Supplementary Table 5.2a. Analysis 1: Spearman's correlations between sleep characteristics and CVD/CMD risk variables among the women (n=37).

Sleep variable	CVD risk score		CMD risk score		BMI		WC		Fasting glucose	
	rho	p-value	rho	p-value	rho	p-value	rho	p-value	rho	p-value
Sleep onset (hh:mm)	–0.296	0.074	0.008	0.964	–0.088	0.602	–0.068	0.686	–0.041	0.818
Sleep offset (hh:mm)	–0.397	**0.014**	–0.169	0.339	–0.057	0.738	–0.149	0.378	–0.393	**0.021**
Midsleep (hh:mm)	–0.422	**0.009**	–0.124	0.485	–0.071	0.677	–0.121	0.477	–0.290	0.096
Sleep duration (h)	–0.125	0.458	–0.166	0.348	0.095	0.576	–0.006	0.972	–0.291	0.096
Total sleep time (h)	–0.122	0.471	–0.151	0.392	0.002	0.990	–0.059	0.724	–0.187	0.288
Sleep efficiency (%)	0.089	0.598	–0.036	0.839	–0.221	0.189	–0.138	0.413	0.156	0.376
WASO (min)	–0.016	0.926	–0.118	0.505	0.137	0.417	0.049	0.770	–0.326	0.059
Sleep Fragmentation Index (%)	0.199	0.237	0.035	0.844	0.053	0.751	0.008	0.959	–0.173	0.326
Midsleep regularity (h)	–0.123	0.468	0.265	0.129	–0.206	0.221	–0.148	0.381	0.224	0.202
Sleep duration regularity (h)	–0.148	0.381	0.252	0.150	0.110	0.517	0.108	0.522	–0.022	0.899

Data are presented as Spearman's rho correlation coefficients with p-values.
BMI: body mass index, CMD: cardiometabolic disease, CVD: cardiovascular disease, WASO: wake after sleep onset, WC: waist circumference.

Supplementary Table 5.2b. Analysis 1: Spearman's correlations between sleep characteristics and CVD/CMD risk variables among the men (n=23).

Sleep variable	CVD risk score		CMD risk score		BMI		WC		Fasting glucose	
	rho	p-value	rho	p-value	rho	p-value	rho	p-value	rho	p-value
Sleep onset (hh:mm)	–0.063	0.774	0.070	0.748	0.119	0.589	0.064	0.772	–0.022	0.919
Sleep offset (hh:mm)	–0.226	0.300	–0.344	0.108	–0.222	0.309	–0.272	0.209	–0.087	0.691
Midsleep (hh:mm)	–0.254	0.242	–0.279	0.196	–0.137	0.532	–0.188	0.389	0.002	0.989
Sleep duration (h)	–0.091	0.676	–0.214	0.326	–0.230	0.290	–0.215	0.324	–0.084	0.703
Total sleep time (h)	–0.195	0.369	–0.404	0.055	–0.366	0.085	–0.369	0.082	–0.127	0.563
Sleep efficiency (%)	–0.183	0.402	–0.372	0.080	–0.083	0.708	–0.147	0.502	–0.116	0.598
WASO (min)	0.054	0.805	0.148	0.498	0.019	0.928	0.114	0.602	0.023	0.916
Sleep Fragmentation Index (%)	0.305	0.157	0.425	**0.043**	–0.041	0.852	0.117	0.593	0.262	0.226
Midsleep regularity (h)	–0.449	**0.031**	–0.272	0.209	–0.403	0.057*	–0.445	**0.033**	–0.183	0.403
Sleep duration regularity (h)	–0.001	0.998	0.047	0.831	–0.285	0.187	–0.263	0.225	–0.072	0.743

Data are presented as Spearman's rho correlation coefficients with p-values. * indicates correlation trending towards significance.
BMI: body mass index, CMD: cardiometabolic disease, CVD: cardiovascular disease, WASO: wake after sleep onset, WC: waist circumference.

Supplementary Table 5.3a. Analysis 2: Spearman's correlations between nocturnal BP and CVD/CMD risk variables among the women (n=36).

BP variable	CVD risk score		CMD risk score		BMI		WC		Fasting glucose	
	rho	p-value	rho	p-value	rho	p-value	rho	p-value	rho	p-value
Nocturnal SBP (mmHg)	0.146	0.394	0.300	0.089	0.187	0.273	0.171	0.318	0.139	0.437
Nocturnal DBP (mmHg)	0.167	0.330	0.198	0.269	–0.071	0.681	–0.056	0.746	0.183	0.306
SBP dipping %	0.098	0.597	–0.238	0.214	–0.191	0.304	–0.178	0.335	–0.235	0.220
DBP dipping %	–0.004	0.981	–0.194	0.312	–0.106	0.570	–0.109	0.557	–0.340	0.070

Data are presented as Spearman's rho correlation coefficients with p-values.

BMI: body mass index, BP: blood pressure, CMD: cardiometabolic disease, CVD: cardiovascular disease, DBP: diastolic blood pressure, SBP: systolic blood pressure, WC: waist circumference.

Supplementary Table 5.3b. Analysis 2: Spearman's correlations between nocturnal BP and CVD/CMD risk variables among the men (n=23).

BP variable	CVD risk score		CMD risk score		BMI		WC		Fasting glucose	
	rho	p-value	rho	p-value	rho	p-value	rho	p-value	rho	p-value
Nocturnal SBP (mmHg)	0.205	0.348	0.656	**0.007**	0.436	**0.037**	0.574	**0.004**	0.418	**0.047**
Nocturnal DBP (mmHg)	0.224	0.303	0.648	**<0.001**	0.252	0.247	0.419	**0.046**	0.322	0.134
SBP dipping %	–0.053	0.816	–0.257	0.247	–0.017	0.940	–0.085	0.708	–0.001	0.998
DBP dipping %	0.019	0.930	–0.239	0.282	0.164	0.464	0.094	0.676	0.120	0.593

Data are presented as Spearman's rho correlation coefficients with p-values.

BMI: body mass index, BP: blood pressure, CMD: cardiometabolic disease, CVD: cardiovascular disease, DBP: diastolic blood pressure, SBP: systolic blood pressure, WC: waist circumference.

Supplementary Table 5.4a. Analysis 3: Spearman's correlations between sleep characteristics and nocturnal BP among the women (n=36).

Sleep variable	Nocturnal SBP		Nocturnal DBP		SBP dipping %		DBP dipping %	
	rho	p-value	rho	p-value	rho	p-value	rho	p-value
Sleep onset (hh:mm)	–0.115	0.503	–0.021	0.904	–0.118	0.525	–0.329	0.070
Sleep offset (hh:mm)	0.062	0.718	0.046	0.786	0.234	0.204	0.079	0.670
Midsleep (hh:mm)	–0.046	0.787	–0.002	0.998	0.013	0.943	–0.204	0.270
Sleep duration (h)	0.171	0.317	0.046	0.788	0.302	0.098	0.392	**0.029**
Total sleep time (h)	0.043	0.800	–0.033	0.848	0.415	**0.020**	0.436	**0.014**
Sleep efficiency (%)	–0.396	**0.016**	–0.272	0.108	0.511	**0.003**	0.376	**0.037**
WASO (min)	0.292	0.084	0.134	0.433	–0.179	0.334	–0.020	0.912
Sleep Fragmentation Index (%)	0.076	0.658	0.095	0.583	–0.162	0.384	0.077	0.678
Midsleep regularity (h)	0.105	0.540	0.287	0.089	0.014	0.938	–0.131	0.483
Sleep duration regularity (h)	0.036	0.833	0.102	0.554	–0.188	0.527	–0.135	0.468

Data are presented as Spearman's rho correlation coefficients with p-values.
BP: blood pressure, DBP: diastolic blood pressure, SBP: systolic blood pressure, WASO: wake after sleep onset.

Supplementary Table 5.4b. Analysis 3: Spearman's correlations between sleep characteristics and nocturnal BP among the men (n=23).

Sleep variable	Nocturnal SBP		Nocturnal DBP		SBP dipping %		DBP dipping %	
	rho	p-value	rho	p-value	rho	p-value	rho	p-value
Sleep onset (hh:mm)	–0.262	0.226	–0.167	0.444	0.030	0.894	–0.060	0.789
Sleep offset (hh:mm)	–0.065	0.769	–0.161	0.463	0.135	0.547	0.207	0.355
Midsleep (hh:mm)	–0.205	0.347	–0.261	0.230	0.180	0.420	0.176	0.431
Sleep duration (h)	0.115	0.602	–0.005	0.980	–0.029	0.898	0.081	0.721
Total sleep time (h)	–0.132	0.546	–0.224	0.304	0.045	0.843	0.228	0.306
Sleep efficiency (%)	–0.468	**0.024**	–0.502	**0.015**	0.055	0.808	0.407	0.060
WASO (min)	0.599	**0.003**	0.503	**0.014**	–0.090	0.689	–0.282	0.202
Sleep Fragmentation Index (%)	0.596	**0.003**	0.589	**0.003**	–0.050	0.833	–0.380	0.081
Midsleep regularity (h)	0.038	0.863	0.085	0.699	–0.030	0.890	–0.212	0.344
Sleep duration regularity (h)	0.184	0.400	0.257	0.235	–0.476	**0.025**	–0.518	**0.014**

Data are presented as Spearman's rho correlation coefficients with p-values.
BP: blood pressure, DBP: diastolic blood pressure, SBP: systolic blood pressure, WASO: wake after sleep onset.

Supplementary Table 5.5a. Descriptive characteristics of SBP and DBP dippers and non-dippers for women (n=31).

	SBP		p-value	DBP		p-value
	SBP dippers (n=12)	SBP non-dippers (n=19)		DBP dippers (n=19)	DBP non-dippers (n=12)	
Age (y)	44 (37, 52)	43 (37, 50)	0.745	44 (36, 50)	43 (39, 51)	0.951
BMI (kg/m^2)	28.9 (25.3, 33.7)	32.3 (25.4, 38.9)	0.543	32.1 (25.4, 36.5)	30.7 (24.7, 37.4)	0.685
Obese (count, %)	5 (41.7)	11 (57.9)	0.379	10 (52.6)	6 (50.0)	0.589
Waist circumference (cm)	97.0 (84.5, 101.3)	98.0 (84.5, 117.5)	0.640	97.5 (84.5, 112.0)	95.6 (84.8, 110.1)	0.626
Clinic SBP (mmHg)	125 (115, 139)	117 (112, 129)	0.340	122 (112, 133)	120 (112, 131)	0.855
Clinic DBP (mmHg)	83 (74, 88)	77 (72, 86)	0.291	78 (74, 87)	77 (72, 83)	0.465
Elevated BP (count, %)	7 (58.3)	10 (52.6)	0.606	9 (47.4)	8 (66.7)	0.249
Hypertension medication (count, %)	3 (25.0)	5 (26.3)	0.552	4 (21.1)	4 (33.3)	0.362
Chronic diseases (count, %)	6 (50.0)	12 (63.2)	0.484	10 (52.6)	8 (66.7)	0.347
Fasting glucose concentration (mmol/L)	4.6 (3.8, 5.2)	5.0 (4.4, 5.6)	0.101	4.6 (4.0, 4.9)	5.4 (4.5, 5.8)	0.054*
Elevated blood glucose (count, %)	0 (0.0)	4 (22.2)	0.100	1 (5.9)	3 (25.0)	0.178
CVD risk score (%)	4.4 (3.2, 10.4)	3.7 (2.5, 6.0)	0.310	3.7 (2.3, 9.6)	4.8 (2.5, 6.2)	0.715
CMD risk score	0.1 (–1.0, 0.7)	0.5 (–0.1, 1.2)	0.333	0.4 (–0.1, 0.9)	0.3 (–0.4, 1.1)	0.773
MVPA (min/day)	34 (19, 56)	30 (20, 50)	0.776	34 (17, 58)	29 (21, 46)	0.612
Smoker (count, %)	5 (41.7)	6 (31.6)	0.403	6 (31.6)	5 (41.6)	0.611
Alcohol use (no. drinks / week)	0 (0, 7.5)	0 (0, 14)	0.929	0 (0, 11)	0 (0, 11)	0.892
Employed (count, %)	3 (25)	2 (10.5)	0.083	4 (21.1)	1 (8.3)	0.342
Education (y)	11 (9, 12)	10.5 (9.0, 11.0)	0.332	11 (9, 11)	11 (9, 12)	0.585

Data are presented as median (interquartile range) or count (%). P-values represent differences between dipper and non-dipper groups determined using Mann-Whitney U or Fisher's exact tests. * indicates differences trending towards significance.

BMI: body mass index, BP: blood pressure, CMD: cardiometabolic disease, CVD: cardiovascular disease, DBP: diastolic blood pressure, MVPA: moderate- to vigorous-intensity physical activity, SBP: systolic blood pressure.

Supplementary Table 5.5b. Descriptive characteristics of SBP and DBP dippers and non-dippers for men (n=22).

	SBP			DBP		
	SBP dippers (n=11)	SBP non-dippers (n=11)	p-value	DBP dippers (n=17)	DBP non-dippers (n=5)	p-value
Age (y)	39 (31, 45)	39 (34, 42)	0.973	39 (34, 43)	40 (38, 42)	0.813
BMI (kg/m^2)	21.9 (20.1, 24.3)	22.4 (19.3, 24.2)	0.922	21.9 (20.1, 23.4)	23.2 (19.9, 24.2)	0.875
Obese (count, %)	1 (9.1)	0 (0.0)	0.500	1 (5.9)	0 (0.0)	0.773
Waist circumference (cm)	82.0 (75.2, 85.0)	82.5 (70.1, 96.0)	0.947	82.0 (75.2, 84.5)	82.5 (71.7, 96.0)	0.814
Clinic SBP (mmHg)	120 (111, 140)	132 (127, 141)	0.309	130 (117, 135)	133 (130, 143)	0.136
Clinic DBP (mmHg)	83 (72, 92)	82 (79, 95)	0.393	82 (73, 92)	89 (82, 98)	0.158
Elevated BP (count, %)	9 (81.8)	6 (54.5)	0.181	10 (58.8)	5 (100.0)	0.114
Hypertension medication (count, %)	0 (0.0)	1 (9.1)	0.500	0 (0.0)	1 (20.0)	0.227
Chronic diseases (count, %)	2 (18.2)	3 (27.3)	0.611	4 (23.5)	1 (20.0)	0.687
Fasting glucose concentration(mmol/L)	5.1 (4.6, 5.2)	5.1 (4.6, 5.8)	0.621	5.1 (4.6, 5.3)	4.8 (4.7, 5.1)	0.968
Elevated blood glucose (count, %)	1 (9.1)	3 (27.3)	0.293	3 (17.6)	1 (20.0)	0.675
CVD risk score (%)	5.6 (4.6, 9.6)	8.0 (3.9, 9.8)	0.718	5.6 (4.6, 9.6)	4.8 (4.7, 5.1)	0.695
CMD risk score	–0.7 (–2.2, –0.5)	–0.3 (–1.1, 1.2)	0.157	–0.7 (–2.2, –0.3)	–0.2 (–0.3, –0.1)	0.136
MVPA (min/day)	49 (30, 86)	77 (57, 95)	0.292	60 (30, 86)	77 (60, 94)	0.255
Smoker (count, %)	9 (81.8)	8 (72.7)	0.500	14 (82.4)	4 (80.0)	0.313
Alcohol use (no. drinks / week)	17 (5, 33)	9 (0, 30)	0.317	17 (5, 30)	0 (0, 16)	0.265
Employed (count, %)	3 (27.3)	2 (18.2)	0.500	3 (17.6)	2 (40.0)	0.313
Education (y)	11 (10, 11)	11 (10, 12)	0.289	11 (10, 12)	11 (10, 12)	0.607

Data are presented as median (interquartile range) or count (%). P-values represent differences between dipper and non-dipper groups determined using Mann-Whitney U or Fisher's exact tests.

BMI: body mass index, BP: blood pressure, CMD: cardiometabolic disease, CVD: cardiovascular disease, DBP: diastolic blood pressure, MVPA: moderate- to vigorous-intensity physical activity, SBP: systolic blood pressure.

Supplementary Table 5.6a. Sleep characteristics of SBP and DBP dippers and non-dippers for women (n=31).

	SBP dippers (n=12)	SBP non-dippers (n=19)	p-value	DBP dippers (n=19)	DBP non-dippers (n=12)	p-value
Sleep onset (hh:mm)	22:09 (21:27, 23:36)	22:15 (21:40, 23:13)	0.626	21:57 (21:26, 22:31)	22:58 (22:14, 23:44)	0.056
Sleep offset (hh:mm)	07:04 (06:31, 08:01)	06:28 (06:2, 07:05)	0.223	06:58 (06:05, 08:00)	06:33 (06:05, 07:07)	0.441
Midsleep (hh:mm)	02:41 (02:11, 03:16)	02:33 (01:58, 03:09)	0.745	02:29 (01:58, 02:54)	02:49 (02:12, 03:16)	0.351
Duration (h)	8.67 (7.69, 9.60)	8.21 (7.69, 8.72)	0.113	8.67 (8.25, 9.62)	7.79 (6.65, 8.63)	**0.018**
Duration category			0.093			0.140
≤9h (count, %)	6 (50.0)	15 (78.9)		11 (57.9)	10 (83.3)	
>9h (count, %)	6 (50.0)	4 (21.1)		8 (42.1)	2 (16.7)	
Total sleep time (h)	7.5 (7.2, 8.2)	6.8 (6.3, 7.5)	**0.038**	7.45 (7.21, 7.99)	6.47 (5.58, 7.31)	**0.013**
Sleep efficiency (%)	83.4 (80.3, 86.1)	79.7 (73.8, 83.2)	**0.047**	82.5 (79.3, 86.5)	79.4 (68.9, 82.2)	**0.032**
WASO (min)	73.83 (61.0, 109.71)	75.64 (69.07, 86.21)	0.841	73.83 (61.0, 111.14)	75.64 (70.17, 85.71)	0.967
Sleep Fragmentation Index (%)	29.90 (20.84, 33.10)	28.79 (25.94, 33.47)	0.779	29.34 (23.8, 34.5)	29.48 (24.62, 32.91)	0.967
Midsleep regularity (h)	0.72 (0.50, 1.08)	0.73 (0.51, 1.06)	0.936	0.72 (0.50, 1.08)	0.73 (0.56, 1.27)	0.807
Sleep duration regularity (h)	1.78 (1.07, 2.09)	1.28 (1.05, 2.31)	0.968	1.43 (1.07, 2.09)	1.56 (1.04, 2.53)	0.903
PSQI	4 (2.0, 5.0)	4.5 (3.0, 6.0)	0.478	4 (2.0, 5.0)	4.5 (3.0, 6.0)	0.519
ESS	2 (1.0, 11.0)	4.5 (3.0, 8.0)	0.717	5 (1.0, 11.0)	3.5 (2.5, 9.5)	0.967
ISI	1 (0.0, 4.0)	2 (0.0, 4.0)	0.885	1 (0.0, 4.0)	2 (0.0, 5.5)	0.603
High OSA risk (count, %)	4 (33.3)	3 (15.8)	0.170	4 (21.1)	3 (25.0)	0.638

Data are presented median (interquartile range) or count (%). P-values represent differences between dipper and non-dipper groups determined using Mann-Whitney U or Fisher's exact tests.

DBP: diastolic blood pressure, ESS: Epworth Sleepiness Scale, ISI: Insomnia Severity Index, OSA: Obstructive sleep apnoea, PSQI: Pittsburgh Sleep Quality Index, SBP: systolic blood pressure, WASO: Wake after sleep onset.

Supplementary Table 5.6b. Sleep characteristics of SBP and DBP dippers and non-dippers for men (n=22).

	SBP			DBP		
	SBP dippers (n=11)	**SBP non-dippers (n=11)**	**p-value**	**DBP dippers (n=17)**	**DBP non-dippers (n=5)**	**p-value**
Sleep onset (hh:mm)	22:00 (21:40, 22:41)	22:22 (21:58, 22:44)	0.450	22:08 (21:48, 22:41)	22:44 (22:22, 22:44)	0.224
Sleep offset (hh:mm)	07:31 (06:57, 08:13)	06:54 (06:00, 07:44)	0.178	07:26 (06:56, 07:44)	06:41 (06:08, 06:54)	0.170
Midsleep (hh:mm)	02:59 (02:23v03:17)	02:49 (02:00, 03:04)	0.308	02:56 (02:23, 03:08)	02:49 (02:26, 02:50)	0.411
Duration (h)	9.22 (7.82, 10.39)	8.15 (7.40, 9.71)	0.375	9.22 (7.82, 10.24)	7.69 (7.69, 8.15)	0.290
Duration category			0.197			0.155
≤9h (count, %)	4 (36.4)	7 (63.6)		7 (41.2)	4 (80.0)	
>9h (count, %)	7 (63.6)	4 (36.4)		10 (58.8)	1 (20.0)	
Total sleep time (h)	7.69 (6.92, 8.08)	6.39 (5.81, 7.91)	0.250	7.48 (6.92, 8.08)	6.23 (5.70, 6.39)	0.077
Sleep efficiency (%)	81.06 (78.13, 83.61)	78.77 (71.48, 81.45)	0.375	81.06 (78.53, 82.89)	71.47 (68.18, 75.56)	**0.017**
WASO (min)	92.25 (75.04, 163.23)	92.86 (69.56, 116.83)	0.869	91.12 (75.04, 103.76)	106.07 (104.81, 119.46)	0.224
Sleep Fragmentation Index (%)	32.04 (23.96, 39.39)	33.48 (27.37, 37.62)	0.622	32.05 (26.96, 37.62)	36.50 (33.48, 37.01)	0.224
Midsleep regularity (h)	0.88 (0.64, 1.30)	0.93 (0.78, 1.35)	0.491	0.90 (0.65, 1.30)	0.90 (0.78, 0.93)	0.968
Sleep duration regularity (h)	1.39 (1.18, 2.04)	2.08 (1.88, 2.41)	**0.016**	1.75 (1.19, 2.07)	2.19 (1.91, 2.41)	**0.038**
PSQI	4.0 (2.0, 6.0)	3.0 (2.0, 4.0)	0.416	3.0 (2.0, 5.0)	3.0 (2.0, 4.0)	0.746
ESS	2.0 (1.0, 5.0)	3.0 (0.0, 8.0)	0.920	3.0 (2.0, 8.0)	0.0 (0.0, 2.0)	0.074
ISI	1.0 (0.0, 3.0)	0.0 (0.0, 1.0)	0.133	1.0 (0.0, 2.0)	0.0 (0.0, 1.0)	0.428
High OSA risk (count, %)	0 (0.0)	2 (18.2)	0.238	0 (0.0)	2 (40.0)	**0.043**

Data are presented median (interquartile range) or count (%). P-values represent differences between dippers and non-dippers groups determined using Mann-Whitney U or Fisher's exact tests.

DBP: diastolic blood pressure, ESS: Epworth Sleepiness Scale, ISI: Insomnia Severity Index, OSA: obstructive sleep apnoea, PSQI: Pittsburgh Sleep Quality Index, SBP: systolic blood pressure, WASO: wake after sleep onset.

Supplementary Table 5.7. Actigraphy-derived sleep characteristics of participants with and without nocturnal hypertension.

	Women (n=36)			Men (n=23)		
	Nocturnal hypertension		p-value	Nocturnal hypertension		p-value
	Yes (n=26)	No (n=10)		Yes (n=11)	No (n=12)	
Sleep onset (hh:mm)	22:23 (21:31, 23:04)	21:56 (21:40, 23:36)	0.832	22:18 (21:48, 22:40)	22:33 (21:59, 22:52)	0.175
Sleep offset (hh:mm)	06:58 (06:08, 08:00)	06:55 (06:14, 07:52)	0.775	07:26 (06:00, 08:34)	07:19 (06:40, 07:39)	0.622
Midsleep (hh:mm)	02:42 (02:07, 03:16)	02:41 (01:58, 04:01)	0.724	02:48 (02:30, 03:00)	02:54 (02:18, 02:18)	0.902
Duration (h)	8.65 (7.71, 9.28)	8.85 (8.25, 9.86)	0.804	9.59 (7.69, 10.24)	8.36 (7.54, 9.67)	0.389
Duration category			0.529			0.263
≤9h (count, %)	16 (61.5)	5 (50.0)		4 (36.4)	7 (58.3)	
>9h (count, %)	10 (38.5)	5 (50.0)		7 (63.6)	5 (41.7)	
Total sleep time (h)	7.35 (6.51, 7.95)	7.35 (6.79, 8.08)	0.887	7.48 (5.98, 7.93)	6.79 (6.29, 8.02)	0.951
Sleep efficiency (%)	80.7 (76.7, 84.4)	80.4 (79.1, 85.3)	0.502	78.87 (68.6, 81.1)	81.66 (76.93, 83.71)	0.175
WASO (min)	75.57 (69.07, 89.35)	84.03 (68.25, 109.71)	0.548	116.83 (88.75, 163.23)	88.10 (65.08, 98.3)	**0.031**
Sleep Fragmentation Index (%)	28.25 (23.32, 33.47)	30.36 (28.6, 33.1)	0.289	36.4 (33.4, 40.8)	29.6 (25.8, 34.7)	**0.019**
Midsleep regularity (h)	0.72 (0.51, 1.06)	0.88 (0.62, 1.03)	0.887	0.9 (0.8, 1.5)	0.9 (0.7, 1.1)	0.498
Sleep duration regularity (h)	1.34 (1.04, 1.97)	1.56 (1.27, 2.09)	0.548	1.9 (1.6, 2.4)	1.9 (1.4, 2.1)	0.538
High OSA risk (count, %)	7 (26.9)	1 (10.0)	0.262	1 (0.1)	1 (8.3)	0.714

Data are presented median (interquartile range) or count (%). P-values represent differences between nocturnal hypertension groups determined using Mann-Whitney U or Fisher's exact tests.

OSA: obstructive sleep apnoea, WASO: wake after sleep onset.

Appendix 6: Supplementary data Chapter 6

Supplementary Table 6.1. Interview guide: guide questions pertaining to participants perceptions and experiences of their sleep habits and environment.

1. Please describe the space where you sleep? *Probes: number of people per room, number of bedrooms in the house, what type of bedding do you have, is it noisy, too light, too hot, too cold)*

2. What changes could you make to improve your sleep environment, if any?

3. Tell me how your sleeping area impacts your sleep? *Probes: do you feel that you struggle to sleep because of your sleeping space*

4. When you are trying to sleep at night, how safe do you personally feel? *Probes: How does physically feeling unsafe affect your sleep. Do people in your home come home drunk etc. If yes, how does that affect your sleep*

5. What do you do to try and make yourself feel safe?

6. Please describe any fears associated with going to sleep? *Probes: Tell me about the fear at home; tell me about the fears in the wider community.*
    a. Do you think this fear/worry/anxiousness/concern impacts your sleep?

7. What is your experience of your neighbourhood after 6pm at night?

8. Is there anything about your community or neighbourhood, or what's happening in the neighbourhood at night, that impacts your sleep?

9. Are there nights where your neighbourhood is more disruptive to your sleep than others? *Probe: which nights, what is it about these nights that is so disruptive*

10. On a scale of 1-10, how safe do you feel your neighbourhood is? *1 being not at all safe and 10 being very safe.*
    a. Describe what factors make it feel safe / unsafe to you?

11. Do your neighbours feel the same way about the neighbourhood as you do? *Probes: Do you discuss the safety of your neighbourhood? Who can you rely on when you feel scared i.e. the Police? Does the community leader know about this?*

12. What do you think good/healthy sleep is?

13. How important is sleep to you and why?

14. How would you describe the quality of your sleep?

15. Has your sleep always been like this or has your sleep changed in the past few years?

16. On an average night, how long do you think you are asleep for? *Probe: does this change on different nights or between week and weekend?*

17. How often are you disturbed during the night? *Probe: every night of the week? Is it once a night or multiple times per night?*
    a. What usually disturbs you?
    b. How severe do these sleep disturbances feel to you?

18. When/if you are disturbed and wake up, what do you do then? *Probes: what causes this behaviour? Is it something that you have always done?*

19. Please describe your routine from when you're getting home to when you get into bed? *If they don't get home, what is the general routine from 5pm onwards? Probe: do you use any sort of technology, do you get ready for the next day? What food, drinks (alcoholic on non-alcoholic, e.g. caffeine) are you consuming?*

20. Can you describe the sleep routine of the other people who share the same sleep environment as you? *Probes: Do you all go to bed at the same time? Does the last person to go to sleep turn the light off / candle? Do people come home late in the evening and disturb other members of the household?*

21. Can you tell me about napping during the day, do you nap during the day? *Probes: if yes, have you always napped? How often do you nap? How long do you nap for? Why do you nap or feel you need to nap? Do you ever fall asleep unintentionally? If so, how often?*

22. How does a lack of sleep or poor sleep affect your daytime functioning? *Probe: How do you feel you function throughout the day? If you sleep well, do you have a better day? Do you feel tired when you wake up in the morning?*

23. To what extent do you think your sleep impacts your physical health? *Probes: are you concerned that your current sleep patterns are affecting your body in any way? Do you feel that poor sleep affects how your body works? Do you think that poor sleep might be the reason for any health problems?*

24. To what extent do you think your sleep impacts your mental health? *Probes: your feelings around being anxious or sad or worried if you don't sleep well?*

25. Can you think of anything that has happened to you in the past that makes it difficult for you to sleep today? *[If yes]: please elaborate*

26. Do you ever feel that it is hard to get good sleep because of feelings of stress/anxiety/worry? *Probe: what is causing these feelings? Are these feelings related to finances, safety, personal problems, work or something else?*

27. Is there anything we didn't ask about that we should have? Anything else you want to tell us?

Supplementary Table 6.2. Visual examples of the housing structures in Khayelitsha.

Image	Source
	Zoe Postman and Denise Patterson (2017). *Hundreds of shacks demolished in Khayelitsha*. GroundUp News. https://groundup.org.za/article/hundreds-shacks-demolished-khayelitsha/ Image: Ashraf Hendricks
	John. *Houses in Khayelitsha Township* (2008). https://www.flickr.com/photos/25643444@N08/2528807722 Image: Flickr/A Guy Called John
	South Africa searches for solutions to shack fires. (2023, January 5). *The New Humanitarian*. https://www.thenewhumanitarian.org/analysis/2013/01/23/south-africa-searches-solutions-shack-fires Image: Bill Corcoran
	John. *Houses in Khayelitsha Township* (2008). https://www.flickr.com/photos/25643444@N08/2528807722 Image: Flickr/A Guy Called John

Appendix 7: Sleep Health Composite Score - Development & Methodology

Guided by the Buysse RU-SATED model[35], we created a sleep health composite score to capture the dimensions of Regularity, Satisfaction, Alertness, Timing, Efficiency and Duration, described in Supplementary Table 7.1 below. For the most part, cut-offs and composite scores have been created based on European and American populations[36–38], which do not necessarily apply to this cohort of African descent individuals living in a low SES environment. We have therefore applied the following adjustments: Sleep regularity for this composite score was calculated as the average of sleep onset regularity + sleep offset regularity + sleep duration regularity. We chose this adjustment for the regularity component (instead of using the SRI) as to not deviate too much from the RU-SATED model, but still incorporate sleep duration regularity as an important component of sleep health. Regularity variables were calculated as the standard deviation of all daily variable values for each participant. Subjective measures of sleep satisfaction and sleepiness (used as a proxy for alertness) were extracted from question 4 of the ISI and the overall ESS score, respectively. Timing was extracted from sleep midpoint. Subsequent to z-scoring midsleep, we applied an absolute transformation to the standardized variable. Similarly, since sleep duration exhibits a U-shaped relationship with CVD risk, creating a standardized linear score for sleep duration is not ideal. Instead, the absolute values of the z-scored sleep duration were used. The purpose of the absolute transformation for both midsleep and sleep duration was to focus on the magnitude of deviations from the mean while disregarding their direction. Since the mean sleep duration in this cohort was ±9h, using the standard cut-points of 7-9h of sleep as being optimal was not appropriate for this population. By taking the absolute value, we ensured that both positive and negative deviations contributed equally to the composite score, making it a measure of the variable's overall deviation from the mean. Sleep efficiency was reverse scored so that higher values represented poorer sleep for all dimensions. All sleep dimensions were treated continuously, z-scored and then summed to create the final Sleep Health Composite score. We used z-scores of the sleep dimensions in order to allow for comparability across sleep dimensions measured on different scales[37]. This sleep health composite score differs from previous binary scores as the individual dimension scores are continuous. We believe this improves the score since it is not overly reliant on cut points to score dimensions as good or poor.

Supplementary Table 7.1. Generation of the Sleep Health Composite Score

Dimension	Variable	Assessment
Regularity	Regularity of sleep onset, sleep offset & sleep duration	• Standard deviation of sleep onset, sleep offset and sleep duration • Summed and divided by 3 • Z-scored
Satisfaction	ISI Question 4	• How satisfied/dissatisfied are you with your current sleep pattern? • Very satisfied (0) to very dissatisfied (4) • Z-scored
Alertness	Sleepiness as a proxy for alertness	• Epworth Sleepiness Scale (ESS) Score • Higher scores indicate higher sleepiness (or lower alertness) • Z-scored
Timing	Sleep midpoint	• Midpoint between sleep onset and sleep offset • Absolute transformation • Z-scored
Efficiency	Sleep efficiency	• Percentage (%) of time asleep • Reverse scored • Z-scored
Duration	Sleep duration	• The time elapsed between start of the sleep interval and the end of the sleep interval • Absolute transformation • Z-scored

Sleep Health Composite Score = z-regularity + z-satisfaction + z-alertness + z-timing + z-efficiency + z-duration. Higher scores indicate worse sleep health.