Sleep Under Stress: The Complex Web of Fear, Hypervigilance and Mental Health in a Low Socioeconomic Status Community in South Africa

By

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DECLARATION

I, Arron Taylor Lund Correia, hereby declare that the work on which this thesis is based is my original work (except where acknowledgements indicate otherwise) and that 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.

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Date: 17 February 2025

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DECLARATION OF INCLUSION OF PUBLICATIONS

I confirm that I have been granted permission by the University of Cape Town's Doctoral Degrees Board to include the following publications in my PhD thesis, and where co-authorships are involved, my co-authors have agreed that I may include the publications:

Correia, A. T. L., *Forshaw, P. E., Roden, L. C., Lipinska, G., Rauch, H. G. L., Lambert, E. V., Layden, B. T., Reutrakul, S., Crowley, S. J., Luke, A., Dugas, L. R., & Rae, D. E. (2024). Associations between fears related to safety during sleep and self-reported sleep in men and women living in a low-socioeconomic status setting. Scientific Reports, 14(1).* *https://doi.org/10.1038/s41598-024-54032-w*

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

Arron Correia (CRRARR001)

17 February 2025

TERMS AND DEFINITIONS

The following list contains useful terms and definitions for concepts presented in this thesis:

Autonomic nervous system – the branch of the nervous system involved in regulating involuntary physiological processes such as heart rate and respiration[1].

Criterion A trauma – a traumatic event meeting the criteria for resulting in post-traumatic stress disorder according to the Diagnostic and Statistical Manual of Mental Disorders. This includes one of the following traumas: death, threatened death, actual or threatened serious injury, or actual or threatened sexual violence; experienced in one of the following way(s): through direct exposure, by witnessing the trauma, by learning that the trauma happened to a close relative or close friend or by indirect exposure to aversive details of the trauma, usually in the course of professional duties (e.g., first responders, medics)[2].

Fear of sleep – the feeling of fear or wariness about falling asleep and the associated vulnerability to potential physical threats or concern over nightmares[3].

Global North – wealthier countries with higher socioeconomic status and more economic development located predominantly in the Northern Hemisphere. Typically includes North America, Europe, Australia, New Zealand and countries in Asia such as Israel and South Korea[4].

Global South – developing countries regarded as having lower socioeconomic statuses, more poverty and poorer infrastructure and also tend to be located more geographically South. Typically includes Africa, Latin America, most of Asia and the Caribbean[4].

Heart rate variability – the variation in time between consecutive heart beats[5].

Hyperarousal – excessive arousal and increased responsiveness to stimuli that is marked by various physiological and psychological symptoms (e.g., increased levels of alertness and anxiety and elevated heart rate and respiration)[6].

Hypersomnia – the inability to stay alert and awake during the day despite getting sufficient sleep at night[7].

Hypervigilance – related to but distinct from hyperarousal; constant state of heightened awareness assessing for potential threats[8].

Mental disorders – disturbances in an individual's cognition, emotional regulation or behaviour, which usually impairs functioning, to a clinically significant extent[9].

Parasympathetic nervous system – the branch of the nervous system responsible for rest and digestion including slowing the heart rate, dilating blood vessels, decreasing respiration and increasing digestion[1].

R-R intervals – the length of time between successive R waves on an electrocardiogram[5].

Sleep efficiency – the percentage of time spent asleep out of time spent in bed trying to sleep[10].

Sleep onset latency – the time elapsed between attempting to fall asleep and the onset of sleep[11].

Socioeconomic status – a combination of income, level of education and employment status to determine a person's social and economic standing or class[12].

Sympathetic nervous system – the branch of the nervous system responsible for preparing the body for physical activity and stress, including increasing the heart rate, constricting blood vessels, increasing respiration and decreasing digestion[1].

ABBREVIATIONS

ANS:	Autonomic nervous system
BAI:	Beck Anxiety Inventory
BDI:	Beck Depression Inventory
BMI:	Body mass index
CBT-I:	Cognitive Behavioural Therapy for Insomnia
CI:	Confidence interval
CFI:	Comparative fit index
CTS:	Continuous Traumatic Stress
DFA:	Detrended fluctuation analysis
DSM 5-TR:	Diagnostic and Statistical Manual of Mental Disorders 5 (Text Revision)
ECG:	Electrocardiography
ESS:	Epworth Sleepiness Scale
FIRST:	Ford Insomnia Response to Stress Test
FoSI:	Fear of Sleep Inventory
GAD:	Generalized Anxiety Disorder
HADS:	Hospital Anxiety and Depression Scale
HF:	High frequency
HPA:	Hypothalamic-pituitary-adrenal
HR:	Heart rate

HRV:	Heart rate variability
ISI:	Insomnia Severity Index
LF:	Low frequency
LMICs:	Low- and middle-income countries
MDD:	Major depressive disorder
METS:	Modelling the Epidemiologic Transition Study
MSE:	Multiscale entropy
NREM:	Non-rapid eye movement sleep
nHF:	Normalised high frequency
nLF:	Normalised low frequency
OR:	Odds ratio
OSA:	Obstructive sleep apnoea
PC-PTSD:	Primary Care PTSD Screen
PHQ-9:	Patient Health Questionnaire-9
PLMS:	Periodic limb movement syndrome
pNN50:	Percent of differences of adjacent R-R intervals greater than 50msec
PNS:	Parasympathetic nervous system
PSG:	Polysomnography
PSQI:	Pittsburgh Sleep Quality Index
PTSD:	Post-traumatic stress disorder

REM:	Rapid-eye movement
RMSEA:	Root mean square error of approximation
RMSSD:	Root mean square of successive differences between R-R intervals
RSA:	Respiratory sinus arrhythmia
SEM:	Structural equation modelling
SES:	Socioeconomic status
SDNN:	Standard deviation of differences between R-R intervals
SCN:	Suprachiasmatic nucleus
SFI:	Sleep fragmentation index
SNS:	Sympathetic nervous system
SRMR:	Standardized root mean square residual
SWS:	Slow-wave sleep
TIB:	Time-in-bed
TST:	Total sleep time
US:	United States of America
WASO:	Wake after sleep onset

ABSTRACT

Introduction: There is a well-established bidirectional relationship between sleep and mental health. Furthermore, low socioeconomic status (SES) environments have been linked to both poorer sleep and mental health, at least in part due to a lack of perceived safety. Specifically, individuals who feel unsafe or vulnerable in their neighbourhoods may either delay sleep in favour of remaining alert to potential threats or experience hypervigilance throughout the night. This state of hypervigilance is typically characterized by heightened sympathetic nervous system activity and reduced parasympathetic tone, which can be quantified through measures of autonomic nervous system function, such as heart rate variability.

Heart rate variability (HRV) is a non-invasive measure of autonomic regulation of the heart which can be divided into time and frequency domain variables. Frequency domain variables are derived from the spectral power of the electrocardiography signal and include very low, low and high frequency power measures (VLF, LF and HF power, respectively). VLF and HF power reflect sympathetic withdrawal and parasympathetic input, respectively while LF is understood to reflect a combination of sympathetic and parasympathetic input. Lower HRV has previously been linked to various mental disorders, including depression and anxiety, and has been included as a contributing factor in the hyperarousal model of insomnia. Altered autonomic regulation may thus provide one potential mechanism underpinning the relationship between sleep and mood- and anxiety-related symptoms.

The purpose of this thesis is to explore the relationship between sleep characteristics, ANS function (as indexed by HRV) and symptoms of depression, anxiety and post-traumatic stress disorder (PTSD) in individuals living in a low SES environment. This purpose was achieved through the following aims: i) to determine whether fears related to perceptions of safety during sleep are associated with self-reported sleep duration, quality, symptoms of insomnia and daytime sleepiness among individuals living in a low SES environment, ii) to conduct qualitative interviews to understand safety-related fears and the consequences thereof in residents of a low SES community, iii) to investigate whether fear of sleep mediates the relationships between sleep measures and symptoms of depression, anxiety and PTSD in individuals living in a low SES neighbourhood, iv) to systematically review the evidence

describing the relationships between sleep-related autonomic regulation (as measured by HRV) with both sleep and mood- and anxiety-related disorder outcomes, v) to characterise HRV in this population and vi) to model the relationships between fear, sleep, sleep-related HRV and mood- and anxiety-related symptoms.

Methods: This thesis comprises four cross-sectional, observational experimental chapters, one qualitative interview chapter and a systematic review exploring associations between heart rate variability and both sleep and mental health outcomes in apparently healthy, sleep disorder and mood-and anxiety-related disorder populations. The participants in all experimental chapters and the qualitative chapter were individuals of African origin (56% women, 29-51y, 40% employed) living in a low-income community (Khayelitsha in Cape Town, South Africa) characterised by informal housing, low employment and high crime rates. All cross-sectional experimental chapters made use of the following sleep questionnaires: Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), Insomnia Severity Index (ISI). The first experimental chapter (n=400) also included select questions regarding fear of not being safe. A subset of these individuals had their sleep objectively measured with seven days of wrist-actigraphy and sleep diaries (n=200) and their fear of sleep and symptoms of depression, anxiety and PTSD were assessed using validated questionnaires (Fear of Sleep Inventory [FoSI], Beck's Depression Inventory [BDI-II], Beck's Anxiety Inventory [BAI] and Primary Care PTSD Screen [PC-PTSD]; n=100; 69% women) for the other three cross-sectional experimental chapters. Ambulatory, 24-hour electrocardiography was collected in a further subset of individuals (n=85, 25-55y, 75% women) alongside their sleep and mental health measures. Finally, one-on-one qualitative interviews were conducted with a further subset (n=15, 53% women) to understand the fears individuals have related to personal safety in this environment and the consequences of this fear on sleep quality and mental health.

Results: Subjective data obtained through questionnaires in Chapter 1 found that safety-related fears were prevalent among most participants, although more women reported "Fear of not being safe during sleep" (p=0.007) as well as "Sleeping with the light on to feel safe" (p=0.001) than men. Participants reporting safety-related fears during sleep had poorer self-reported sleep quality compared to participants not reporting such fears although, surprisingly, this relationship was stronger among men than women (Men: OR: 9.09 (3.31-24.99), p<0.001; Women: OR: 3.61 (1.80-6.54), p<0.001). Fears described by participants were

largely driven by various neighbourhood characteristics: high crime, darkness, alcohol use and lack of policing. The consequences of this include hypervigilance, disturbed sleep and poor mental health. Individuals have also adopted various coping mechanisms: i) securing their homes; ii) social strategies; iii) avoidance and iv) vigilance to try and deal with these fears.

In Chapter 2, questionnaire data revealed that 37% of participants reported mild and 27% reported moderate symptoms of depression and anxiety, while 44% were likely to suffer from PTSD. Women reported more severe depression ($p=0.005$) and PTSD ($p<0.001$) symptoms than men. Spearman's correlations showed that individuals with more fear of sleep had higher BDI-II ($p<0.001$), BAI ($p=0.002$) and PC-PTSD ($p=0.006$) scores. However, fear of sleep did not mediate the relationships between sleep and mental health. Rather, given the high prevalence of trauma and co-morbidity between clinically significant symptoms of PTSD and depression observed, exploratory analyses found that fear of sleep mediated the relationship between more severe symptoms of PTSD and depression.

Findings from the systematic review showed that the presence of mood-, anxiety- or sleep-related disorders was associated with reduced sleep-related HRV and altered indices of sympathovagal modulation. In line with these review findings, investigation of HRV parameters in Chapter 6 found dampened HRV and sympathetic dominance in majority of participants. While there were significant difference between wake- and sleep-related HRV measures, both wake and sleep HRV values remained lower than previously published data. Structural equation modelling showed that, in women, fear of sleep directly contributed to symptoms of depression and anxiety but not through dampened markers of parasympathetic activity or disrupted sleep. In anxiety models, dampened markers of parasympathetic activity were associated with more fragmented sleep, although neither markers of parasympathetic activity nor disrupted sleep were in turn associated with more severe symptoms of anxiety.

Conclusion: Individuals living in a low-income, high crime environment experience chronic fear for their safety, driven by various neighbourhood characteristics, which appears to result in a state of hypervigilance and impaired sleep quality. We propose, based on key findings from these studies, that individuals in these environments experience a Vigilance-Sleep Trade-Off, such that heightened vigilance as an adaptive response to perceived threats, which negatively impacts the physiological health of individuals through disrupted sleep patterns and reduced heart rate variability, but paradoxically provides psychological benefits as

a coping mechanism. This research underscores the systemic barriers to restorative sleep in this community which may create and perpetuate mental health disparities. Given that neighbourhood characteristics lie at the root of safety-related fears and thus the subsequent effects, this may explain some of the socio-economic disparities in health and well-being observed globally.

Chapter 1

General background

CHAPTER 1: GENERAL BACKGROUND

The purpose of this thesis is to explore the relationships between sleep characteristics, autonomic nervous system (ANS) function, as indexed by heart rate variability (HRV) and symptoms of depression, anxiety and PTSD in individuals living in a low socioeconomic status (SES) environment. Specifically, we seek to understand the role of the social environment and fears related to safety in the sleep-ANS-mental health relationship.

Individuals living in low SES communities in South Africa face a unique combination of challenges, with enormous potential to impact their health and well-being. Informal settlements in South Africa epitomize these low SES communities, in which residents face poverty, limited resources, and high rates of crime and violence. Khayelitsha in Cape Town, the site of interest for this thesis, is one such neighbourhood in which residents live in small one- to two-room homes, typically built with a mixture of brick and temporary materials such as wood and zinc. Approximately half of all households in Khayelitsha survive on a monthly income of R1,600.00 ($84.47) or less, with 55% of its population residing in informal dwellings lacking basic services[13]. Furthermore, Khayelitsha has some of the highest reported rates of violent crime, particularly of murder and sexual assault, in the country[14]. Therefore, in addition to the challenges inherent to the suboptimal housing and financial stress, it seems plausible that this environmental may also frequently expose individuals to trauma and create a state of constant vigilance among residents, who must remain perpetually alert to potential threats, affecting both their physical and psychological well-being. The need for heightened awareness and defensive readiness likely contributes to hypervigilance which may disrupt typical autonomic nervous system regulation (promoting hyperarousal), impair sleep quality and exacerbate chronic stress, anxiety and post-traumatic stress disorder (PTSD). Thus, while adaptation towards vigilance is potentially protective in dangerous environments, the knock-on consequences may have detrimental long-term health implications.

There has been a growing awareness of the importance of mental health, particularly in the wake of the COVID-19 pandemic. Mental health is defined by the World Health Organization as “a state of mental well-being that enables people to cope with the stresses of life, realize

their abilities, learn well and work well, and contribute to their community."[18] For many people, though, achieving this state of mental health remains out of reach, with mental disorders being one of the leading contributors to global disease burden[19]. Estimates suggest that, in 2019, 970 million people were living with a mental or addictive disorder[20]; a number which subsequently rose following COVID-19 and is continuing to rise[9], costing the global economy close to five trillion US dollars in 2022[21]. This cost is expected to rise to $6 trillion by 2030. One of the reasons for this is that over and above treatment costs and lost productivity, mental disorders increase the risk for communicable and non-communicable diseases[22]. Therefore, as outlined by Prince et al. (2007) there can be "no health without mental health"[22].

Low- and middle-income countries (LMICs) bear a disproportionate share of this burden with around 80% of all individuals with mental disorders globally residing in an LMIC and accounting for between 8.8-16.6% of disease in an LMIC[23,24]. Although the prevalence of mental disorders is similar in high-income countries (about 15%)[4], there are various factors to consider. One is the relative population size and make-up. LMICs tend to be more densely populated which means more individuals affected and tend to have a greater proportion of children under 10y (who are less likely to report a mental health condition) which decreases their prevalence rate[4]. One study, however, in 232,243 adults from 45 LMICs found the incidence of 12-month depression to be 6.2% and that rates of depression in almost all countries were closed linked to residents' perceived stress, such that higher stress was linked to more severe depression[25]. A meta-analysis on depression and anxiety in older adults living in LMICs found that depression prevalence ranged from 0.5-62.7% while the range for anxiety was 0.2-32.2%[26].

The other thing to consider is the financial aspect. Countries with higher gross domestic products and better infrastructure (such as high-income countries) are better equipped to deal with the burden of mental disorders. Thus, in part, the problem is the gap between the treatment resources available and those who need it. One global return on investment analysis suggests that the treatment gap for lower-middle income countries is 86% for depression and 90% for anxiety, and that these numbers are even higher for low-income countries (depression: 93% and anxiety: 95%)[27]. This means that of the individuals suffering

from depression in lower-middle income countries, 86% are not receiving treatment while 90% of those who require treatment for anxiety are not receiving said treatment. The burden of poor mental health in low-income countries, however, also stems from the environment and associated social issues related to poverty and poor sleep[28–32]. PTSD is more common in low SES settings[33], likely due to increased exposure to trauma coupled with limited support[24]. As one might anticipate, the relative prevalence of depression, anxiety and PTSD tends to be above global and regional averages in populations exposed to adverse events[34]. This may provide one insight as to why South Africa has higher rates of depression, anxiety and PTSD than other countries given the country's high rate of crime, violence and poverty[35]. Thus, finding effective points of intervention to address this burden is imperative. Sleep has been highlighted as one such lifestyle and behavioural factor with potential for intervention.

Decades of literature conclude that sleep is paramount for maintaining optimal physical and mental health. Results from numerous studies underscore the pivotal role sleep plays in the functioning of almost every facet of the human body including the cardiovascular system, immunity, metabolic regulation and, most importantly for the scope of this thesis, mental health[36–40]. Current guidelines for sleep duration suggest adults 18-64y need 7-9h of sleep for optimal physical and mental health[41]. Sleep that is of poor quality, shorter or longer than these recommended guidelines, irregular and/or mistimed has been associated with increased risk of various poor health outcomes, including all-cause mortality, cardiovascular disease, cancer, impaired autonomic function and depression and anxiety[37–39,42]. Given the focus of this thesis, the critical relationship between sleep and mental health will be discussed in more detail in Section 1.2.5. Numerous factors influence the quality of sleep including gender and SES. For example, women are 1.58 times more likely to report poor sleep and insomnia than men[43] and residents of low SES environments are more likely to report poor quality sleep than those living in higher SES areas[44]. Gender and SES both also happen to be risk factors for mental disorders[45]. This overlap suggests common pathways and interrelatedness between sleep, mental health and sociodemographic factors like gender and SES. One such contributor may be impaired autonomic function, which will be further explored in this thesis.

SES is a concept that tries to capture a person's quality of life, social standing within society

and the opportunities afforded to them. It extends beyond income to also include educational attainment, occupation (and its perceived value or importance), and subjective perceptions of social status and social class[12]. The effect of SES on both sleep quality and mental health is also likely moderated by other sociodemographic factors such as ethnicity and gender. For example, increasing SES appears to be more protective against depressive symptoms in women compared to men and in Black individuals compared to other racial/ethnic groups[31]. The vulnerability of Khayelitsha's inhabitants is further complicated by South Africa's apartheid legacy, where SES divisions largely parallel racial lines with low SES areas predominantly populated with African-origin individuals[15,16]. Alex Neitzke (2015) frames depression as a disorder related to power dynamics, emerging in groups oppressed through intersecting factors such as gender, class, and race[17]. This framework raises particular concerns for the mental health of low SES residents in South Africa's informal housing communities, especially women of African-origin, who face particular vulnerability through their positioning at the intersection of these marginalized groups. Their significant representation within South Africa's population, combined with these complex challenges, underscores the critical importance of targeted research and intervention efforts in these communities.

This introductory chapter will address the key concepts of i) mental disorders, specifically depression, anxiety and PTSD, as a specific concern for individuals living in low SES areas, ii) sleep health, as a modifiable risk factor for mental health disorders particularly in a low SES environment, iii) fear of safety as a characteristic of low SES environments and its role in poor sleep and iv) heart rate variability, a marker of hyperarousal as one potential factor linking the environment and subsequent fears to sleep quality and its role in mental disorders.

1.1. Mental disorders

Mental disorders are characterised by “a clinically significant disturbance in an individual’s cognition, emotional regulation, or behaviour” and encompass a variety of mood, anxiety, affective and neurodevelopmental disorders[9]. These include conditions such as schizophrenia, bipolar, and autism spectrum disorder, among others[9], but the scope of this thesis will be limited to mood- and anxiety-related disorders, specifically depression,

generalised anxiety disorder (GAD) and PTSD and the symptoms thereof.

1.1.1. Depression

In 2023, an estimated 5% of all adults experienced depression (defined as meeting the clinical threshold for either the Diagnostic and Statistical Manual of Mental Disorders or International Classification of Disease criteria), with a disproportionate percentage of these being women[46]. Numbers are even higher in South Africa, with rates of depression nearly five times that of global estimates. A recent study found 25.7% of nationally representative respondents (n=3,402; 50.8% female; 27.5% unemployed; across all provinces in South Africa) reported scores on the Patient Health Questionnaire-9 (PHQ-9; a 9-item Likert scale) indicative of probable depression (scores of $\geq$10)[47]. The rate of probable depression in South Africa is higher than those of high-income countries like the United States, as might be expected given the aforementioned link between LMICs and mental health concerns, but is also higher than Brazil, a similarly middle-income country with comparative levels of economic inequality[47]. This suggests that there may be factors specific to the South African context driving the development of depression which warrant further investigation.

Depression is characterised by low mood, loss of pleasure or loss of interest for a prolonged period[31]. The symptoms include: depressed mood; notably diminished interest or pleasure in most or all activities; significant weight loss (or poor appetite) or weight gain; frequent, regular insomnia or hypersomnia; noticeable psychomotor changes (e.g. walking or talking slowly or pacing and fidgeting); fatigue or loss of energy; feelings of worthlessness; indecisiveness or trouble concentrating and recurrent thoughts of death (not just fear of dying), or suicidal ideation, plan, or attempt. Five or more of these symptoms - at least one of which must include depressed mood or loss of interest or pleasure - need to be present for at least two weeks and cause significant impairment to qualify as a major depressive episode according to the most recently revised Diagnostic and Statistical Manual of Mental Disorders v5 text revision (DSM-5-TR)[2,48]. Depression is frequently comorbid with other conditions, with roughly three quarters of individuals with depression also reporting at least one other mental disorder, commonly generalised anxiety disorder or PTSD[49]. There are many proposed, likely interacting, factors implicated in the development of depression, including genetic risk factors, altered neurotransmitter signalling, neuroinflammation and gender[17,49,50].

Women are reported to be 1.5 times more likely to develop depression than men and are also more likely to develop anxiety and PTSD[17,18,51–53]. The reasons for this appear to be biological, psychological and social in nature. There is evidence to suggest that depression is linked to hormonal fluctuations given that the prevalence of women reporting depression is higher around times of hormonal change such as puberty, pregnancy and perimenopause[54]. There is also a neurobiological model that suggests there are sex differences in the brain structure and transcriptional networks of patients with depression[55]. This may go some way to explaining why we see different patterns of symptom presentation and response to treatment between men and women[55]. Women are not just biologically different to men, though, they have different experiences of the world. As outlined above, it has been suggested that depression is linked to power dynamics with women more likely to experience marginalisation and poverty than men[17].

1.1.2. Generalised anxiety disorder

Similarly, anxiety disorders affected an estimated 4% of the global population in 2023 (as defined by the clinical thresholds for either the DSM-5-TR or International Classification of Disease criteria), with only about 25% of individuals receiving treatment[51]. As with depression, however, the estimated prevalence in South Africa far exceeds the global average with 17.8% of South Africans considered to have probable anxiety[47]. Anxiety disorders include a variety of disorders, including social anxiety disorder, phobias, and panic disorder, among others[2,48]. In this thesis, we will be focusing on GAD and hence forth any use of the term anxiety is understood to refer to GAD and the general symptoms thereof. According to the DSM-5-TR, anxiety disorders are characterised by excessive anxiety or worry about various events, typically accompanied by physical symptoms, over a six month period which cause clinically significant distress. Associated symptoms include: restlessness, fatigue, difficulty concentrating, sleep disturbances, muscle tension and irritability (at least three of which need to have been present for most of the six month period for a diagnosis)[2,48]. As with depression, there are numerous factors at play in the development of anxiety disorders, including genetic factors, the presence of other health disorders, oxidative stress and inflammation, experiencing adverse events, and gender[51,56].

1.1.3. Post-traumatic stress disorder

PTSD can develop after exposure to a traumatic event, which includes exposure to actual or threatened death, violent assault, sexual assault or natural disasters (Criterion A trauma). This exposure can be directly experienced by the individual, witnessed by the individual, the result of learning that a close family member or friend experienced a trauma or through repeated or exposure to details of traumatic events in the line of work[2,48]. Although it is suggested that as many as 70% of individuals will experience a criterion A trauma in their lifetime, only about 5.6% of these individuals go on to develop PTSD[52]. This raises the question as to what risk factors increase a person's vulnerability to developing PTSD and what promotes resilience. Trauma type is one key determinant in predicting whether an individual will go to develop PTSD, with particularly high rates of PTSD in individuals exposed to sexual violence or those exposed to violent conflict[52]. This is particularly relevant in South Africa, where over 678,000 contact crimes were recorded for the 2023/2024 year, over 50,000 of which were sexual offenses[35]. Contact crimes are defined as those in which "the victims are the targets of violence or instances where the victims are in the vicinity of property that criminals target and are subjected to the use of/or threats of violence by perpetrators"[35].

Once again, as with depression and anxiety, women are more likely to develop PTSD than men. While, this may have something to do with women being more likely to experience sexual violence than men[35,52], it has been indicated that higher risk for exposure to sexual violence does not entirely explain women's greater risk for PTSD. Women are more likely to develop PTSD even after controlling for the type of trauma (tollin ref). PTSD is characterised by one or more of the following which began after trauma exposure: repeated, intrusive memories of the event, repeated distressing dreams related to the traumatic event, dissociative reactions in which the individual re-experiences the trauma and significant distress (either physiological or psychological) at cues related to the traumatic event[2,48]. Other symptoms of PTSD are clustered as hyperarousal symptoms, where individuals are increasingly vigilant to potential threats due a heightened sense of danger[52].

1.1.4. Socioeconomic status and symptoms of depression, anxiety and PTSD

Evidence suggests a strong relationship between poverty, trauma, and mental disorders, with individuals facing poverty more likely to experience mental disorders like depression and

PTSD[57,58]. Lower SES is associated with an increased burden of mental disorders, with more severe symptomology[28–32], and with impaired treatment efficacy[59]. This may be due to additional financial and psychosocial stresses associated with low SES environments and limited access to mental health resources. Persistence of symptoms after treatment may be due to sustained exposure to crime, violence and socioeconomic deprivation which remain even when treatment concludes[59]. These disorders are exacerbated by traumatic events, substance abuse, lower educational outcomes, food insecurity, and disability, further disadvantaging those living in challenging socioeconomic contexts[57]. It may be that chronic stress from socioeconomic-related challenges elicits physical consequences such as neuroinflammation and altered neurocircuitry[50,56] in addition to the psychological stress. This has implications for those living in informal settlements, which are prevalent in South Africa[60], as they face heightened risks of mental disorders due to adverse living conditions, including poverty, violence, crime, and a lack of government support, all of which perpetuate mental health issues and social marginalization[57,58,61–63].

1.1.5. Measurement of depression, anxiety and PTSD symptomology

The assessment of depression, anxiety, and PTSD symptoms often involves validated self-report tools that measure symptom severity and impact. The Beck Depression Inventory (BDI) is widely used to quantify depressive symptomatology, evaluating both cognitive, affective[64] and physical symptoms associated with depression. Similarly, the Beck Anxiety Inventory (BAI) provides a focused measure of anxiety, assessing the somatic and subjective aspects of anxiety experiences[65]. For PTSD, the Primary Care PTSD Screen (PC-PTSD) is a screening tool commonly used in primary care settings to identify individuals who may require further assessment for PTSD[66]. While there are other tools, such as the PHQ-9 for depression, these tools have demonstrated reliability and validity across various populations, including South Africa, making them critical instruments for accurately identifying symptom presence and severity in clinical and research contexts[67–70].

Table 1.1: Validated questionnaires to investigate depression, anxiety and PTSD symptom severity and their respective scoring parameters.

Questionnaire	Use	Scoring
Beck Depression Inventory (BDI-II)[64]	The BDI-II assesses symptoms of depression over the previous two weeks. Participants are presented with various feelings associated with depression including sadness, tiredness and guilt and asked to select the statement which they feel most applies from not feeling to feeling that emotion strongly or frequently.	This tool comprises 21 questions which are summed for a global score. Total scores range from 0-63. Higher scores are indicative of more severe symptoms of depression. Scores can also be categorised according to the following depression risk categories: 0-13: minimal; 14-19: mild; 20-28 moderate; 29-63: severe.
Beck Anxiety Inventory (BAI)[65]	The BAI assesses cognitive and somatic symptoms of anxiety over the last month. Individuals are presented with various symptoms of anxiety and asked to rate how much they have been bothered by that symptom from "*Not at all*" to "*Several times a week*".	Responses to 21 questions are summed to obtain a total score (0-63), with "*Not at all*" assigned a score of 0 and "*Several times a week*" being assigned a score of 3. Higher scores indicate more severe symptoms of anxiety. The following cut-points are used to stratify participants into anxiety risk categories: 0-7: minimal anxiety; 8-15: mild anxiety; 16-25 moderate anxiety; 26 and above: severe levels of anxiety.

Primary Care Post-Traumatic Stress Disorder (PC-PTSD)[66]	The PC-PTSD screens for trauma and psychological stress in line with the DSM-5 PTSD diagnostic criteria. If participants answer "yes" to experiencing a traumatic event and then "yes" to any four of the five item statements, they are understood to exhibit significant symptoms of PTSD.	Each "yes" answer is assigned a score of 1. This tool yields a total score ranging from 0-5 with higher scores indicating more severe symptoms of PTSD. Scores of ≥4 indicate likely presence of PTSD with high specificity.

PTSD: post-traumatic stress disorder

1.2. Sleep

Sleep is a universal constant with almost every species exhibiting some form of rest period[71]. This evolutionary preservation of sleep suggests that sleep is essential for survival and, as such, should be considered a basic human right. Sleep is characterised by a period of reduced i) consciousness, ii) response to environmental stimuli and iii) voluntary movement[40]. It is a complex and dynamic process driven by various neurotransmitters acting on the arousal systems of the brain. During sleep, neurotransmitters typically inhibit these arousal systems which would otherwise promote wakefulness[38]. The sleep-wake controlling regions of the brain, such as the ventrolateral preoptic nucleus and the periaqueductal grey, are also implicated in autonomic control; involved in regulating both sympathetic activity and wakefulness[72]. Alteration of the neuronal signals controlling sleep (such as where an individual is disturbed from sleep through arousals or hypoxia etc.), therefore, promotes sympathetic activity, inducing hyperarousal of the central nervous system[72].

Seep can be broken down into stages broadly categorized based on neural activity into non-rapid eye movement (NREM) and rapid eye movement (REM) sleep. NREM sleep consists of stages 1, 2 and 3 sleep. NREM stage 1 sleep is a very light, transitory stage which should only comprise about 5% of an individual's total sleep time[38]. NREM stage 2 sleep is deeper than

stage 1 and constitutes the bulk of one's sleep with most people spending roughly half their time in this stage[38]. NREM stage 3, also known as deep or slow-wave sleep, makes up around 20% of a person's total sleep time and is thought to be responsible for muscle repair and immune function[38]. Finally, REM sleep typically comprises nearly a quarter of one's sleep and is tasked with emotional regulation[73]. REM is characterised by rapid eye movements, muscle atonia and distinctive saw-tooth brainwaves[73]. The typical structure of sleep involves cycling through each of these four stages and most people will complete 4-5 cycles throughout the night, although the exact structure of these cycles changes as the night progresses[38]. Throughout the night the proportion of time spent in REM sleep per cycle lengthens, whereas most of our deep sleep occurs in the initial phase of sleep as illustrated in Figure 1.1[74]. Sleep staging can only be reliably measured using polysomnography, which will be discussed along with other methods of assessing sleep in the next section.

During NREM sleep, parasympathetic tone typically dominates while sympathetic tone is reduced, allowing the cardiovascular system a period of rest to promote recovery[74]. This balance of autonomic nervous system activity is a key indicator of physical and mental health. Altered autonomic regulation, has been associated with cardiovascular disease, and mental disorders including depression, anxiety and PTSD[75–78]. Disruption in typical sleep architecture appears to alter activity of the sympathetic and parasympathetic nervous systems which exhibit sleep stage-dependent interactions[72]. As such, sympathovagal activity emerges as a crucial consideration when investigating the effect of insufficient and/or disrupted sleep on mental health.

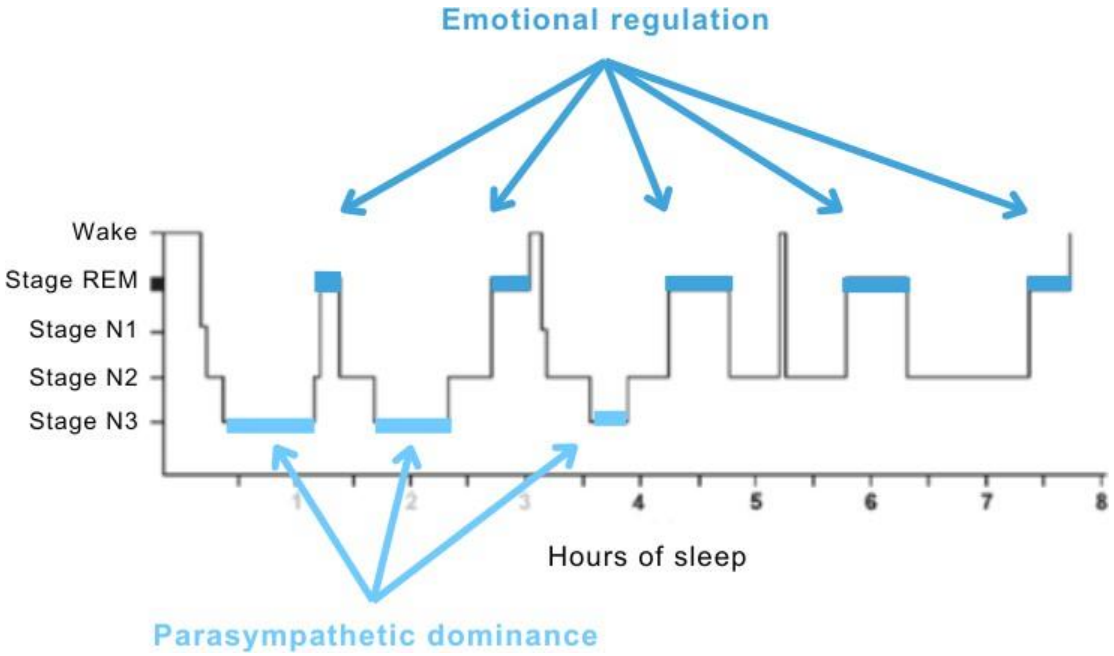

Figure 1.1. Hyponogram representing the distribution of the various sleep stages across the night. *Stage N1: Non-REM Stage 1; Stage N2: Non-REM Stage 2; Stage N3: Non-REM Stage 3; Stage R: Rapid Eye Movement (REM) Sleep; Stage W: Wake.*

Thus, healthy sleep is understood to be sleep that is of sufficient duration, minimally disrupted, regular and appropriately timed to both the light-dark cycle and an individual's own intrinsic clock and with adequate time spent in each sleep stage. Insufficient sleep has long been linked to poor physical and mental health outcomes but the negative consequences of irregular, disrupted and mistimed sleep (including all-cause mortality, diabetes mellitus, cognitive impairment, stress and depression) are also emerging[79–84]. This motivates the need to consider sleep health in its entirety rather than focusing solely on duration and will be explored in more detail below.

Sleep health may be impaired because of either a sleep disorder or disordered sleep – related but distinct concepts in sleep medicine. Sleep disorders are clinically diagnosed conditions that meet specific medical criteria and disrupt normal sleep patterns[85,86]. The two most prevalent sleep disorders are insomnia and obstructive sleep apnoea (OSA)[87]. Insomnia typically reduces overall sleep duration, while OSA fragments sleep through repeated breathing interruptions (apnoea or hypopneas) throughout the night[85]. Other recognized

sleep disorders include restless legs syndrome and narcolepsy[85,86]. These conditions generally require professional medical intervention and treatment.

Disordered sleep, on the other hand, describes poor sleep that does not necessarily meet the criteria to be diagnosed as a clinical sleep disorder but still affects sleep quality and health. These irregularities might include inconsistent sleep schedules, frequent nighttime awakenings due to stress, or sleep disruptions from caffeine consumption or environmental factors. While disordered sleep often improves with lifestyle modifications and better sleep hygiene practices, sleep disorders typically demand more comprehensive medical management.

1.2.1. Sleep health

Researchers are beginning to consider a multidimensional model of sleep that extends the traditional focus on duration. Sleep health encompasses duration, efficiency, regularity, timing, alertness and perceived quality[88]. Each of these components are associated with physical and mental health, although the exact health outcomes vary between components and between studies[36,79,80,82–84].

1.2.1.1. Sleep duration

Sleep duration is the most extensively studied aspect of sleep health, referring to the total hours of sleep obtained in a 24h period. It is a fundamental determinant of both physical and mental health[36,89–94]. Sleep duration differs from an individual's sleep opportunity which is their time-in-bed or the time between bedtime and wake-up time during which an individual is trying to sleep. Sleep duration is also frequently referred to as total sleep time and measures the amount of sleep achieved. In individuals with healthy sleep, sleep opportunity and sleep duration or time-in-bed and total sleep time respectively will be very similar. The National Sleep Foundation in the United States recommends 7-9 hours of sleep per night for adults aged 18 to 64y[41], noting that individual needs may vary due to age, lifestyle, and genetic differences. Duration is understood to have a U-shaped relationship with health as

both short (<7h) and long (>9h) sleep have been associated with mortality, cardiovascular disease and mental disorders[36,39,41,42].

1.2.1.2. Sleep efficiency

Sleep efficiency is a measure of how much time an individual spends asleep out of their total sleep opportunity, typically expressed as a percentage. A higher sleep efficiency typically reflects minimal disruptions, contributing to more restorative, better quality sleep. Conversely, low sleep efficiency may indicate a long time taken to fall asleep (also known as sleep onset latency) or sleep which is fragmented or disturbed, as is common in sleep disorders such as insomnia. The longer the time spent awake after being disturbed, the lower the sleep efficiency will be. Time spent awake after having initially fallen asleep during the intended sleep period is known as wake after sleep onset (WASO). Sleep efficiencies regularly lower than 85% is one of the criteria of sleep maintenance-type insomnia[10]. Poor sleep efficiency has been shown to predict incidence of cardiovascular disease and depression[95,96].

1.2.1.3. Sleep fragmentation

Sleep that is increasingly fragmented - with frequent arousals and disturbances - can disrupt sleep staging and has been associated with poorer physical and mental health[79–81]. Fragmentation of REM sleep, in particular, is emerging as a key feature in both perceived insomnia (where individuals underestimate duration)[73,97] and in the development of hyperarousal by impairing resolution of emotional distress and potentially even reinforcing perceived emotional and physical distress[73,97]. This has implications for the development of disorders related to emotional distress such as depression and PTSD. In depression, REM fragmentation may contribute to the persistence of negative emotional memories and mood, while also disrupting the brain's natural ability to regulate emotional responses to daily stressors. In PTSD, fragmented REM sleep may impair the processing and integration of traumatic memories, potentially maintaining their emotional intensity and contributing to recurring nightmares and flashbacks[98,99]. Additionally, this fragmentation can heighten the hypervigilance characteristic of PTSD, as the brain's ability to appropriately categorize and respond to potential threats becomes compromised[98,99]. The Sleep Fragmentation Index (SFI),

which is further detailed in Chapters 3 and 7 of this thesis, provides an index of restlessness during sleep, quantified as a percentage. This metric, alongside sleep efficiency, allows for a more comprehensive assessment of sleep continuity and quality, highlighting the effects of disturbances on sleep health.

1.2.1.4. Sleep regularity

Sleep regularity, or "the day-to day consistency in sleep-wake timing", plays a significant role in sleep quality and overall health[83]. Recent research has shown that sleep regularity was a stronger predictor of all-cause mortality than sleep duration in a longitudinal study of 60,977 UK Biobank participants. More regular sleep is associated with lower risk of all-cause, cancer and cardiometabolic mortality[83]. This may be due to the effect of irregular, shifting sleep times in disrupting the various physiological processes that follow circadian rhythms, such as immune function and hormone secretion. One example is the HPA axis and the release of adrenocorticotropin, which should be high in the morning and low at night but is also activated in response to circadian disruption and sleep deprivation. Chronic HPA activation and adrenocorticotropin release subsequently results in dampened immune response, increased heart rate and blood pressure and altered metabolism[100,,101]. Given that our circadian rhythms take time to adjust to changes, individuals who shift their sleep timing frequently may experience misalignment between their sleep-wake cycle and their circadian rhythm[100,101].

1.2.1.5. Sleep timing

Sleep timing refers to the specific hours at which sleep begins and ends and is typically using the midpoint of sleep. This midpoint represents the precise centre of an individual's sleep period and may provide deeper insights into an individual's chronotype. Chronotypes are the behavioural expression of an individual's natural sleep-wake preferences. An individual's chronotype is largely genetically determined, with environmental factors and age also playing influential roles[102]. Sleep timing (and by extension the midpoint of sleep) thus varies significantly across different chronotypes. Chronotypes exist on a spectrum ranging from more morning-orientated to more evening-orientated. "Morning-types" experience peak

alertness and productivity during early daylight hours and tend to sleep and wake early with earlier sleep midpoints, while “evening-types” reach their cognitive and productive peak later in the day, with correspondingly later sleep and wake times and a later sleep midpoint[102]. In healthy sleep, sleep timing would align with an individual’s chronotype for optimal health benefits. Misalignment between sleep timing and the body’s natural biological clock (or circadian rhythms), may be due to various causes including shift work, jet lag, social jet lag or erratic sleep schedules. This misalignment can disrupt sleep quality and lead to adverse health outcomes[84]. Earlier sleep timing and better regularity have been associated with lower cardiometabolic risk and lower incidence of depression[84] among other outcomes, which may be linked to better circadian rhythmicity as outlined below.

Circadian rhythms

Circadian rhythms are the endogenous rhythms of our bodies, which have an approximately 24h period[103]. These rhythms are entrained to the external environment in response to various signals known as *zeitgebers,* which include light, temperature, exercise, meal timing, and social influences with the light-dark cycle acting as a key entrainer[104]. In humans, the suprachiasmatic nucleus (SCN)[103] in the hypothalamus acts as the master clock and provides entrainment signals about the light environment to the rest of the body. Light is perceived by retinal ganglion cells and this signal is sent to the SCN which then orchestrates the alignment of internal peripheral clocks with the external environment. This sophisticated mechanism ensures that biological activities correspond precisely with the 24-hour light-dark cycle[74].

The sleep-wake cycle is one clear example of circadian rhythmicity at work. In fact, the two-process model of sleep[105] proposes that our circadian rhythm, working in tandem with the sleep homeostat, is pivotal in ensuring wakefulness during the day and promoting sleep at night (Figure 1.2). The sleep homeostat is thought to sense “sleep pressure” – the sensation of sleepiness or drive to fall asleep, which accumulates with prolonged wakefulness and dissipates during sleep (Process S). The circadian component (Process C) represents a sine function of alertness, which reaches its peak during the day and its nadir at night, thus counteracting sleep pressure during the day to maintain wakefulness[105,106]. As darkness falls, however, the SCN signals the pineal gland to release melatonin, a hormone that signals the body's transition from active to rest phase. During the day, melatonin production diminishes,

promoting wakefulness. The combination of high propensity to sleep and low alertness facilitates initiation and maintenance of sleep at night[105,106].

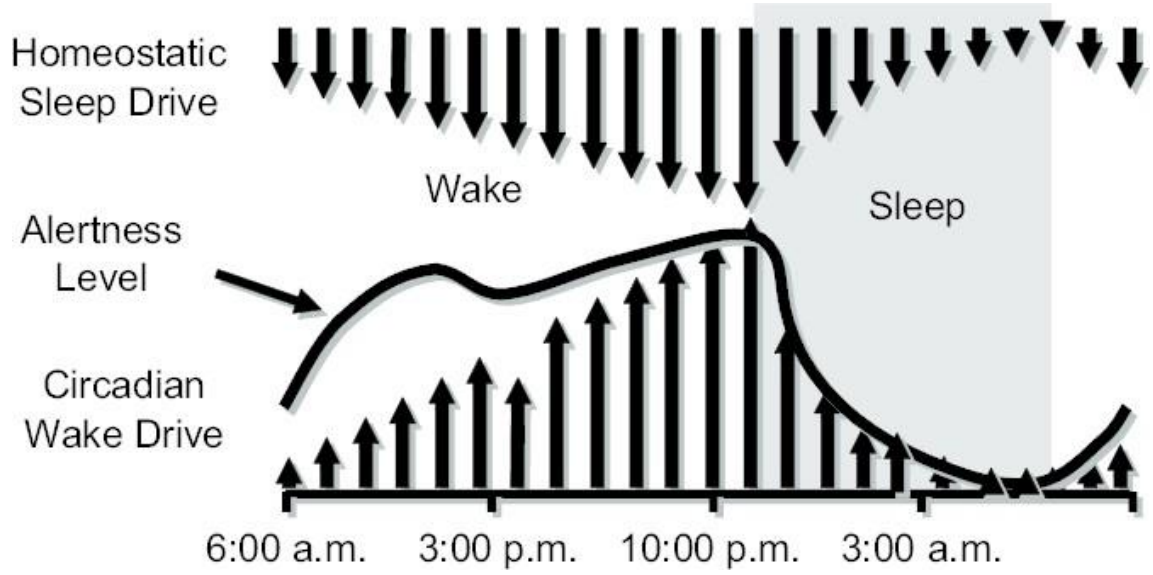

Figure 1.2. The two-process model of sleep regulation. *Homeostatic drive to sleep (Process S) increases with prolonged wakefulness and declines during sleep. The circadian wake drive (Process C) also increases across the day to maintain alertness, decreasing in the evening and rising again the following morning. The decrease in Process C, in conjunction with high Process S, provides the stimulus for sleep onset. (Source: Owens, Judith & Gruber, Reut & Brown, Thomas & Corkum, Penny & Cortese, Samuele & O'Brien, Louise & Stein, Mark & Weiss, Margaret. (2013). Future Research Directions in Sleep and ADHD: Report of a Consensus Working Group)*

1.2.1.6. Sleep quality

Sleep quality encompasses several dimensions, including subjective perceptions of restfulness and objective measures such as sleep depth and continuity. Sleep depth refers to progressive loss of awareness to the surrounding environment as we progress through the various stages of sleep detailed below. High-quality sleep is understood to be characterised by sufficient time spent in deep sleep and REM stages, with minimal interruptions or arousals.

1.2.2. Measuring sleep

There are various tools available to assess sleep, broadly divided into subjective and objective

measures. Subjective measures are largely self-report or perception-based and rely on the individual's assessment of their sleep and other related constructs, whereas objective measures use data from physiological measures like electroencephalography (EEG), heart rate or movement to build a picture of sleep.

1.2.2.1. Subjective measures

Subjective measures include perceived sleep quality, daytime sleepiness, daytime function, and risk for various sleep disorders. These constructs are typically measured using validated questionnaires and sleep diaries. While there are a large number of these tools, only those specifically utilised in this thesis are described in detail below (see Table 1.2). Perceived sleep quality questionnaires typically ask a person to consider their ability to fall asleep and stay asleep, their duration, continuity, sleep depth and how refreshed and alert they feel during the day to try and gauge a person's overall impression of their sleep and its restorative value. Daytime sleepiness refers to an individual's propensity to fall asleep during the day and is assessed as a symptom of poor sleep based on the premise that, in the absence of a sleep disorder or disordered sleep, a person should feel alert and energised during the day. Daytime function tools measure a person's ability to complete daily tasks, perform higher order cognitive processes and sustain focus and energy. Finally, risk for insomnia and OSA are frequently assessed given that these are the two most common sleep disorders[87]. Risk for insomnia tools assess difficulties falling asleep, staying asleep or waking too early and their impact on daytime functioning while questionnaires assessing risk for sleep apnoea measures the presence of known risk factors such as a high body mass index (BMI) or being male. Both fear of sleep and risk for sleep disorders are important considerations as factors which can disrupt sleep.

The strengths of subjective measures are that they allow researchers to quantify an individual's experience of their sleep and are easy to administer which allows for larger sample sizes. Unfortunately, given the self-report nature of subjective measures, they are vulnerable to participant recall bias and cannot capture aspects of sleep such as sleep architecture.

Table 1.2: Validated questionnaires to investigate sleep quality, daytime sleepiness, insomnia symptom severity, fear related to sleep and risk for sleep apnoea and their respective scoring parameters.

Questionnaire	Use	Scoring
Pittsburgh Sleep Quality Index (PSQI)[107]	The PSQI assesses perceived sleep quality over the last month. Participants are asked about time-in-bed, sleep duration and to rate how frequently they have been disturbed by various stimuli from "*Not in the last month*" to "*Three or more times a week*".	This tool comprises 19 questions, the scores of which are summed for a global score (0-21). Similar questions are combined to create 7 subcomponent scores ranging from 0-3. Higher scores are indicative of poorer sleep quality. A cut-point of 5 or less is used to denote good sleep quality.
Epworth Sleepiness Scale (ESS)[108]	The ESS measures participants' habitual levels of daytime sleepiness over the last month. Participants are presented with 8 scenarios and are asked to rate how likely they are to fall asleep ranging from "*Not at all*" to "*Almost certainly*".	Responses to eight questions are summed to obtain a total score (0-24), with "*Not at all*" assigned a score of 0 and "*Almost certainly*" being assigned a score of 3. Higher scores indicate greater levels of daytime sleepiness. A score of 10 or more is categorized as excessive daytime sleepiness.
Insomnia Severity Index (ISI)[109]	The ISI is a 7-item questionnaire assessing the nature, severity, and impact of insomnia. It evaluates 7 items over the last month using a 5-point Likert scale.	This tool yields a total score ranging from 0-28 with higher scores indicating more severe symptoms of insomnia. The score can also be stratified into risk categories: 0-7: absence of insomnia; 8-14: sub-threshold insomnia; 15-21: moderate insomnia and 22-28: severe insomnia.

STOP-BANG questionnaire[110]	The STOP-BANG questionnaire is a screening tool for OSA. It includes 8 binary yes/no questions related to snoring, tiredness, observed apnoeas, blood pressure, body mass index, age, neck circumference and gender.	Each item is awarded either a 0 for the absence or 1 for the presence of the risk factor. Scores for each item are summed and respondents are categorised as follows based on their total score: 0-2 - low risk, 3-4 - moderate risk and 5-8 - high risk for OSA.

OSA: obstructive sleep apnoea

1.2.2.2. Objective measures

Polysomnography

Polysomnography (PSG) is widely recognized as the gold standard for assessing sleep structure, including sleep stages and sleep-related respiratory disorders. It employs a comprehensive array of measurements, including electroencephalography (EEG), electrooculography (EOG), chin electromyography (EMG), electrocardiography (ECG), nasal airflow, pulse oximetry, and chest and abdominal respiratory effort. In the research context, it is primarily used to characterise sleep stages from a single night and as such does not provide insight into habitual sleep. Furthermore, other limitations of PSG are that it is labour-intensive to set up, requires specialised staffing and can be uncomfortable for participants, potentially disrupting their sleep and thus skewing results[111].

Outcome variables of PSG include: Total sleep time (actual time spent asleep; h), sleep onset latency (time taken to fall asleep; min), number of arousals, WASO (min), sleep efficiency (%), time (min) and proportion (%) of night spent in NREM sleep (i.e. stages 1, 2 and 3) and REM sleep, REM latency (min) and the apnoea-hypopnea index.

Actigraphy

In contrast, actigraphy, another method of objective sleep measurement (Figure 1.3), offers several advantages, especially for population-based research. Actigraphy is based on

accelerometer-measured movement during the day and night, which is used to estimate whether the individual is asleep or awake within any given 30s epoch of time[11]. These data are typically visualised on an actogram such as the one displayed in Figure 1.3 showing night-by-night data. Actigraphs are typically worn for at least a week and are fairly non-invasive, providing a better reflection of habitual sleep patterns. They are easy both to set up and for participants to use, making them a more practical choice for large-scale studies. Despite these benefits, actigraphy does not provide the detailed sleep stage information that PSG does but rather makes predictions of sleep / wake states based on accelerometer-derived activity patterns. Thus, actigraphy is a useful alternative for certain types of sleep research including larger epidemiological studies[111].

Outcome variables of actigraphy include: bedtime, wake-up-time, time-in-bed (elapsed time between bedtime and wake-up time), total sleep time (h), sleep efficiency (%), arousals, WASO (min) and SFI (further detailed in Chapters 3 and 7 of this thesis; %).

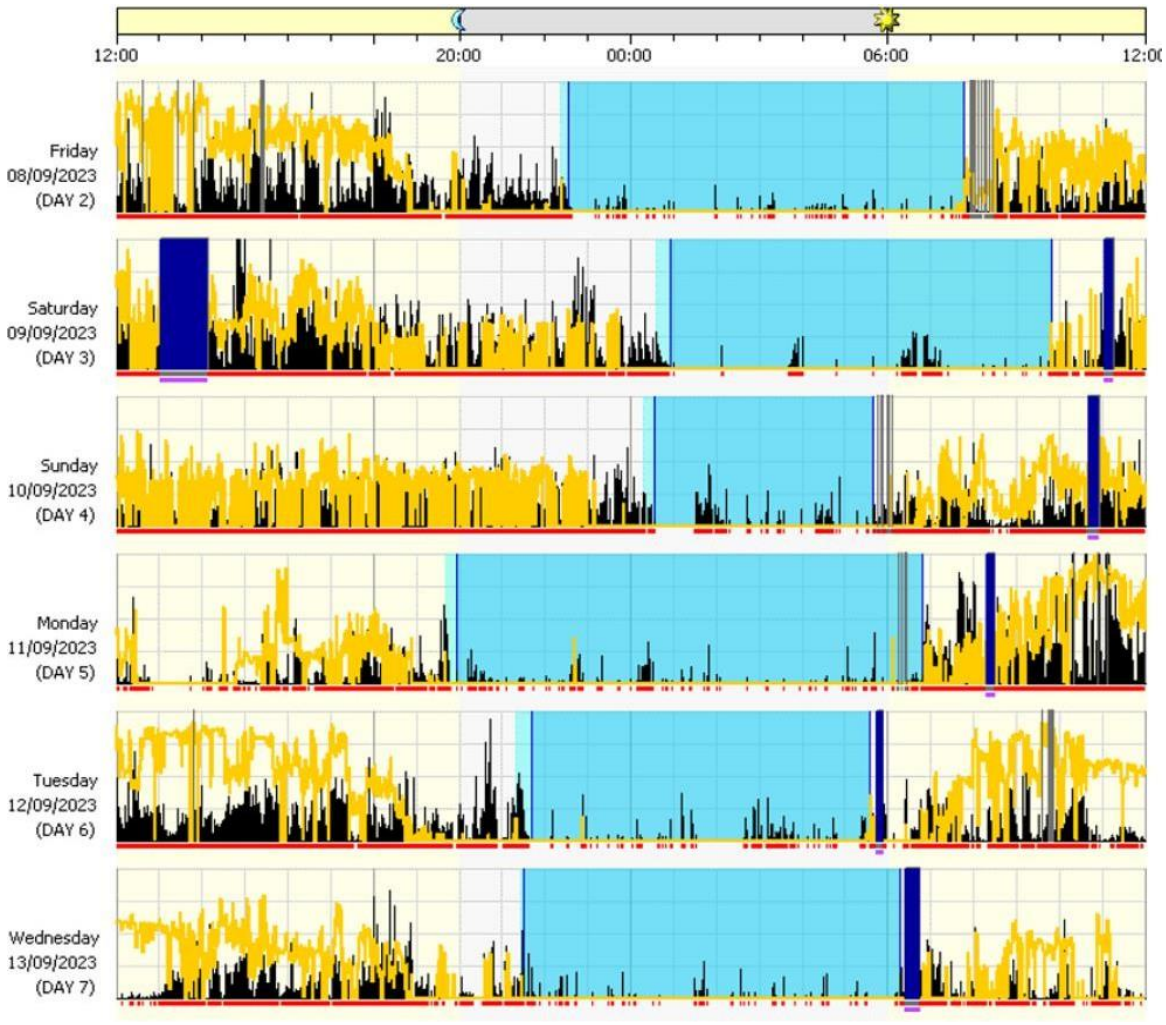

Figure 1.3. An example of an actogram. *The actogram shows both the wake and sleep period (light*

blue) over six days. Each bar starts at midday on the date listed on the left and continues for 24 hours until midday the following day. The black lines represent activity, the yellow lines represent light, and the red lines represent epochs scored as wake. Dark blue areas are excluded intervals which are not scored. During each sleep period, bursts of movement (black vertical lines) underlined by red show arousals or awakenings, and thus provide insight into the disturbance experienced by the participant. The above actogram shows an example of irregularly timed, disturbed sleep.

1.2.3. Sleep in a low socioeconomic setting

Just as sleep health is multidimensional, so too are the factors that influence it. The Socio-Ecological Model of Sleep Health proposes that various factors at the i) individual, ii) family and iii) neighbourhood level interact to influence sleep health (illustrated in Figure 1.4). The socioecological determinants of sleep encompass individual behaviours and risk factors as well as the wider social and physical environment[112].

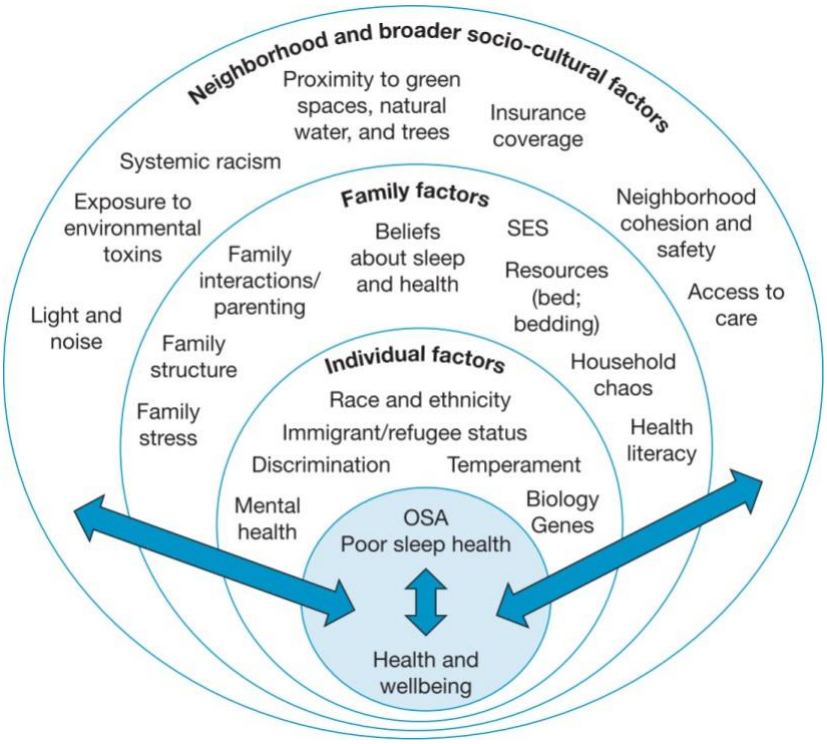

Figure 1.4. Individual, family and neighbourhood level factors which may influence sleep health and overall health and wellbeing. *Living in a low socioeconomic status area increases the likelihood that one or more of these factors from all three levels impair sleep health. (Source: Billings ME, Cohen RT, Baldwin CM, Johnson DA, Palen BN, Parthasarathy S, Patel SR, Russell M, Tapia IE,*

Williamson AA, Sharma S. Disparities in Sleep Health and Potential Intervention Models: A Focused Review. Chest. 2021 Mar;159(3):1232-1240. doi: 10.1016/j.chest.2020.09.249. Epub 2020 Sep 30. PMID: 33007324; PMCID: PMC7525655.)

Lower SES areas have previously been associated with both poorer health outcomes and poorer sleep compared to higher SES areas[113–115]. In fact, one review found that 29% of the relationship between SES and health outcomes can be attributed to the effect of poor sleep such that low SES environments impair sleep quality which in turn negatively affects health[113]. SES is understood to compromise sleep health in a number of ways (see Figure 1.4). For example, residents of lower SES communities may live in suboptimal housing in which poor ventilation and overcrowding may contribute to disturbed sleep[116]. Low SES areas also tend to be characterised by more noise and light and with higher population densities than high SES areas. Excess noise and light as well as higher indoor temperatures at night are all associated with poor sleep quality and increase the risk of insufficient sleep. Excess light at night impedes melatonin secretion, while high temperatures interfere with dropping core body temperature which can alter circadian rhythmicity, delay sleep timing and increase sleep onset latency[117]. Additionally, traffic, crowding and pollution undermine the walkability of the environment, which may indirectly lead to sleep disruptions by limiting physical activity and contributing to psychosocial stress[44,117–119].

Additionally, the social environment of low SES areas also modifies sleep for residents of these areas. An adverse social environment, characterised by high disorder and low safety and social cohesion, has been associated with shorter self-reported sleep duration[120] and higher daytime sleepiness[120,121] after adjustment for the physical environment, neighbourhood socioeconomic status as well as individual level sociodemographic characteristics and other short sleep risk factors. For example, Johnson et al. (2016) used data from 5,301 Americans in the Jackson Health Study and observed shorter and poorer quality sleep associated with high self-reported frequency of neighbourhood violence[122]. It may also be that anxiety around circumstances pertaining to socioeconomic status or past traumatic events contribute to poor sleep in low SES communities[123–125]. A study in urban-dwelling African Americans reported associations between the indicators of stressful environments with increased sympathetic and decreased parasympathetic nervous system activity (hyperarousal) during sleep[126]. Given that longitudinal data suggest that 8 out of 10 South Africans lived in poverty between 2008 and 2017[127], as well as the clear link between sleep and health, the environmental effect on

sleep is a public health concern.

1.2.4. Gender differences in sleep

Another factor in the socioecological determinants of sleep is gender. This may have a physiological basis related to the biological sex of men and women, as there is evidence females tend to report more sleep problems than males from puberty and particularly during menopause – times of large hormonal change[128]. Throughout the reproductive years, across the menstrual cycle, changes in sleep are observed which may be linked to fluctuating hormone levels[128]. Hormones, however, are not the sole difference at play between men and women. As outlined earlier, prevalence of depression, anxiety and PTSD are higher in women than men[17,46,51–53], which, given the close relationship between sleep and mental health, likely has a role in the higher prevalence of poor sleep among women[129]. South African women are also more likely to be unemployed and live in poverty[127,130]. Previous research found that the relationship between gender and poor sleep was halved after taking SES into account, suggesting that SES mediates much of the gender disparity in sleep complaints[131]. Furthermore, women are also more likely to be exposed to violence, particularly in South Africa, where gender-based violence and intimate partner violence are rife, particularly in lower SES households[62,132,133]. This may translate to women experiencing fears for their safety in their home environments, which may further impair their sleep. Mellman et al. (2018) found that women exposed to violence also experienced more autonomic dysregulation, which may contribute to these sleep difficulties due to elevated levels of arousal and hypervigilance[126].

1.2.5. Sleep and mental health

Sleep and mental health have a well-established bidirectional relationship[134–137]. Poor sleep increases the risk for development of mental disorders (most significantly anxiety, depression, and PTSD) while sleep complaints are a hallmark feature of most mental disorders[81,134,135,138–144]. Poor sleep also worsens the symptoms of these disorders[139,140,143] and can contribute to development of insomnia. Individuals with PTSD, for example, have been shown to have decreased sleep depth and more fragmented sleep compared to those without PTSD[142]. Major

depression and generalised anxiety are also both characterised by disruptions in sleep continuity[145].

Mood- and anxiety-related disorders in individuals with poor sleep are also more likely to remain intractable to treatment and such individuals are more likely to relapse post-recovery compared to individuals without sleep complaints[138,146]. A recent meta-analysis of randomised control trials designed to improve sleep (largely using cognitive behavioural therapy for insomnia; CBT-I) found that improving sleep quality has a direct dose-response effect on improving symptoms of depression, anxiety and stress. Sleep improvements were quantified using either: global sleep quality measures (like the PSQI), disorder-specific measures assessing sleep continuity and daily impact (such as the ISI), or composite scores of self-reported sleep continuity measures (combining metrics like sleep onset latency and wake after sleep onset). This meta-analysis found that studies that showed greater effect sizes of the intervention on sleep quality paralleled greater effect sizes on mental health symptoms. Specifically, greater improvements in sleep quality led to greater improvements in mental health outcomes, further emphasizing the causal relationship between sleep and mental health[147]. This also highlights sleep as a potential point of intervention for under-resourced communities with limited access to mental health support. While the exact mechanism underpinning this relationship remains unclear, and is likely multifactorial, the current evidence suggests that altered patterns of arousal and fragmented REM sleep may play a role[73]. Given the roles of SES and gender in risk for both poor quality sleep and mental disorders, these also need to be considered when investigating the comorbidity of sleep and mental disorders.

1.3. Fear and chronic stress

As outlined above, low SES environments are frequently associated with high rates of crime and violence. It, therefore, seems plausible that residents in low SES communities may experience chronic stress through persistent feelings of fear for their safety. Previous studies on fear of safety or fear of crime confirm this, with both being associated with low socioeconomic status, specifically with poorer perceived quality neighbourhoods and housing[148–150]. While fear of not being safe and fear of crime are two separate constructs, they are closely related. Fear of not being safe has also been implicated as a determinant of

physical and mental health with fears related to safety associated with poorer physical and mental health outcomes (general self-rated health and psychological distress respectively)[148,150]. This may be one mediating factor linking socioeconomic status with poorer health outcomes, particularly mental health disorders.

1.3.1. Sleep and fear

Fear of sleep is distinct but related to fear of crime or not being safe. Fear of sleep refers to the dread or anxiety around falling asleep which can stem from various causes, including previous traumatic experiences related to sleep, such as sleep paralysis, or concern about loss of alertness or control while unconscious[3,123,124]. Individuals with fear of sleep may worry about potential dangers occurring while they sleep or may feel a heightened sense of vulnerability as they drift off. This may then interfere with an individuals' ability to relax, let their guard down and fall asleep or remain asleep[3].

Sleep and fear appear to have a bidirectional relationship: fears fragment sleep, and disrupted sleep subsequently reinforces and intensifies fear responses (Figure 1.5). Living in low SES environments increases the likelihood of experiencing trauma [151,152]. Past trauma may directly disturb sleep through nightmares; feelings of not being safe enough to sleep or negative associations between the sleep environment and the past traumatic experiences[3,123,124]. Safety-related fears in turn may either trigger a fear of sleep itself (due to the inherent vulnerability stemming from the loss of alertness and vigilance associated with reduced consciousness) or disrupt sleep directly. Previous research has shown that fear of sleep in individuals who have experienced trauma is associated with insomnia and poorer quality sleep[3,123,153].

Emerging research increasingly emphasizes the critical role of sleep in emotional regulation and emotional reactivity[154,155]. Emotional regulation refers to the ability of individuals to manage and respond to emotional states, while emotional reactivity describes the intensity and speed of emotional responses to stimuli. This critical role of sleep in processing and regulating emotional responses extends to fear-related reactions[156,157].

Thus, compromised sleep quality and increased risk of insomnia in low SES environments may significantly amplify individuals' emotional vulnerability and fear responses[154,155]. Residents in such settings are also more likely to experience traumatic events or persistent safety

concerns, which can affect sleep[3,123,153]. Overall, this creates a cycle whereby fear may impair sleep quality which in turn amplifies emotional reactivity, increasing feelings of fear while dampening the ability to emotionally regulate that fear.

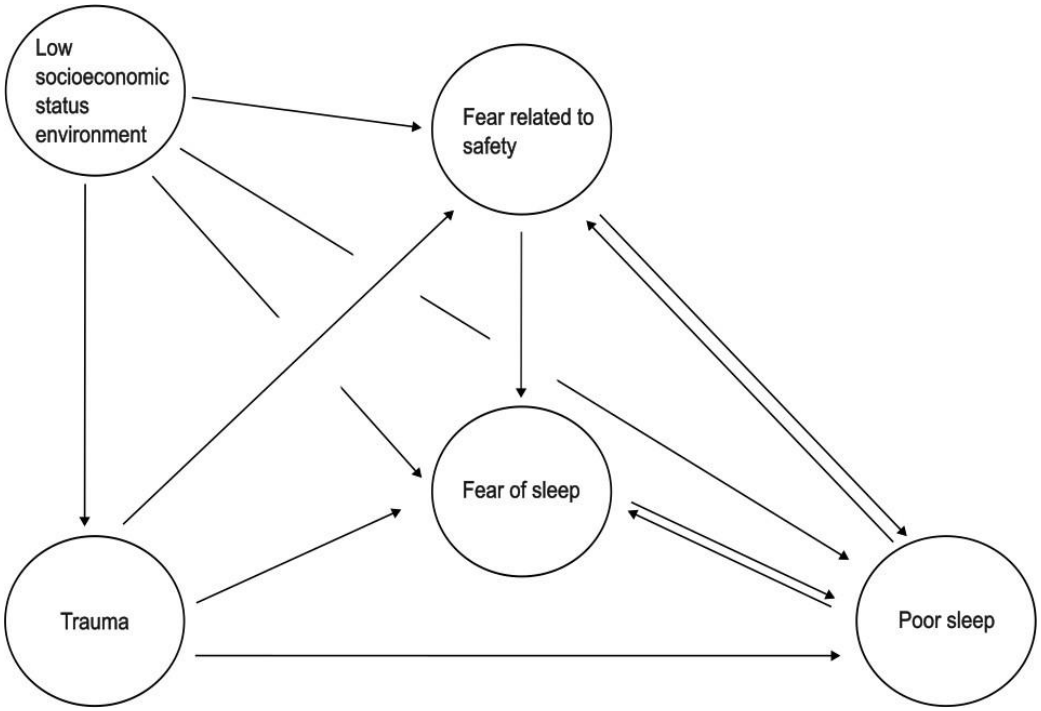

Figure 1.5. Proposed web of relationships between low socioeconomic status environments, fear and sleep. *Living in a low socioeconomic status area increases the likelihood that residents experience trauma or fears related to safety, which may in turn i) lead to fear of sleep (and the associated vulnerability) or ii) disrupt sleep. Arrows represent proposed relationships based on previous research outlined in this introduction.*

1.4. Heart rate variability

Heightened fear responses may impair sleep by creating a state of hyperarousal[158]. Hyperarousal is understood to be heightened sensitivity to stimuli, characterised by physiological and psychological symptoms such as raised alertness, increased anxiety, elevated heart rate, and faster respiration reflecting autonomic dysregulation and excessive sympathetic activity[6]. Given the link between the autonomic nervous system and cardiovascular modulation, heart rate variability (HRV) has previously been used as an index

of sympathetic and parasympathetic input. As such, this thesis will include HRV as an indication of autonomic function, specifically as a measure of potential hyperarousal.

The autonomic nervous system (ANS) is divided into two branches: the sympathetic nervous system (SNS; amongst others, effects our fight-or-flight response) and the parasympathetic nervous system (PNS; amongst others effects our rest-and-digest response). Alteration of ANS balance to predominantly sympathetic activity has been associated with various mood- and anxiety-related disorders and with objectively measured poor sleep which are frequently co-morbid[159]. For this thesis, we will be using HRV as a method of indirectly assessing sympathovagal activity and hyperarousal given that it is minimally invasive, can be assessed over a prolonged period and allows for more ecologically valid measurement than lab-based measures such as measurement of neurotransmitter levels or sympathetic skin response tests (which measure the changes in skin electrical resistance in response to activation of sweat glands).

HRV is a measure of variability in the time between R-R peaks and is used as an indirect index of ANS activity. These variations reflect the interplay between autonomic neural activity, blood pressure, respiration, hormones and the heart-brain axis[160]. There are various measures of HRV which can be broadly categorised into i) time-domain, ii) frequency-domain and iii) non-linear measures. The time-domain measures include root mean square of successive differences between R-peak to R-peak (R-R) intervals (RMSSD), standard deviation of differences between R-R intervals (SDNN), and percent of differences of adjacent R-R intervals greater than 50msec (pNN50)[161]. Frequency domain measures are derived from spectral power analysis of R-R intervals and provide an index of cardiac ANS regulation. These include very low frequency (VLF; 0.003-0.04 Hz), low frequency (LF; 0.04-0.15 Hz) and high frequency (HF; 0.15-0.4 Hz) power[161]. The physiological basis purported to be driving VLF, LF and HF power measures are afferent vascular rhythms[160], baroreflex-mediated modulation of the heart[162] and the spontaneous breathing rate on heart rate respectively[163] (Figure 1.6). This variation in heart rate linked to the breathing cycle is known as respiratory sinus arrhythmia. While VLF power predominantly reflects sympathetic activity[160] and HF cardiac spectral power reflects only PNS activity[163], LF cardiac spectral power reflects contributions from both the sympathetic and parasympathetic branches of the ANS[160]. HRV is naturally related to heart rate (HR) as the lower the heart rate, the more time between beats which allows for

more variability. This relationship is known as cycle length dependency[160].

Heart rate variability can be assessed across recordings of various lengths, each offering distinct advantages and limitations[161]. The Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology make the following recommendation in their guidelines: "Two types of recordings should be used whenever possible: (a) short-term recordings of 5 min made under physiologically stable conditions processed by frequency-domain methods, and/or (b) nominal 24-h recordings processed by time-domain methods"[161]. Twenty-four-hour recordings, typically obtained through Holter ambulatory monitoring, provide the most comprehensive view of autonomic function across sleep-wake cycles and various daily activities and are relatively stable measures in both apparently healthy and clinical populations[161]. These long-term measurements capture circadian rhythms and allow for analysis of both day and night variations[161]. However, a limitation with 24-hour recordings is that an element of noise is introduced as with ambulatory measurement the environment will differ from person to person and factors such as posture, physical activity or emotional state will influence the ECG[161]. At least 18h of analysable data, which include the whole nocturnal period, are required to be considered a valid analysis as a substantial part of the variation in HRV over 24h is derived from diurnal differences[161]. While time-domain measures are particularly well-suited to this length of recording, frequency domain measures are also acceptable[161].

Short-term measurements (approximately 5 minutes) represent a widely-used compromise between accuracy and practicality, providing sufficient data for frequency domain analyses, able to be carefully controlled under laboratory conditions and can effectively capture acute autonomic responses to specific stimuli or interventions[161]. A standardized recording time also allows for comparisons between studies as HRV increases as recording length increases[161]. For short-term recordings frequency domain measures are preferable to time-domain measures. Ultra-short-term measurements (<5 minutes, often 1-2 minutes) are beginning to be used[164]. While these brief recordings are efficient, their reliability remains debated and these ultra-short recordings may be more susceptible to artifact from variables such as gender than longer recordings[164]. The choice of recording duration thus depends on the specific research questions, required HRV parameters, and practical constraints of the study context.

Low HRV is considered an indicator of pathophysiology given its association with increased risk of mortality, cardiovascular disease, psychiatric disorders and other detrimental health outcomes[159,165–167]. This is true across various ages, sex, populations and recording lengths. When looking at overall mortality, similar hazard ratios are seen across HRV parameters (RMSSD vs SDNN vs HF etc.)[168].

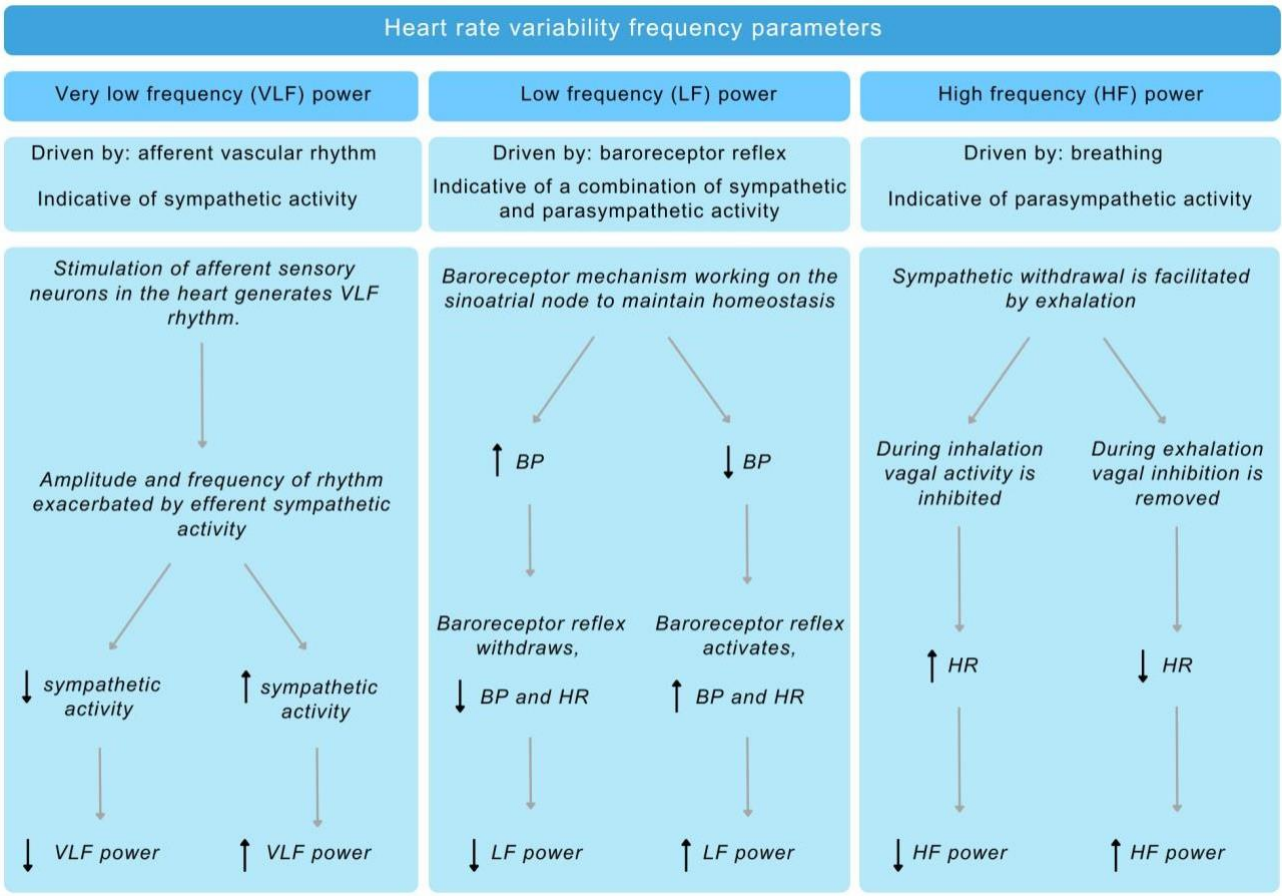

Figure 1.6. Proposed physiological basis for frequency domain parameters of heart rate variability. *BP: blood pressure; HF: high frequency HR: heart rate; LF: low frequency; VLF: very low frequency.*

1.4.1. Diurnal variation in HRV and the effect on sleep

HRV, like many of the body's other processes, is dynamic and has been shown to exhibit circadian rhythmicity[169,170]. During the day, sympathetic activity is expected to be higher than at night, given the movement, eating, and necessity of responding to environmental stimuli that are characteristic of diurnal activities. Meanwhile, at night, parasympathetic activity

should peak[169]. Alteration of this pattern has been associated with various detrimental mental health outcomes[171,172]. Sustained sympathetic activity and/or insufficient rise in parasympathetic activity at night is one proposed mechanism in the development and maintenance of insomnia by creating a state of alertness at odds with initiating or maintaining sleep[173]. Long- term exposure to a stress stimulus could manifest as altered ANS functioning, specifically in the predominance of the sympathetic arm of the ANS system[76,172], impairing HRV rhythmicity. Thus, the stressful settings and hypervigilance towards potential threats experienced by people residing in low SES environments may facilitate a constant state of hyperarousal characterised by low HRV with dampened diurnal variation. The association between hyperarousal of the ANS, sympathetic states, and living in low SES environments has previously been outlined[174].

1.4.2. HRV and mental health

Altered HRV has been consistently associated with mood- and anxiety-related disorders, independent of the effects of the medications to treat these disorders[175]. Individuals with mood- and anxiety-related disorders consistently show lower HRV values than healthy controls, and lower HRV is also associated with more severe symptoms of depression and anxiety[159]. While this is likely in part due to the medications used to treat these disorders, certain antidepressants in particular have shown associations with lower HRV[175], the effect on patients' HRV remains even for non-medicated patients[175]. Lower HRV may explain why mental disorders are often comorbid with both cardiovascular disease and insomnia[176,177].

1.5. Thesis outline

Given the information presented above, this thesis addresses six research questions:

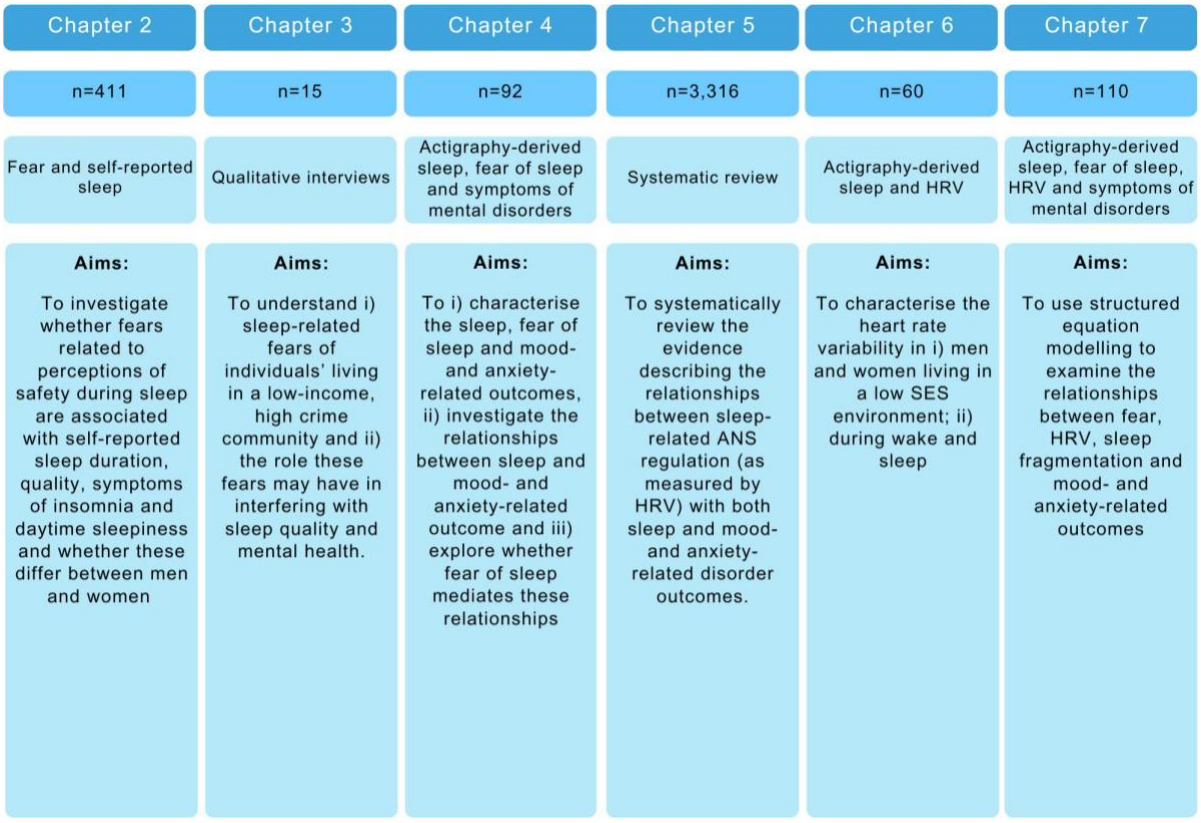

Figure 1.7. Thesis outline by chapter. *ANS: autonomic nervous system, HRV: heart rate variability, PTSD: post-traumatic stress disorder, SES: socioeconomic status.*

1.5.1. Is there an association between fears related to not being safe during sleep and self-reported markers of sleep quality in individuals living in a low SES setting?

Chapter 2 utilised linear and logistic regression models to investigate the relationships between fears related to safety during sleep and markers of sleep quality including self-reported sleep quality, daytime sleepiness and symptoms of insomnia in men and women. As such, this chapter lays the groundwork and provides rationale to focus attention on fear of sleep and sleep characteristics of residents of a low SES community in subsequent chapters.

1.5.2. What fears do individuals living in a low SES, high crime environment have and what are the drivers/consequences of these fears?

One-on-one qualitative interviews were conducted for Chapter 3 to better understand the drivers of fear and the consequences thereof for individuals living in a low SES environment. Since participants shared that fears related to being unsafe during sleep may be linked to poor sleep quality as well as to symptoms of poor mental health, the following chapter aimed to better quantify these relationships. In addition, the emergence of fear-related hypervigilance from multiple interviewees prompted further investigation into the underlying physiology of hypervigilance (as indexed by HRV) in subsequent chapters.

1.5.3. Are there any associations between objectively measured sleep characteristics and symptoms of fear of sleep, depression, anxiety and PTSD?

Chapter 4 builds on the previous chapters by introducing objective sleep measurement in the home environment and by extending the data collected on fear of sleep and symptoms of depression, anxiety and PTSD. Stark gender differences in trauma exposure and mental health outcomes emerged, with associations suggesting that trauma and fear of sleep may contribute to depression, anxiety and PTSD symptoms in South African adults but do not solely explain the disrupted sleep observed.

1.5.4. What are the established associations between measures of HRV and both sleep and mood-/anxiety-related outcomes?

A systematic review was conducted in Chapter 5 to assess the associations between measures of HRV (time and frequency domain variable) and both sleep outcomes (including both quality and duration) and mood-/anxiety-related symptoms (specifically depression, anxiety, PTSD

and stress). The review provides evidence that ANS dysregulation appears to be independently associated with both disordered sleep and mood- and anxiety-related disorders. Specifically, HRV during sleep or just prior to sleep seems to be a promising area in the sleep and mental health relationship. Research modelling the interaction of these factors, however, was noticeably absent and thus Chapter 7 aimed to fill that gap.

1.5.5. Does HRV differ with fear of sleep or sleep quality?

Given the fear-hypervigilance-sleep relationship described by participants in Chapter 3, this chapter aimed to characterise HRV during wake and sleep in this cohort. HRV was used to try and non-invasively assess hypervigilance. Altered autonomic regulation was observed in both women and men with women experiencing lower HRV at night compared to men. Models investigating how this altered autonomic regulation is related to fear, sleep quality and mood- and anxiety-related outcomes are still required.

1.5.6. What role does HRV play in the relationship between sleep and mood-/anxiety-related outcomes?

Structured equation modelling was used in Chapter 7 in women to test the hypotheses that i) trauma exposure (and associated PTSD symptoms in the depression model) will be associated with more fear of sleep, ii) fear of sleep will be directly associated with a smaller changes in HRV between sleep and wake, indicative of sustained sympathetic activity intruding into sleep or diminished parasympathetic activity, iii) damped HRV changes will be directly associated with poorer sleep quality and shorter total sleep time and iv) poorer sleep quality and/or shorter total sleep time will be associated with more severe symptoms of depression and anxiety.

Chapter 2

Fears related to safety during sleep and the associations with sleep duration, sleep quality, daytime sleepiness and symptoms of insomnia.

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2.1. Introduction

In the United States of America (US), an adverse social environment, characterised by high disorder, low safety and low social cohesion has been associated with shorter self-reported sleep duration and higher daytime sleepiness[120]. In contrast, we, and others, have previously shown that South Africans of African-origin living in similar adverse communities self-report long, rather than short, time-in-bed (around 8.75h)[178] and total sleep times (between 8.5-10.0h)[179–182]. Previously, individuals reporting higher perceived neighbourhood safety in the South African setting were less likely to report long sleep[182]. Perhaps fears of being unsafe at night or even anxiety related to past traumatic events erode sleep quality, causing individuals to extend their sleep to compensate.

In South Africa, 24% of the population live in urban townships, characterised by temporary housing which provide individuals with little to no security regarding their residence, usually lack basic services and often have buildings which may not comply with government regulations[60]. Khayelitsha, is one such township, in which 55% of residents live in informal dwellings, 38% are unemployed and nearly 75% earn less than R38,200 ($2,680.32) annually[13]. According to the 2020 South African crime statistics, low socioeconomic status (SES) communities like Khayelitsha have the highest number of contact crimes reported, defined as incidents where victims are subjected to violence or threats of violence including murder or attempted murder, sexual offences, and assault or robbery[14]. In particular, Khayelitsha had the fifth highest number of contact crimes nationwide[14]. It seems plausible that individuals living in such a setting may well experience fears related to personal safety, especially at night when trying to sleep.

South African women may be particularly vulnerable to fears related to personal safety given that they are exposed to high levels of gender-based violence. Most sexual offences occur in the home by perpetrators known by the victim, particularly in low SES communities[132,133]. This may translate to women experiencing fears for their safety in their home environments which may further impair their sleep. In fact, Lipinska and Thomas (2017) found that women in South Africa with post-traumatic stress disorder slept better in an unfamiliar bed at the laboratory due to feeling safer than they do at home[183]. There is also a well-established gender disparity

in the prevalence of insomnia, with women around 1.25-1.41 times more likely to report insomnia than men[43,184,185]. Previous research has shown that this gender disparity can largely be explained by socioeconomic factors with the lower SES of women mediating the gender difference in reported sleep problems[131]. Therefore, in a low SES setting, such as Khayelitsha, risk for poor sleep may be higher among women, since a greater percentage of women live in poverty[186] and are unemployed[187] compared to men. For these reasons, we split our analyses by gender as it seems likely that there may be barriers to sleep which are greater for women compared to men.

We hypothesise that individuals experiencing fear related to safety during sleep will have poorer sleep and that this relationship will be stronger in women compared to men. Therefore, the aims of this study are to investigate whether fears related to perceptions of safety during sleep are associated with self-reported sleep duration, quality, symptoms of insomnia and daytime sleepiness, and to compare these associations between South Africans men and women living in a low SES neighbourhood.

2.2. Methods

2.2.1 Study overview and design

This study is a sub-study of the "Modelling the Epidemiologic Transition Study (METS) – Microbiome", a prospective longitudinal study investigating associations between the gut microbiota, short chain fatty acids, adiposity and risk for cardiometabolic disease in individuals of African-origin from five countries varying by economic development. As protocols for both METS-Microbiome, as well as its parent study, METS,[188,189] have been previously published, we present only methodological information specific to the current analysis. This cross-sectional, observational study made use of the South African participants enrolled in METS-Microbiome. While we obtained demographic and medical history data collected as part of the METS-Microbiome baseline clinic visit (2018-2019), we supplemented data collection by adding in questionnaires to assess sleep and fear, as these were outside the scope of METS-Microbiome. Participants presented to the METS clinic in Khayelitsha, an urban low socioeconomic status informal township in Cape Town. Trained fieldworkers, speaking the home language of the participants, administered questionnaires and made

anthropometric measurements. METS-Microbiome as well as the current study were approved by the University of Cape Town's Faculty of Health Sciences Human Research Ethics Committee (HREC numbers: 696/2018 and 154/2020) and the studies were conducted in accordance with the Declaration of Helsinki[190]. All participants signed informed consent in their home language (English or isiXhosa).

2.2.2 Participants

Data were collected on all 411 participants enrolled in the South African arm of METS-Microbiome. Participants were South African adults of African-origin between the ages of 25 and 50y (n=411, 57% women), living in Khayelitsha. Pregnant or lactating women and individuals with active infections (e.g. HIV, and malaria) were excluded. All participants lived in a combination of formal and semi-formal housing and had been living in Khayelitsha for a minimum of two years. None of the participants in this study were from the same household.

2.2.3 Questionnaire data

Demographic, medical history and lifestyle information were obtained from the METS-Microbiome questionnaires[188,189]. Participants provided markers of SES status, including highest education level achieved (no formal education, primary school, secondary school, tertiary education), employment status (assessed by the question "Did you do any work for pay in the last month?"), and housing density (assessed by the question "How many people are part of this household, including yourself? The household is defined as people who regularly live and eat together and sleep in the house on at least 4 nights of the week"). Participants indicated whether or not they suffered from any chronic diseases and used any chronic medication. Smoking status was categorized as current smoker, ex-smoker, occasional smoker and non-user ("Never smoked regularly). Given the small number of individuals in the occasional smokers group, this group was combined with the current smokers group. Current alcohol use (units per week) was also recorded.

Additional measurements collected specifically for this study include the following: the Epworth Sleepiness Scale (ESS)[108], the Pittsburgh Sleep Quality Index (PSQI)[107] and the Insomnia Severity Index (ISI)[109], which were used to quantify daytime sleepiness, sleep quality

and insomnia symptom severity, respectively. The ESS is comprised of 8 questions that are summed to obtain a total score (0-24), with higher scores indicating greater levels of daytime sleepiness[108]. Scores above 10 are indicative of excessive daytime sleepiness. The PSQI contains 19 questions, the scores of which are summed for a global score. A cut-point of >5 is used to denote poor sleep quality[107]. Bedtime, wake-up time, sleep onset latency and total sleep time (TST) were obtained directly from the PSQI. Time-in-bed (TIB) was calculated as the difference between bedtime and wake-up time reported in the PSQI. The PSQI subcomponent categorical scores for sleep disturbances (None, Slight, Moderate, Severe) and daytime dysfunction (None, Slight, Moderate, Severe) were also used in these analyses. Finally, the ISI is a 7-item questionnaire assessing the nature, severity, and impact of insomnia. It evaluates 7 dimensions over the "last month" using a 5-point Likert scale yielding a total score ranging from 0-28. Scores above 14 indicate clinically significant insomnia symptoms[109]. We used a customised questionnaire adapted from the Fear of Sleep Inventory[191] to investigate perceptions of safety during sleep. Participants were asked to indicate (Yes/No) whether any of the following scenarios normally made it difficult for them to either fall asleep or stay asleep at night: "Fear of not being safe while asleep", "Fear of being attacked while asleep", "Fear of falling asleep", "Being awakened by strange noises out of sleep", "Dreams about past traumatic experiences" and "Sleeping with the light on to feel safe". This questionnaire is presented in Appendix 2.1. Cronbach's alpha and factor analyses were done to assess the most appropriate way to analyse the fear of sleep questions. We analysed each question individually as the Cronbach alpha score (alpha=0.60) was deemed unacceptable, indicating it would be inappropriate to create a composite score from the questions. Therefore, each of the fear items were treated individually as binary variables.

2.2.4 Anthropometrics

Trained fieldworkers measured the height (m) to the nearest 0.1cm and weight (kg) to the nearest 0.5kg. Body mass index (BMI) was calculated (kg/m^2) and participants were classified as normal weight (BMI $<25kg/m^2$), overweight (BMI $\geq 25kg/m^2$ and $<30kg/m^2$) or obese (BMI $\geq 30kg/m^2$).

2.2.5 Data and statistical analysis

All data were analysed using Stata (v.13, StataCorp LLC, College Station, TX, US) and a value of $p<0.050$ was deemed statistically significant. Data are presented as mean and standard deviation, median and interquartile range or count (percentage). Normality was assessed using the Shapiro-Wilk test. Between group comparisons were made using independent t-tests, Mann-Whitney U, Chi-squared or Fisher's exact tests.

Logistic regression analyses were used to assess associations between self-report measures of TIB, TST, daytime sleepiness, sleep quality, insomnia symptom severity and daytime dysfunction (dependent variables) and the fear-related items (independent variables) stratified by gender. Given the focus on long sleep in this cohort, TIB and TST were dichotomized into short/normal ($\leq$9h) and long ($>9\mathrm{h}$). Age was included as a covariate in all analyses *a priori* and we used univariate analyses to identify other covariates (BMI, smoking status, alcohol consumption, household density, presence of young children, annual household income, employment status and level of education) for each model (Appendices 2.2 and 2.3 for the men and women, respectively). Identified covariates with a significance level of $p<0.150$ were included in each model.

2.3. Results

2.3.1 Demographic, sleep and fear characteristics

The descriptive characteristics of the men and women are presented in Table 2.1. Women had a higher BMI ($p<0.001$), were less likely to be employed ($p<0.001$), lived in households with more people ($p=0.002$), were less likely to be smokers ($p<0.001$) and consumed less alcohol ($p<0.001$) than men.

Table 2.1: Descriptive characteristics of participants.

	Women (n=234)	**Men (n=177)**	**p-value**
Age (y)	34 [29-42]	36 [31-42]	0.191
BMI ($kg.m^{-2}$)	32.71 [26.70-38.21]	21.44 [19.39-24.22]	**<0.001**

Chronic disease (count, %)	60 (25.6)	37 (20.8)	0.251
Employed (count, %)	69 (29.6)	94 (53.4)	**<0.001**
Highest degree of formal education (count, %)			0.239
None	2 (0.9)	3 (1.7)	
Primary	142 (60.9)	110 (62.5)	
Secondary	75 (32.2)	47 (26.6)	
Tertiary	14 (6.0)	16 (9.0)	
Household density (people per house)	5 [3-6]	4 [2-5]	**0.002**
Presence of young children (count, %)	187 (79.4)	88 (50.0)	**<0.001**
Under 2 years old	57 (24.5) *	20 (11.4) *	
Between 3 and 15 years old	171 (73.4) *	83 (47.2) *	
Smoking (count, %)			**<0.001**
Non-smoker	187 (79.9) *	38 (21.9) *	
Smoker	42 (18.0) *	128 (71.9) *	
Ex-smoker	5 (2.1) *	11 (6.2) *	
Alcohol consumption (standard drinks per week)	0 [0-7]	16 [0-36]	**<0.001**

Data are presented as median [interquartile range] or count (percentage). P-values were determined using Mann-Whitney U and Chi-squared tests. BMI: body mass index. * *indicate post hoc differences between men and women determined using Fisher's exact tests.*

Self-reported sleep characteristics are presented in Table 2.2. Mean time-in-bed reported by both men and women was longer than 9h, with roughly a third of participants reporting poor sleep quality (PSQI>5) and excessive daytime sleepiness (ESS>10). Men reported longer sleep onset latencies than women (p=0.013). PSQI sub-component distributions for sleep disturbances and daytime dysfunction are displayed in Figure 2.1. The distribution of sleep disturbance severity differed between men and women, with more women reporting moderate (men: 31.3% vs women: 47.9%, p=0.001) and more men reported slight (men: 61.4% vs women: 47.0%, p=0.003) sleep disturbances. The distribution of daytime dysfunction related to sleep was similar between men and women, with roughly half reporting some degree of daytime dysfunction (men: 46.0% vs women: 53.4%, p=0.245).

Table 2.2: Self-reported sleep characteristics of participants.

	Women (n=234)	**Men (n=177)**	**p-value**
PSQI bedtime (hh:mm)	21:30 [21:00-22:00]	22:00 [21:00-22:00]	0.579
PSQI wake-up time (hh:mm)	7:00 [6:00 – 8:00]	7:00 [6:00 – 8:00]	0.951
PSQI sleep onset latency (min)	20 [10-30]	30 [15-30]	**0.013**
PSQI time-in-bed (h)	9.31 ± 1.55	9.17 ± 1.65	0.376
<7h	9 (3.9)	11 (6.3)	
7-9h	109 (46.8)	84 (47.7)	0.492
>9h	115 (49.4)	81 (46.0)	
PSQI total sleep time (h)	8.79 ± 1.53	8.53 ± 1.61	0.138
<7h	22 (9.4)	26 (14.7)	
7-9h	120 (51.3)	95 (53.7)	0.050
>9h	92 (39.3)	56 (31.6)	
PSQI score	4 [3-6]	4 [3-6]	0.513
Poor sleep quality (PSQI >5)	67 (28.6)	53 (30.1)	0.744

ESS score	7 [4-11]	7 [3-10]	0.137
Excessive daytime sleepiness (ESS >10)	80 (34.3)	49 (27.8)	0.162
ISI score	3 [1-6]	2 [1-5]	0.084
Clinically significant insomnia symptoms (ISI >14)	13 (5.6)	9 (5.1)	0.834

Data are presented as mean ± standard deviation, median [interquartile range] or count (percentage). P-values were determined using independent t-tests, Mann-Whitney U and Chi-squared tests ESS: Epworth Sleepiness Scale; ISI: Insomnia Severity Index; PSQI: Pittsburgh Sleep Quality Index

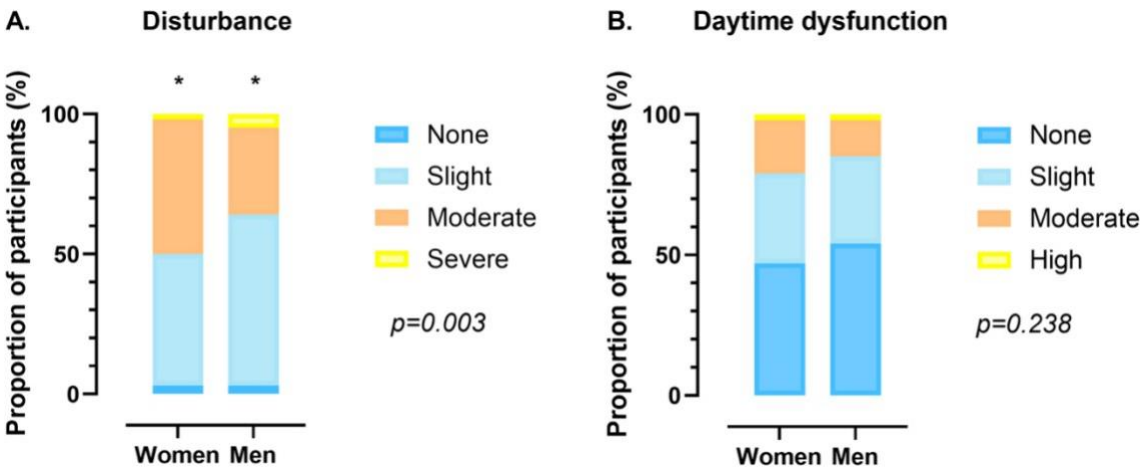

Figure 2.1: The distribution of scores for the PSQI subcomponents: A) disturbance and B) daytime dysfunction in women (n=234) and men (n=177). *Chi-squared tests were used to compare distributions between men and women. * indicate post hoc differences between groups determined using a Fisher's exact test.*

Figure 2.2 presents participant responses to the fear of sleep questions. Among both men and women, the most common fear response was "Being awakened by strange noises out of sleep". In addition, more women reported "Fear of not being safe during sleep" (p=0.007) as well as "Sleeping with the light on to feel safe" (p=0.001) than men.

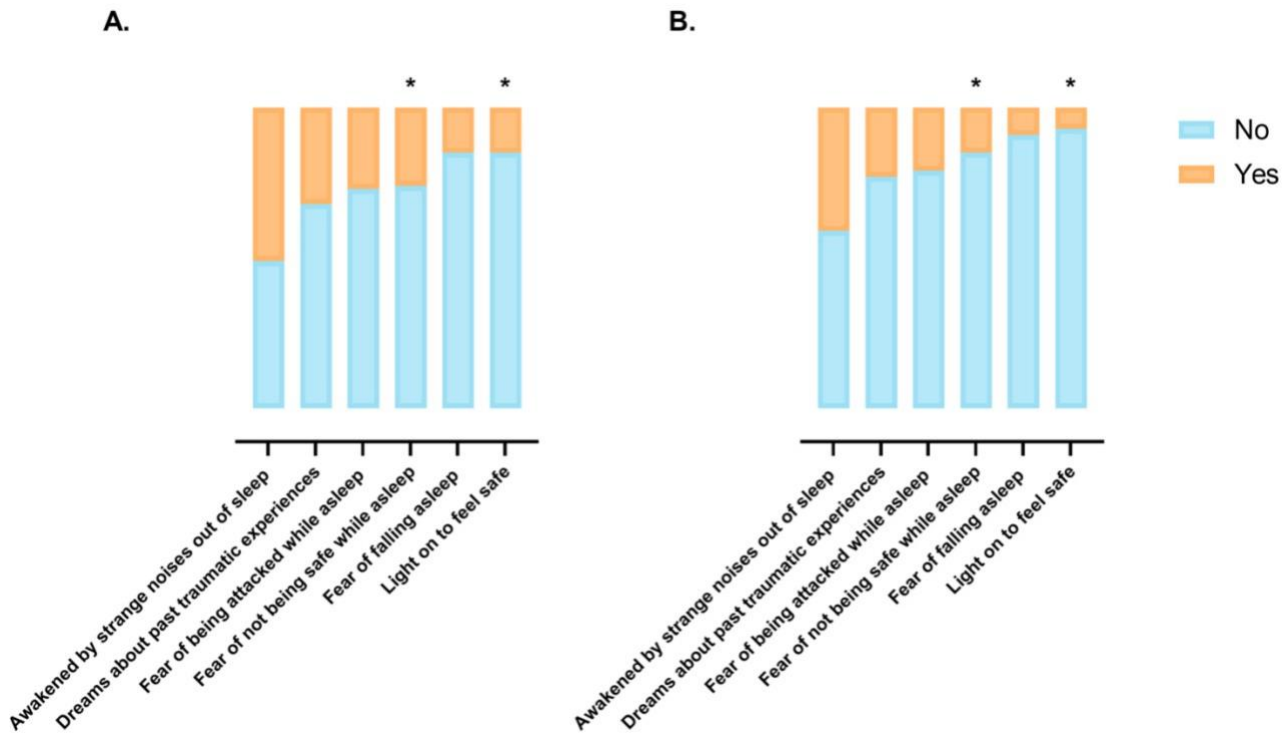

Figure 2.2: The proportion of A) women (n=234) and B) men (n=177) who reported fears related to sleep (Yes) compared to those who reported no fears related to sleep (No). *Data are presented as frequencies. Chi-squared tests were used to compare distribution differences between men and women. * indicate post hoc differences between groups determined using a Fisher's exact test.*

2.3.2 Associations between fear of sleep and sleep characteristics

Men

Among the men, adjusted models show that men who reported "Fear of being attacked during sleep", "Fear of not being safe during sleep", "Fear of falling asleep" and "Sleeping with the light on to feel safe" were more likely to report excessive daytime sleepiness than those who did not report fears related to sleep (Table 2.3). Men who reported any of the fears related to sleep as well as those who were older were more likely to report poor sleep quality. Additionally, "Dreams about past traumatic experiences", "Fear of not being safe while asleep" or "Fear of falling asleep" along with the covariates alcohol consumption and smoking were associated with increased likelihood of moderate to severe symptoms of insomnia. All

fear items (except “Fear of being attacked during sleep”) as well as age, alcohol consumption and smoking were associated with more disturbed sleep. Moderate to severe daytime dysfunction was only associated with the “Fear of falling asleep” fear item. For the time-in-bed models, only age and body mass index showed significant associations with PSQI-derived time-in-bed. Shorter total sleep time was associated with “Fear of not being safe during sleep” and “Sleeping with the light on to feel safe” as well as older age and a higher body mass index.

Table 2.3: Logistic regression model summaries for associations between customised questions around fear related to safety during sleep (independent variable) and self-reported sleep characteristics (dependent variable) in men (n=177)

Fear items	Excessive daytime sleepiness (ESS>10)	Poor sleep quality (PSQI>5)	Clinically significant insomnia symptoms (ISI>14)	PSQI disturbance item	PSQI daytime dysfunction item	PSQI time-in-bed	PSQI total sleep time
"Awakened by strange noises"	1.46 (0.74-2.88), p=0.278	3.24 (1.56-6.70), **p=0.002**	2.68 (0.56-12.94), p=0.218	1.86 (0.98-3.52), p=0.057	1.24 (0.69-2.21), p=0.476	1.87 (0.99-3.52), p=0.052	1.11 (0.60-2.08), p=0.728
"Dreams about past traumatic experiences"	1.60 (0.74-3.45), p=0.231	5.91 (2.51-13.88), **p<0.001**	6.89 (1.38-34.38), **p=0.019**	2.35 (1.15-4.84), **p=0.020**	1.22 (0.62-2.43), p=0.560	1.25 (0.60-2.60), p=0.969	0.90 (0.45-1.81), p=0.771
"Fear of being attacked during sleep"	2.44 (1.13-5.25), **p=0.023**	3.96 (1.73-9.06), **p=0.001**	2.79 (0.61-12.77), p=0.185	3.38 (1.58-7.22), **p=0.002**	1.23 (0.60-2.50), p=0.570	1.21 (0.57-2.56), p=0.619	0.54 (0.26-1.12), p=0.098
"Fear of not being safe during sleep"	2.73 (1.15-6.47), **p=0.023**	9.09 (3.31-24.99), **p<0.001**	6.50 (1.37-30.87), **p=0.019**	7.19 (2.96-17.47), **p<0.001**	2.20 (0.99-4.90), p=0.054	1.04 (0.44-2.47), p=0.931	0.40 (0.17-0.93), **p=0.033**
"Fear of falling asleep"	3.40 (1.17-9.87), **p=0.024**	6.71 (2.10-21.48), **p=0.001**	13.85 (2.22-86.37), **p=0.005**	5.40 (1.83-15.92), **p=0.002**	4.18 (1.53-11.43), **p=0.005**	1.30 (0.44-3.80), p=0.637	0.41 (0.15-1.13), p=0.085
"Sleeping with the light on to feel safe"	5.00 (1.30-19.27), **p=0.019**	4.90 (1.19-20.20), **p=0.028**	3.42 (0.30-38.89), p=0.322	6.33 (1.63-24.56), **p=0.008**	1.59 (0.45-5.67), p=0.471	0.38 (0.10-1.43), p=0.152	0.17 (0.04-0.64), **p=0.009**

Data are presented as odds ratio (95% confidence interval), p-value. Logistic regression models were adjusted for age a priori and then further adjusted for covariates which had a p-value <0.150 in univariate analyses (Appendix 2.2). Additional covariates were as follows: for excessive daytime sleepiness model: body mass index (BMI); for poor sleep quality model: annual household income and level of education; for insomnia symptoms model: smoking, alcohol consumption, presence of young children and household density; for sleep disturbances model: BMI, smoking and alcohol consumption; for the time-in-bed models: employment status and level of education and for total sleep time models: BMI, employment status, smoking and level of education.

Women

Fully adjusted models also show that women who reported fears related to sleep (with the exception of “Sleeping with the light on to feel safe”) were more likely to report excessive daytime sleepiness and poor sleep quality than those not reporting any fear related to sleep (Table 2.4). All fear items (with the exception of “Dreams about past traumatic events” and “Fear of being attacked during sleep”) as well as age were associated with increased likelihood of moderate to severe symptoms of insomnia. Unlike in the men, only one fear item, “Dreams about past traumatic events”, was associated with more disturbed sleep. Finally, while women who report “Fear of not being safe while asleep” and “Fear of being attacked while asleep” were more likely to report longer time-in-bed, those who were employed were less likely to report long time-in-bed. In the models for both time-in-bed and total sleep time, a higher BMI was significantly associated with longer time-in-bed and shorter sleep respectively.

Table 2.4: Logistic regression model summaries for associations between customised questions around fear related to safety during sleep (independent variable) and self-reported sleep characteristics (dependent variable) in women (n=234)

Fear item	Excessive daytime sleepiness (ESS>10)	Poor sleep quality (PSQI>5)	Clinically significant insomnia symptoms (ISI>14)	PSQI disturbance item	PSQI daytime dysfunction item	PSQI time-in-bed	PSQI total sleep time
"Awakened by strange noises"	2.62 (1.45-4.72), **p=0.001**	3.45 (1.82-6.55), **p<0.001**	4.98 (1.04-23.86), **p=0.045**	1.53 (0.92-2.55), p=0.105	1.00 (0.61-1.62), p=0.988	1.36 (0.79-2.33), p=0.261	0.91 (0.54-1.54), p=0.735
"Dreams about past traumatic experiences"	2.05 (1.12-3.74), **p=0.020**	2.18 (1.18-4.05), **p=0.013**	2.44 (0.75-7.97), p=0.140	2.11 (1.21-3.70), **p=0.009**	1.15 (0.68-1.93), p=0.612	1.67 (0.94-2.99), p=0.081	1.13 (0.65-1.99), p=0.661
"Fear of being attacked during sleep"	3.42 (1.81-6.43), **p<0.001**	2.13 (1.12-4.03), **p=0.020**	2.30 (0.70-7.58), p=0.170	1.28 (0.72-2.28), p=0.408	1.15 (0.66-1.98), p=0.627	2.01 (1.12-3.91), **p=0.021**	1.58 (0.86-2.88), p=0.138
"Fear of not being safe during sleep"	2.43 (1.29-4.57), **p=0.006**	3.61 (1.80-6.54), **p<0.001**	3.77 (1.14-12.48), **p=0.030**	1.30 (0.72-2.33), p=0.375	1.29 (0.74-2.25), p=0.365	2.16 (1.14-4.09), **p=0.018**	1.31 (0.71-2.40), p=0.382
"Fear of falling asleep"	3.44 (1.13-5.28), **p=0.023**	3.30 (1.53-7.12), **p=0.002**	3.74 (1.04-13.44), **p=0.043**	1.38 (0.67-2.82), p=0.384	1.25 (0.66-2.37), p=0.488	1.76 (0.82-3.77), p=0.147	0.94 (0.45-1.97), p=0.865
"Sleeping with the light on to feel safe"	1.91 (0.91-4.00), p=0.086	1.57 (0.73-3.37), p=0.246	5.92 (1.54-22.77), **p=0.010**	0.80 (0.40-1.60), p=0.530	0.95 (0.49-1.85), p=0.890	1.11 (0.54-2.29), p=0.776	1.08 (0.54-2.15), p=0.820

Data are presented as odds ratio (95% confidence interval), p-value. Logistic regression models were adjusted for age a priori and then adjusted for covariates which had a p-value <0.150 in univariate analyses (Appendix 2.3). Additional covariates were as follows: for excessive daytime sleepiness model: smoking, alcohol consumption, household density and level of education; for poor sleep quality model: alcohol consumption per week, level of education and presence of young children in the house; for insomnia symptoms model: alcohol consumption and level of education; for the time-in-bed models: BMI, employment status, presence of young children and household density and for the total sleep time models: BMI and employment status

2.4. Discussion

We present sleep quality data from the METS-Microbiome study, in which we explored the relationship between sleep-related fear and self-reported measures of sleep duration and quality as well as daytime sleepiness and dysfunction among South African adults living in a low SES environment. The most commonly reported sleep-related fear item was being awakened by strange noises, followed by dreams of past traumatic experiences, fear of being attacked while asleep and then fear of not being safe while asleep. Our study confirms previous findings indicating longer sleep time and time-in-bed among low-SES South Africans[178–182]. Notably, almost half of our participants spent more than 9h in bed. Accompanying the observed long time-in-bed, approximately half the participants reported some degree of sleep disturbance and daytime dysfunction related to sleep, and about one third reported excessive daytime sleepiness. Thus, despite self-reported long sleep opportunities, participants report disturbed sleep, which in turn may affect their daytime function.

One might hypothesise that in the context of these low SES adults, longer sleep opportunities may be to compensate for poor sleep quality, driven at least partially, by fear for their safety during sleep. Our findings confirm that there is an inverse association between sleep-related fear and sleep quality and that women who reported feeling unsafe during sleep were more likely to report longer sleep opportunities (time-in-bed >9h) but without corresponding longer total sleep times. Furthermore, participants who answered “Yes” to any of the fear- related sleep items were more likely to report more daytime sleepiness, poorer sleep quality and more insomnia-type symptoms than those who feel safe during sleep. The latter finding is similar to previous work by Mellman et al. (2018) which showed that fear of sleep was correlated with insomnia severity[126] in urban African-Americans living in the US. In contrast, however, we did not observe any association between shorter sleep and fear among the METS participants. This may be because METS participants compensated with long sleep opportunities, with very few being classified as short sleepers based either on time-in-bed or total sleep time. Alternatively, the high unemployment rate, leading to a lack of work obligations and subsequently more free time but less expendable income for entertainment, combined with a lack of infrastructure, may help explain why longer sleep durations are only observed in this population but not in urban African-Americans in the US. Thus, in the South

African context, fears regarding safety at night appear to reduce sleep quality, despite a seemingly adequate sleep opportunity. Fears related to safety during sleep may lead to hypervigilance and hyperarousal, increasing sleep disturbances and reducing overall sleep quality. This idea is supported by the same study mentioned above which showed that in a US urban, low SES environment, higher fear of sleep scores correlated with markers of autonomic dysregulation during sleep[126].

While the focus of this study was to explore associations between fear and self-reported sleep parameters, we also observed some of the expected relationships between sleep and covariates, such as age, alcohol consumption, smoking status and BMI[192–195]. Specifically, among the men, independent of the fear items, an older age was associated with poorer sleep quality scores and more disturbed sleep, participants who used alcohol or smoked were more likely to reported moderate to severe insomnia symptoms and smoking, and older participants as well as those with higher BMI's were more likely to report shorter sleep durations. In contrast, among the women older age was associated with increased likelihood of moderate to severe symptoms of insomnia and those with a higher BMI were more likely to report longer time-in-bed but shorter total sleep time, independent of the fear items. Compared to the fear-related items, however, the contributions of these covariates were small, which gives us confidence that over and above these well-documented relationships [192–195], the fear items are still independently related to, and give some additional explanations for poor or short sleep.

Between men and women, we saw both similarities and differences in the associations between fear of sleep and sleep parameters. Answering "Yes" to any of the fear-related items (except "Sleeping with the light on to feel safe") was associated with increased odds for poor quality sleep in both men and women. In women, however, sleep-related fears were also consistently associated with increased odds for excessive daytime sleepiness, while in men the associations were consistently associated with increased risk for more disturbed sleep. While both men and women demonstrated associations between fears related to safety and markers of poor sleep, the associations were stronger among the men, especially for poor sleep quality and disturbed sleep, which was contrary to our hypothesis. This is in contrast to a previous study which found women were more vulnerable to fear-based sleep disruptions and that their autonomic nervous system during sleep may be more sensitive to

environmental stress, especially when that stress was related to exposure to violence[126]. There are several possible reasons underlying our observations. Firstly, it may be linked to methodological differences as the above study by Mellman et al. (2018) used objective sleep measures whereas this study utilized subjective sleep measures, and we investigated the effect of presence or absence of fears related to sleep as opposed to severity of fear symptoms. Alternatively, given South Africa's high prevalence of gender-based violence it is possible that women in this community frequently feel vulnerable and thus potentially have become desensitized to fears related to safety. One might hypothesise that although the level of fear experienced by men and women does not appear to be different during sleep, sleep is disrupted to a lesser extent in the women because of a blunted emotional and/or physiological response to fear-related stimuli. Therefore, they may have a higher threshold for fear-related responses to affect their sleep. Finally, it may be that men feel a societal responsibility to protect their family at night causing a state of alertness to threats which results in a state of hyperarousal unconducive to sleep[196].

This is one of the few studies confirming the relationship between perceptions of safety and sleep outcomes in populations outside of American or European populations. Notably it is the first study to investigate the association between sleep-related fear and sleep quality, daytime sleepiness, and insomnia in South African adults of African-origin. We are aware of only two other studies which have investigated the associations between fear of sleep and insomnia[121,182]. Our study, therefore, extends that research by also including measures of sleep quality and daytime sleepiness. Previous work, including one study in South Africa among 3,854 older (60±12y) adults, has largely looked at associations between perceived neighbourhood safety and self-reported sleep quality whereas we investigated the association between people's feelings of safety in their homes prior to and during sleep with self-reported sleep measures. Although Poindexter et.al. (2022) found that perceptions of the neighbourhood environment were linked to fear of sleep, Simonelli et al. (2014) found that after accounting for feelings of home safety, neighbourhood safety did not impact sleep among adults living in Argentina[197]. These findings indicate that perceptions of the safety of an individual's immediate sleep environment may be more relevant than their neighbourhood safety. Additionally, this is the first study to investigate how the relationship between perceived safety and sleep quality varies between men and women. Our research

highlights the importance of improving community and home safety to allow for better sleep quality, rather than sleep duration, which may have knock-on effects on physical and mental health. Improving sleeping conditions may provide one opportunity of breaking the vicious cycle of poverty and poor health.

Our study is not without limitations, including the exclusive use of self-report data for all the sleep measures. As self-reported total sleep time has consistently been shown to overestimate measured sleep duration[198], the problem may be even more significant than what we have found in this study. Furthermore, the binary "yes/no" outcomes of the fear of sleep questions as opposed to Likert scale answers may limit the sensitivity of this measurement. The binary nature of these variables also limited our ability to conduct a mediation analysis to directly test the relationship between fears related to safety during sleep, sleep quality and long time-in-bed. Additionally, there may be other variables which were not investigated in this study, such as childcare or other societal responsibilities, length of residence in the community, sleep disorders, psychiatric disorders or measures of distress, all of which may influence both the association between fear and sleep and the differences observed between men and women. Thus, qualitative research as well as more detailed demographic, sleep and psychiatric questionnaires in future studies are recommended to provide further insights. Future research including physiological measures such as cortisol level assessment or heart rate variability may also be useful to elucidate whether autonomic dysregulation does underpin the association between fear-related stimuli and markers of poorer sleep. Finally, we acknowledge the cross-sectional study design which prevents us from inferring causality. It may be that poor sleep quality heightens feelings of vulnerability or fear as opposed to the other way around. Subsequent studies should utilise longitudinal data to draw more definitive conclusions about the extent to which fear of sleep impairs sleep quality.

2.5. Conclusion

We present some of the first data outside of the European and American settings showing that African-origin South African adults living in a low-SES, high-crime environment who report fear related to feeling unsafe during sleep experience low-quality sleep accompanied with daytime sleepiness and dysfunction. This may have long-term implications for physical

and mental health outcomes in people already experiencing reduced access to healthcare as a result of living in a low-SES setting[199–203]. Further research to understand i) the lived experiences, drivers and consequences of nocturnal fears related to sleep, ii) habitual sleep characteristics, including objectively measured sleep behaviour, and iii) mental health symptoms, such as past trauma, depression and anxiety, especially as they relate to nocturnal fears around sleep, are warranted. Additionally, further unpacking the sexual dimorphism in the experience and perception of fears related to safety during sleep is necessary.

Chapter 3

A qualitative study to understand sleep-related fears in a low SES, high crime community.

3.1. Introduction

Individuals living in low SES environments consistently exhibit poorer sleep quality compared to those living in higher SES environments[44,115]. The mechanisms through which living in these low SES neighbourhoods disrupt sleep are almost certainly multifactorial, driven by numerous challenges which frequently characterise these communities. These challenges may relate to both the physical environment (e.g. poor ventilation, extreme temperature fluctuations, household density, noise, and inopportune light)[44,116,117,204] and the social environment (e.g. exposure to neighbourhood violence, high crime levels and high neighbourhood disorder)[117,204]. These in turn likely compound the effects of individual-level challenges (e.g. financial stresses and family concerns) on sleep quality.

This presents a social dilemma given that sufficient, good quality sleep is essential for optimal physical and mental health[36,92,134] and the inability to attain healthy sleep may have serious long-term implications for individuals. Low SES areas are known to be associated with poorer long-term health outcomes for residents compared to residents of high SES areas[205] – a relationship that is partially mediated through sleep quality[206]. In fact, 20% of the relationship between perceived neighbourhood quality and health status could be explained by self-reported sleep quality[206].

Given that high rates of crime and violence plague many low SES neighbourhoods, many individuals may fear for their safety, particularly during sleep when they are more vulnerable. Thus, fear owing to low perceived safety, may be one way in which residents in these neighbourhoods experience impaired sleep quality. Previous studies have found that perceived safety significantly influences perceived and actigraphy-derived sleep quality, specifically sleep continuity, but not necessarily duration[197,207–209]. Troxel et al. (2018) reported that residents who perceived their neighbourhood to be safer had higher sleep efficiencies and less wake after sleep onset (WASO)[208]. Similar findings showed that higher counts of violent crime, particularly those in the immediate neighbourhood, were associated with lower ratings of perceived safety and more WASO[209]. This work is largely limited to the Global North[191,208,210,211], with only a handful of studies investigating perceived safety in the Global South[182,197].

Research to date has almost exclusively used quantitative methods to describe the neighbourhood social environment[118] with most studies focusing on the effect of perceived neighbourhood safety, exposure to neighbourhood violence or objective crime metrics[197] on sleep. Neighbourhood safety and exposure to violence are usually assessed in the form of one or two questions such as: "How safe do you feel when walking down your street alone after dark?" or "In general, how safe from crime and violence do you feel when you are alone at home?"[182]. While these questions have highlighted a link between perceived safety and sleep, we still have limited understanding of how feelings of safety—or lack thereof—influence sleep patterns. In particular, we know little about how people experience and cope with fears specifically related to safety and sleeping at night.

Perceived safety is a particularly relevant topic for South Africa, which has one of the highest crime rates in the world, currently ranked seventh globally for organised crime[212]. South Africa is also marked by large socioeconomic disparities, with roughly 63% of individuals living below the poverty line (about $55.23 income/person/month)[213,214]. Official census numbers estimate that 8.1-24.4% of the population live in townships[215–217], neighbourhoods characterised by poverty, informal housing and high crime rates.

Both low perceived safety, and poor quality sleep have implications for mental health outcomes. Poor sleep quality increases the risk for, and severity of, mood- and anxiety-related disorders while sleep disturbances are a hallmark and key symptom of mood- and anxiety-related disorders[140,141,177,218]. Meanwhile, low perceived neighbourhood safety has previously been linked to more severe symptoms of depression[219,220]. Thus individuals living in low SES areas characterised by high crime rates and violence[221,222], may face increased risk for mood- and anxiety-related disorders stemming, in part from low perceived safety and poor sleep quality, both independently undermining an individual's mental health.

In Chapter 2 it was shown that fears related to not feeling safe during sleep are prevalent among the inhabitants of Khayelitsha and that the presence of these fears was linked to poorer sleep quality[223]. As such, the purpose of this study is to use a qualitative approach to understand i) fears related to safety in individuals' living in a low SES, high crime community and ii) the role these fears may have on sleep quality and mental health.

3.2. Methods

3.2.1 Study design and approach

This study made use of a qualitative research design, based on semi-structured interviews conducted with residents living in Khayelitsha, South Africa. This is a low SES community, characterised by high-density temporary and informal housing, high rates of crime and unemployment[14,130]. Given our prior findings that fear of not feeling safe during sleep is widely prevalent and associated with poorer sleep quality, we wanted to better understand these fears, including what drives feelings of fear and the consequences thereof. As such, we designed an interview guide, covering four main areas: 1) the physical sleep environment, 2) safety, 3) the neighbourhood environment and 4) attitudes and understandings about sleep. Since this full interview is part of a larger study, only any themes related to safety and fear are explored here.

The interviews were conducted in the home language of participants, by an isiXhosa-speaking field worker. Although trained and experienced in qualitative data collection methods, they received additional training in interview techniques, such as active listening and maintaining neutrality. The field worker had no prior relationship with the participants, to minimize bias and ensure the confidentiality of responses, but lived in the same area, to maximise cultural sensitivity, effective communication and rapport building during the interviews. The home language of the participants was used to ensure responses were fluent and detailed. Interviews took place at the Health through Physical Activity, Lifestyle and Sport Research Centre at the University of Cape Town, as opposed to participants homes, to protect the privacy of individuals and to encourage them to speak freely without censoring themselves in the presence of other household members. An individual interview approach was chosen to ensure the participants felt comfortable answering questions, some of which were sensitive in nature around mental health and past trauma. Ethical approval for this study was obtained from the University of Cape Town's Faculty of Health Sciences Human Research Ethics Committee (HREC number: 154/2020). All participants provided written informed consent and this study was conducted in accordance with the Declaration of Helsinki[190].

3.2.2 Participants

Fifteen isiXhosa-speaking adults from Khayelitsha (29-52y, 53% women, 73% unemployed, all

high school educated) took part in this study. Participants were recruited from the South African cohort of a large five country study known as "Modelling the Epidemiologic Transition Study (METS) – Sleep". METS-Sleep extended the previously described METS-Microbiome study[189], to investigate associations between sleep and meal timing with risk for cardiometabolic disease in individuals of African-origin living in Ghana, South Africa, Jamaica, Seychelles and the US. While METS-Sleep did include self-reported and objective sleep measures across all five sites, it had no qualitative component. Thus, for this thesis chapter, no variables from the METS-Sleep study were used; rather we just recruited our participants for the qualitative interviews from the South African METS-Sleep cohort. The decision to interview fifteen participants was based on the homogeneity of participants' experiences such that data saturation was reached at that point[224,225].

3.2.3 Data collection

The interview began with general demographic questions such as, "How long have you lived in Khayelitsha" to encourage participants to feel more comfortable with the interviewer before delving into more open-ended questions (Appendix 3.1). These included: "Please describe any fears associated with going to sleep", "What is your experience of your neighbourhood after 6pm at night?" and "How would you describe the quality of your sleep?". Probe and follow-up questions were employed to elicit detailed responses and to capture a holistic understanding of the participants' perspectives and experiences. All interviews were audio recorded, translated into English and then transcribed by the same fieldworker who conducted the interview to maintain accuracy.

3.2.4 Analysis

Thematic analysis was employed to identify recurrent themes and patterns within the qualitative data212,213. The transcripts were deductively and inductively coded, with the assistance of NVivo (v.14.23.2, Lumivero, Denver, US). Themes were identified and refined through an iterative process involving multiple rounds of review and discussion among the research team. Both ATLC and PEF independently reviewed the interview transcripts and coded the interviews. Discrepancies between codes were discussed, revised and resolved.

3.2.5 Trustworthiness

A subset of the interviews were subsequently also coded by DER to assess intercoder reliability. Direct quotations were incorporated into the analysis to support and illustrate key findings, promoting transparency and authenticity. Confidentiality and anonymity were maintained throughout the study, with deidentified participant numbers used to protect participants' identities. Method triangulation was employed in this study by incorporating multiple data sources, including participant observations and interviewer field notes, while investigator triangulation was achieved through participation of multiple researchers (ATLC, PEF, DER and MD) in devising the interview questions and in discussing and analysing the data, collectively enriching the depth and breadth of the analysis[228]. Given that the researchers analysing the data (ATLC and PEF) are from outside the Khayelitsha community, it was important to reflect on potential biases. ATLC, PEF and DER were regularly involved in collection of quantitative data within this community and as such had some first-hand knowledge of living conditions and challenges experienced by participants. By regularly engaging in rigorous peer questioning to scrutinize the conclusions drawn and their alignment with the collected data, the researchers critically evaluated their interpretations, thereby reducing the influence of preconceptions or external biases.

3.3. Results

Four overarching themes, with subthemes listed in brackets, were identified from the interviews: i) Contributors to fear (suboptimal living conditions, excessive crime and violence, personal and community trauma, and lack of community trust); ii) Consequences of feeling fearful (symptoms of hypervigilance and disturbed sleep); iii) Responses to feelings of fear (adaptive behaviours and resignation) and iv) Poor mental health outcomes. The subthemes appear to be driven by various environmental factors (Figure 3.1). In this context, fears were found to be almost exclusively related to lack of safety, particularly at night and even when individuals are inside their homes, including fears that family members would be hurt due to danger in the neighbourhood. Participants describe persistent fear throughout their daily lives, with daytime experiences of crime, violence, and general unsafety creating an atmosphere of anticipated danger that intensified during nighttime hours and extended to fears of not being safe during sleep. As such, fear and safety appear to be inextricably linked in this context. It is also worth noting that women were more emotional when describing their

fears and experiences, were more detailed in their interview answers, and perceived their area to be less safe than men.

> *"You constantly are in fear if you live there."* – P2 (female, 41y)
>
> *"You might die anytime in that place … I am unsafe completely."* – P4 (female, 50y)
>
> *"Otherwise, Cape Town generally in informal settlements there is no safety."* – P14 (male, 38y)

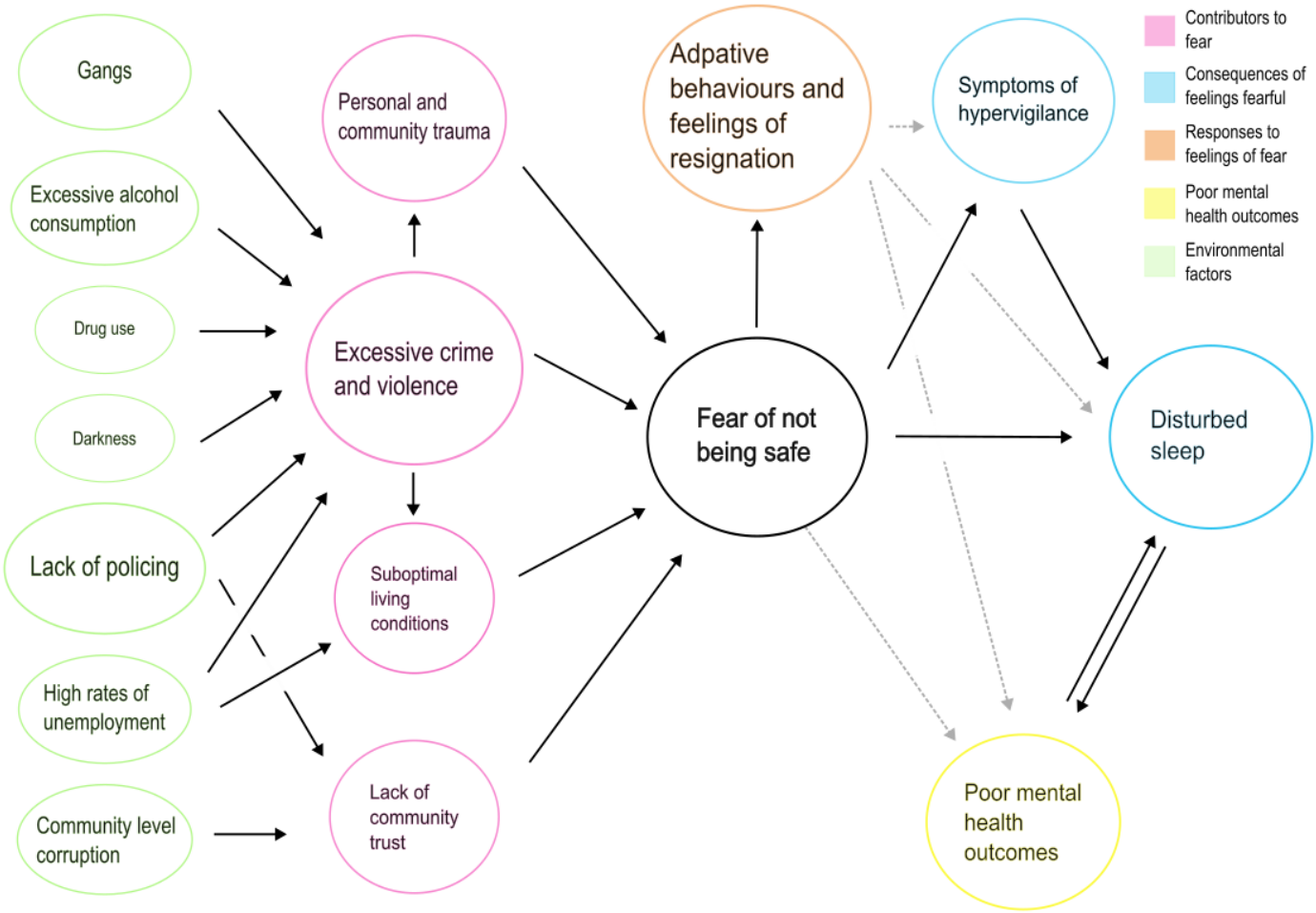

Figure 3.1: Overview of the relationships between environmental factors and various subthemes. *Size indicates relative frequency with which that particular concept was mentioned. Colours indicate the theme to which a particular subtheme belongs. Solid black arrows indicate relationships which are understood to directly contribute to a particular subtheme as described by participants. Dotted grey arrows indicate possible relationships between subthemes, but where the effect is unclear or varies.*

3.3.1. Contributors to fear

3.3.1.1. Excessive crime and violence

Khayelitsha, as described by all participants, is characterised by high neighbourhood disorder, including gang activity, drinking and drunk behaviour in the streets, drug-dealing, conflict and low social cohesion (lack of trust amongst neighbours), which cultivates high levels of crime and violence. Crime and violence are the root of almost all of the participants' feelings of fear and lack of perceived safety. These participants rely solely on public transport and walking to get to work, shops or to visit friends and family. Concerns about being attacked/robbed while commuting were voiced by the majority of participants. More than half said they felt unsafe because of shootings in their neighbourhoods. According to many participants, they are more fearful of leaving their house when it is dark and on the weekend when there is more drinking, given the associated increase in crime.

"*Our environment is not good at all especially now that its winter and it gets dark earlier than it is in summer because there are these boys that are doing criminal activities by robbing people.*" – P7 (female, 50y)

"There is always noise that is unbearable, shooting and every other chaos that is there… there isn't much joy and happiness living in the area." – P8 (male, 52y)

The perceived ineffectiveness of the South African Police Service (SAPS) was raised by almost all participants as a barrier to feeling safe in their homes in the evenings. Only one participant described SAPS officers as quick to respond and helpful. Two main issues repeatedly raised were i) SAPS taking too long to respond and ii) SAPS officers themselves being afraid for their own safety in this neighbourhood.

"*SAPS only respond when it's too late and there is no help at all that they provide.*" – P4 (female, 50y)

"*Even though when we call them at a time of need they arrive after some time. Even if you were to die they would probably arrive after you've died*." – P7 (female, 50y)

"At the moment I trust my partner not anyone else because SAPS is also scared of that area." – P1 (female, 45y)

One participant also expressed dissatisfaction with the government's response to safety concerns, stating "*We feel that our government is very ignorant and not considerate of us because this has been reported several times.*" – P8 (male, 52y)

3.3.1.2. Personal and community trauma

Often closely linked to the excessive crime and violence in the area, many individuals described that past trauma influences their current perceptions of safety and fear. Loss of a close family member (son, brother, or grandmother, etc.) was the most common past trauma described by participants. Three individuals also described past break-ins, two described shootings of members in the community and another described being mugged at knifepoint.

"*If I hear gunshots … these gunshots bring back memories. And if they do happen around then I start thinking heavily.*" – P4 (female, 50y)

3.3.1.3. Suboptimal living conditions

For many participants, living in temporary housing (shacks) was a barrier to safety as the materials used to build these homes (zinc and wood) are not sturdy enough to deter individuals trying to break in or to stop stray bullets from entering the home.

"*Random shooting that's usually happening outside can also be harmful to us because what if you are caught in a crossfire of the bullet penetrates through your walls.*" – P2 (female, 41y)

In addition to the structure of the home, the location also affected perceived safety. Shacks within close proximity to the road, shebeens (an informal establishment which may or may not be licensed, typically in a township, selling alcohol) or abandoned houses present additional safety concerns because of increased foot traffic, including drunk neighbours, or criminals using abandoned houses to ambush individuals and to use or deal drugs. Shacks located in these areas are at increased risk of opportunistic break-ins and robbery. Given the dense arrangement and flammable building materials of shacks, fire is another fear shared by many participants. Fires may start for multiple reasons including: individuals cutting electricity cables to steal the copper and appliances that are left on during loadshedding (scheduled power-outages across the country to reduce electricity demands) and are unattended when

the power comes back.

Many of the interviewees mentioned unemployment as a contributor to lack of safety in the context of their living conditions. Participants had aspects about their home, specifically their sleep environment, that they would like to improve to make it more conducive to safety and/or good sleep, but did not have the financial means to do so. The most commonly mentioned "improvement" was relocating to a better area, but individuals also mentioned building themselves a safer, brick house.

"*Those things [unemployment and money issues] comes to mind now and again when I am trying to sleep at night. Just wondering how life could have been if all was well. The house I've longed to have of my own and a proper one and so forth.*" – P6 (male, 43y)

3.3.1.4. Lack of community trust

There were a variety of responses regarding trust in the community. For about half of the individuals, trust in the community was undermined by the perception that community leaders themselves were involved in criminal activities or trying to protect perpetrators who are relatives or neighbours. The ineffectual policing adds to this lack of trust, as participants describe having no-one to rely on.

"*We have no trust in anything. Even when you are crying out loud for help when they kick down your door, no one really comes out because everyone is scared."* – P11 (male, 29y)

On the other hand, the remainder of the participants who did trust their neighbours and their wider community tended to perceive their area as being safer. This trust appeared to stem from the community taking action against crime or other concerns in the area. Individuals who trusted their community described community watches, patrols and the community eliminating drug trade or recovering stolen property.

"*There are people who at least are trying to patrol the area who volunteered to watch the area even though they don't have means and rights resources for safety keeping… We trust each other as the community because once there is a cry we all come out*." – P5 (male, 45y)

3.3.2. Consequences of feeling fearful

3.3.2.1. Symptoms of hypervigilance, anxiety and disturbed sleep

Numerous participants conveyed symptoms indicative of hypervigilance, characterised by an enhanced awareness of potential threats, particularly during nocturnal hours. In particular, many participants described a pervasive sense of apprehension, constantly monitoring their surroundings and concerns about the safety of their environment at night. This state of hypervigilance is compounded by the suboptimal living conditions experienced by most individuals, given the vulnerability to external dangers such as shootings or break-ins. Personal experiences of past traumas, such as home invasions, also appear to exacerbate these symptoms of hypervigilance and anxiety, leading to disturbances in sleep patterns and persistent feelings of paranoia.

> *"So you just sit in anticipation of anything as a result you are constantly on your guard and live in fear."* – P4 (female, 50y)
>
> *"I am always on my guard"* – P8 (male, 52y)
>
> "*I barely sleep peaceful because any kind of movement or slight noise I wake up and always thinking what if it is them [the robbers] again.*" – P13 (male, 38y)

Participants described these symptoms of hypervigilance eroding their sleep quality: finding it difficult to fall asleep, being easily disturbed and waking up frequently. The sound of gunshots or whistles from their neighbours (alerting them to suspicious activity) awakens many of the participants during the night and they struggle to fall asleep afterwards. These sleep difficulties are directly related to the environment as many participants describe their sleep problems getting worse as the crime and violence in the neighbourhood has increased. When probed about anything that makes it difficult for them to sleep currently, only one participant said that they have no difficulties sleeping.

"*So sometimes even when you hear mouse footsteps you do not rest because you aren't aware what or where the noise is coming from. So you hardly sleep thoroughly.*" – P3 (female, 45y)
"Sometimes you are trying to sleep, and you hear gunshots from outside and from there it's difficult to go to sleep." – P7 (female, 50y)

3.3.3. Responses to feelings of fear

3.3.3.1. Adaptive behaviours

Under this chronic threat of danger, participants developed various adaptive behaviours to try and mitigate these safety concerns, although in most cases these strategies made no discernible difference to individuals' perceived safety. These included: i) securing their homes, ii) social strategies, iii) avoidance and iv) vigilance. Almost all participants secure their homes with security gates and locked doors but three participants also described barricading their front door with furniture and another described keeping weapons for protection.

Most participants described some sort of social strategy to improve their neighbourhood safety including community patrols and "whistle-blower" initiatives - where everyone on the street gets a whistle and watches out for any suspicious activity to alert others. A few participants also described befriending the criminals in the area to deter them from being targeted and to have their homes protected. Avoidance encompasses staying indoors after dark and restricting their children's movements to avoid areas where there may be criminals or shootings. One woman chose to send her children to live in her more rural home village to remove them from the dangerous urban environment, although this had the unintended consequence of exchanging fear for their safety to worry for their well-being. One man used alcohol to avoid ruminating on previous trauma of having his home broken into and to dull feelings of fear so that he is able to sleep, to the point that he can no longer sleep without it. Lastly, while many participants reported disturbed or poor quality sleep linked to the threat of danger, some participants purposefully try to remain awake at night to stay vigilant and guard their families. This is related but separate to the hypervigilance described above as this is a behavioural choice rather than a physiological/psychological response.

"*Each one of us have their own weapon that we hide somewhere in our rooms. One has a hammer and I have an axe in my room.*" – P4 (female, 50y)

"*I would stay awake most of the times and guard my son until the next morning*" – P2 (female, 41y)

"*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.*" – P7 (female, 50y)

3.3.3.2. Feelings of resignation

Finally, most participants seemed resigned to their circumstances. Resignation appears to be another strategy to cope given the systemic nature of the abovementioned challenges and participants' inability to change their environment.

"*Because there is no other place that I can go to so I have to endure."* and *"There is nothing I can do about them so it is what it is.*" – P5 (male, 45y)

3.3.4. Poor mental health consequences

Most participants described feelings of stress and anxiety or of lingering responses to trauma which make it difficult to sleep. Some of these poor mental health outcomes were related to fear (particularly due to past traumas or worry for family) but for many individuals their stress or anxiety was related to financial concerns. As such, poor mental health outcomes emerged as a separate, but interacting, theme to consequences of fear. All participants who mentioned experiencing past traumas described current distress related to the trauma (frequently triggered by cues such as gunshots) and subsequent trouble sleeping. Only one participant mentioned receiving any form of psychiatric treatment to address severe depression. Another mentioned planning to seek free counselling but for all other participants there was no mention of any sort of support, professional or social, to address symptoms of depression or anxiety. Almost half of the participants struggled to sleep because of stress related to current unemployment/financial concerns and concern about not being able to purchase essential goods.

"My experience of the break-in made things worse and I can no longer sleep the way I did in the past." – P3 (female, 45y)

"I don't think we have enough finances to be able to do everything necessary to do at home and it's causing anxiety that results in my sleeping pattern being affected." – P4 (female, 50y)

"*Those things [unemployment and money issues] comes to mind now and again when I am trying to sleep at night. Just wondering how life could have been if all was well. The house I've longed to have of my own and a proper one and so forth.*" – P6 (male, 43y)

"The only thing that has caused me anxiety and lack of sleep was the passing of my close cousin but I am okay now." – P15 (female, 30y)

Participants did not spontaneously discuss their perception of sleep's effect on mental health, however, when probed all participants acknowledged that they thought sleep had some impact on mental health, functioning and mood.

Overall, most participants generally believed that sleep could affect mental health, although many participants discussed this as an abstract concept rather than as their own experience (using distancing language such as "you" and "your" as opposed to "I").

"When you don't sleep you can't really think straight and your mind can't function well." – P5 (male, 45y)

"It [lack of sleep] might affect you. You end up having stress which might lead also to depression. Sleep is very important" and "it does cause something in your spirit, just not being happy and you constantly are feeling moody and you feel down" – P7 (female, 50y)

"…on the days where I don't sleep I think a lot and get carried away with thinking a lot of things and I notice that my brain isn't functioning as it should. Sometimes I feel that I am not well mentally." – P13 (male, 38y)

3.4. Discussion

This study found that residents of a low SES urban neighbourhood, specifically characterised by high levels of crime, face numerous challenges to their perceived safety, which for some,

manifests as fear related to sleep. The findings from this qualitative study help us understand the context behind the reasons individuals may feel unsafe or fearful and how these influence their sleep, mental health and behaviours. One key finding from this study is that while the contributors to fear are multifaceted, they are all inextricably linked to the neighbourhood in which these individuals live and perceptions of not being safe. This is supported by work which showed that in trauma-exposed individuals perceived neighbourhood stress accounted for a similar amount of variance in fears related to sleep as PTSD symptom severity[229].

This fear related to safety during sleep was one of the major factors impairing participants' sleep. A plethora of quantitative evidence has linked low SES environments to shorter, poorer quality sleep when compared to the sleep of individuals in higher SES environments[44,116,121,122]. This is attributable to individual-level challenges (e.g. financial stresses and family concerns) experienced by residents of lower SES communities being compounded by both physical (e.g. inopportune light and noise) and social (e.g. violence, high crime and high social disorder) neighbourhood-level challenges[44]. The effect of these social challenges was highlighted in this study, as the neighbourhood chaos and violence eroded participant's feelings of safety, primarily during sleep when individuals are especially vulnerable and cannot protect themselves from threats in their environment. These fears related to sleep and associated hypervigilance (being alert to potential threats and easily disturbed from sleep) indirectly impaired sleep while the adaptive, watchful behaviours (purposefully staying up throughout the night or waking up regularly to check for potential danger) directly impaired sleep.

Similar results are seen in studies conducted in predominantly African-American populations living in low SES settings utilising objective crime measures, where higher crime rates were associated with lower sleep efficiencies and higher WASO[210,230]. This is likely because in areas with high crime rates individuals are constantly concerned for their safety, as described by our participants, and fear of crime and violence or high social neighbourhood disorder may impair sleep through dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis[117,231] or the autonomic nervous system (ANS)[126,211,232]. Sleep is a time where an individual experiences "perceptual disengagement from and unresponsiveness to the environment", leaving an individual vulnerable to threat[233]. Therefore, these fears may make it difficult to relax sufficiently and withdraw from the environment. As such, instead of parasympathetic activity

dominating at night as one would expect, associated predominantly with sleep onset and deep sleep[169], individuals may still experience sympathetic dominance and heightened arousal which is a key pillar of the hyperarousal model of insomnia[234,235].

To make matters worse, poor sleep quality is exacerbated by sleep-related behaviours that arise in response to fear, worsening the already fear-disturbed sleep many individuals experience. For example, purposefully delaying sleep to remain alert to any threats likely shortens the sleep opportunity and may also contribute to circadian misalignment. Meanwhile, purposefully waking up throughout the night fragments sleep, which has been linked to adverse health consequences including emotional distress and increased risk for mood disorders, hypertension, cardiovascular disease, metabolic diseases and all-cause mortality[39,79] Increased activity of the sympathetic nervous system and HPA axis as well as circadian disruption may be some of the mechanisms underpinning the relationship between sleep fragmentation and poor health[39]. This may mean that the fear-related adaptive behaviours employed by these individuals may compound the effects of the environment as both appear to alter activity of the ANS and HPA axis. This has implications for the physical and mental health of individuals living in low SES environments and may provide further insight into the potential links between living in adverse environments and the associated poorer sleep and mental health outcomes[113,210,230,236].

In this context, the hypervigilance and watchful behaviours described by participants may still be considered adaptive behaviours, despite reducing individuals' quality of life, as the threat (from excessive crime and violence) is ongoing. Therefore, the paradigm of "continuous traumatic stress" (CTS)[237] may be applicable in this environment. Although exposure to trauma, symptoms of hypervigilance, and avoidance are characteristics of PTSD, CTS describes "the experience of living in contexts of realistic current and ongoing danger"[238] rather than symptoms stemming from discrete past events. The findings of this study align closely with a qualitative study that interviewed women suffering from PTSD, living close to the Israeli-Gaza border under constant threat of political violence[239]. Changes in arousal and reactivity, subsequent trouble sleeping, negative changes to mood and cognition and avoidance were similarly described by their participants with a notable absence of flashbacks and nightmares[239]. CTS has been associated with more PTSD and depressive symptoms as well as more sleep disturbances[240], similar to experiences described by our participants.

The major limitation of this study is that, due to language barriers, the researchers who analysed the data did not conduct the interviews, which may have resulted in some nuance being lost. To minimise any loss in meaning the same fieldworker who conducted the interviews also translated the transcripts. Participants in this study were also from a single township neighbourhood. Future research should explore the perceptions and experiences of individuals living in other urban informal settlements and rural settings across South Africa and other Global South countries to determine the extent to which the environmental influences on fear are common to other settings.

3.5. Conclusion

This qualitative study sheds light on the multifaceted challenges faced by residents living in a high-crime, low SES community over and above the typical expected stresses related to unemployment and lack of finances, particularly concerning their perceived safety. Our findings highlight the pervasive influence of the environment on fear (especially at night) and the knock-on effect this fear has on behaviour and sleep quality. Participants report fear of not being safe associated with a state of hypervigilance which disrupts sleep as well as driving behaviours in an effort to cope with these fears for personal safety that further impair sleep quality. Overall, this study reveals how past trauma and deeply embedded fears about safety as well as stress and anxiety related to fear and poverty profoundly shape sleep experiences in low-resource communities. Improving the safety of these communities at the policy level is, therefore, a public health concern. Potential targets for intervention include: housing, strategies to improve the efficacy of the police force and introducing strategic lighting plans.

Chapter 4

Too scared to sleep – the interplay between trauma, fear, sleep and mental health in a low socioeconomic status setting

4.1. Introduction

Sleep and mental health are inextricably linked. Sleep disturbances are a key clinical feature of many mental health disorders including major depression, generalized anxiety and PTSD[2]. Findings from the previous chapter echo this by highlighting the destructive role that past trauma, fear and poverty-related stress and anxiety have on sleep quality of low SES residents. Poor sleep, in turn, increases the risk for developing these disorders[134,136,138,144,176] and may exacerbate the symptoms of these disorders, even in sub-clinical populations[39,139]. Research has shown that poor subjective sleep quality, lower actigraphy-derived sleep efficiency, short and long total sleep time and shorter REM latency are correlated with more severe symptoms of depression[39,145,241]. Likewise, worse subjective sleep quality, shortened sleep, reduced sleep efficiency, longer wake after sleep onset time and less slow-wave sleep are observed in individuals diagnosed with anxiety and PTSD compared to controls[145,242,243].

Previous work suggests the prevalence of depression and anxiety in South Africa is higher than the estimated global averages (depression: 25.7% in South Africa vs 5% globally and anxiety: 17.8% in South Africa vs 4% globally)[47]. Similar results have been seen in other low- to middle-income countries (LMICs). According to a recent review, the prevalence of depression and anxiety in older individuals in LMICs ranges from 0.5% to 62.7% and 0.2% to 32.2% respectively, with the pooled prevalence of depression indicated as 10.5%[26]. Another review also found a high prevalence of depressive and anxiety-related disorders in South Asia, which varied according to age and presence of comorbid conditions[244]. This link between low SES and mental health is in part mediated through sleep disturbances [113] such that low SES is associated with disturbed, poor quality sleep[44,196,245,246] and that disturbed sleep in turn increases the risk for mental health. Within low SES areas, stressors related to poverty/unemployment and environmental factors such as loud noise, excessive light-at-night and high household densities are all potential barriers to healthy sleep[44]. Ultimately, however, it is not only the physical neighbourhood or home environment in low SES communities that can influence sleep, but also perceptions of neighbourhood safety.

This is in line with what was found in the previous chapter, with many participants describing that past traumas, fears related to their safety and the safety of their family during sleep all had the potential to disrupt their sleep through hypervigilance. Residents of neighbourhoods with low perceived safety and low social cohesion have shorter, poorer quality sleep

compared to the sleep of those residing in safe neighbourhoods with high social cohesion[44,197,204]. It may be that individuals who feel unsafe or vulnerable in their neighbourhoods either delay sleep in favour of remaining alert to potential threats or experience hypervigilance throughout the night, both of which could affect both sleep duration and quality[173,235].

Trauma, defined as exposure to distressing events or circumstances that cause severe lasting emotional shock or pain, is a pervasive reality for many in low SES environments. These experiences often stem from violence, chronic stress, or systemic inequities that create a constant sense of insecurity[247]. Trauma not only disrupts psychological well-being but also has physiological consequences, affecting stress-response systems and interfering with the ability to achieve restorative sleep[123]. This is in line with lived experiences recounted by participants in Chapter 3, as many described past break-ins or other traumas making it difficult for them to sleep currently. Thus, in this context, trauma may prompt fears of not being safe, fear of sleep and/or symptoms of anxiety and depression which in turn impair sleep. This would be in line both with what was found in Chapter 2 – that fear of not being safe impairs markers of sleep quality – as well as the literature. Sleep disturbances and insomnia frequently ensue following a traumatic event[3,123,124,248], while poor sleep in turn can amplify trauma-related symptoms such as intrusive thoughts, emotional dysregulation, and heightened arousal[3,123,156,249], creating a feedback loop that heightens the risk for mental health conditions like depression, anxiety, and PTSD.

While anxiety and PTSD are distinct but historically overlapping disorders, it is unsurprising that they are frequently comorbid[250]. It is also commonly accepted that depression and PTSD are independent but frequently comorbid. Up to 50% of individuals with PTSD also exhibit symptoms of major depression, which may represent a specific trauma-related phenotype[251,252]. Current research suggests that this comorbidity may stem from negative affect symptoms in depression, anxiety and PTSD[250]. Fear of sleep or poor sleep quality may present other potential pathways for this clustering of symptoms and help us understand this co-morbidity. For individuals with a history of trauma, sleep may become associated with vulnerability, recurring nightmares, or a loss of control, leading to avoidance or difficulty initiating and maintaining sleep, referred to as fear of sleep.

Therefore, it makes sense that fears related to sleep have been associated with both symptoms of insomnia[3,211] and more severe symptoms of PTSD. The potential associations between fear of sleep and symptoms of depression and anxiety, however, have yet to be investigated. It may be that fear of sleep is one mechanism underpinning the established link between disturbed sleep and mental disorders such as depression, anxiety and PTSD in certain environments. It may even be that fear of sleep post-trauma contributes to the progression of PTSD.

The first two aims of this study were to i) to assess the traditional relationship between sleep and symptoms of depression, anxiety and PTSD in South Africans living in a low SES community and ii) investigate the relationships between fear of sleep and both sleep and mental health measures (specifically symptoms of depression, anxiety and PTSD). Poor sleep quality and/or short sleep duration is expected to be associated with more severe symptoms of depression, anxiety and PTSD. Fear of sleep, in turn, is expected to be associated with poorer sleep and more severe symptoms of depression, anxiety and PTSD. Given that the analyses largely failed to find the established relationships between sleep and mental health laid out in aim 1 as well as any relationship between fear of sleep and sleep quality in women, a third *post priori* aim was created to understand the role fear plays in mental health outcomes. This aim was to explore whether fear of sleep mediates the relationship between trauma and PTSD symptomology and whether fear of sleep or sleep quality mediates the relationship between depression and PTSD. Given the gender-specific relationships between fear and markers of sleep quality in Chapter 2, an *a priori* decision was made to analyse data for the men and women separately.

4.2. Methods

4.2 1 Study overview and design

This is a cross-sectional observational sub-study of the longitudinal five-country study entitled "Modelling the Epidemiologic Transition Study (METS) – Sleep" described in Chapter 3. Protocols for the parent studies METS-Microbiome and METS[188,189] have been published previously. We present only methodological information specific to the current analysis, for which we supplemented METS-Sleep data collection with mental health and fear variables in the South African cohort only. At their annual clinic visit, participants completed

questionnaires to assess sleep quality, daytime sleepiness, symptoms of insomnia, sleep apnoea, PTSD, and fears related to sleep. They were then given a wrist-worn actigraphy device to measure habitual sleep characteristics over a period of seven days. METS-Sleep and the current study were approved by the University of Cape Town's Faculty of Health Sciences Human Research Ethics Committee (HREC numbers: 696/2014 and 154/2020), conducted in accordance with the Declaration of Helsinki[190] and included only participants who had given informed consent.

4.2.2 Participants

South African adults (25-55 years of age) enrolled in METS-Sleep were invited to participate in this study. This was not an entirely random sample, since we included the first 100 volunteers who consented to take part in this sub-study. Participants were of African-descent and lived in Khayelitsha, a low SES community, characterised by high-density, temporary and informal housing as well as high rates of crime and unemployment. Shift-workers and women who were pregnant or breastfeeding were excluded. After excluding individuals with missing (n=6) or invalid (n=2) data, the final sample comprised 92 participants (41.1±8.2y of age, 70% women).

4.2.3 Questionnaire data

Demographic questionnaires were completed as part of the parent study to capture age, gender, education, employment status, smoking status, weekly alcohol consumption and medical history. A person was classified as suffering from a chronic disease if they had a history of cardiovascular disease (heart attack, rheumatic heart disease, stroke, etc.), cancer, high cholesterol, diabetes mellitus, osteoarthritis, rheumatoid arthritis, kidney failure, a diagnosed mental disorder or any other chronic disease. No individuals in this study reported a diagnosed mental health disorder. The Pittsburgh Sleep Quality Index (PSQI)[107], Epworth Sleepiness Scale (ESS)[108] and Insomnia Severity Index (ISI)[109] were used to assess subjective sleep quality, daytime sleepiness and symptoms of insomnia respectively. The same scoring system and cut-points were used as outlined in Chapters 1 and 2. A

modified version of the STOP-BANG questionnaire[110], omitting neck circumference, was used to assess risk for obstructive sleep apnoea.

Depression and anxiety symptom severity were assessed using the Beck Depression Inventory, second edition (BDI-II) and the Beck Anxiety Inventory (BAI) respectively. The BDI-II is a 21-item questionnaire that evaluates the severity of a participant's depressive symptoms. Total BDI-II scores range from 0-63 with higher scores indicating higher depressive symptom severity. Participants were also classified into a depression risk category: 0-13: minimal; 14-19: mild; 20-28 moderate; 29-63: severe[64]. For the BAI, the responses to 21 questions are summed to determine an overall BAI score from 0-63 with higher scores indicating higher anxiety symptom severity. The following cut-points were used to stratify participants into anxiety risk categories: 0-7: minimal; 8-15: mild; 16-25 moderate; ≥26: severe[65]. The Primary Care Post-Traumatic Stress Disorder (PC-PTSD) was used to screen for symptoms of psychological stress and trauma. It is a short 5-item measure reflecting the DSM-V PTSD diagnostic criteria, with total scores ranging from 0-5. If participants answer "yes" to experiencing a traumatic event and then "yes" to any four of the five item statements, they are understood to exhibit significant symptoms of PTSD[66].

This information was also used to classify trauma status: no trauma exposure: those who answered "no" to a traumatic event in their lifetime; trauma exposure but resilient: those who answered "yes" to experiencing a traumatic event but answered "yes" to fewer than four of the five item statements; trauma exposure and likely presence of PTSD: "yes" to experiencing a traumatic event and "yes" to any four of the five item statements. Fears related to sleep were assessed using the Fear of Sleep Inventory (FoSI), a 23-item tool employing a 5-point scale to rate traumatic events in the context of sleep within the last month. FoSI scores range from 0-92, with higher scores indicating more fear of sleep[191]. The FoSI has five subscale domains which are: i) fear of sleep, ii) fear of loss of vigilance, iii) fear of re-experiencing trauma, iv) nighttime vigilant behaviours and v) fear of the dark.

4.2.4 Actigraphy-derived sleep measures

Participants wore an actigraph on their non-dominant wrist (Actiwatch Spectrum Plus, Philips Respironics, Bend, OR, US) for seven consecutive days to measure habitual home-based sleep

characteristics. Participants were instructed to wear the device 24h a day, only taking it off to shower/bath, and to push the marker button at intended bedtime at night and wake-up time in the morning. Only data sets with five days of valid actigraphy (including at least one weekend night) were included in analyses. Actiwatches were programmed to collect activity and light data in 30s epochs. Timing of sleep periods were established manually based on published guidelines[238]. Sleep onset was defined as five minutes of continuous immobility, while sleep offset was marked by zero minutes of immobility, using a wake threshold of 40 counts per minute to classify each epoch as sleep or wake. Data were processed using Philips Actiware software (v6.3, Philips Respironics, Bend, OR, US).

The outcome variables included bedtime (hh:mm), wake-up time (hh:mm), time-in-bed (time between bedtime and wake-up time, hours), total sleep time (actual hours spent asleep), sleep efficiency (%), wake after sleep onset (WASO, minutes), arousal index (arousals.h^{-1}), sleep fragmentation index (SFI, %), bedtime regularity, wake-up time regularity, time-in-bed regularity and total sleep time regularity. Regularity variables were calculated as the standard deviation of daily values for each participant for each variable. Long sleep was defined as time-in-bed exceeding 9 hours, and poor sleep efficiency was classified as less than 85%. Midsleep was calculated as the midpoint between bedtime and wake-up time. Due to the limited accuracy of actigraphy in estimating sleep onset latency, this variable was not examined.

The SFI, derived using Actiware software (v6.3, Philips Respironics, Bend, OR, US), measures the extent to which physical movement disrupts sleep such that higher SFI values indicate more disrupted sleep. It is calculated using the formula:

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

4.2.5 Data and statistical analysis

Normality was assessed using a Shapiro-Wilk test and data are presented as mean ± standard deviation, median [interquartile range] or count (percentage). Between group differences were assessed using independent t-tests, Mann-Whitney U, Kruskal-Wallis ANOVA, Chi-squared and Fisher's exact tests with Sidak post-hoc tests. Associations between sleep

variables (dependent variables) and fear of sleep and the five fear of sleep subscales were investigated for men and women separately given evidence in Chapter 2 that the fear-sleep relationship differs between men and women[209]. Spearman's correlations were chosen to assess these relationships for continuous variables because the data were largely non-parametric. To limit the number of correlations, given the large number of sleep variables measured, an *a priori* decision was made to restrict the analyses to two measures of actigraphy-derived sleep duration (TIB and TST), two measures of actigraphy-derived efficiency (SE and SFI), and two self-reported sleep measures (ESS and PSQI).

Logistic regressions were run between selected sleep variables (daytime sleepiness, subjective sleep quality, time-in-bed, total sleep time, sleep efficiency and SFI) and binary outcome variables for moderate-severe depression and anxiety. The 'medeff" and "gsem" packages in Stata were used to conduct mediation analyses. Owing to the small sample size of men, the mediation analyses were limited to women only. Only sleep-mental health relationships with $p<0.06$ and a related fear variable ($p<0.06$) were selected for mediation analysis. Due to the high prevalence of trauma reported and the significant differences in fear and symptoms of depression and anxiety between trauma groups (no exposure to trauma, exposed to trauma but resilient and those exposed to trauma with symptoms of likely PTSD) which emerged, fear as a mediator of the trauma-mental health gradient was also examined. Data were analysed using Stata (v15, StataCorp, College Station, TX, US) and significance accepted at $p<0.050$.

4.3. Results

4.3.1 Descriptive characteristics

Descriptive characteristics of the participants are displayed in Table 4.1. Women had a higher body mass index (BMI, $p<0.001$), were less likely to smoke ($p<0.001$) and drank less alcohol each week ($p<0.001$) than men; while more men had tertiary education compared to women ($p=0.009$). Collectively, these participants had long actigraphy-derived sleep opportunities (9.1±1.3h) but 67% had poor sleep efficiency (<85%). This contrasts with only 20% self-reporting poor sleep quality, 10% with excessive daytime sleepiness and 5% with clinically significant moderate to severe insomnia symptoms (Table 4.2). Men and women differed

across all actigraphy-derived measures. Men went to bed earlier (p=0.038), woke up later (p=0.011) and had correspondingly longer time-in-bed (p=0.019) and total sleep times (p=0.010) than women. Men also had worse actigraphy-derived markers of sleep quality with lower sleep efficiencies (p=0.032), more wake after sleep onset time (p=0.003) and higher arousal indices (p=0.003) than women. In contrast, women had higher risk of sleep apnoea (p<0.001) and higher ESS (p<0.001) and ISI (p=0.047) scores than men (Table 4.2).

Mental health characteristics data are presented in Table 4.3. Women had higher BDI-II (p=0.005), PC-PTSD (p<0.001) and FoSI (p=0.024) scores than men. Among all participants, nearly three quarters had experienced a trauma and 45% screened as likely to suffer from PTSD. Women were more likely to have experienced a trauma (p<0.001) and report symptoms indicative of likely PTSD (p<0.001) than men. Participants whose PC-PTSD scores were suggestive of the likely presence of PTSD reported higher FoSI scores (21±9, n=41) than those less likely to have PTSD (14±10, n=50, p<0.001). FoSI scores did not differ between those who spent >9h (FoSI: 17±9) or ≤9h (FoSI: 18±10) in bed (p=0.346). FoSI scores were also similar among those getting <7h (FoSI: 20±11), 7-9h (FoSI: 16±9) or >9h (FoSI: 18±9) sleep (p=0.150). Analysis of the FoSI subscales indicated that women reported higher fear of sleep (p<0.001), fear of trauma re-exposure (p<0.001) and fear of the dark (p=0.026) subscale scores compared to men.

Table 4.1: Descriptive characteristics of participants.

	All (n=92)	**Women (n=64)**	**Men (n=28)**	**p-value**
Age (y)	41.0 ± 8.2	41.0 ± 8.5	41.1 ± 7.6	0.966
Female (count, %)	64 (70)	64 (100)	0 (0)	
BMI ($kg.m^{-2}$)	27.9 [23.2-36.5]	32.3 [24.7-38.5]	22.4 [19.4-24.9]	**<0.001**
Chronic disease (count, %)	58 (63)	44 (69)	14 (52)	0.126
Employed (count, %)	27 (30)	19 (30)	8 (30)	0.996

Highest degree of formal education (count, %)				**0.020**
None	2 (2)	1 (2)	1 (4)	
Primary	3 (3)	2 (3)	1 (4)	
Secondary	79 (88)	59 (93)*	20 (73)*	
Tertiary	6 (7)	1 (2)*	5 (19)*	
Smoking status (count, %)				**<0.001**
Non-smoker	48 (53)	45 (70)*	3 (11)*	
Smoker	38 (42)	16 (25)*	22 (82)*	
Ex-smoker	5 (5)	3 (5)	2 (7)	
Alcohol consumption (standard drinks/ week)	0 [0-14]	0 [0-5]	14 [0-28]	**<0.001**

*Data are presented as mean ± standard deviation, median [interquartile range] or count (percentage). BMI: body mass index; PTSD: post-traumatic stress disorder. Presence of chronic disease was classified as anyone having a history of cardiovascular disease (heart attack, rheumatic heart disease, stroke, etc.), cancer, high cholesterol, diabetes mellitus, osteoarthritis, rheumatoid arthritis, kidney failure, a diagnosed mental disorder or any other chronic disease. P-values represent comparisons between the men and women determined using independent t-tests, Mann-Whitney U, Kruskal Wallis ANOVA, Chi-squared and Fisher's exact tests. * indicate significant post hoc differences (p<0.050) between men and women as determined using Fisher's exact test.*

Table 4.2: Actigraphy-derived and self-reported sleep characteristics of participants.

	All (n=92)	**Women (n=64)**	**Men (n=28)**	**p-value**
Bedtime (hh:mm)	22:05 [21:35-22:52]	22:08 [21:41-22:58]	21:46 [21:27-22:26]	**0.038**
Wake-up time (hh:mm)	7:17 ± 1:08	7:07 ± 1:08	7:46 ± 1:02	**0.011**

Time-in-bed (h)	9.08 ± 1.45	8.72 ± 1.39	9.89 ± 1.24	**0.019**
Long sleep (TIB >9h)	43 (47)	23 (36)	20 (71)	**0.002**
Total sleep time (h)	7.36 ± 1.31	7.15 ± 1.31	7.85 ± 1.21	**0.010**
TST <7h	37 (40)	31 (48)*	6 (21)*	
TST 7-9h	44 (48)	26 (41)*	18 (64)*	
TST >9h	11 (12)	7 (11)	4 (14)	
Sleep efficiency (%)	82 [78-86]	83 [80-87]	80 [77-83]	**0.032**
Low sleep efficiency (<85%)	62 (67)	39 (61)	23 (82)	**0.046**
Wake after sleep onset (min)	83 [62-104]	75 [59-100]	94 [82-124]	**0.003**
Arousal index (number.h^{-1})	7 [6-10]	7 [5-8]	9 [7-10]	**0.003**
SFI (%)	28.77 ± 8.96	27.07 ± 8.77	32.42 ± 8.38	**0.013**
Bedtime regularity	1.15 [0.82-1.87]	1.05 [0.68-1.65]	1.64 [0.95-1.94]	**0.035**
Wake-up time regularity	0.94 [0.75-1.36]	0.94 [0.77-1.33]	0.95 [0.70-1.38]	0.932
TIB regularity	1.57 [1.09-2.27]	1.55 [1.06-2.02]	1.81 [1.13-2.39]	0.373
TST regularity	1.41 [0.93-1.75]	1.35 [0.87-1.62]	1.61 [1.16-1.88]	*0.052*
Modified STOP-BANG score	2 [2-3]	3 [2-3]	1 [1-2]	**<0.001**
PSQI score	4 [2-5]	4 [3-5]	3 [2-5]	0.136
Poor sleep quality (PSQI >5)	18 (20)	15 (24)	3 (12)	0.190
PSQI disturbance subcomponent	1 [1-2]	1 [1-2]	1 [1-1]	0.067
ESS score	3 [1-7]	5 [3-8]	1 [0-4]	**0.004**
Excessive daytime	9 (10)	9 (14)	0 (0)	**0.038**

sleepiness (ESS >10)				
ISI score	1 [0-4]	2 [0-6]	1 [0-2]	**0.038**
Clinically significant insomnia symptoms (ISI >14)	5 (6)	3 (5)	2 (7)	0.616

*Data are presented as mean ± standard deviation, median [interquartile range] or count (percentage). ESS: Epworth Sleepiness Scale; ISI: Insomnia Severity Index; PSQI: Pittsburgh Sleep Quality Index; SFI: Sleep Fragmentation Index; TIB: time-in-bed; TST: total sleep time. Regularity measures were derived from the standard deviation of the bedtimes, wake-up times, total sleep times, time-in-bed or midpoint of sleep respectively over the week of actigraphy. P-values represent comparisons between the men and women determined using independent t-tests, Mann-Whitney U, Kruskal Wallis ANOVA, Chi-squared and Fisher's exact tests. * indicates significant post hoc differences (p<0.050) between men and women as determined using Fisher's exact test.*

Table 4.3: Mental health, trauma and fear of sleep characteristics of participants.

	All (n=91)	**Women (n=64)**	**Men (n=27)**	**p-value**
BDI-II score	14 [10-24]	18 [11-27]	12 [8-14]	**0.005**
Moderate-severe depression symptoms (BDI-II >19)	34 (37)	28 (44)	6 (22)	0.077
BAI score	10 [6-16]	11 [6-16]	8 [4-13]	0.203
Moderate-severe anxiety symptoms (BAI >15)	25 (27)	19 (30)	6 (22)	0.895
PC-PTSD score	3 [0-4]	4 [2-5]	0 [0-2]	**<0.001**
Likely presence of PTSD (PC-PTSD score >3)	41 (45)	37 (58)	4 (15)	**<0.001**
Trauma status				**<0.001**
No trauma	22 (24)	7 (11)*	15 (55)*	
Yes, resilient	28 (31)	20 (31)	8 (30)	

Yes, symptoms indicative of PTSD	41 (45)	37 (58)*	4 (15)*	
FoSI score	18 ± 10	19 ± 10	14 ± 9	**0.024**
Fear of sleep subscale	2 [0-4]	3 [1-5]	0 [0-3]	**<0.001**
Fear of loss of vigilance subscale	4 [2-6]	4 [2-6]	3 [2-6]	0.680
Fear of trauma re-exposure subscale	2 [1-3]	2 [1-4]	1 [0-2]	**<0.001**
Nighttime vigilant behaviour subscale	7 [3-8]	7 [3-8]	6 [5-8]	1.00
Fear of the dark subscale	0 [0-3]	0 [0-4]	0 [0-0]	**0.026**

*Data are presented as median [interquartile range] or count (percentage). Trauma status calculated from whether or not individuals have experienced a trauma (Yes/No) and if yes, whether they report symptoms suggestive of PTSD (PC-PTSD>3) or not (resilient; PC-PTSD≤ 3). BAI: Beck Anxiety Inventory; BDI-II: Beck Depression (II) Inventory; FoSI: Fear of Sleep Inventory; PC-PTSD: Primary Care Post-traumatic Stress Disorder. P-values represent comparisons between the men and women determined using independent t-tests, Mann-Whitney U, Chi-squared and Fisher's exact tests. * indicates significant post hoc differences (p<0.050) between men and women as determined using Fisher's exact test.*

4.3.2 Associations between sleep characteristics with mental health characteristics and fear of sleep

Figure 4.1 summarises the significant relationships between sleep, symptoms of depression, anxiety and PTSD and fear of sleep. The full correlation tables for these associations are presented in Appendices 4.1 (women) and 4.2 (men). Similarly, logistic regressions exploring associations between sleep characteristics and moderate-severe symptoms of depression, moderate-severe symptoms of anxiety and symptoms indicative of likely PTSD are presented in Appendices 4.3 (women) and 4.4 (men).

Among women, fragmented sleep was correlated with higher scores on the fear of trauma re-exposure subscale (rho=0.290, p=0.030) while higher scores on the nighttime vigilant

behaviour subscale showed a trend with more daytime sleepiness (rho=0.255, p=0.054). When looking at the results of the logistic regression analyses in women, only one relationship emerged such that those categorized as reporting moderate-severe symptoms of anxiety had more daytime sleepiness than those with no or only mild symptoms of anxiety [odds ratio (OR) (95% confidence interval (CI): 1.22 (1.06-1.41); p=0.007)].

For men, poorer subjective sleep quality was correlated with more severe symptoms of depression (rho=0.628, p=0.001), anxiety (rho=0.481, p=0.015) and PTSD (rho=0.454, p=0.023). Higher ESS scores were correlated with higher depression scores in the men (rho=0.460, p=0.021). Furthermore, more fragmented sleep (rho=-0.418, p=0.047) and more severe symptoms of anxiety (rho=0.433, p=0.039) were associated with higher nighttime vigilance subscale scores. Poorer sleep quality was associated with higher fear of sleep subscale scores (rho=0.489, p=0.018) and a trend towards higher fear of trauma re-exposure (rho=0.403, p=0.056) subscale scores. In men, self-reported sleep quality was significantly worse in the group exposed to trauma with symptoms of PTSD (median PSQI score: 6 [interquartile range: 5-10] compared to both the no trauma exposure group (3[2-4], p=0.001) and the resilient group (3[2-4], p=0.003; Appendix 4.7).

4.3.3 Associations between fear of sleep and trauma with depression, anxiety and PTSD

When separated by gender, both women and men showed associations between fear of sleep with symptoms of depression, anxiety and PTSD (Appendix 4.5 for women and 4.6 for men). Specifically, higher depression symptom scores were correlated with higher global fear of sleep scores (women: rho=0.435, p<0.001; men: rho=0.599, p=0.001) and higher scores on the fear of sleep (women: rho=0.378, p=0.002; men: rho=0.453, p=0.030) and fear of trauma re-exposure (women: rho=0.256, p=0.042; men: rho=0.516, p=0.012) subscales. Similarly, higher anxiety symptom scores were associated with higher global fear of sleep scores (women: rho=0.450, p<0.001; men: rho=0.628, p=0.001) and higher scores on the fear of sleep (women: rho=0.456, p<0.001; men: rho=0.559, p=0.006), and fear of trauma re-exposure (women: rho=0.409, p-value<0.001; men: rho=0.639, p=0.001) subscales. More severe symptoms of PTSD were associated with higher global fear of sleep scores (women: rho=0.323, p=0.009; men: rho=0.434, p=0.023) and a higher fear of trauma re-exposure (women: rho=0.318, p=0.010; men: rho=0.481, p=0.020) subscale score.

In just the women, a higher PTSD score was associated with a higher score on the fear of sleep subscale (rho=0.308, p=0.013). In addition, higher scores on both the nighttime vigilance and fear of the dark subscales also correlated with higher depression (vigilance: rho=0.273, p=0.029 and dark: rho=0.241, p=0.055) and anxiety (vigilance: rho=0.348, p=0.005 and dark: rho=0.256, p=0.042) symptom scores among the women. In women, depression and anxiety symptoms were significantly worse in the group exposed to trauma with symptoms of PTSD compared to the resilient group (depression: p=0.034; anxiety: p=0.014; Appendix 4.8). There was a trend towards higher depression symptom scores between the likely PTSD group and the no trauma group (p=0.056). Similarly, in men, depression symptoms were significantly worse in the group exposed to trauma with symptoms of PTSD (median BDI-II score: 22 [interquartile range: 18-28] compared to the no trauma exposure group (8[3-12], p=0.001; Appendix 4.8).

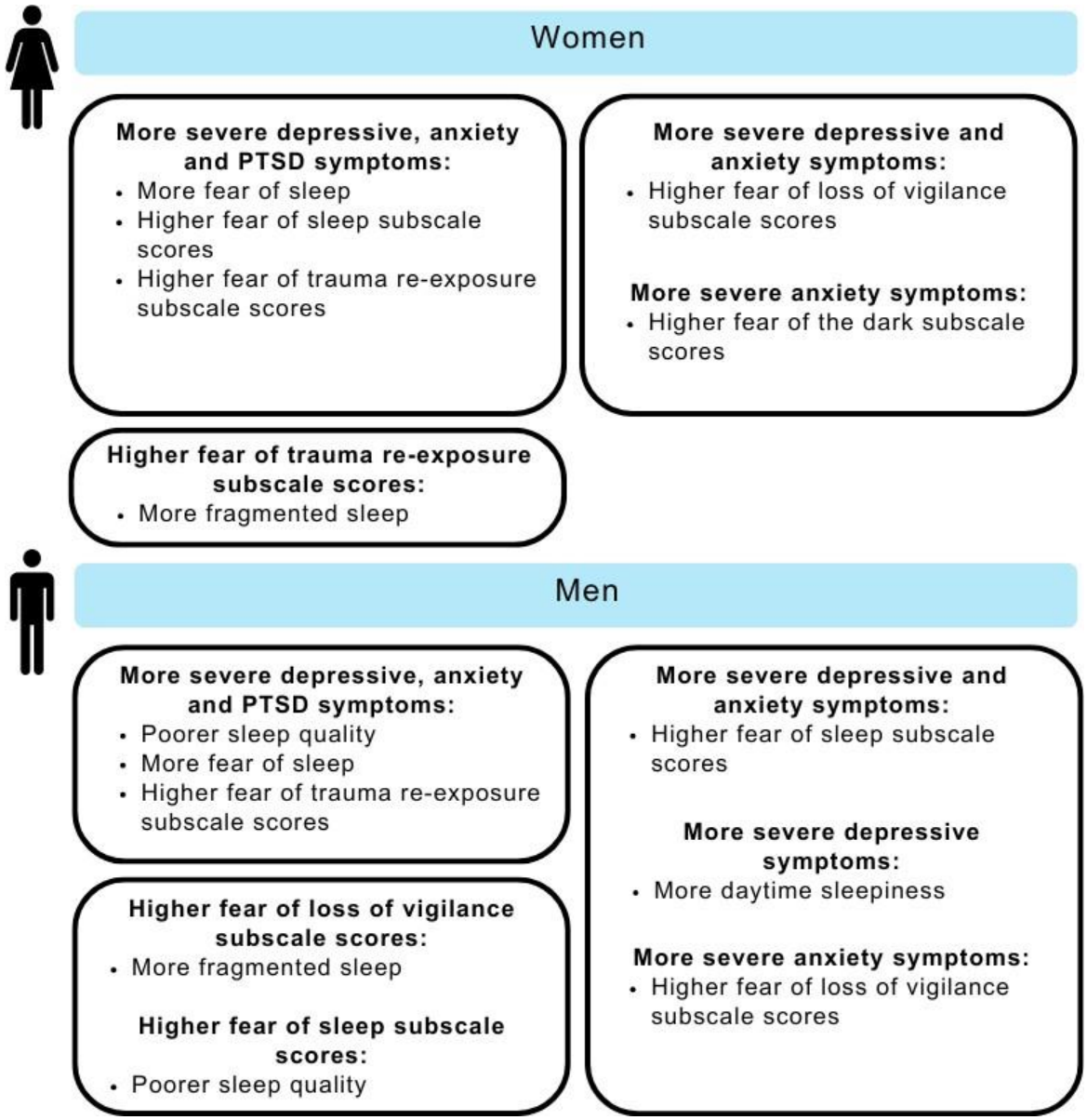

Figure 4.1: Summary of the significant relationships between sleep, fear of sleep and symptoms of depression, anxiety and PTSD as determined using Spearman's rank order correlations. *Full correlation tables are provided in Appendices 4.1, 4.2, 4.5 and 4.6. Significance was accepted as p<0.050. Fear of sleep and its related subscales were obtained from the full Fear of Sleep Inventory. PTSD: post-traumatic stress disorder*

Mediation analyses

In women, only ESS, fear of vigilance and moderate-severe symptoms of anxiety emerged as candidates for mediation but in the mediation analysis neither the direct relationship between ESS and anxiety or indirect effect were significant (direct effect: β=0.150, p=0.146;

indirect effect: β=0.022, p=0.569; total effect: β=0.172, p=0.122). Fear of sleep did not mediate the relationship between trauma exposure and PTSD symptom severity (direct effect: β=3.331, p<0.001; indirect effect: β=0.289, p=0.203; total effect: β=3.621, p<0.001; Figure 4.2A). Fear of sleep, however, did mediate 43% of the relationship between PTSD symptom severity and moderate-severe depressive symptoms (p<0.05) such that the relationship between PTSD symptom severity and moderate-severe depressive symptoms was no longer significant after accounting for the indirect effect through fear of sleep (Figure 4.2B). None of the sleep variables emerged as candidates for mediation between PTSD symptom severity and moderate-severe symptoms of depression.

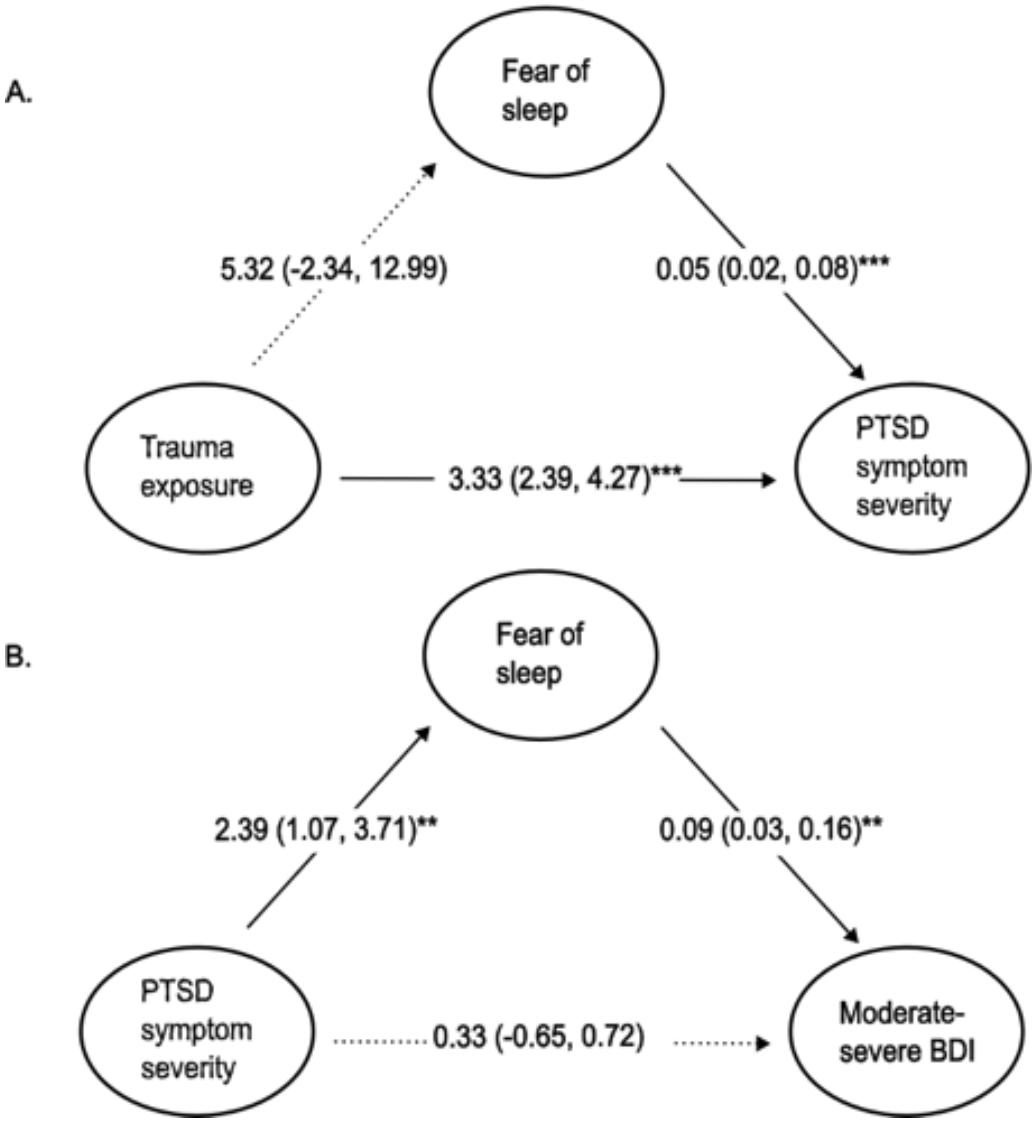

Figure 4.2: Mediation analyses between symptoms of PTSD, fear of sleep and A) moderate-severe depressive symptomology and B) moderate-severe symptoms of anxiety in women (n=64). *PTSD symptom severity and fear of sleep were assessed using the Primary Care PTSD and Fear of Sleep Inventory respectively. Depression symptoms were assessed using the Beck Depression Inventory-II (BDI) where moderate-severe symptoms were classified as scores >19. Statistics displayed are the beta coefficients (95% confidence intervals). Solid lines represent significant paths. *p < 0.05. **p < 0.01. ***p < 0.001. PTSD: post-traumatic stress disorder.*

4.4. Discussion

Data are presented on the sleep characteristics and symptoms of depression, anxiety and PTSD in a group of South Africans living in an urban township. Urban townships are reflective of the living circumstances of an estimated 8.1% to 24.4% of South African households[215–217]. Given the well-established links between low SES and both sleep[44,197,246,253] and mental health[113,245,254], coupled with the bidirectional relationship between sleep and mental health[93,138,141,176,177,255], one would hypothesise that many of these individuals living in a low SES community would experience both poor sleep and more severe symptoms of mood- and anxiety-related disorders.

In line with this hypothesis, the overall picture presented by these results is of short, irregular and poor quality sleep, despite long sleep opportunities. Although many individuals are meeting the recommended sleep duration guidelines[41], we observed low sleep efficiencies, high WASO and fragmented sleep in the majority of the participants. We confirmed the previously self-reported long time-in-bed[180,181,223,256] in South Africans living in low SES areas, which may be an attempt to compensate for the poor quality of sleep observed. Despite this, very few participants reported poor quality sleep, excessive daytime sleepiness or clinically significant symptoms of insomnia.

While discrepancies between self-report and objectively measured sleep are common, individuals typically tend to underestimate the amount of sleep they are getting - the “sleep state misperception” insomnia subtype[97,257] - which is proposed to stem from differences in the microstructure of sleep with less stage 3 NREM sleep and more wake-like brain activity[258]. However, the converse overestimation of sleep is less frequently reported and more poorly

understood. It is possible that the wording of instruments like the PSQI and ISI, which emphasize the perceived severity of sleep disturbances, may be influenced by cultural and contextual factors. Nearly all participants in this study had spent their entire lives in Khayelitsha, a low socioeconomic setting, described in the previous chapter to be marked by environmental disruptions to sleep. As a result, their perceptions of what constitutes a significant sleep issue may have been shaped by this environment, potentially raising their threshold for reporting sleep problems. This highlights the importance of considering cultural and contextual relevance when applying these tools, and future research should explore their appropriateness in such settings.

Moderate-to-severe symptoms of depression and anxiety were reported by a third and a quarter of participants respectively, with nearly half reporting trauma symptomology suggestive of PTSD, much higher than national estimates[259]. Fear of sleep scores similar to those in other studies with trauma-exposed individuals[229,253] were observed, regardless of sleep duration. We did not observe the expected relationships between objectively measured sleep variables with mood- and anxiety-related measures[134,218,260,261]. This may be because some individuals are more resilient to the effects of disturbed sleep than others. Alternatively, it may be that individuals have adopted adaptive behaviours (as described in Chapter 3) which help to mitigate the effects of fear, anxiety or depressive symptoms on sleep. In line with this, for women, higher scores on many of the fear subscales were associated with severe symptoms of depression, anxiety or PTSD, except for the vigilant behaviour subscale, which includes locking doors and keeping windows shut and in men, more vigilant behaviours was even associated with less fragmented sleep.

A striking finding of this study is that fear of sleep was consistently associated with symptoms of depression, anxiety and PTSD and that fear of sleep mediates the relationship between PTSD symptom severity and moderate-severe symptoms of depression. Individuals with both PTSD and depressive symptoms are more likely to have more severe symptoms and a poorer prognonsis[252], making understanding this comorbidity key. While there are suggestions that there may be an epigenetic component[252], these results suggest that these symptom clusters may be related, at least in part, through fear of sleep. To date, few studies have investigated the role of fear of sleep in disorders outside of PTSD. Similar results were observed in a group of first responders where they found individuals with clinically significant symptoms of

depression, anxiety and PTSD reported more fear of sleep than individuals with mild symptoms[153]. A study of sleep quality in deaf individuals by Carr et al. (2023)[262] and a study in individuals with epilepsy and healthy controls by Norton et al. (2023)[263] also investigated associations between fear of sleep and depression and anxiety. More fear of sleep was associated with more severe depression in both of these studies and with more severe anxiety in patients with epilepsy. There was also a trend towards more anxiety in deaf individuals who reported more fear of sleep, although this was no longer significant after correcting for multiple testing[262].

Fear of sleep has been the focus of a lot of research in individuals with PTSD or at risk for PTSD, such as active military personnel[3,99,123,264–266]. These studies found a specific subtype of individuals with PTSD who report fears related to sleep. These individuals were more likely to report sleep disturbances and insomnia than those who didn't report fear related to sleep, likely linked to pre-sleep arousal and hypervigilance[123,265]. In this chapter, we observed gender-specific associations between fear of sleep and the sleep measures. More fear of sleep and fear of loss of vigilance was associated with poorer subjective sleep quality and more fragmented sleep in men respectively whereas for women fear of experiencing trauma re-exposure was associated with more fragmented sleep. Interestingly, when looking at the vigilant behaviours subscale, this did not correlate with any of the mental health outcomes (although trends were observed). One could speculate that this may be because in a high crime area, such as Khayelitsha, behaviours which help secure an individual's home like locking doors, checking windows before they go to bed, trying to remain awake as long as possible and other behaviours outlined in this subscale are reasonable security measures. While these behaviours may occasionally disturb sleep, they may help people feel safer, improving their mental health and the quality of the sleep they do get.

We observed clear gender differences in fear of sleep and symptoms of depression and PTSD, with women reporting more fear of sleep and more severe symptoms of depression and PTSD. Most studies[191,211,229,263] did not investigate how fear of sleep may differ between men and women but those that did also reported gender disparities in fear of sleep reported[153,223]. This may be because women are more often victims of sexual assault, particularly in South Africa[133,267,268]. In line with this, we found that a disproportionate number of women had experienced a trauma and reported symptoms suggestive of clinically significant PTSD.

Additionally, our mediation results suggest that, in women, the link between more severe PTSD symptoms may be associated with more severe clinical symptoms of depression through fear of sleep. Although we didn't collect data on type of trauma, certain trauma types, particularly sexual assault and threat of death, are more likely to trigger fear of sleep, more severe symptoms of PTSD and are more strongly associated with negative cognition and mood[124,153,248,269]. These traumas are also more likely to occur in the home which may be the reason these traumas are more closely associated with fear of sleep as individuals may feel more fear in bedrooms or sleep-related contexts[3,153]. This fear of sleep may impair sleep quality by making it difficult for individuals to let their guard down enough to go to sleep. It may be that this fear of sleep triggers hypervigilance in individuals which in turn leads to hyperarousal of the autonomic nervous system. Collectively, these findings suggest that past trauma and fear of sleep are key to understanding the sleep and mental health paradigm in a low SES context.

This study adds to the literature investigating the relationship between sleep characteristics and symptoms of depression, anxiety and PTSD outside of the Global North. Moreover, to our knowledge, this study is one of the first to investigate the relationship between fear of sleep and symptoms of depression and anxiety. Future research should consider the impact that fears related to sleep can have outside the scope of PTSD. The cross-sectional nature of this study limits the conclusions on the directionality or causality of these relationships and as such, longitudinal work is necessary to elucidate whether fears related to sleep are subsequent to or precede symptoms of depression, anxiety or PTSD. Our sample may be subject to some selection bias as our participants were comprised of the first 100 individuals to volunteer from the larger parent study, rather than a completely random sample. As such, our sample was also predominantly women, which limited our ability to do the mediation analyses for men. Additionally, there may be other factors which were not investigated in this study, such as social support systems or time since the trauma occurred, which may influence the relationship between trauma, fear of sleep, mental health outcomes and/or sleep. Finally, including physiological measures, such as heart rate variability, may help to better understand resilience as well as elucidate the contribution to sleep disruption of fear of sleep.

4.5. Conclusion

In a low SES neighbourhood, trauma and fear of sleep likely contribute to the high prevalence of depression, anxiety and PTSD symptoms in South African adults but is largely unable to explain the disrupted sleep observed. Over and above the trauma and fear of sleep, other factors characteristic of low SES environments such as noise or poverty-related stress are superimposed and may fragment sleep both independently or in tandem. Notably, our findings suggest that South African women may have more past trauma than men, heightening feelings of fear during sleep, and that fear of sleep ultimately may fragment sleep through hyperarousal and worsen symptoms of depression, anxiety and PTSD. This highlights hyperarousal as a key avenue of investigation to better understand the effect of fear of sleep.

Chapter 5

Associations between sleep-related heart rate variability and both sleep and symptoms of depression and anxiety: A systematic review.

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5.1. Introduction

Sleep is essential for the functioning of many of the body's systems, including the brain[85]. According to a recent systematic review, between 20-43% of adults report poor quality or insufficient sleep[270]. Mental illness is one of the leading health concerns globally, with anxiety and depressive disorders having estimated global prevalences of 3.6% and 4.4%, respectively pre-2020[129] with estimated increases of 25.6% and 27.6% respectively due to the subsequent Covid-19 pandemic[271]. Both poor sleep and mood- and anxiety-related disorders are independently associated with increased all-cause mortality[92,272,273].

5.1.1. Sleep and mood- and anxiety-related disorders

Psychiatric disorders have long been linked to sleep abnormalities[80,142,146,274,275] in a bidirectional manner[135]. Poor sleep increases the likelihood of developing mood- and anxiety-related disorders, specifically[81,136,176]. Almost all patients with major depressive disorder (MDD) report some form of sleep complaint[276]. Depressed patients with comorbid sleep difficulties usually exhibit more severe symptoms, including increased suicidal ideation, and are more resistant to treatment, while resolving sleep issues appears to improve outcomes, including decreasing symptom severity and increasing rate of recovery[138,277]. Furthermore, patients with anxiety disorders, such as generalised anxiety disorder and post-traumatic stress disorder (PTSD), frequently report sleep disturbances and problems initiating sleep[268]. In fact, individuals with PTSD and concurrent sleep difficulties often remain refractory to treatment, while treating sleep issues improves overall symptoms [143,249].

5.1.2. Autonomic nervous system function and heart rate variability

Both poor sleep and mood- and anxiety-related disorders are associated with altered 24h autonomic nervous system (ANS) function[166,167,279]. The ANS is composed of two branches: the sympathetic nervous system (SNS) and parasympathetic nervous system (PNS). Heart rate variability (HRV) has been widely used as a marker of autonomic functioning due to its non-invasive nature. HRV is an index of vagal activation of the heart that has both chronotropic

and modulatory effects. The dorsal motor vagal nuclei in the medulla control cardiac chronotropy (i.e., heart rate), while the nucleus ambiguous in the medulla regulates cardiac modulatory effects[280]. High frequency vagal input into the heart is typically modulated by the spontaneous breathing rate and is also known as respiratory sinus arrhythmia (RSA)[280].

The predominant parasympathetic vagal traffic below the diaphragm involves the gut-brain axis and as such falls outside the scope of our review (which is focusing on HRV). It is worth noting, however, that part of the feedback from the gut-brain axis - associated with disorders such as depression and PTSD[281] - occurs via the vagus nerve. And *vice versa*, stimulation of the vagus nerve is a treatment option for mood and anxiety disorders[281] as well as for inflammatory bowel disease and pro-inflammatory cytokine production[282].

Methods of HRV analysis typically used can collectively be broken down into time-domain, frequency-domain and non-linear analyses, with the former two comprising more traditional and the latter more recent methodologies. Time-domain measures of HRV include root mean square of successive differences between R-peak to R-peak (R-R) intervals (RMSSD), standard deviation of differences between R-R intervals (SDNN) and percent of differences of adjacent R-R intervals greater than 50msec (pNN50).

Frequency domain measures derived from spectral power analysis of R-R intervals, provide an index of cardiac ANS regulation. Cardiac spectral power in the low frequency band (LF; 0.04-0.15Hz) is purported to be due to baroreflex-mediated modulation of the heart[162], while high frequency variability (HF; 0.15–0.4Hz) is typically due to the influence of the spontaneous breathing rate on heart rate, referred to as RSA. While HF cardiac spectral power reflects only parasympathetic activity[163], LF cardiac spectral power reflects contributions from both the sympathetic and parasympathetic branches of the ANS. Given the large parasympathetic influence on LF cardiac spectral power, the physiological relevance of LF/HF ratio has been disputed[283] and should be interpreted with caution.

Furthermore, non-linear HRV measures (including multiscale entropy (MSE), sample entropy (SampEn), and detrended fluctuation analysis (DFA)) give a global indication of the complexity of heart rate dynamics, specifically the beat-to-beat fluctuations in R-R intervals. Lower complexity in the HRV signal makes the signal more predictable and less healthy, e.g., such as occurs during chronic heart failure[284]. On the other hand, if there is too much randomness or

chaos in the HRV signal it is indicative of impeded cooperation in the physiological control systems. Non-linear analyses have begun providing new insights into HRV, but clinical translation has not occurred to date.

5.1.3. Sleep and HRV

There is extensive research looking at the relationship between sleep and 24h HRV[285,286]. In healthy, neurotypical individuals, wakefulness and rapid eye movement (REM) sleep is predominantly associated with LF power[285–287] in the cardiac spectrogram. On the other hand, HF power in the cardiac spectrogram is increased during sleep compared to during wake and this index of parasympathetic dominance increases with increasing sleep depth[286]. Alteration of this pattern of parasympathetic dominance may impair sleep by inducing a state of alertness (hyperarousal) unconducive to sleep[173]. This hyperarousal is commonly regarded as a contributing factor in insomnia models[173]. While the macrostructure of sleep architecture is associated with altered autonomic activation, it is also important to consider the microstructure. Cyclic alternating pattern of arousal during sleep (characterised by regular fluctuations between greater and lesser arousal) within sleep stages is also associated with less parasympathetic input compared to non-cyclic alternating pattern (which represents more stable sleep)[288–290]. Disrupted sleep is associated with an increase in sympathetic tone[39,80]. Burgess et al. (1997) found that short sleep predominantly impacts sympathetic activation (assessed using pre-ejection period) with parasympathetic activation (assessed using RSA) being mediated more by circadian influence[291]. Given that HRV is not a direct measure of ANS function, however, but only provides an indirect index of ANS function, the current evidence is still too varied for any definitive conclusions to be drawn. Despite this, HRV impairment in insomnia is a widely accepted concept[5].

5.1.4. Mood- and anxiety-related disorders and HRV

While greater complexity in 24h and daytime HRV measures appear to be a characteristic of healthy individuals, disorders such as MDD and generalised anxiety-disorder are associated with decreased complexity[166,292,293]. Several studies show lower 24h and daytime resting HRV

in patients with depression- and anxiety-related disorders[166,294], although there are discrepant results. In a review of HRV, various psychiatric disorders and psychotropic medications, studies with only non-medicated patients showed that there was a significantly lower long-term (24h) and short-term (5min daytime rest) HRV in patients with mood- and anxiety-related disorders than controls[175]. This lower HRV also seems to be exacerbated by the psychotropic medications used to treat these disorders[154,287]. Other studies, however, showed no correlation between psychiatric symptom severity and HRV[296,297].

Given these established links between (i) sleep and mood- and anxiety-related disorders, (ii) poor sleep and 24h HRV, and (iii) mood- and anxiety-related disorders and 24h HRV, we propose that ANS dysregulation, specifically during sleep, is a critical factor in explaining the relationship between poor sleep and mood- and anxiety-related disorders. On one hand, a sleep-related ANS imbalance, where there is a shift away from the usual physiological patterns of sympathetic and parasympathetic control, may impair sleep[298]. Additionally, individuals with high levels of anxiety or PTSD may experience hypervigilance or a state of vulnerability at night, making falling asleep or staying asleep difficult. This impaired sleep may then exacerbate any symptoms of anxiety or depression experienced during the day[81,261]. While the mechanisms by which impaired sleep worsens symptoms of anxiety and depression are still unclear, some previously proposed pathways include elevated glucocorticoids associated with the stress response[81,261] and altered brain plasticity leading to altered communication between regions of the brain involved in regulating mood[81]. Similarly, nocturnal ANS imbalance may underly sleep impairment (for example, expressed as insomnia) and contribute to mood- and anxiety-related disorders, either independently or in conjunction with the previously proposed pathways. Additionally, the presence of a mood- and anxiety-related disorder may be associated with an ANS imbalance which may then contribute to difficulties with sleep.

Thus, while the bidirectional relationships between sleep and mood- and anxiety-related disorders are commonly reported, potential underlying mechanisms, such as sleep-related ANS dysregulation, warrant further investigation. Therefore this review will focus specifically on sleep-related HRV, as that is where we hypothesise ANS dysregulation will have the greatest effect on sleep quality and therefore on mood- and anxiety-related disorders. The aim of this study is to systematically review the evidence describing the relationships between

sleep-related ANS regulation (as measured by HRV) with both sleep and mood- and anxiety-related disorder outcomes.

5.2. Methods

5.2.1. Search strategy

Prior to conducting the literature search for this systematic review, the aims and methods were registered with PROSPERO (ID: CRD42020179952). Three databases (PubMed, Scopus and Web of Science) were searched for all peer-reviewed studies published prior to 02 April 2022 using the following search terms: "sleep, insomnia, nervous system, autonomic nervous system, ANS, parasympathetic nervous system, PNS, sympathetic nervous system, SNS, hyperarousal, heart rate variability, HRV, mental health, mental illness, mental disease, mental disorder, depression, anxiety, post traumatic stress disorder, PTSD, post-traumatic stress disorder, posttraumatic stress disorder" (Appendix 5.1). Filters were applied to each search limiting the results to journal articles written in or translated to English. The reporting was conducted according to the "*Preferred Reporting Items for Systematic Reviews and Meta-Analyses*" (PRISMA) guidelines[299].

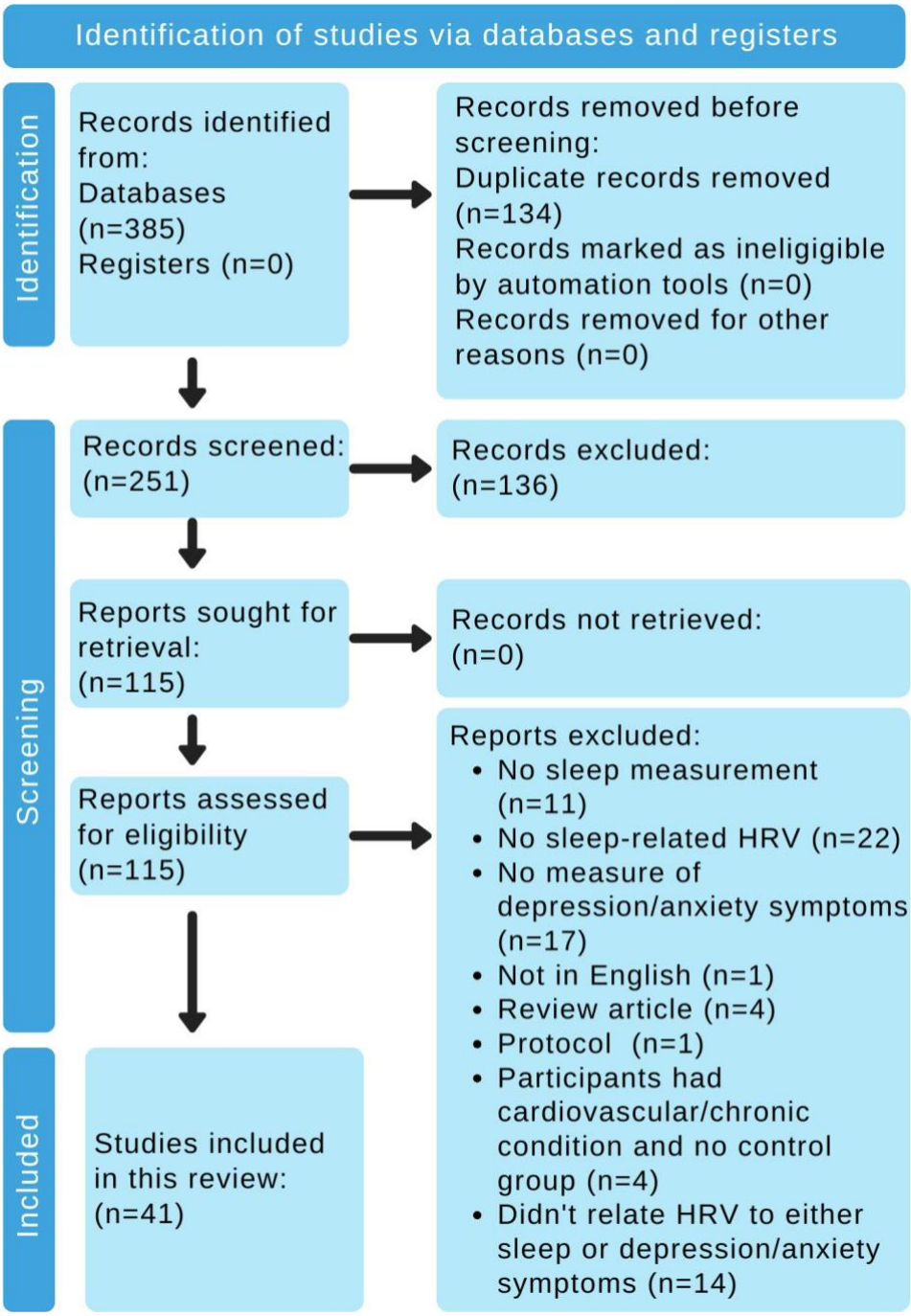

Figure 5.1: Flow diagram depicting the method of article selection.

5.2.2. Study selection

Figure 5.1 depicts the article selection process. The initial database search yielded 385articles. Following removal of duplicates, two reviewers (ATLC and PEF) independently scanned titles and abstracts of the remaining 251 articles to determine whether they potentially fit the following inclusion criteria: 1) primary research study published in a peer-reviewed journal, 2) participants had no conditions other than diagnosed sleep, mood- or anxiety-related

disorders, 3) participants were between the ages of 18 and 65 years, 4) at least one sleep quality or duration-related outcome was reported, 5) a measurement of HRV during sleep was provided and 6) anxiety, depression or stress symptom severity outcomes were measured. In studies comparing individuals with exclusionary conditions (e.g. fibromyalgia) to controls, the Control groups were included in this review, provided sleep-related HRV, and mood-, anxiety- or stress-related measures were conducted. Control groups with scores above clinical cut-offs on questionnaires assessing depression or anxiety symptoms were grouped with diagnosed individuals even though the original study classified them as healthy.

Sleep-related HRV was defined as the inter-beat variability extracted from either the electrocardiogram (ECG) component of polysomnography (PSG) or ambulatory recording (e.g. Polar heart rate monitor) measured during the sleep period. Studies with either or both frequency domain (HF and LF power) and time domain (RMSSD, SDNN, pNN50) measures during sleep were included. Reviews, conference abstracts and case studies were excluded but longitudinal, cohort and cross-sectional studies were included. Any studies which could not be definitively excluded based on their title and abstract were retained for full text screening. Full texts were screened by ATLC with any queries discussed and resolved with PEF, DER and GL. The references of the included studies were manually examined for other potentially relevant studies. The screening process is presented in Figure 5.1. Where there were queries about the method of the study the authors were contacted to clarify. One hundred and fifteen studies were assessed for eligibility and of these, 74 were excluded for reasons provided in Figure 5.1. Ultimately, 41 studies were included in this review, the bias and quality of which was assessed by ATLC using the Joanna Briggs Institute Critical Appraisal Checklist for Analytical Cross-Sectional Studies[300] (Appendix 5.2).

5.3. Results

5.3.1. Study characteristics

Table 5.1 presents the characteristics of all included studies. Participant mean ages range from 19.6±1.8 to 55.6±4.0 years; 36 studies included both men and women[171,232,296,301–319], two and three studies included only women[320,321] or men[75,308,322], respectively.

Table 5.1: Characteristics of participants and included studies.

Citation	Study design	Population (n)	Method to assign to group	Sleep disorders assessed and method of assessment	Age (y)	Female (%)
Agorastos et al., 2013	CS	PTSD (7)	CAPS, SCID	Not reported	26.3±4.0	0.0
		Control (8)			30.9±10.6	
Alomri et al., 2021	CS	Non-OSA (12)	PSG, AHI	OSA: PSG	33.7±14.8	36.1
		Mild OSA (26)			37.4±11.5	
		Moderate OSA (16)			44.1±12.4	
		Severe OSA (20)			46.5±10.4	
Bassett et al., 2016	CS	Remitted Bipolar Type 1 (29)	MINI	Not reported	36.9±13.5	66.7
		Recurrent MDD (41)			42.0±13.1	75.8
		Control (38)			43.0±9.7	45.9
Beilharz et al., 2020	CS	Childhood trauma (22)	CTQ-SF	Not reported	22.3±4.9	68.1
		No childhood trauma (89)			21.7±4.4	62.9
Bertram et al., 2014	CS	PTSD (56)	SCID	Sleep apnoea: self- reported history of diagnosis and usage of a CPAP machine via questionnaires	53.4±11.3	0.0
		Control (54)			54.5±9.5	0.0

Brosschot et al., 2007	CS	"Healthy participants" (52)		Not reported	33.8±13.9	75.0
Brupbacher et al., 2021	RCT	Exercise intervention (46)	SCID	RLS: validated cut off in the RLS screening questionnaire, sleep apnoea: oxygen desaturation >15 in baseline PSG	46 (37-53)	70.0
		Control (46)			48 (43-51)	72.0
Burton et al., 2010	CS	"Healthy participants" (20)		Patient history	36.0±13.2	75.0
		Insomnia (10)			27.1±6.3	70.0
Chen et al., 2017	CS	Good sleeper: high vulnerability to insomnia (10)	PSG, ISI, FIRST	Semi-structured interview, questionnaires	26.0±4.0	80.0
		Good sleeper: low vulnerability to insomnia (10)			26.9±5.8	50.0
Cosgrave et al., 2021	CS	Poor sleepers (23)	ISI, PSQI	Not reported	23.7±3.5	60.9
		Good sleepers (20)			22.7±3.2	55.0
Dennis et al., 2014	CS	PTSD (105)	CAPS	Not reported	30.8±5.3	45.7
		Control (120)			28.0±5.5	53.3
Dennis et al., 2017	CS	PTSD (93)	CAPS	Not reported	28.9±5.6	51.0
		Control (104)				

De Zambotti et al., 2011	CS	Insomnia (8)	PSQI, AIS, ISI	Questionnaires, semi-structured interviews, actigraphy, sleep diaries	23.3±2.4	50.0
		Control (8)			23.3±3.2	62.5
Eddie et al., 2020	CS	MDD (39)	HAM-D, ISI, BDI-II	Questionnaires, patient history	28.1±9.2	69.2
		Insomnia (14)			32.14±9.1	85.7
		Control (20)			31.5±14.6	75.0
Farina et al., 2014	CS	Insomnia (85)	ICSD-2, SCID	Neurologic and psychiatric evaluation	53.2±13.6	44.7
		Control (55)			54.2±13.9	41.8
Fatt et al., 2020	CS	"Healthy participants" (24)	Clinician assessment	Patient history	35.4±12.0	75.0
Furutani et al., 2011	CS	High chronic stress (6)	Stress response questionnaire	Not reported	20.3±0.5	63.6
		Low chronic stress (5)				
Hall et al., 2004	CS	Stress exposure (31)	Random assignment	Insomnia: patient history	19.6±1.8	49.0
		Control (28)				
Hall et al., 2013	CS	European American (160)	Race	Sleep apnoea: patient history, PSG	51.2±2.2	100.0
		African American (119)			51.0±2.2	100.0
		Chinese American (53)			51.7±2.2	100.0
Idiaquez et al., 2014	CS	Mild OSA (23)	PSG, AHI	OSA: PSG	41.2±8.8	8.7
		Severe OSA (35)			48.9±8.5	8.6

Israel et al., 2012	CS	Insomnia (54)	DSM criteria for self-report data, SCID	Clinical interviews, patient history	34.6±9.7	55.6
		Control (22)			26.5±7.3	86.4
Jarrin et al., 2018	CS	Insomnia: objectively short sleep (46)	ICSD, SCID, ISI, PSG	Clinical interviews	51.6±10.8	52.2
		Insomnia: nearly normal sleep (134)			49.3±11.5	66.4
Kobayashi et al., 2014	CS	PTSD (20)	SCID, CAPS	Sleep breathing and movement disorders: PSG	24.0±5.6	75.0
		Resilient (18)			21.7±3.7	61.1
Kobayashi et al., 2016	CS	PTSD (38)	SCID, CAPS	Sleep apnoea: PSG	22.5±4.7	65.8
		Resilient (33)			22.7±3.8	51.5
Kwon et al., 2019	CS	MDD (30)	Interview with certified psychiatrist	Sleep breathing disorders: PSG	50.5±14.5	50.0
		Control (30)			50.0±17.5	50.0
Leistedt et al., 2011	CS	Unmedicated MDD in depressive episode (25)	DSM-IV-TR criteria	PSG, patient history	39.0±19.6	0.0
		Control (20)			36.0±25.5	0.0
Mellman et al., 2004	Longitudinal	PTSD (9)	SCID, CAPS	Sleep apnoea: PSG	37.1±10.8	31.6
		Control (10)				

Migliorini et al., 2015	Longitudinal	Bipolar patients during depressive episode (15) Bipolar patients during non-depressed episode (15)	Previous diagnosis of bipolar disorder (I or II), QUIDS	Not reported	Not reported	Not reported
Nishith et al., 2003	Cohort	PTSD (6)	CAPS	PSG, patient history	30.7±9.8	100.0
Orr et al., 2000	CS	"Healthy participants" (15)	Bowel symptom frequency questionnaire, PSQI, BDI	Patient history	36.2±2.3	86.7
Ottaviani, Medea, et al., 2015	CS	Healthy males (19) Healthy females (23)	Sex	Not reported	26.9±5.9 26.5±9.5	0.0 100.0
Ottaviani, Shahabi, et al., 2015	CS	MDD (18) Control (18)	SCID or MINI	Not reported	38.4±12.1 30.1±10.5	66.7 61.1
Rissling et al., 2016	CS	PTSD (97) Control (114)	CAPS	Not reported	28.1±5.5 30.5±5.4	48.3 52.0
Saad et al., 2020	CS	Depressed (25) Control (31)	Medical history, BDI	Sleep apnoea: PSG	33.8±12.2 37.2±12.4	84.0 58.1
	CS	Nightmare (19)		Not reported	20.9±1.6	47.4

Simor et al., 2014		Control (21)	Dream Quality Questionnaire, Hungarian version of the Van Dream Anxiety Scale, 7-point Likert scale on nightmare frequency		21.6±1.5	47.6
Spiegelhalder et al., 2011	CS	Insomnia (58)	DSM-IV criteria	Clinical interview, patient history	39.5±11.8	62.1
		Control (46)			37.3±11.4	58.7
Tan et al., 2019	CS	Younger (22)	Age at time of study	Not reported	55.6±4.0	64.0
		Older (23)			67.4±5.2	61.0
Ulmer et al., 2018	CS	Poor sleepers (31)	PSQI	OSA, RLS and PMLS: clinical interview, PSG	40.9±17.2	54.8
		Good sleepers (53)			35.2±14.3	47.2
	CS	PTSD veterans (29)	CAPS, SCID		31.0±8.7	12.9
		Control veterans (33)			33.0±7.4	
Woodward et al., 2009	CS	PTSD (22)	CAPS, SCID	PSG, patient history	42.2 ±12.8	Not reported
		PD (13)			42.1±11.0	
		PTSD + PD (11)			42.0 ±13.9	
		Control (13)			39.6±10.8	

Wu et al., 2015	CS	PLMS OSA (30)	PSG	PSG, patient history	54.9±12.8	23.3
		Non-PLMS OSA (30)			45.5±15.3	40.0
Yang et al., 2011	CS	MDD (52)	Interview with psychiatrist based on DSM-IV criteria	Not reported	42.7±10.2	61.5
		Primary insomnia (47)			43.9±10.4	66.0
		Healthy control (88)			41.6±11.7	62.5

Data are presented as mean ±SD or percentage. AHI: apnoea hypopnoea index; AIS: Athens Insomnia Scale; BDI: Beck Depression Inventory; BMI: Body mass index; CAPS: Clinician-administered PTSD Scale; CPAP: Continuous positive airway pressure; CS: Cross-sectional; CTQ-SF: Childhood Trauma Questionnaire Short Form; DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders, 4th edition (text revision); FIRST: Ford Insomnia Response to Stress Test; HAM- D: Hamilton Depression Rating Scale; ISCD-2:International Classification of Sleep Disorders–second edition; ISI: Insomnia Severity Index; MDD: Major depressive disorder; MINI: Mini-international Neuropsychiatric Interview; OSA: Obstructive sleep apnoea; PD: Panic disorder; PLMS: Periodic limb movement syndrome; PSG: Polysomnography; PSQI: Pittsburgh Sleep Quality Index; PTSD: Post-traumatic stress disorder; QUIDS: Quick Inventory of Depressive Symptomology; RLS: Restless legs syndrome; SCID: Structured Clinical Interview for DSM-IV.

Included studies reported sleep outcomes, mood- and anxiety-related outcomes and sleep-related HRV in various populations. For ease of understanding, we present the data first for apparently healthy participants (to indicate normative values and associations), then for participants with defined sleep disorders, and lastly for participants with diagnosed anxiety-mood-related disorders.

5.3.2. Healthy participants

Six studies report on sleep-related HRV outcomes in healthy participants[312,321,323–326] (Appendix 5.3). Two studies measured HRV during various sleep stages and observed that sleep-related HRV varies according to individual sleep stages with greater markers of parasympathetic activity during non-rapid eye movement (NREM) compared to REM sleep[324] and wake[326] indicated by higher HF power (p<0.001) and lower LF/HF (p<0.001) ratios[324]. HF power values were also lower during REM compared to wake (p<0.050)[324,326]. Another study showed that this varied further by ethnic group such that European Americans had higher normalized LF power and LF/HF ratios and lower normalized HF values (i.e. indicative of less parasympathetic activity) during NREM Stage 2 and REM sleep than the African- and Chinese American groups[321].

Poorer sleep quality (β=0.31, 95% confidence intervals (CI): 0.18, 0.44, p<0.001), younger age (β=-0.06, 95% CI: -0.10, -0.001, p=0.012) and lower sleep-related HRV (β=-0.02, 95% CI: -0.04, -0.01, p=0.011) were predictors of more severe psychological symptoms[312], while higher trait worry and rumination were predictors of lower HRV[304]. Lower sleep-related HRV correlates with subjective severity of sleep difficulties (β =-0.47, p=0.005)[325] while higher indices of vagal activity during sleep are linked to better subjective sleep quality[325,326] (β =0.43, p=0.007)[325].

5.3.3. Participants with sleep-related disorders

5.3.3.1. Insomnia

Ten studies reported on sleep-related HRV in participants with and without insomnia[297,317,318,327,328] (Appendix 5.4). Five of these studies found differences in sleep-

related HRV measures between insomnia and control groups[297,314,316,327,329]. Participants with significantly shorter sleep duration or lower sleep quality had lower overall sleep-related HRV[314,316,329] and markers of parasympathetic activity [314,316,329] than controls. Time domain measures (RMSSD[314], SDNN[314,316] and pNN50[314]) during sleep were lower in insomnia groups than controls, and participants with insomnia also showed lower HF power [314] and higher LF power[297,314] and LF/HF ratios[297,329] during sleep compared to controls[297,314]. Furthermore, participants with objective insomnia (measured by PSG) had lower HF power and higher LF/HF ratios during sleep than those with subjective insomnia[327]. Spiegelhalder et al. (2011) observed a trend towards lower sleep-related RMSSD, pNN50 and HF power values in insomnia participants compared to controls, which reached statistical significance when limited to only participants with insomnia and objectively-measured short sleep (RMSSD: p=0.046; pNN50: p=0.024; HF: p=0.037)[316]. Cosgrave et al., 2021 showed similar results, with differences in SDNN only significant when comparing participants with objectively short sleep to controls[329]. Jarrin et al. (2018) found sleep-related HRV differences in objectively-measured short sleepers even after adjusting for covariates (including depressive symptoms) compared to participants with nearly normal objectively-measured sleep duration, but who had subjective insomnia[327]. One study found that during sleep, patients with insomnia also showed diminished MSE[314]. Collectively these findings suggest that short-sleepers and individuals with insomnia, characterised by objectively measured sleep, versus those with insomnia with near-normal objectively measured sleep and control participants, have lower HRV measures, except for measures more typically associated with sympathetic activation, which show higher values in the former group.

Looking at the relationships between sleep and sleep-related HRV measures, the LF/HF ratio was positively correlated with objectively measured wake after sleep onset (WASO) (r=0.40; p=0.037) in both insomnia and control participants[317]. Furthermore, daytime sleepiness (ESS scores) negatively correlated with awake and sleep measures of RMSSD (awake: r=−0.446, p=0.015; sleep: r=−0.362, p=0.054) and HF power (awake: r=−0.488, p=0.007; sleep: r=−0.402, p=0.031) and positively with the LF/HF ratio (wake: r=0.353, p=0.061; sleep: r=0.399, p=0.032) only in participants with insomnia[314]. Additionally, one study found sex-linked differences in sleep-related HRV with females (both those with insomnia controls) having lower time domain HRV values compared to males (SDNN F(97,1)=15.38, p<0.001, β(female)=-12.39); RMSSD (F(97,1)=6.21, p=0.014, β(female)=-7.56; and pNN50 (F(97,1)=12.48, p<0.001,

β(female)=-7.08)[316].

5.3.3.2. Other sleep disorders

Three studies reported on sleep-related HRV and depression/anxiety-related symptoms in participants with obstructive sleep apnoea (OSA)[319,330,331] and one reported on participants with frequent nightmares[332]. In participants with severe OSA, one study reported the sleep-related cardiac spectral power values were mostly in the LF band and reduced in the HF band. There was no association between depressive symptoms and markers of sleep-related ANS function[330]. The log LF/HF ratio was associated with respiratory arousal index (β=0.36; p<0.001) with significantly higher log LF/HF ratios in the severe OSA group than in the non-OSA group[331].

Despite no significant differences in sleep duration or sleep architecture in OSA participants with and without periodic limb movement syndrome (PLMS), the OSA participants with PLMS had lower sleep-related HRV measures, with lower RMSSD (p=0.032), SDNN (p=0.028), HF (p=0.047) and normalised HF (nHF) (p=0.004) and higher normalised LF (nLF) (p=0.003) and LF/HF ratios (p=0.018) than those without PLMS. After adjusting for age, the presence of PLMS in participants with OSA was still independently associated with sleep-related RMSSD (β=-20.16; 95% CI: -39.90, -0.42, p=0.046), nHF (β=-0.09; 95% CI: -0.16, -0.02, p=0.013) and the LF/HF ratio (β=0.54; 95% CI: 0.04, 1.03, p=0.036). After adjusting for sex, PLMS in participants with OSA was also still independently associated with sleep-related nLF (β=0.09; 95% CI: 0.02, 0.16, p=0.008). There was no significant difference in Hospital Anxiety and Depression Scale (HADS) scores between the two groups[319], so the authors did not investigate the influence of this variable on HRV.

In participants suffering from recurrent nightmares, RMSSD (p=0.002), HF power (p=0.004) and LF power (p=0.006) values were reduced during non-transitory NREM periods compared to controls. Additionally, HRV measures in the nightmare group were similar before and after REM periods, whereas controls had greater RMSSD, HF and LF power values after REM periods compared to before REM sleep[332].

5.3.4. Sleep and sleep-related HRV in participants with mood-, anxiety- and stress-related disorders

5.3.4.1. Mood-related disorders

Eight studies reported on participants with MDD and one study reported on participants diagnosed with bipolar disorder who were experiencing a depressive episode (Appendix 5.5). Of these studies, three found that MDD groups reported higher PSQI scores[305,314,322]. Sleep-related time domain measures (RMSSD[305,311,314], SDNN[302,305,333] and pNN50[305,314]) and HF power[302,305,314] were all lower in MDD compared to control participants. Sleep-related LF power[305,314] and LF/HF ratios[302,305] were higher in participants with MDD than control participants. Basset et al. (2016) found that even after adjusting for covariates (age, sex, PSQI, waking at night and medications) in an extended multivariate model, the presence of depression was still a significant predictor of decreased sleep-related RMSSD (β=-21.86, 95% CI: -32.12, -11.60, $p<0.05$) and SDNN (β=-20.88, 95% CI: -36.73, -5.03, $p<0.05$) compared to controls[305]. Sleep-related HF power was significantly lower in participants with MDD than controls after adjusting for age, sex, PSQI and waking at night, but was no longer significant after accounting for medications[305].

Yang et al. (2011) and Ottaviani et al. (2015) found lower HRV during both wake and sleep in participants with MDD compared to controls while Kwon et al. (2019) only found lower HRV during wake in MDD than control participants in time and frequency domain measures[302,311,314]. Saad et al. (2020) found there was a group-sleep stage interaction with the difference in sleep-related HRV between the MDD and control groups widening with increasing sleep depth such that the difference in HRV between groups was greater in NREM Stage 3 than in Stages 1 or 2 (data not shown), although they found no differences during wake[333]. Brupbacher et al. (2021) found no differences in time or frequency domain HRV measures across any sleep stage in participants with MDD after either a bout of aerobic exercise or reading magazines[334].

Non-linear measures (MSE[314], DFA alpha-1[302] and SampEn[322]) of sleep-related HRV were also lower in MDD groups during sleep compared to controls. A stepwise regression analysis showed the DFA alpha-1 correlated with Beck Depression Inventory (BDI) scores (r=0.36,

p=0.005) and accounted for 12.9% of the variance in BDI scores. The effect size of this association, however, was small[302]. Leistedt et al. (2011) found sleep-related SampEn (MDD: median 15.4; range 6.9–19.8 compared to control: 17.6; 13.8–19.4; p<0.04) was associated with HADS score in participants with MDD (r=-0.40; p=0.05)[322]. Yang et al (2011) found that PSQI score correlated with LF/HF ratio (r=0.345, p=0.057), RMSSD (r=-0.404, p=0.024), pNN50 (r=-0.359, p=0.047) and HF power (r=-0.376, p=0.037) during wake in the MDD group, with no similar observations among the controls [314].

5.3.4.2. Anxiety-related disorders

Eight studies reported on participants with PTSD (Appendix 5.5) while no studies reported on HRV and sleep in any other diagnosed anxiety-related disorders. All the studies which used PSQI found significantly higher scores in PTSD groups than controls[301,304,306,308]. Mellman et al. (2004) found an interaction effect between PTSD group and sleep stage on ANS function[303]. Time-in-bed nHF power was lower in participants with PTSD than controls (p<0.05)[232], as were SDNN, log HF power and log LF power, and none of these measures varied by current comorbid MDD status[301]. Participants with PTSD had higher heart rates during sleep than controls in multiple studies, even after adjusting for age (p=0.017), combat exposure (p=0.003), sleep and activity (p<0.05)[75,306,308]. One model showed a significant interaction between PTSD symptom severity and interval (sleep, rest or activity periods) for HF power (p=0.028, Cohen's d=0.12) where more severe PTSD symptoms predicted lower HF values during sleep only[171].

While Ulmer et al. (2018) found no overall difference in sleep-related HF power between groups after adjusting for covariates, the participants with PTSD had lower HF power during NREM (p=0.047), specifically during the first and fourth NREM cycle, but not during REM (p=0.16) sleep. This diminished HF power in participants with PTSD during NREM sleep remained significant after adjusting for age, sex, apnoea hypopnea index, and BDI-II scores (excluding the sleep questions). Based on this, the authors proposed that PTSD status may mediate the NREM-REM differences in HRV, although this interaction did not reach significance (p=0.074)[304]. Agorastos et al. (2013) found positive correlations between clinician-administered PTSD scale scores and heart rate, LF/HF ratio (all p<0.01) and DFA alpha

($p<0.05$). Depression severity was also positively correlated with the LF/HF ratio and daytime DFA[75].

In another study, the PTSD-resilient group's (those exposed to trauma but who did not develop PTSD) total sleep time was correlated with nHF power ($r=0.75$, $p=0.001$) and LF/HF ratios ($r=-0.64$, $p=0.008$) during time-in-bed but this relationship was absent in the PTSD group[232]. Another study found heart rate ($r=0.332$, $p<0.05$) and RSA magnitude ($r=-0.333$, $p<0.05$) during sleep were both correlated with PSQI scores in both the PTSD and control groups. Their final model accounted for 37% of the variance in PSQI scores (adjusted $R^2=0.371$, $p<0.001$) and included RSA magnitude and Beck Anxiety Inventory (BAI) scores as significant predictors of sleep quality (RSA: $\beta=-0.28$, $p<0.05$; BAI: $\beta=0.41$, $p<0.01$)[306].

One study reported on "healthy participants" who had clinically significant scores on questionnaires assessing symptoms of anxiety[335]. These participants showed that worry duration correlated with lower sleep-related HRV and that lower sleep-related HRV correlated with poorer sleep quality[335].

5.3.4.3. Stress-related exposure

Sleep and sleep-related HRV data describing participants with stress-related exposure was reported in three studies (Appendix 5.4). Two of these studies used participants where cases and controls both reported questionnaire scores suggesting the presence of clinical levels of anxiety[313,315] whereas Furutani et al. (2011) included participants who were chronically stressed and healthy controls[309]. In the acute stress study by Hall et al. (2004), this stress exposure was in the form of being told they would have to prepare and present a speech in the morning while control groups were told they would be asked to read a magazine. HF was consistently higher in the control group during REM ($p<0.01$) and across all NREM periods ($p<0.02$) while the stress group showed higher LF/HF ratios than controls during NREM ($p<0.05$). The LF/HF ratio during NREM was negatively correlated with sleep maintenance ($r=-0.43$, $p<0.01$)[315].

Meanwhile, in another study, the high chronic stress group had higher LF/HF ratio before sleep onset compared to during sleep (all $p<0.01$), whereas in the low chronic stress group

there were no differences between LF/HF ratios measured before or after sleep onset. In the high and low chronic stress groups, both the HF power (p=0.03) and LF power values (p=0.04) showed significant time effects when comparing pre-, during and post-sleep onset, such that HF power increased and LF power decreased as the participants transitioned from wake to sleep[309].

Finally, participants exposed to childhood trauma also reported poorer quality sleep, based on PSQI scores (p<0.001)[313], compared to controls. Whilst the trauma group showed only a trend towards lower sleep-related HRV, when this group was split and analysed based on the type of trauma experienced, the physical abuse subgroup showed significantly lower HF power values than controls in the early hours of the night [313].

5.3.5. Risk of bias

There was considerable bias in many of the included studies (Appendix 5.2). Potential confounders such as age (which ranged widely in these studies), sex and comorbidities were not considered in many of the HRV analyses[232,297,302,309,313,318,320,324,325,328,330,332,336]. Additionally, most studies did not adequately describe the study participants in sufficient detail, making it difficult to compare populations and thus limiting the generalisability of the results[75,297,301,305,306,309,313,316,318–320,322,324,330,332,333,335,336].

5.4. Discussion

This review found that 29 of the 35 studies assessed (excluding the 6 studies with apparently healthy individuals only) reported lower HRV during sleep (as measured using time-domain, frequency-domain or non-linear methods) in participants with both mood- and anxiety-related disorders and sleep disorders compared to participants without these disorders. This suggests that sleep-related ANS dysfunction may be a common but independent factor to both sets of disorders. That is, ANS dysfunction during sleep may play a role in both sets of disorders, but that the mechanism by which of sleep-related ANS may associate with these disroders is likely specific to either the mood-, anxiety- or sleep-related disorders. It may, however, be an underlying reason for the frequent co-occurrence of these conditions, especially given that in healthy individuals, both poor sleep and lower sleep- related HRV are

predictors of more severe psychological symptoms[323]. This review is unable to categorically show that ANS dysregulation plays a role in the relationship between sleep and mood/anxiety-related symptoms, given a) the heterogeneity of the sleep, HRV and mood- and anxiety-related disorder symptom measures, b) that the majority of the included studies were cross-sectional in design, c) that many did not control for known confounders, including three studies where participants were taking psychotropic medications, six studies where the authors did not state whether or not participants were taking psychotropic medications and 15 studies which did not report excluding participants with comorbid sleep disorders and d) that there are at present no mediation analyses of sleep, HRV and mood- and anxiety-related symptoms. Despite this, we did find that the presence of mood-, anxiety- or sleep-related disorders was associated with reduced sleep-related HRV and altered indices of sympathovagal modulation. In sleep-related disorder populations, this relationship appears limited to objectively-measured shorter, poorer quality or more disordered sleep.

We considered the relationships between depressive- and anxiety-related symptoms and sleep-related HRV in populations with sleep disorders such as insomnia and OSA. Specifically, results from seven studies showed that objectively-measured short, poor quality or more severely disordered sleep (e.g. more severe OSA) may be associated with ANS dysregulation[297,316,319,327,329–331]. Meanwhile, insomnia groups with significantly higher subjective measures of poor sleep (PSQI and/or ISI scores) unanimously reported more severe depressive or anxiety-related symptoms but the majority showed no differences in measures of HRV[314,316–318,328]. Given the limited sample sizes of these studies, they may have been underpowered to detect HRV differences. Seven of the nine studies where participants with insomnia had objectively-measured shorter, poorer quality or more severely disordered sleep than controls showed they had lower HRV during sleep compared to controls. This suggests that objective measures of quality or disordered sleep may be necessary for the categorisation of insomnia that manifests with detectable changes in HRV.

Given the complexity of the physiology underlying psychiatric disorders and insomnia it may also be that those studies that include insomnia groups with significantly higher subjective

measures of poor sleep exhibit a scenario where other factors, such as psychological factors (e.g. rumination)[176], either a) compound subtle alterations in ANS regulation which the studies were underpowered to detect or b) are the predominant drivers of the observed relationship between poor sleep and mood- and anxiety-related disorders (as proposed in our model in Figure 5.2 by the arrows which bypass sleep-related ANS dysregulation).

Participants with MDD, PTSD, and acute stress all had lower sleep-related markers of PNS activity[232,301,302,305,314,315] and overall HRV[302,305,311,314,333] compared to controls. All participants diagnosed with a mood disorder showed some evidence of lower overall HRV, and time-domain HRV measures remained significant even after adjusting for medication usage. These differences widened with increasing sleep depth[333] such that differences in HRV between MDD-diagnosed individuals and controls were greater in Stage 3 NREM than in Stage 1 NREM sleep. There was a significant interaction between PTSD symptom severity and interval (sleep, rest or activity periods) for HF power, where more severe PTSD symptoms predicted lower HF power values during sleep only[333]. This finding specifically highlights the association between symptom severity and sleep-related HRV dysregulation. In the stress-related studies sleep-stage specific ANS dysregulation was found with differences in sympathovagal modulation in chronically high-stressed participants during NREM sleep and negatively correlated with sleep maintenance. Collectively, these results suggest that these lower HRV values during sleep (and during NREM sleep specifically), indicative of sleep-related hyperarousal, are linked to more severe symptoms of anxiety (including stress) and depression as well as the presence of sleep disorders and, by extension, poor sleep quality.

We also considered sleep parameters in participants with mood- and anxiety-related disorders and lower sleep-related HRV. In individuals diagnosed with or self-reporting MDD- and PTSD, lower sleep-related HRV measures were associated with poorer self-reported sleep quality[301,304–306,314,322,335], whereas controls had higher sleep-related HRV. Measures of hyperarousal also negatively correlated with sleep quality[308,315,335] although this relationship was absent in some PTSD-diagnosed participants[232]. None of the included studies focused on the potential mediation relationship between sleep, sleep-related HRV and mood- and

anxiety-related disorders and few studies controlled for the effect of poor sleep and depressive- or anxiety-related symptoms on HRV. There were clear differences, however, in sleep-related indices of ANS regulation between healthy participants and those with sleep or mood- and anxiety-related disorders. The healthy participants displayed markers of more parasympathetic activity/less sympathetic activity during sleep than the disordered groups. Additionally, many of these differences were sleep stage specific in the participants diagnosed with depression- or anxiety-related disorders. This supports our hypothesis that ANS dysregulation may influence the observed relationship between sleep and mood- and anxiety-related disorders and suggests that it may be sleep stage specific.

Based on this, we propose that ANS dysregulation during sleep may influence the apparent bidirectional relationship between poor quality or disordered sleep and mood- or anxiety-related disorders (see Figure 5.2). Robust studies are required to test this hypothesis. Since parasympathetic input usually predominates during sleep[286], indices of parasympathetic input are positively correlated with good sleep quality and lower HRV during sleep predicts increased severity of sleep difficulties in apparently healthy individuals[323]. Thus, attenuation of parasympathetic activity at night, potentially contributing to a state of hyperarousal, is likely unconducive to good quality sleep. This is in line with the current literature which accepts hyperarousal as a factor in insomnia[234,337] and that there may in fact be a continuum of ANS dysfunction which parallels the range in sleep complaint severity. Additionally, this continuum of dysfunction may be as a result of a "natural continuum of basal arousal levels" making some individuals more prone to hyperarousal than others [234,337] and thus more prone to insomnia. If an individual does develop hyperarousal leading to poor quality sleep, this would then potentially exacerbate any depressive/anxiety-related symptoms. Alternatively, we found both depression- and anxiety-related disorders to be associated with lower overall sleep-related HRV and, specifically, sleep-related parasympathetic modulation. This may push an individual into a state of hyperarousal which then impacts on sleep and leads to the development of co-morbid insomnia. This also concurs with other literature which proposes a hyperarousal subtype of PTSD[338] and that hyperarousal may also present in anxiety[339], stress[340], depression[338], and insomnia[337]. This in turn may also explain why some patients experience sleep disturbances and others do not[341].

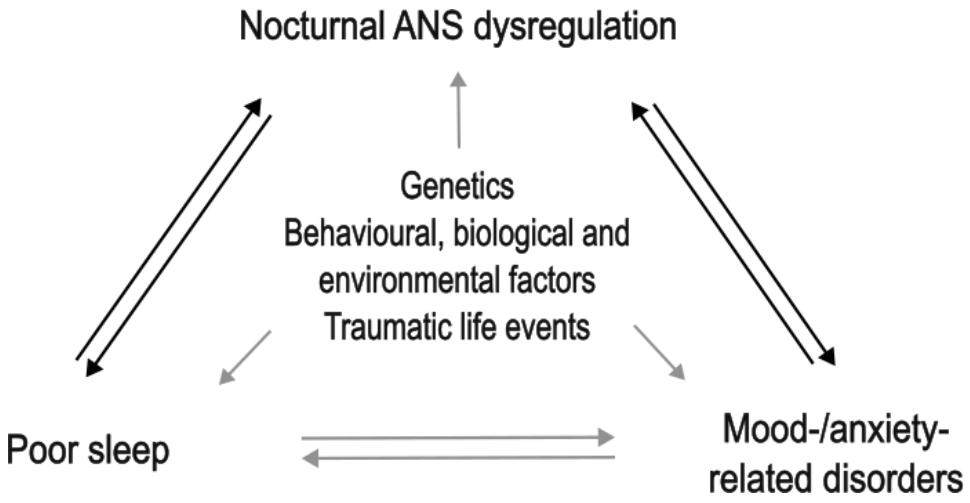

Figure 5.2: Diagram depicting the proposed relationship between sleep, autonomic nervous system (ANS) dysregulation and mood- and anxiety-related disorders. *The arrows indicate the direction of the relationships such that ANS dysregulation can be either a contributing causal factor to and / or a consequence of poor sleep and mood- and anxiety-related disorders. Light grey arrows indicate established relationships which are not the focus of this review.*

Kohler et al. (2016) proposed a hypothesis by which poor sleep quality and hyperarousal may exacerbate depression- and anxiety-related symptoms. They suggest that activation of the SNS without the corresponding counter-action of the PNS leads to systemic inflammation[342], which itself may be exacerbated by consequent sleep disruption[135]. This, in turn, creates an environment which leaves the brain vulnerable to the development of symptoms of a psychiatric disorder[342]. Thus, ANS dysregulation may influence the relationship between sleep and depression-/anxiety-related disorders.

The limitations of this review are that most of the included studies used observational designs and therefore are unable to demonstrate causality. There were no studies investigating how sleep-related HRV may mediate the relationship between disordered sleep and mood- and anxiety-related disorders, as most just looked at HRV as an outcome in populations diagnosed with or self-reporting disordered sleep or mood- and anxiety-related disorders. Only a few studies in sleep disorder populations accounted for symptoms of anxiety and depression in

their analyses of the relationship between sleep quality and HRV[317,327]. Additionally, none of the 41 reviewed studies looked at generalised anxiety-disorder or non-diagnosed anxiety in the general population. Given the high-stress nature of our current society and that hyperarousal is a characteristic of anxiety-related disorders, this appears to be a gap in the literature and an important direction for further research. Additionally, longitudinal studies and mediation analyses are required to further determine the relationship between sleep quality, ANS dysregulation and mood- and anxiety-related disorders. Finally, future research should focus on sleep stage differences as almost all studies which included PSG found HRV differences only during specific sleep stages or found different patterns of HRV compared to controls during the different sleep stages.

5.5. Conclusion

While the current evidence is too varied to conclusively state that ANS dysregulation plays a role in the relationship between disordered sleep and mood- and anxiety-related disorders, we did find that ANS dysregulation appears to be independently associated with both disordered sleep and mood- and anxiety-related disorders. This variation is likely largely due to methodological differences such as using PSG vs subjective sleep quality assessments as HRV differences may be sleep stage specific and particularly associated with objectively shorter, poorer quality or more disordered sleep. Included studies largely showed lower sleep-related HRV, lower markers of sleep-related parasympathetic activity and altered sleep-related sympathovagal balance in populations with sleep or mood- and anxiety-related disorders versus controls which could be a marker of hyperarousal in these populations. Hyperarousal is widely considered a factor of insomnia and is a characteristic of anxiety-related disorders such as PTSD. This provides common ground between sleep and psychiatric disorders and provides support for the hypothesis that sleep-related ANS dysregulation influences the observed bidirectional relationship between sleep and mood- and anxiety-related disorders. However, longitudinal studies (accounting for confounding factors) and mediation analyses are necessary to further elucidate the relationship between sleep, HRV and mood- and anxiety-related disorders. In light of these findings, subsequent experimental chapters will i) investigate sleep versus wake HRV (Chapter 6) to assess whether these findings

of lower sleep-related HRV hold true for our population - in whom we expect to observe markers of hypervigilance and hyperarousal given their qualitative descriptions - and ii) use Structural Equation Modelling (Chapter 7) to directly test whether sleep-related ANS dysregulation is a key contributor to the relationship between poor sleep and symptoms of mood- and anxiety-related disorders.

Chapter 6

Characterising heart rate variability in individuals living in a low socioeconomic status environment

6.1. Introduction

Individuals living in low socioeconomic status (SES) environments are more vulnerable to impaired sleep[44,117,119]. The reasons for this are multifactorial but have roots in both physical and social aspects of the environment. Individuals in low SES areas frequently live in suboptimal housing, which can present challenges such as noise and light pollution, extreme temperatures and poor ventilation, which all have implications for sleep[44,117,119]. As characterised in Chapter 3, low SES environments, such as the one in which the participants of this study reside, also tend to be areas of high crime and high neighbourhood disorder (including violence, lack of trust, gang activity and drunk and disorderly behaviour) [44,117,119]. High crime rates and perceived neighbourhood disorder have been associated with short, poor quality sleep[211,223,229]. This may be because individuals feel unsafe in these environments leading to fear of sleep and, consequently, impaired sleep [211,223,229]. The negative effects of fear of sleep on sleep may be through dysregulation of the autonomic nervous system (ANS) at night in response to chronic stress. During sleep, particularly non-REM sleep, there is dominance of the parasympathetic nervous system (PNS)[343,344]. Persistent activation of the sympathetic nervous system (SNS), driven by fear and stress[165,345,346], may impair the body's ability to achieve parasympathetic dominance at night. In fact, there is evidence to suggest that neighbourhood stress has been linked to increased nocturnal SNS activity[126].

Dysregulation of the ANS is reflected in reduced heart rate variability (HRV) as HRV is regulated by the brain's neural control of the heart via the ANS. The ANS comprises two branches: the SNS, responsible for the "fight-or-flight" response, and PNS, which governs our "rest-and-digest" state[161]. Typically, low HRV is understood to reflect a shift towards sympathetic dominance (with excess sympathetic activity or insufficient parasympathetic activity) and, consequently, one would expect to see higher HRV during sleep than wake[291,344]. There are various HRV metrics that are categorized into time domain, frequency domain, or non-linear domain measures[161]. Time domain metrics include the root mean square of successive differences between R-peak to R-peak (R-R) intervals (RMSSD) and the standard deviation of differences between R-R intervals (SDNN). Time domain measures are the preferred choice for 24h length recordings, however, these measures are also appropriate for short-term measures (5 minute long)[161]. Frequency domain metrics encompass very low

frequency (VLF), low frequency (LF), and high frequency (HF) powers, which are derived from the frequency-transformed R-R intervals[161]. Similarly to time-domain variables, frequency domain variables are appropriate for both short-term and 24h measurement, however, for frequency domain measures the recordings can be as short as 2 minutes[161]. While SDNN is predominantly driven by PNS activity during rest (and correlates more closely with HF power), in ambulatory monitoring SDNN is more related to the lower frequencies and represents a combination of various signals controlling HRV. Higher RMSSD and HF values are largely indicative of vagal input. LF power, however, represents baroreflex feedback regulation mediated by both sympathetic vasomotor nerves and cardiac vagal nerves and the physiologic basis of VLF is still unclear, although higher values correspond to reduced sympathetic and greater parasympathetic activity[164].

HRV follows distinct diurnal patterns, with peak vagal activity occurring during nighttime hours, marked by elevated high-frequency components and decreased sympathetic dominance, and reaching its nadir during the day[161]. Dampened 24h HRV, characterized by a smaller amplitude between HRV measures during the day and night, and representative of reduced vagal tone and limited autonomic flexibility, has been linked to various pathophysiological states[161,347]. Reduced nocturnal HRV not only reflects impaired autonomic regulation but may compromise sleep architecture and quality as it may reflect nocturnal hyperarousal. Previous research, which was outlined in Chapter 5, suggests that altered sleep-related HRV is frequently observed in people with short and/or disturbed sleep. Specifically, higher parasympathetic activation during sleep, measured through HF power, correlates positively with sleep quality, while diminished HRV is linked to increased sleep fragmentation and difficulties with both sleep initiation and maintenance[159]. Fragmented sleep in turn may disrupt the expected diurnal variation in HRV as awakenings after sleep onset cause repeated increases in heart rate and sympathetic activity instead of sympathetic withdrawal[348], potentially creating a self-reinforcing cycle of autonomic and circadian dysregulation.

The implications extend beyond sleep alone; poor sleep and reduced HRV[84,147,349–352] – whether assessed during short-term daytime measures[353], longer sleep-related measures[159,354] or the diurnal difference between sleep and wake[347] - are individually associated with adverse health outcomes, including increased cardiovascular disease risk, impaired cognitive functioning, and heightened susceptibility to mood and anxiety

disorders[150,236,355]. These outcomes are particularly pronounced in populations already burdened by the stressors of low SES, underscoring the importance of understanding and addressing the intersection of HRV, sleep, and environmental stress.

Individuals in low SES environments may be particularly vulnerable to the effects of stress on sleep due to safety concerns, which may exacerbate nocturnal hypervigilance[126,356]. One could speculate that nocturnal hypervigilance is associated with sustained sympathetic input into the evening. This has implications specifically for sleep-related HRV and the diurnal difference in HRV. Therefore, this study aimed to i) characterise HRV in men and women living in a low SES environment and ii) compare their heart rate variability metrics during wake and sleep. As a previous meta-analysis suggests that there are gender differences in HRV measured over 24h[357] and that gender-based differences have been observed throughout the chapters in this thesis, an *a priori* decision was made to investigate women and men separately.

6.2. Methods

6.2.1. Study design and overview

This is a cross-sectional observational sub-study of the longitudinal five-country study entitled "Modelling the Epidemiologic Transition Study (METS) – Sleep" as outlined in Chapters 3 and 4. Protocols for the parent studies METS-Microbiome and METS[188,189] have been published previously. We present only methodological information specific to the current analysis, for which we supplemented METS-Sleep data collection with 24h ambulatory electrocardiogram (ECG) and fear of sleep questions in the South African cohort only. At their annual clinic visit, participants completed questionnaires to assess sleep quality, daytime sleepiness, symptoms of insomnia, sleep apnoea and fears related to sleep. They were then given a wrist-worn actigraphy device to measure habitual sleep characteristics over a period of seven days. METS-Sleep and the current study were approved by the University of Cape Town's Faculty of Health Sciences Human Research Ethics Committee (HREC numbers: 696/2014 and 154/2020), conducted in accordance with the Declaration of Helsinki[190] and included only participants who had given informed consent.

6.2.2. Participants

South African adults (25-55 years of age) of African-origin enrolled in METS-Sleep were invited to participate in this study. The participants were residents of Khayelitsha, a low SES community characterised by high-density, temporary, and informal housing, along with high rates of crime and unemployment. This sample was not entirely random, as we included the first 85 volunteers who agreed to participate in this sub-study. The sample size was limited to 85 for practical considerations given difficulties with participant compliance, limited heart rate monitors, time constraints (participants had to wear the monitor for at least 24h and collection days were limited to Monday-Thursday to minimise the effects of weekend drinking and reflect typical routine). Shift workers and women who were pregnant or breastfeeding were excluded. After excluding individuals with invalid data (n=26), the final sample consisted of 59 participants (average age 43.6±7.8 years, 81% women).

6.2.3. Questionnaire data

Demographic information, chronic diseases, medications, employment status, education level, smoking status and weekly alcohol consumption were collected as part of the parent study. Individuals also completed the Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS) and Fear of Sleep Inventory (FoSI) questionnaires as described in Chapter 4.

6.2.4. Actigraphy-derived sleep measures

As per the methodology outlined in Chapter 4, participants were equipped with a wrist-worn accelerometer (Actiwatch Spectrum Plus, Philips Respironics, Bend, OR, US) to wear on their non-dominant wrist continuously for seven days while maintaining a sleep diary. Only participants with a minimum of five days of valid actigraphy data were included in the

analysis. Sleep periods were manually identified based on established guideline[11]. Data were processed using Philips Actiware software (v6.3, Philips Respironics, Bend, OR, US).

The outcome variables included average bedtime (hh:mm), wake-up time (hh:mm), time-in-bed (h) total sleep time (actual hours spent asleep), sleep efficiency (%), wake after sleep onset (WASO, minutes), arousal index (arousals.h^{-1}) and the sleep fragmentation index (SFI, %). Long sleep was defined as average sleep duration exceeding 9 hours, and poor sleep efficiency was classified as less than 85%.

6.2.5. Heart rate variability

Free-living ambulatory HRV was recorded over 24 hours at a 1000Hz sampling rate using a portable ECG chest strap (eMotion Faros Sensor, Mega Electronics LTD, Kuopio, Finland). Participants were asked to maintain their usual routines during monitoring, limited to weekdays (Monday-Thursday) to mitigate weekend lifestyle effects. HRV assessment took place during the actigraphy measurement period so that actigraphy-derived bedtime and wake-up time could be used to set the wake and sleep HRV periods individually for each participant. ECG data were processed with Kubios HRV Premium software (v3.5.0, Kubios Oy, Kuopio, Finland), which automatically removed ectopic beats and artifacts and was then manually inspected to remove any additional artifact. An ECG dataset was considered valid if it contained $\geq$18h of analysable data and was worn throughout the sleep period[161]. The 24h ECG data were segmented into sleep and wake periods corresponding to each individual's own actigraphy-derived bedtime and wake-up time for the night they wore it. For both the sleep and wake periods, average time and frequency domain variables were calculated. Specifically, RMSSD and SDNN were calculated, and the R-R intervals were transformed to calculate power spectral densities in the VLF power, LF power and HF power frequency bands of the cardiac spectrogram using Fast Fourier Transformation. Outcome variables include: Sleep and wake heart rate, RMSSD (ms), SDNN (ms), VLF power (ms^2), LF power (ms^2) and HF power (ms^2) as well as the delta values for each of these variables (calculated as sleep values minus wake values, such that negative values represent HRV higher during the day than night).

6.2.6. Data and statistical analysis

Given the uneven sample sizes and small number of men, the choice was made to use non-parametric statistics to compare men and women. Actigraphy data was utilized in two ways: i) the average of all valid days for descriptive purposes and ii) to determine the sleep period versus wake period for the night participants' HRV data was collected. Data are presented as median and interquartile range (IQR) or count (percentage). Mann-Whitney U, Chi-squared and Fisher's exact tests were used to assess differences between independent groups while Wilcoxon- matched pairs tests compared diurnal (wake) and nocturnal (sleep) averages of SDNN, RMSSD, VLF, LF, and HF power variables. Data were analysed using Stata (v15, StataCorp, College Station, TX, US) and significance accepted at $p<0.050$.

6.3. Results

6.3.1. Participant characteristics

Table 6.1 shows the demographic characteristics of participants. This sample was predominantly comprised of women. Compared to men, women had higher a body mass index (BMI; $p<0.001$) were more likely to report cardiometabolic disease (p-0.030, were more likely to be non-smokers ($p=0.009$) and consumed less alcohol per week ($p=0.008$) than the men. Differences in sleep characteristics between genders were also observed (Table 6.2), with men waking later ($p=0.020$), but going to bed at a similar time, and thus spending more time-in-bed ($p=0.027$) than women. Women reported more daytime sleepiness ($p=0.020$), had higher ISI ($p=0.035$) and FoSI ($p=0.011$) scores and more nighttime vigilant behaviour than men ($p=0.043$).

Table 6.1. Descriptive characteristics of participants.

	All (n=59)	**Women (n=47)**	**Men (n=12)**	**p-value**
Age (y)	43 [38-50]	44 [38-51]	41 [38-45]	0.492
BMI ($kg.m^{-2}$)	29.52 [23.68-37.96]	32.34 [25.44-38.67]	21.59 [18.89-23.68]	**<0.001**

Chronic disease (count, %)	39 (67)	32 (68)	7 (64)	0.777
Cardiometabolic disease	15 (26)	15 (32)	0 (0)	**0.030**
HIV	9 (16)	8 (17)	1 (9)	0.513
Chronic medication	21 (36)	19 (40)	2 (18)	0.167
Hypertensive medication	10 (17)	10 (21)	0 (0)	0.093
Statins	5 (9)	5 (11)	0 (0)	0.258
ARVs	7 (12)	6 (13)	1 (9)	0.736
Employed (count, %)	18 (31)	16 (33)	2 (18)	0.325
Highest degree of formal education (count, %)				0.215
None	2 (3)	2 (4)	0 (0)	
Primary	3 (5)	1 (6)	0 (0)	
Secondary	52 (87)	42 (88)	10 (82)	
Tertiary	3 (5)	1 (2)	2 (18)	
Smoking status (count, %)				**0.009**
Non-smoker	31 (53)	30 (63)*	1 (9)*	
Smoker	24 (39)	14 (29)*	10 (82)*	
Ex-smoker	5 (8)	4 (8)	1 (9)	
Alcohol consumption (standard drinks/ week)	0 [0-8]	0 [0-6]	12 [0-16]	**0.008**

*Data are presented as median [interquartile range] or count (percentage). ARV: antiretroviral; BMI: body mass index; HIV: human immunodeficiency virus. Presence of chronic disease was classified as anyone having a history of cardiovascular disease (heart attack, rheumatic heart disease, stroke, etc.) cancer, high cholesterol, diabetes mellitus, osteoarthritis, rheumatoid arthritis, kidney failure, a diagnosed mental disorder or any other chronic disease. Presence of chronic medication was anyone taking at least one long-term daily medication. P-values represent comparisons between the men and women determined using independent t-tests, Mann-Whitney U, Chi-squared and Fisher's exact tests. * indicates significant post hoc differences (p<0.05) between groups as determined using Fisher's exact tests.*

Table 6.2. Actigraphy, self-reported sleep and fear of sleep characteristics.

	All (n=59)	**Women (n=47)**	**Men (n=12)**	**p-value**
Bedtime (hh:mm)	22:07 [21:23-22:36]	22:05 [21:23-22:53]	22:17 [21:11-22:29]	0.954
Wake-up time (hh:mm)	7:14 [6:19-7:47]	6:57 [6:09-7:44]	7:26 [7:17-8:19]	**0.010**
Time-in-bed (h)	9.13 [8.37-9.97]	8.88 [8.08-9.87]	9.89 [8.98-10.44]	**0.042**
Long sleep (TIB >9h)	30 (50)	21 (44)	9 (75)	0.070
Total sleep time (h)	7.45 [6.88-7.95]	7.42 [6.34-7.99]	7.54 [7.33-7.93]	0.278
TST <7h	18 (31)	17 (37)	1 (8)	
TST 7-9h	36 (62)	26 (56)	10 (84)	
TST >9h	4 (7)	3 (7)	1 (8)	
Sleep efficiency (%)	82.2 [78.9-85.8]	82.5 [79.5-85.9]	80.0 [77.4-83.2]	0.156
Low sleep efficiency (<85%)	39 (67)	29 (63)	10 (83)	0.182
Wake after sleep onset (min)	85.2 [68.2-104.8]	83.7 [61.0-102.1]	87.5 [79.2-123.6]	0.120
Arousal index (number.h^{-1})	8 ± 2	7 ± 2	8 ± 2	0.173
SFI (%)	31.8 [26.2-36.0]	30.9 [23.3-35.5]	33.5 [28.4-36.3]	0.296
PSQI score	3 [2-5]	4 [2-5]	2 [2-4]	0.094
Poor sleep quality (PSQI >5)	11 (19)	10 (22)	1 (9)	0.340
ESS score	3 [1-8]	4 [2-8]	1 [0-3]	**0.020**
Excessive daytime sleepiness (ESS >10)	7 (12)	7 (15)	0 (0)	0.177

ISI score	1 [0-3]	1 [0-4]	0 [0-1]	**0.035**
Clinically significant insomnia symptoms (ISI >14)	2 (3)	2 (4)	0 (0)	0.491
FoSI score	15 [10-22]	18 [12-24]	11 [6-15]	**0.011**
Fear of sleep subscale	2 [0-4]	2 [0-5]	2 [1-3]	0.853
Fear of loss of vigilance subscale	4 [2-7]	4 [2-7]	5 [2-5]	1.00
Fear of trauma re-exposure subscale	2 [1-3]	2 [1-3]	2 [0-3]	0.394
Nighttime vigilant behaviour subscale	6±3	7±3	4±3	**0.043**
Fear of the dark subscale	0 [0-0]	0 [0-0]	0 [0-2]	0.670

Data are presented as mean ± standard deviation, median [interquartile range] or count (percentage). ESS: Epworth Sleepiness Scale; FoSI: Fear of Sleep Inventory; ISI: Insomnia Severity Index; PSQI: Pittsburgh Sleep Quality Index; SFI: Sleep Fragmentation Index; TIB: time-in-bed; TST: total sleep time. P-values represent comparisons between the men and women determined using independent t-tests, Mann-Whitney U, Chi-squared and Fisher's exact tests.

6.3.2. HRV characteristics of participants

Gender differences were observed across all measures of HRV (with the exception of the wake values of heart rate, RMSSD, SDNN and HF power and change in SDNN between wake and sleep, Table 6.3). Specifically, men had a lower heart rate during sleep, higher HRV values for all measures, as well as larger increases in HRV from wake to sleep. The figures below

compare wake and sleep time and frequency domain measures in all participants (Figures 6.1 and 6.2 respectively) as well as in women (Figures 6.3 and 6.4) and men (Figures 6.5 and 6.6.) separately. With the exception of LF power (p=0.720), all HRV variables measured during sleep were higher than those measured during wake (all p<0.010).

Table 6.3: Heart rate variability characteristics of participants.

	All (n=59)	**Women (n=47)**	**Men (n=12)**	**p-value**
Heart rate wake (bpm)	92 [82-96]	94 [84-98]	88 [81-92]	0.118
Heart rate sleep (bpm)	75 [68-82]	77 [70-86]	72 [64-78]	**0.046**
RMSSD wake (ms)	19.1 [14.7 – 25.9]	19.4 [14.6 – 24.8]	20.4 [15.4 – 37.1]	0.438
RMSSD sleep (ms)	27.5 [19.7 – 40.0]	27.5 [19.4 – 36.9]	47.7 [23.2 – 65.3]	**0.012**
RMSSD Δ (ms)	8.8 [0.4 – 17.1]	7.1 [-0.1 – 15.5]	17.1 [8.8 – 18.9]	**0.044**
SDNN wake (ms)	26.2 [19.2 – 32.1]	25.8 [19.0 – 31.8]	30.8 [23.9 – 39.4]	0.121
SDNN sleep (ms)	30.3 [23.1 – 37.4]	28.9 [20.4 – 35.9]	49.7 [26.5 – 62.8]	**0.005**
SDNN Δ (ms)	4.4 [-2.6 – 12.9]	2.5 [-3.4 – 10.8]	11.9 [1.7 – 17.4]	0.056
VLF power wake (ms^2)	77.8 [39.9 – 115.5]	69.0 [34.3 – 97.7]	121.4 [83.2 – 146.1]	**0.004**
VLF power sleep (ms^2)	104.3 [61.9 – 157.5]	84.6 [59.0 – 142.1]	184.4 [85.2 – 286.1]	**0.002**
VLF power Δ (ms^2)	34.7 [-4.9 – 70.5]	30.1 [-6.4 – 57.6]	77.5 [22.5 – 129.8]	**0.036**
LF power wake (ms^2)	414.4 [277.3 – 624.2]	405.3 [241.0 – 537.0]	635.6 [434.8 – 903.4]	**0.009**
LF power sleep (ms^2)	431.4 [217.9 – 646.2]	359.1 [195.6 – 570.7]	721.5 [431.4 – 1874.1]	**0.003**
LF power Δ (ms^2)	11.2 [-218.9 – 209.3]	-25.5 [-248.7 – 168.7]	202.4 [-140.3 – 881.3]	**0.035**

HF power wake (ms^2)	166.5 [84.6 – 253.3]	169.2 [70.9 – 250.0]	152.0 [90.9 – 433.4]	0.554
HF power sleep (ms^2)	287.5 [135.9 – 568.6]	278.9 [135.9 – 526.3]	665.9 [220.2 – 1255.4]	**0.031**
HF power Δ (ms^2)	118.4 [11.5 – 383.3]	93.0 [-5.2 – 361.1]	383.3 [52.5 – 596.6]	**0.028**

Data are presented as median [interquartile range] or count (percentage). Δ variables were calculated as the difference between sleep and wake values such that a negative indicates higher values during wake than sleep. Bpm: beats per minute; HF: high frequency; LF: low frequency; RMSSD: root mean square of successive differences between R-peak to R-peak (R-R) intervals; SDNN: standard deviation of differences between R-R intervals; VLF: very low frequency. P-values represent comparisons between the men and women determined using Mann-Whitney U tests.

There was a subgroup of individuals, however, who showed higher HRV values during wake than sleep. In all participants, this reverse pattern was present in 23% of participants for RMSSD, 35% for SDNN, 27% for VLF power, 46% for LF power and 22% for HF power. When split by men and women, the proportions weren't significantly different for RMSSD (women: 27%, men:1 0%, p=0.216), SDNN (women: 39%, men: 18%, p=0.202), VLF (women: 30%, men: 18%, p=0.449) and LF (women: 51%, men: 27%, p=0.155), although there was a trend for HF (women: 27%, men: 0%, p=0.05). There were no differences in any HRV measures between participants with chronic disease and those with no chronic disease (Appendix 6.1) or those between taking chronic medication and those not taking chronic medication (Appendix 6.2), including the proportion of individuals with reverse versus expected diurnal HRV metrics (Appendix 6.3). Similarly, there was no difference in age, perceived sleep quality, total sleep time or fragmentation between those with the reverse versus expected diurnal pattern of HRV for any of the HRV metrics (Appendix 6.3).

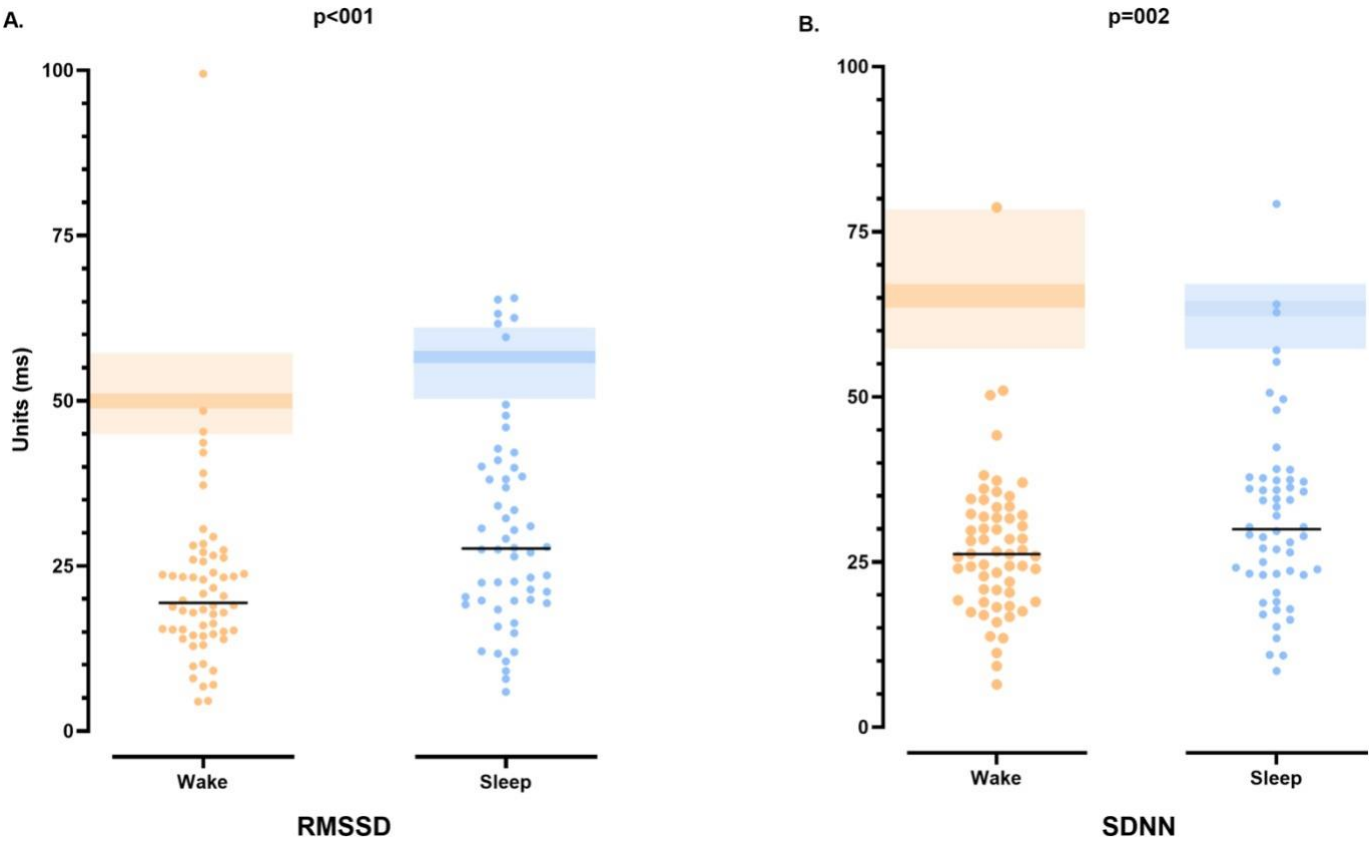

Figure 6.1: Time domain variables A) RMSSD and B) SDNN during wake and sleep in all participants (n=59). *Data for each individual is presented, with the black horizontal line representing the group median value. Darker orange and blue shading represent mean values from Spiegelhader et al. (2011) and Eddie et al. (2020) during wake and NREM Stage 2 sleep respectively shown as a comparison data obtained obtained from apparently healthy adults. Lighter orange and blue shading represent corresponding one standard deviation ranges. Mean and standard deviation ranges overlap in the figure. NREM: non-rapid eye movement; RMSSD: root mean square of successive differences between R-peak to R-peak (R-R) intervals; SDNN: standard deviation of differences between R-R*

intervals. P-values represent comparisons between wake and sleep determined using Wilcoxon signed-rank tests.

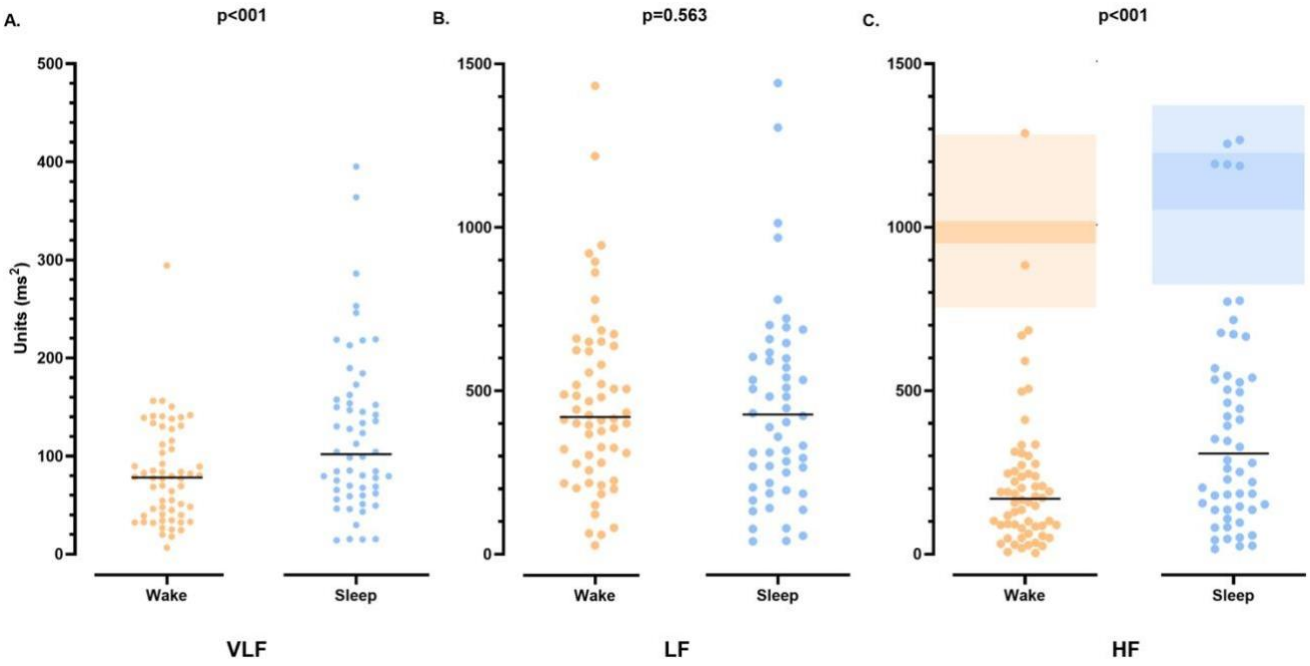

Figure 6.2: Frequency domain variables A) VLF power, B) LF power and C) HF power during wake and sleep in all participants (n=59). *Data are presented as ms². Data for each individual is presented, with the black horizontal line representing the group median value. Darker orange and blue shading represent mean values from Spiegelhader et al. (2011) and Eddie et al. (2020) during wake and NREM Stage 2 sleep respectively shown as a comparison data obtained obtained from apparently healthy adults. Lighter orange and blue shading represent corresponding one standard deviation ranges. Mean and standard deviation ranges overlap in the figure. HF: high frequency; LF: low frequency; VLF: very low frequency. P-values represent comparisons between wake and sleep determined using Wilcoxon signed-rank tests.*

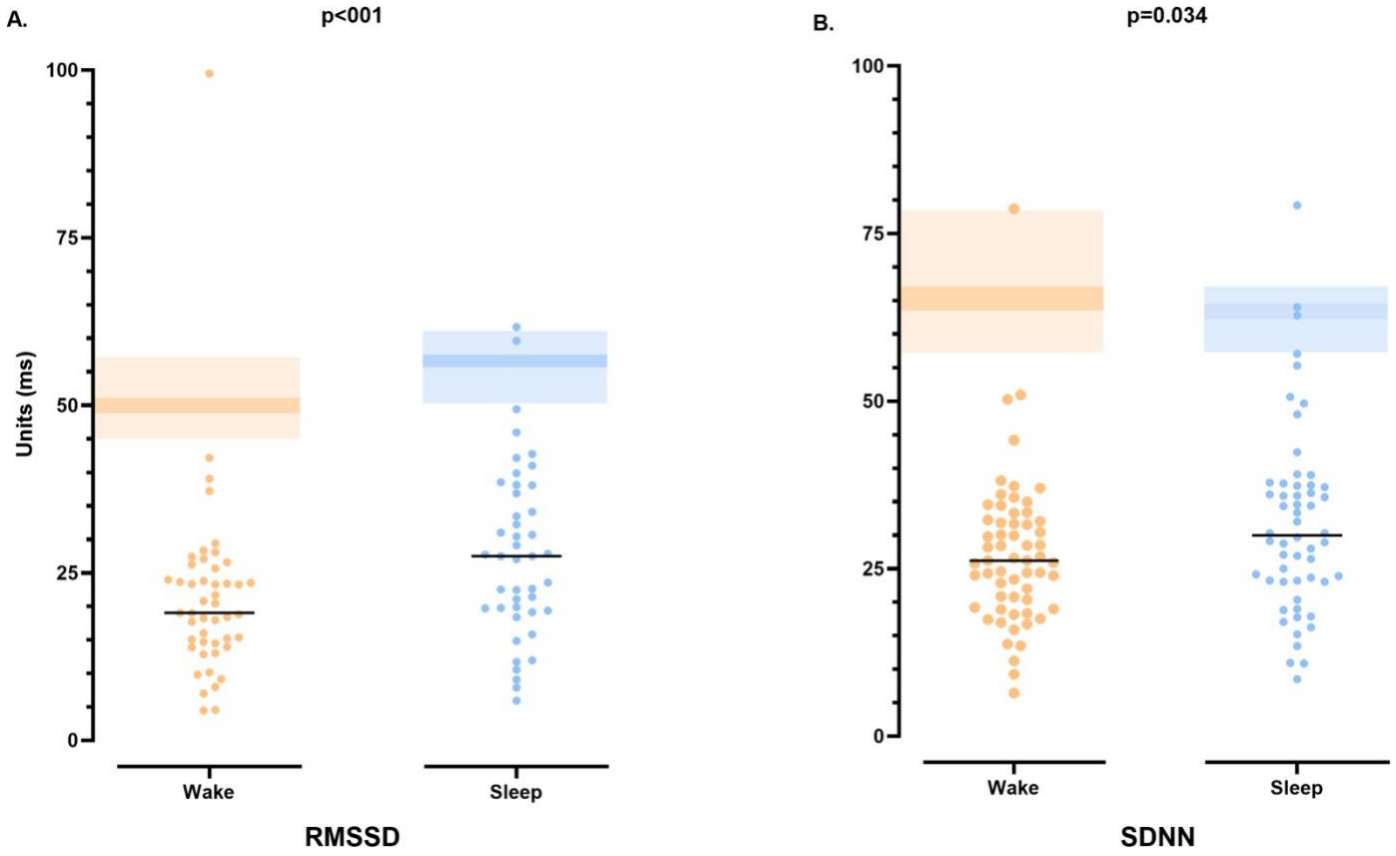

Figure 6.3: Time domain variables A) RMSSD and B) SDNN during wake and sleep in women (n=47). *Data for each individual is presented, with the black horizontal line representing the group median value. Darker orange and blue shading represent mean values from Spiegelhader et al. (2011) and Eddie et al. (2020) during wake and NREM Stage 2 sleep respectively shown as a comparison data obtained obtained from apparently healthy adults. Lighter orange and blue shading represent corresponding one standard deviation ranges. Mean and standard deviation ranges overlap in the figure. NREM: non-rapid eye movement; RMSSD: root mean square of successive differences between R-peak to R-peak (R-R) intervals; SDNN: standard deviation of differences between R-R intervals. P-values represent comparisons between wake and sleep determined using Wilcoxon signed- rank tests.*

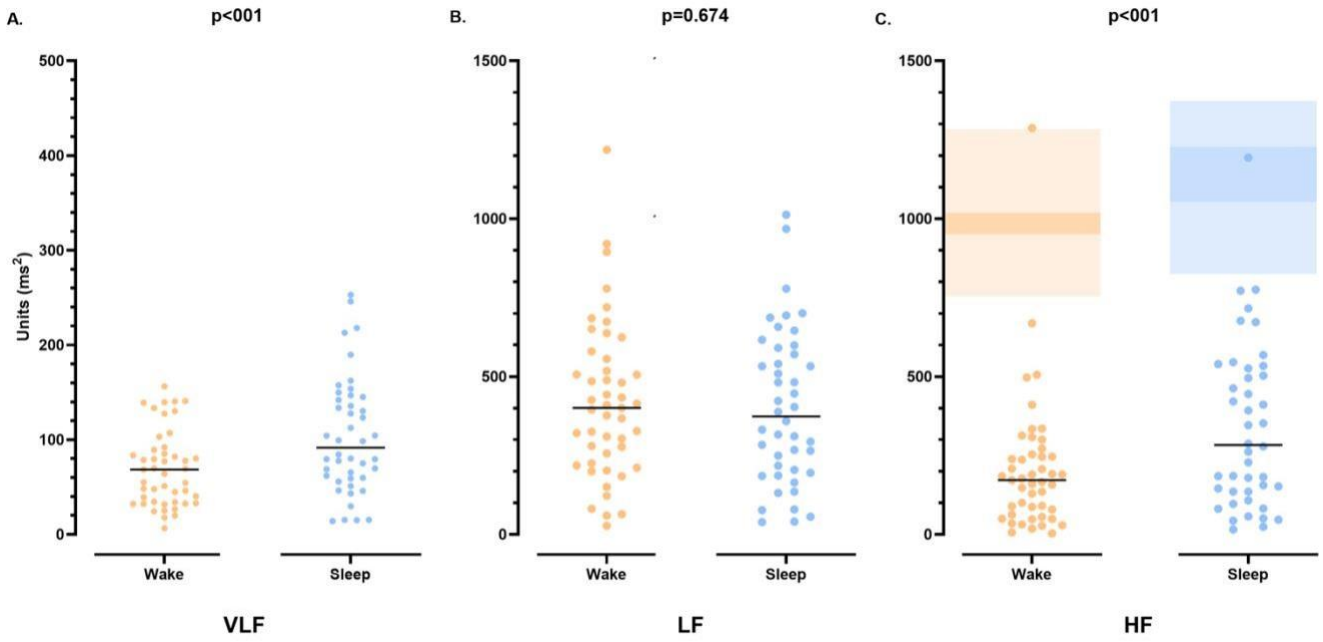

Figure 6.4: Frequency domain variables A) VLF power, B) LF power and C) HF power during wake and sleep in women (n=47). *Data are presented as ms^2. Data for each individual is presented, with the black horizontal line representing the group median value. Darker orange and blue shading represent mean values from Spiegelhader et al. (2011) and Eddie et al. (2020) during wake and NREM Stage 2 sleep respectively shown as a comparison data obtained obtained from apparently healthy adults. Lighter orange and blue shading represent corresponding one standard deviation ranges. Mean and standard deviation ranges overlap in the figure. HF: high frequency; LF: low frequency; VLF: very low frequency. P-values represent comparisons between wake and sleep determined using Wilcoxon signed-rank tests.*

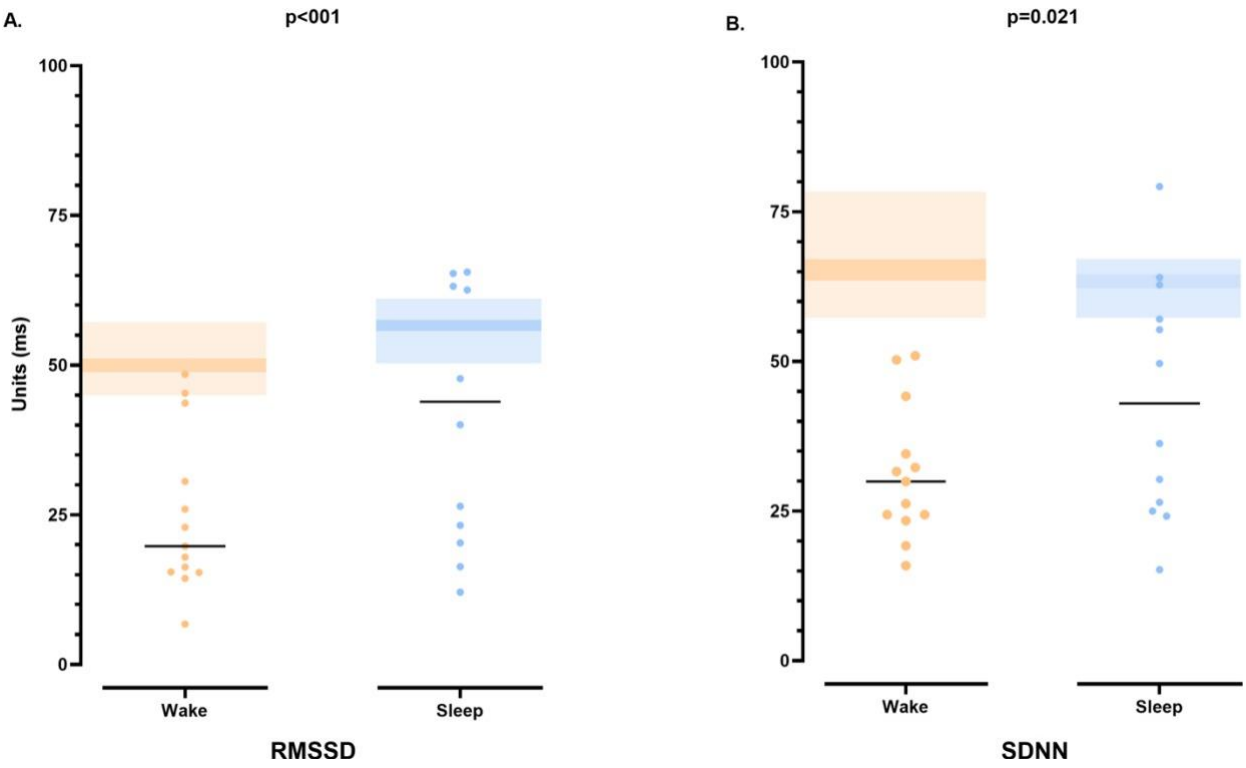

Figure 6.5: Time domain variables A) RMSSD and B) SDNN during wake and sleep in men (n=12). *Data for each individual is presented, with the black horizontal line representing the group median value. Darker orange and blue shading represent mean values from Spiegelhader et al. (2011) and Eddie et al. (2020) during wake and NREM Stage 2 sleep respectively shown as a comparison data obtained obtained from apparently healthy adults. Lighter orange and blue shading represent corresponding one standard deviation ranges. Mean and standard deviation ranges overlap in the figure. NREM: non-rapid eye movement; RMSSD: root mean square of successive differences between R-peak to R-peak (R-R) intervals; SDNN: standard deviation of differences between R-R intervals. P-values represent comparisons between wake and sleep determined using Wilcoxon signed-rank tests.*

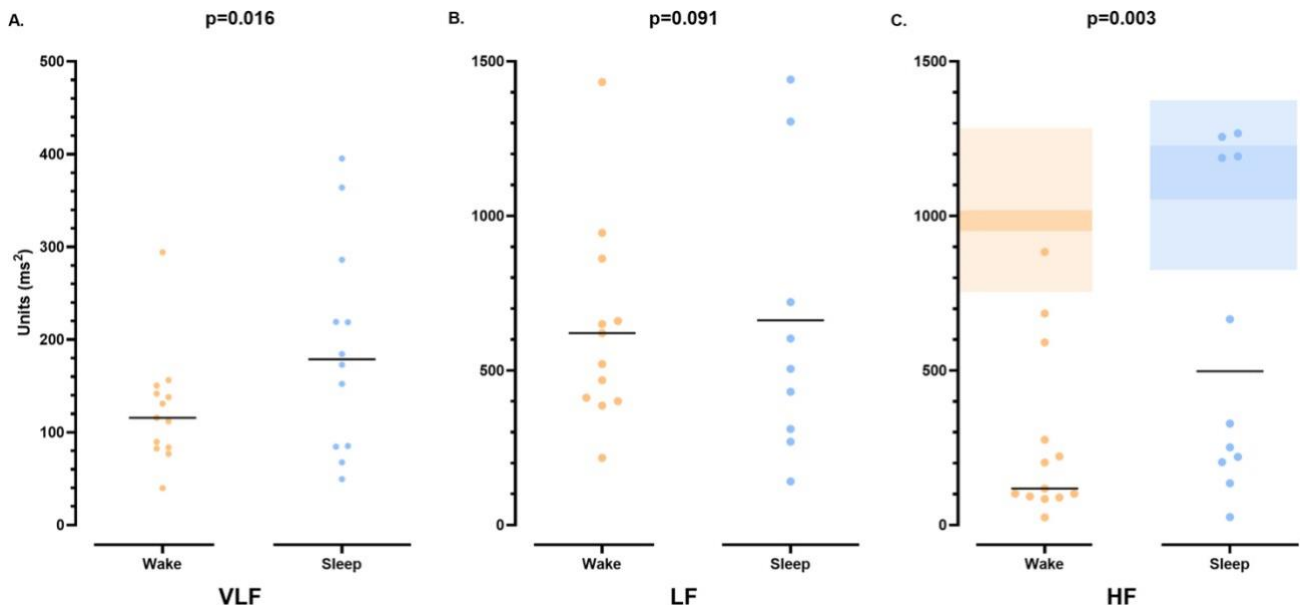

Figure 6.6: Frequency domain variables A) VLF power, B) LF power and C) HF power during wake and sleep in men (n=12). *Data are presented as ms². Data for each individual is presented, with the black horizontal line representing the group median value. Darker orange and blue shading represent mean values from Spiegelhader et al. (2011) and Eddie et al. (2020) during wake and NREM Stage 2 sleep respectively shown as a comparison data obtained obtained from apparently healthy adults. Lighter orange and blue shading represent corresponding one standard deviation ranges. Mean and standard deviation ranges overlap in the figure. HF: high frequency; LF: low frequency; VLF: very low frequency. P-values represent comparisons between wake and sleep determined using Wilcoxon signed-rank tests.*

6.4. Discussion

This study characterised HRV patterns in residents of a high-crime, low SES community in South Africa. Compared to published comparative data from high-income countries, where median wake RMSSD values typically range from 40-51ms and HF power from 951- 10911ms^2 and median sleep RMSSD values typically range from 56-64ms and HF power from 1054-1374ms^2 for apparently healthy controls[316,358], our participants showed notably lower HRV values during both wake (median RMSSD: 28.4ms; HF: 225.6ms^2) and sleep periods (median RMSSD: 31.2ms; HF: 298.4ms^2). These reduced HRV values in our participants are closer to what has been observed in populations with insomnia and major depressive disorder (median wake RMSSD values typically range from 34-50ms and HF power from 545- 640ms^2, and median sleep RMSSD values typically range from 41-50ms and HF power from 902-1210ms^2) [316,358].

The lower HRV values during both sleep and wake likely stem from multiple factors disproportionately prevalent in this population including chronic diseases such as hypertension[77], type II diabetes mellitus[359] and human immunodeficiency virus (HIV)[267,] as well as poor sleep[285,316,327] and chronic poverty-related stresses[315,346,360]. These chronic diseases can impair autonomic function through various mechanisms: for example, hypertension through altered baroreceptor sensitivity[361], diabetes through autonomic neuropathy[359], and HIV through direct viral effects[362,363]. While we did not observe significant differences in our measures of HRV between groups with and without chronic diseases, suggesting other factors may have stronger influences in this context, the high prevalence of these conditions may contribute to the overall reduced HRV observed in our population. Poor sleep, which will be explored in detail in the following chapter, may also impact HRV through disrupted autonomic regulation during sleep. The chronic stress associated with poverty, including financial strain, resource insecurity, and environmental challenges, may have particularly profound effects on autonomic function through persistent activation of stress response systems[165].

While participants showed the expected increase in HRV during sleep compared to wake periods[169,344] (except for LF power), these sleep-related values were still consistently lower than published data for HRV during sleep measured in both apparently healthy people and

in clinical populations, such as those with Major Depressive Disorder and insomnia[316,358]. Thus, the delta HRV values observed in this study, which are indicative of the degree of diurnal variation in HRV, are smaller than what would be expected in a healthy population. This dampened diurnal variation may reflect a state of chronic hyperarousal, where persistent activation of stress response systems reduces HRV both during the day and night[346,364,365]. A subset of participants exhibited higher HRV during wake than sleep (indicated by negative delta values) - a pattern indicating nocturnal hyperarousal that may reflect reduced stress resilience and greater vulnerability to autonomic dysregulation [345,366]. Both these blunted and reversed diurnal patterns are particularly concerning as they suggest disruption of the normal nocturnal dominance of parasympathetic activity, which is crucial for restorative sleep and physiological recovery[325]. Given that demographics (age, gender, presence of chronic disease or chronic medication) and sleep variables (duration or fragmentation) were not different between these individuals with higher HRV at night, it is plausible that this is rather linked to chronic stress. Chronic hyperarousal can create a self-perpetuating cycle whereby elevated nighttime sympathetic activity leads to sleep disruption, which in turn further compromises autonomic regulation and stress resilience[6,158,234]. Moreover, this disrupted circadian pattern of autonomic function may have broader implications for health.

Gender differences in autonomic regulation emerged as another finding. During wake periods, men and women showed similar HRV patterns in both time-domain measures and HF power. During sleep, however, men exhibited significantly higher HRV values, suggesting reduced parasympathetic activation in women during the nocturnal period. This pattern diverges from previous literature, predominantly from high-income Global North countries, which typically shows minimal gender differences in 24h HRV measures[357,367]. We propose that this divergence therefore reflects the profound impact of environmental stress on autonomic regulation, rather than merely physiological gender differences. As suggested in previous chapters, individuals living in a high-crime neighbourhood understandably report feeling fearful for their safety. While both men and women in our study reported elevated levels of fear, women consistently demonstrated higher fear scores, which may be reflected in these HRV differences. Such feelings, particularly during periods of increased vulnerability such as sleep, may drive sympathetic activation and symptoms of hypervigilance. However,

these gender-based findings should be interpreted with caution given our relatively small sample size of men. The relationship between fear and autonomic regulation will be explored further in the next chapter.

Several limitations should be noted related to this study. Given that the recruitment process was not entirely random but rather limited to the first 85 volunteers, this cohort had i) an oversampling of women, and ii) possible selection bias as participants could have volunteered for specific reasons, such as experiencing sleep problems, making them different from those who did not volunteer. This bias could also be a source of the difference between men and women within the sample. The observational design based on a single 24h period prevents causal inferences. HRV, while a useful proxy for autonomic function, cannot fully distinguish between sympathetic and parasympathetic contributions, particularly in metrics like LF power and ambulatory SDNN. Aggregated HRV may overlook dynamic, within-night variations, and individual differences in resilience, emotional regulation, and mental health—potentially key moderators of these associations—were not investigated. Additionally, external factors such as light exposure, physical activity, diet and napping, which may influence autonomic regulation, were not measured and/or statistically controlled for. Lastly, the consistently low HRV values observed in this analysis raised concern over potential measurement or analytical error. While the inclusion of a control group (i.e. participants living in a higher SES community) would be one way to contextualise the HRV measures obtained in this study, such an approach was not within the scope of this thesis. To address this concern, comparison HRV data from two apparently healthy Caucasian researchers (25y and 44y respectively) residing in higher socioeconomic areas were collected. These data show noticeably higher wake and sleep HRV values with larger deltas (Appendix 6.4), suggesting the lower than expected HRV values measured in our participants are likely valid and reflect genuine physiological differences rather than measurement error.

6.5. Conclusion

This study highlights apparent autonomic dysregulation in adults living in a high-crime, low SES setting. The combination of consistently low HRV values during both wake and sleep as well as blunted wake-sleep differences observed in all participants suggests significant ANS

dysregulation. Given the chronic environmental stressors faced by residents in this community, it would be reasonable to propose that this pattern of autonomic dysregulation stems from persistent exposure to environmental stress, with particularly pronounced effects observed in women. The blunted diurnal variation in HRV suggests hyperarousal during sleep, and future research should consider the role past trauma and fear may play in that hyperarousal and the role hyperarousal may in turn play in disrupting sleep in a low SES environment.

Chapter 7

The role of heart rate variability in the relationship between fear of sleep, markers of sleep quality and mood-/anxiety-related symptoms

7.1. Introduction

Low socioeconomic status (SES) environments increase the likelihood of i) experiencing a trauma[33,152], ii) elevated levels of crime and violence eroding individuals' feelings of safety[151], iii) experiencing nocturnal hypervigilance and hyperarousal[126,205], iv) short and/or disturbed sleep[44,210,230] and v) developing depression, anxiety and post-traumatic stress disorder (PTSD)[58,59,63,245]. Many of these factors, such as sleep and mental health, are also interrelated. Therefore, low SES areas may create a perfect storm where the detrimental effects of fear, hypervigilance and short or disturbed sleep compound to drive poor mental health outcomes. Thus, it is insufficient to investigate each factor individually but rather in the context of all the challenges faced by residents of low SES communities.

Chapters 3 and 4 confirmed the high prevalence of trauma exposure in this population, with 76% of individuals having experienced a trauma; a disproportionate number of them being women (89% of women vs 45% of men). Sleep disturbances and problems initiating sleep following trauma[278] are frequently reported as a hallmark feature of PTSD[2,142,264], which may be due to feelings of vulnerability and subsequent fear of not being safe[3]. Aside from PTSD, trauma is a common risk factor for developing depression or anxiety, with depression and PTSD occurring co-morbidly in up to half of all individuals with PTSD[251,252]. It is less clear, however, how PTSD symptoms may lead to and exacerbate symptoms of depression. One way we can potentially understand this comorbidity is via the influence of fear on autonomic nervous system (ANS) regulation and sleep.

Fear—whether stemming from unsafe surroundings or trauma-associated fear of sleep itself—can trigger a state of hypervigilance[123], characterized by sympathetic nervous system (SNS) dominance and reduced parasympathetic nervous system (PNS) activity. This is supported by the polyvagal theory which proposes that typically the stress response is only actively inhibited by increased vagal activity under conditions of perceived safety. This autonomic imbalance can be quantified through heart rate variability (HRV), a non-invasive measure that provides insight into ANS regulation. Low HRV specifically indicates reduced parasympathetic activity and has been associated with both acute and chronic stress

responses[346]. When fear and hypervigilance persist, they can significantly impact sleep through multiple mechanisms: delaying sleep onset, increasing sleep fragmentation, and reducing overall sleep efficiency[3]. In healthy individuals lower HRV predicts increased severity of sleep difficulties and parasympathetic input correlates positively with sleep quality[323]. In turn, fragmented sleep and multiple awakenings from sleep disrupt the normal parasympathetic dominance expected during healthy sleep[158,279], dampening diurnal variation in HRV[170]. The sustained sympathetic activity we observed in our population, evident in the dampened diurnal HRV patterns described in the previous chapter, could not be fully explained by demographic or sleep parameters alone and suggests that chronic stress and hypervigilance may play a crucial role in disrupting both autonomic regulation and sleep patterns in this high-stress environment. As such, this chapter utilises sleep fragmentation and the change in HRV as key measures of interest.

In addition to poorer objectively measured sleep outcomes, Chapter 5 also showed that lower nocturnal HRV is consistently associated with more severe mood- and anxiety-related outcomes[159]. Given the well-established link between sleep and mental health[134,135,137,368,369], it may be that the hyperarousal underpinning low HRV, is implicated in sleep disturbance, which in turn worsens symptoms of depression and anxiety. Alternatively, ANS dysregulation may be a consequence or byproduct of mood- and anxiety-related disorders and therefore may be independently associated with symptoms of depression and anxiety. Brosschot et al.'s (2016) "*Generalized Unsafety Theory of Stress*" (GUTS) theory supports this[364,370]. In anxiety-related disorders in particular, there is a generalisation of fear such that even under conditions of objective safety, individuals perceive neutral stimuli as a threat[371] and may subsequently fail to inhibit their stress response as per the above mentioned polyvagal and GUTS theories[364,370,372].

Thus, this chapter aims to i) investigate the proposed associations between fear, HRV, sleep and mental health outcomes and ii) use structural equation modelling (SEM) to investigate the complex interplay between trauma, fear of not being safe, HRV, sleep quality and both depression and anxiety as independent outcomes. Based on the literature and findings from the previous chapters we aimed to test the following hypotheses: i) trauma exposure (and associated PTSD symptoms in the depression model) will be associated with more fear

of sleep, ii) fear of sleep will be directly associated with a smaller changes in HRV between sleep and wake, indicative of sustained sympathetic activity intruding into sleep or diminished parasympathetic activity, iii) damped HRV changes will be directly associated with poorer sleep quality and shorter total sleep time and iv) poorer sleep quality and/or shorter total sleep time will be associated with more severe symptoms of depression and anxiety.

7.2. Methods

7.2.1 Study design, setting, participants and measures

The design, setting, participants, and data collection measures related to questionnaires, actigraphy and 24h ambulatory ECG of this cross-sectional study are the same as those described in Chapters 4 and 6. As such, only methodological information specific to the current analysis is presented here. One hundred and twenty two participants were recruited, 12 participants had invalid datasets and the final sample consisted of 110 participants (median age 41 [interquartile range: 35-48] years, 75% women). METS-Sleep and the current study were approved by the University of Cape Town's Faculty of Health Sciences Human Research Ethics Committee (HREC numbers: 696/2014 and 154/2020), conducted in accordance with the Declaration of Helsinki[190] and included only participants who had given informed consent.

7.2.2 Data and statistical analysis

Shapiro-Wilk tests were used to evaluate normality of continuous data. Descriptive data are presented as median and interquartile range or count (percentage). Given the difficulty in recruiting men for the study (n=27), the relatively small sample size resulted in insufficient power to address the aim using SEM. For the men, therefore, a Mann-Whitney U test was used to test hypothesis 1 (FoSI score differences between trauma status groups and Spearman's correlations were used to test bivariate relationships addressing hypotheses 2-4. To limit the number of correlations, given the large number of sleep and HRV variables measured, an *a priori* decision was made to restrict the analyses to two measures of actigraphy-derived sleep duration (TIB and TST), two measures of actigraphy-derived

efficiency (sleep efficiency, SE and sleep fragmentation index, SFI), two self-reported sleep measures (Epworth Sleepiness Scale, ESS and Pittsburgh Sleep Quality Index, PSQI), one time-domain measure of HRV (RMSSD during wake, sleep and the delta) and one frequency domain measure (HF power during wake, sleep and the delta). Descriptive and correlation data were analysed using Stata (v15, StataCorp, College Station, TX, US) with significance accepted at $p<0.050$.

For the women, analyses to test the proposed hypotheses were conducted using SEM using the "lavaan" package in R Statistical Software (v4.4.2, R Core Team 2024, Vienna, Austria). All continuous data were scaled prior to analysis. Confirmatory factor analysis (CFA) was used to determine whether the chosen indicators explained the latent variables. Latent variables included Fear (fear of sleep, fear of loss of vigilance, fear of trauma re-exposure, nighttime vigilant behaviours and fear of the dark subscales), Change in parasympathetic activity (define (RMSSD) and high frequency (HF) power differences between sleep and wake), Fragmentation (sleep fragmentation index (SFI) score derived from actigraphy), Depression (Beck Depression II Inventory (BDI-II) score) and Anxiety (Beck Anxiety Inventory (BAI) score). While the results are considered preliminary given the relatively small sample size (n=83), the analysis on this sample is justified as a previous simulation study has demonstrated that models with strong measurement properties and well-defined factors can produce reliable results with samples of 50-100 participants[373]. The measurement model was thus developed considering both psychometric and practical constraints. While SEM traditionally uses individual items as indicators, we employed a parcelling approach using validated factors for two reasons: (i) the depression, anxiety and fear of sleep measures used (BDI-II, BAI and Fear of Sleep Inventory (FoSI) scores, respectively) have demonstrated reliability and strong psychometric properties and factor dimensionality in previous validation studies[70] and (ii) using fewer factors reduces model complexity and improves parameter stability in smaller sample sizes[374,375]. The previously proposed three-factor model of depression which groups BDI-II-assessed symptoms into cognitive, affective and somatic domains was used as the basis for the BDI-II parcels as this structure has repeatedly been shown to be a suitable construct[376,377]. The BAI was used as a global score given that previous studies, including one in South Africans[70], found it to be unidimensional in structure. For the FoSI, the subscale domains were used as the parcels given that throughout Chapters 4 and 6 the subscales showed differing associations

with markers of sleep quality, HRV and symptoms of depression, anxiety and PTSD. Additionally, these subscales were validated in a similar group of trauma-exposed, urban African-American adults[191]. This approach reduced the number of estimated parameters while maintaining construct validity.

Once these measurement models were identified, the structural models were estimated with the latent and observed variables. To assess models with continuous data, given the missing data in the dataset, full information maximum likelihood estimation was used to reduce bias and maximum likelihood estimation with robust standard errors to ensure multivariate normality. Pathways which were non-significant and did not improve model fit were removed. Comparative fit index (CFI) and the standardized root mean square residual (SRMR) were deemed the most appropriate parameters to assess model fit as our sample size was <250[378]. CFI and SRMR values of >0.95 and <0.1 respectively were deemed close fit[378], but significant models were retained even if they did not meet both criteria[379]. Root mean square error of approximation (RMSEA) and 95% confidence intervals (CI) were also reported.

7.3. Results

7.3.1 Descriptive variables

The descriptive demographic, sleep, trauma, fear, depression and anxiety characteristics of the participants are presented in Appendices 7.1-7.3 since the data are almost identical to what was presented in Chapters 4 and 6. Observations relevant to this chapter are that participants displayed long actigraphy-derived sleep opportunities: 8.94 [8.11-10.08] h, 49% sleep >9h, total sleep time: 7.36 [6.59-8.05] h, sleep efficiency: 81.67 [77.45-85.76] %, 69% with poor sleep efficiency, sleep fragmentation index: 29.24±9.21 %, PSQI score: 3 [2-5], 19% classified as poor sleep quality, ESS score: 4[1-8] and 10% classified as having excessive daytime sleepiness. Despite no participants reporting a diagnosed mental health disorder, 33% had moderate-to-severe symptoms of depression, median BDI-II score: 14 [8-22], 23% had moderate-to-severe symptoms of anxiety, median BAI score: 9 [4-15] and 34% described symptoms indicating likely presence of PTSD, median PC-PTSD score: 2 [0-4]. Approximately equal numbers of participants were categorized as having experienced No trauma (35%),

Trauma, resilient (30%) and Trauma, persisting symptoms of PTSD (35%). Participants median FoSI score was 14 [9-24], with the Nighttime vigilant behaviour and Fear of loss of vigilance at nighttime subscales scoring higher than other FoSI subscales. Participants whose PC-PTSD scores indicated the likely presence of PTSD reported higher median FoSI scores (19 [14-28], n=71) than those less likely to have PTSD (11 [5-18], n=37, p<0.001). FoSI scores did not differ between those who spent >9h (FoSI:14 [9-24], n=51) and ≤9h in bed (FoSI: 14 [9-24], n=54, (p=0.964). Similarly, FoSI scores were comparable among those with total sleep time less <7h (15 [6-27], n=40), 7-9h (14 [10-19], n=55), or >9h (14 [9-25], n=10, p=0.780).

Descriptive HRV statistics were presented in Chapter 6 (Table 6.3). Overall, all measures of wake and sleep HRV were low in these participants. With the exception of LF power (p=0.720), HRV measured during sleep was higher than that measured during wake for all variables (all p<0.010, Figures 6.1 and 6.2).

7.3.2. Bivariate correlations (men only)

Figure 7.1 presents the significant correlations observed in the men (full correlation tables are in Appendices 7.4-7.6). Higher PSQI scores, indicating poorer sleep quality, were associated with more severe symptoms of depression (rho=0.534, p=0.005) and anxiety (rho=0.387, p=0.046) as well as higher RMSSD (rho=0.785, p=0.012) and HF power (rho=0.858, p=0.003) values (indicative of more parasympathetic activity) during wake. More daytime sleepiness was associated with worse symptoms of depression (rho=0.401, p=0.042) and PTSD (rho=0.483, p=0.011). More severe symptoms of depression and anxiety were associated with higher RMSSD (depression: rho=0.819, p=0.007; anxiety: rho=0.780, p=0.013) and HF power (depression: rho=0.869, p=0.002; anxiety: rho=0.814, p=0.008) wake values as well as more fear of sleep (depression: rho=0.524, p=0.006; anxiety: rho=0.651, p<0.001) and higher scores on the fear of sleep (depression: rho=0.482, p=0.013; anxiety: rho=0.573, p=0.002) and fear of trauma re-exposure (depression: rho=0.692, p<0.001; anxiety: rho=0.696, p<0.001) subscales. PTSD symptomology showed similar correlations with global fear of sleep (rho=0.512, p=0.006), higher fear of sleep (rho=0.431, p=0.025), fear of loss of vigilance at night (rho=0.395, p=0.041) and fear of trauma re-exposure (rho=0.530, p=0.005) subscale scores.

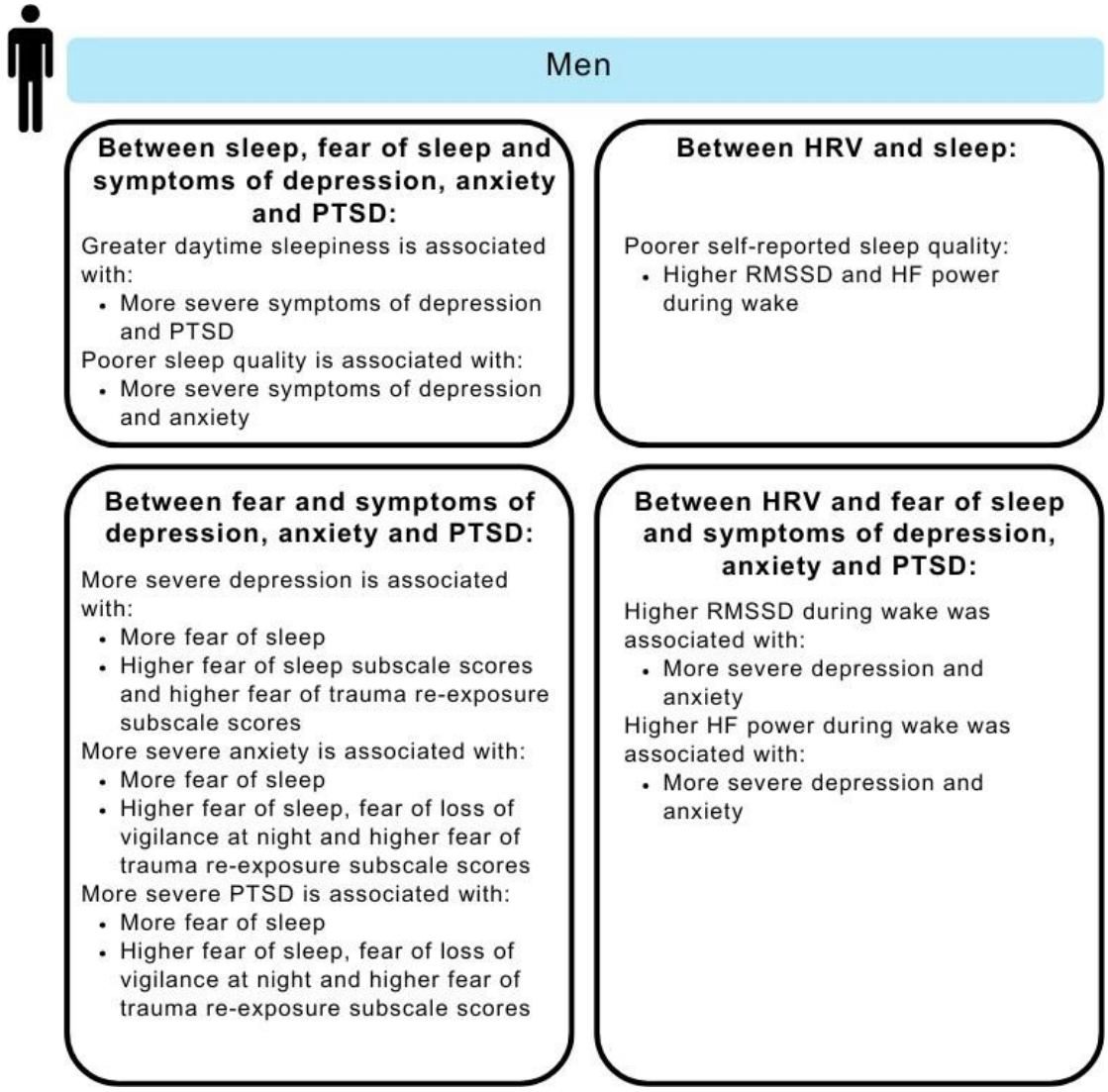

Figure 7.1. Summary of significant correlations between fear of sleep, HRV, sleep and mental health variables in men as determined using Spearman's rank order correlations. *Full correlation tables are provided in Appendices 7.4-7.6. Significance was accepted at p<0.050. Fear of sleep refers to the full Fear of Sleep Inventory score. HF: high frequency; HRV: heart rate variability; PTSD: post-traumatic stress disorder; RMSSD: root mean square of successive differences between R-peak to R-peak (R-R) intervals.*

7.3.3 SEM testing in women

Depressive symptoms

Goodness-of-fit indices of the hypothesised measurement model were just outside the acceptable range (p<0.001, CFI=0.921, SRMR=0.079, RMSEA=0.085 and 95% CI=0.051 – 0.116, Appendix 7.7), however, given the overall significance of the model we retained it as per Kline's (2018) recommendations. Following the establishment of the measurement model, we estimated the relationships hypothesised between the latent variables (see Figure 7.2 and Table 7.1). The final structural model achieved an acceptable fit (p=0.034, CFI=0.950, SRMR=0.077, RMSEA=0.081 and 95% CI=0.064 – 0.180).

To test our structural hypotheses, we evaluated three competing models. First, we tested our primary hypothesized model (p=0.040, CFI=0.943, SRMR=0.087, RMSEA=0.079 and 95%CI=0.017 – 0.120), however, we also tested two alternative models. One contained a pathway between fear and SFI (p=0.034, CFI=0.950, SRMR=0.077, RMSEA=0.081 and 95% CI=0.064 – 0.180) and another retained the only direct pathways between fear of sleep and HRV to depressive symptoms (p=0.057, CFI=0.955, SRMR=0.079, RMSEA=0.078 and 95% CI=0.068 – 0.183). One contained an additional pathway between fear and SFI (p=0.031, CFI=0.943, SRMR=0.089, RMSEA=0.080 and 95% CI=0.025 – 0.124) and another retained the only direct pathways between fear of sleep and HRV to depressive symptoms (p=0.034, CFI=0.950, SRMR=0.077, RMSEA=0.081 and 95% CI=0.064 – 0.180). The final model is illustrated in Figure 7.3. Fear of sleep demonstrated a significant, although small, direct relationship with depression symptoms (β=0.079, p<0.001), rather than the hypothesized pathway through HRV.

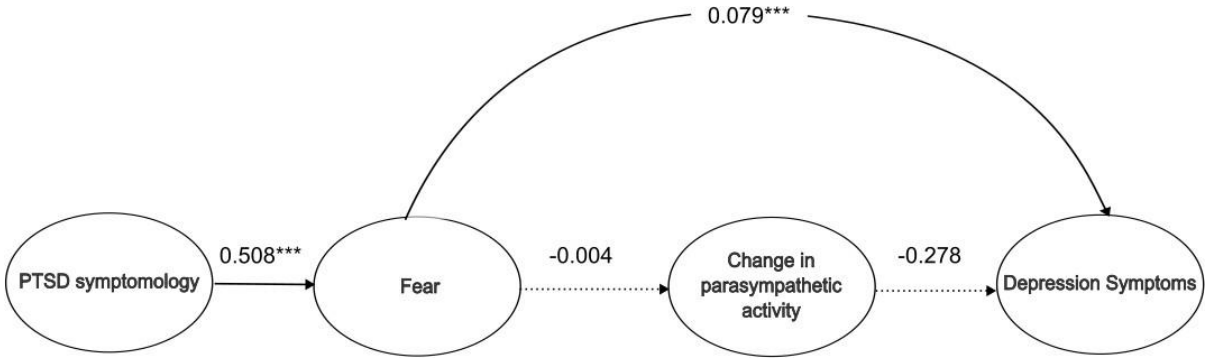

Figure 7.2. Structural equation models predicting depressive symptoms in women (n=83). *These structural equation models predict depression symptoms from PTSD symptoms, fear and change in HRV (specifically in parasympathetic activity. Change in parasympathetic activity was calculated as the difference between RMSSD and HF power variables during sleep and wake such that positive values indicate greater HRV during sleep than wake.* Values displayed are ß coefficients. Solid *black lines indicate significant pathways. *p<0.050, ***p<0.001. HF: high frequency; HRV: heart rate variability; PTSD: post-traumatic stress disorder; RMSSD: root mean square of successive differences between R-peak to R-peak (R-R) intervals.*

Anxiety symptoms

The measurement and structural models were systematically tested to evaluate the hypotheses. The initial measurement model demonstrated adequate fit (p=0.047, CFI=0.950, SRMR=0.082, RMSEA=0.097, 95% CI=0.012 – 0.163), with standardized factor loadings ranging from 0.550 to 1.281 (Appendix 7.8). We achieved this fit by removing the "Fear of the dark" subscale from the FoSI. While these indices fell just below the predetermined cut-offs for good fit, however, given its overall significance, the final model was retained following Kline's (2018) recommendations363.

The final structural model showed good fit (p=0.041, CFI=0.961, SRMR=0.081, RMSEA=0.056, 95% CI: 0.000-0.127). Three models were tested. First, our original hypothesised model, which did not converge. Then two alternative models: one with trauma exposure removed and sleep fragmentation retained which was our final model (p=0.041, CFI=0.933, SRMR=0.085, RMSEA=0.086, 95% CI: 0.024-0.135) and one with trauma exposure retained and sleep fragmentation removed, which again did not converge. Fear of sleep demonstrated a significant direct relationship with anxiety symptoms (β=0.668, p<0.001), rather than the hypothesized pathway through HRV. Sleep-wake differences in parasympathetic activity were significantly associated with sleep fragmentation (β=-0.700, p=0.016), with smaller or changes in an unexpected direction predicting more fragmented sleep.

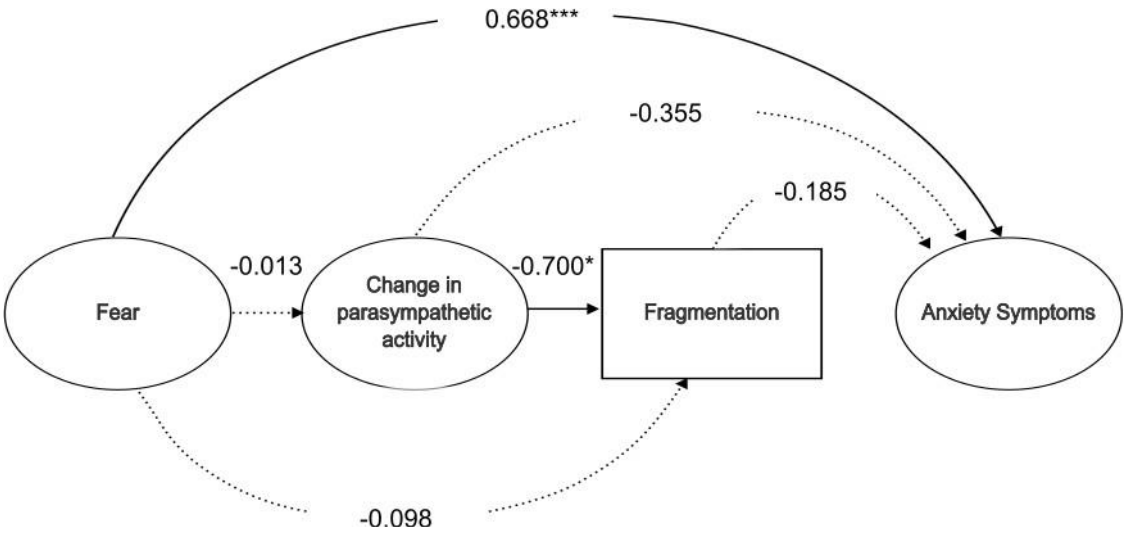

Figure 7.3. Structural equation models predicting anxiety symptoms in women (n=83). *These structural equation models predict anxiety symptoms from fear, change in HRV (specifically in parasympathetic activity) and sleep fragmentation. Change in parasympathetic activity was calculated as the difference between RMSSD and HF power variables during sleep and wake such that positive values indicate greater HRV during sleep than wake.* Values displayed are ß coefficients. Solid *black lines indicate significant pathways. *p<0.050, ***p<0.001. HF: high frequency; HRV: heart rate variability; PTSD: post-traumatic stress disorder; RMSSD: root mean square of successive differences between R-peak to R-peak (R-R) intervals.*

Table 7.1: Results of structural equation models predicting depression symptoms in women (n=83).

			95% CI	
Effects	b value	p-value	Lower limit	Upper limit
Direct				
PTSD symptomology → Fear	0.511	**<0.001**	0.260	0.763
Fear → Change in parasympathetic activity	-0.004	0.569	-0.017	0.010
Fear → Depression	0.079	**<0.001**	0.049	0.110

Change in parasympathetic activity→ Depression	-0.278	0.194	0.697	0.142

β standardized path coefficient. Change in parasympathetic activity was calculated as the difference between sleep and wake such that positive values indicate greater HRV (specifically RMSSD and HF; measures indicating parasympathetic activity) during sleep than wake. HF: high frequency; HRV: heart rate variability; RMSSD: root mean square of successive differences between R-peak to R-peak (R-R) intervals.

Table 7.2: Results of structural equation models predicting anxiety symptoms in women (n=83).

			95% CI	
Effects	b value	p-value	Lower limit	Upper limit
Direct				
Fear → Change in parasympathetic activity	-0.013	-0.106	-0.250	0.225
Change in parasympathetic activity → Fragmentation	-0.700	**0.016**	--1.286	-0.131
Fear → Fragmentation	-0.098	0.516	-0.393	0.197
Fragmentation → Anxiety	-0.185	0.168	-0.448	0.078
Fear → Anxiety	0.668	**<0.001**	0.434	0.901
Change in parasympathetic activity → Anxiety	-0.355	0.201	-0.901	0.190
Indirect				
Change in parasympathetic activity → Fragmentation→ Anxiety	0.129	0.271	-0.101	0.360
Total	-0.226	0.304	-0.657	0.205

β standardized path coefficient. Change in parasympathetic activity was calculated as the difference between sleep and wake such that positive values indicate greater HRV (specifically RMSSD and HF; measures indicating parasympathetic activity) during sleep than wake. HF: high frequency; HRV: heart

rate variability; RMSSD: root mean square of successive differences between R-peak to R-peak (R-R) intervals.

7.4. Discussion

To the best of our knowledge this is first study to use SEM to model fear, HRV, sleep and mental health measures collectively as interacting factors. These data, which must be interpreted with caution because of sample size-related concerns, indicate that among the women PTSD symptoms may drive more fear of sleep, and that fear of sleep has a small but direct effect on depressive symptomology. The anxiety model also shows that fear of sleep has direct effects on anxiety symptomology. In the context of anxiety, autonomic dysregulation also has a direct effect on sleep fragmentation, but fragmentation does not in turn directly influence anxiety as hypothesised. The commonalities in the effect of fear in both depression and anxiety may help explain why these conditions are frequently comorbid, particularly in trauma-exposed women[380,381] as trauma exposure has been linked to the presence of fears-related to sleep[3,123]. Meanwhile, the differences likely speak to specific physiological pathways distinct to the development of these disorders.

Reduced change in parasympathetic activity between wake and sleep measures of heart rate variability could indicate either sympathetic intrusion into sleep periods or insufficient parasympathetic tone - both markers of physiological hyperarousal, a common characteristic of anxiety disorders[159]. Thus, the relationship between autonomic dysregulation and sleep fragmentation aligns with existing literature: hyperarousal has been implicated in sleep disruption in anxiety-related disorders like PTSD[338,341] as well as in REM instability (or fragmentation) in insomnia[6], while fragmented sleep itself may impair normal autonomic regulation by increasing activity of the sympathetic nervous system and hypothalamic-pituitary-adrenal (HPA) axis at night with each awakening and disrupting circadian rhythmicity. This may be the reason OSA patients tend to exhibit low HRV that decreases with increasing OSA severity (a higher apnoea to hypopnoea index likely means, by extension, more fragmented sleep)[331].

Attenuated parasympathetic change likely also reflects significant circadian disruption, as

parasympathetic activity usually predominates during sleep[169]. Circadian disruption is emerging as a common feature of depression and anxiety, although much of the evidence is currently cross-sectional in nature[382–384] and may partly explain the pathway between ANS dysfunction and more severe depression and anxiety independent of sleep disturbance. A recent review by Francis and Porcu (2023) outlines a role for stress-related disruption to the neuronal clock gene expression in the development of depression and anxiety[385]. Over and above the role of sympathetic dominance in disrupting sleep, the low HRV observed likely reflects chronic stress experienced by participants living in this low-SES environment. Recent animal studies have suggested that chronic stress can alter clock gene expression and circadian rhythmicity[385]. Although, this may not directly translate to human populations, chronic stress has been well-documented to impact both HRV and circadian rhythms in humans[385], potentially contributing to the development or worsening of mood- and anxiety-related disorders[103,382,384]. Although our models did not show significant associations between dampened HRV and symptoms of depression or anxiety, this may reflect the context-specific nature of heightened vigilance in this community. In a neighbourhood with legitimate safety concerns such as Khayelitsha, increased vigilance may represent a necessary adaptation for all residents, rather than a marker of psychopathology.

A surprising finding in our model, contrary to the initial hypothesis, was that sleep fragmentation has no significant relationship with anxiety symptoms among the women, which is in contrast to previous research linking poor quality sleep to anxiety[159]. This may reflect the adaptive nature of vigilant behaviours described by our participants in Chapter 3, such as waking to check on family members. Such behaviours, while physiologically disruptive and the root of some of the observed fragmentation of sleep, may provide psychological reassurance that helps manage anxiety symptoms, similar to safety behaviours observed in anxiety disorders[386,387]. This finding aligns with recent work showing that perceived control over one's environment may moderate the relationship between physiological arousal and anxiety symptoms[388].

Women with smaller wake-sleep changes in parasympathetic input did experience more fragmented sleep, as hypothesised. This suggests that while security-conscious behaviours may feel necessary in this context and may be protective against symptoms of depression and anxiety, they may paradoxically impair women's autonomic regulation and sleep quality, by

fragmenting and/or reducing deep sleep. Strategies such as purposefully delaying sleep to remain alert to any threats may restrict sleep opportunities resulting in partial sleep deprivation while purposefully waking up throughout the night fragments sleep, curtailing the expected increase in parasympathetic activity and increasing sympathetic activity[158,291,344]. Increased activity of the sympathetic nervous system and HPA axis as well as circadian disruption may be some of the mechanisms underpinning both poor sleep and health outcomes in this community[39]. These findings highlight how gender-specific responses to environmental threats can have distinct physiological consequences, potentially contributing to gender differences in sleep health disparities in high-stress environments.

Among the men, poorer perceived sleep quality and more severe symptoms of depression and anxiety were associated with markers of more parasympathetic activity during wake. Typically, one would expect parasympathetic activity to be high during the sleep[169,291,344] and would expect both poor sleep quality and more severe depressive and anxiety symptoms to be associated with lower HRV, given the literature outlined in Chapter 5[159]. Men reporting more fear and poorer sleep quality were also more likely to report worse symptoms of depression and anxiety. Together, these findings suggest this autonomic dysregulation in men with more severe symptoms of depression and anxiety may linked to men feeling safer during the day. Men who feel fears related to safety at night may experience poorer quality sleep at night, as suggested by findings in Chapter 2, and may feel safer during the day driving them to take daytime naps. Given the aforementioned link between sleep and parasympathetic activity[344], this may explain the higher HRV during wake in individuals with more severe symptoms of depression and anxiety. Poorer sleep quality was also associated with more severe symptoms of depression and anxiety, which is in line with the well-established relationship between sleep and mental health[134,138,141,218,260]. It is worth noting that the men in this study reported high levels of alcohol consumption. This sort of risk-taking behaviour has previously been linked to mental disorders[254]. Additionally, alcohol consumption is known to fragment sleep[195] and so may contribute to this observed relationship between poor sleep and depression.

Several limitations should be considered when interpreting the results of this study. First, the sample size, while adequate for basic structural equation modelling, may have limited the ability to detect smaller effects and constrained the ability to conduct more complex models.

There may additional variables, such as BMI, which may have contributed to the autonomic impairment observed. Second, limiting our models to female participants, while providing valuable insights into women's mental health in low socioeconomic contexts, limits the generalizability of our findings to men. This is particularly relevant given the gender-specific relationships highlighted in previous chapters. Third, the parcelling of indicators introduces the possibility of masking the potential poor fit of individual items. This may have artificially improved the model fit. The cross-sectional nature of the data precludes causal inferences about the relationships observed. Although, a delta value was chosen to try and capture the circadian aspect of HRV as well as relative night-time stress/arousal, the bluntness of the parasympathetic activity variable limits our understanding of the effects of the dynamic nature of autonomic nervous system functioning. Finally, the sample represented a low socioeconomic status population in a particularly safety-relevant context, and the findings may not generalize to other socioeconomic groups or cultural contexts.

7.5. Conclusion

This novel study provides compelling, although preliminary, evidence for the complex interplay between physiological and psychological factors in the presentation of depression and anxiety among women from low socioeconomic backgrounds. The findings demonstrate that fear responses, but not sleep disturbances or attenuated parasympathetic flexibility, contribute to more severe depressive and anxiety symptoms in this vulnerable population. These results highlight the importance of considering both psychological and physiological mechanisms, the multifaceted nature of mental health outcomes and the moderating role of adaptive behaviours. The identified relationships between fear and symptoms of depression and anxiety as well as the relationship between autonomic dysfunction and sleep disruption suggest potential targets for intervention, particularly in low-resource settings.

Chapter 8

General discussion

8.1. Introduction

The purpose of this thesis was to explore the relationship between sleep characteristics, autonomic nervous system (ANS) function (as indexed by heart rate variability; HRV) and symptoms of depression, anxiety and post-traumatic stress disorder (PTSD) of individuals living in a low socioeconomic status (SES) environment. This thesis further aimed to understand the role of the social environment and fears-related to safety in the sleep-ANS-mental health relationship. Individuals living in Khayelitsha in the Western Cape province of South Africa were chosen as the population of interest given that the low SES of this urban township and the high crime rate in the area mean that this cohort may be particularly vulnerable to both poor quality sleep and mental health challenges. The vast majority of women (34 (29-42) y) and men (36 (31-42) y) who took part in this study reported disturbed sleep (women: 96.6%, men: 97.2%), and poor quality sleep (women: 28.6%, men: 30.1%). This was confirmed by actigraphy-derived measures. Actigraphy shows long time-in-bed (women: 8.72 ± 1.39h, men: 9.89 ± 1.24h) but low sleep efficiencies (women: 83% (80-87) , men: 80% (77-83)) and high wake after sleep onset values (women: 75 (59-100) min, men: 94 (82-124) min). The mental health data was even bleaker: moderate-to-severe symptoms of depression and anxiety were reported by a third and a quarter of participants respectively, with nearly half reporting trauma symptomology suggestive of PTSD, much higher than national estimates (depression: 25.7%, anxiety: 17.8% and PTSD: 0.6-14.9%)[47,259], with a disproportionate percentage of those flagged with likely PTSD being women (90% of all participants flagged as having probable PTSD were women).

8.2. Summary of main findings

The main findings of this thesis are summarised in Figure 8.1.

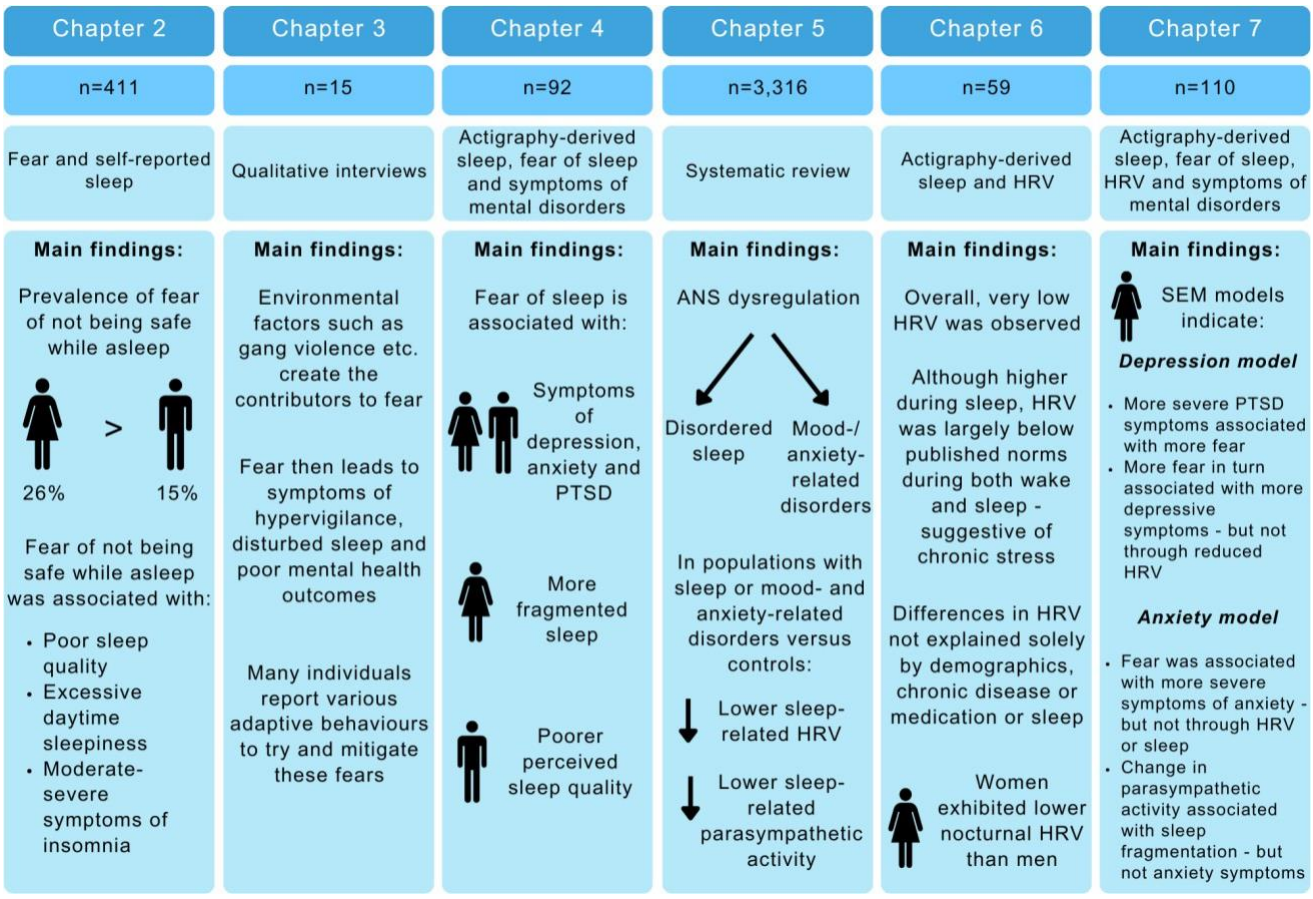

Figure 8.1. Overview of thesis findings by chapter. *ANS: autonomic nervous system; HRV: heart rate variability; PTSD: post-traumatic stress disorder; SEM: structural equation modelling.*

Chapter 2

This study presented this is one of the first studies in an African population and some of the first data outside of the European and American settings showing that African-origin South Africans adults living in a low-SES, high-crime environments who report fear related to feeling unsafe during sleep experience low-quality sleep accompanied with daytime sleepiness and dysfunction. Both men and women were more likely to report poor quality sleep if they experienced any sleep-related fears, however, gender-specific responses also emerged. In women, sleep-related fears were consistently associated with increased odds for excessive daytime sleepiness, while in men the associations were consistently associated with increased risk for more disturbed sleep. While both men and women demonstrated associations between fears related to safety and markers of poor sleep, the associations were stronger among the men, especially for poor sleep quality and disturbed sleep. This highlights the

importance of research in understudied populations to understand context-related barriers to good quality sleep.

Chapter 3

Given the reports of sleep-related fears and the observed association with poor sleep quality in the previous chapter, Chapter 3 utilised qualitative methods to better understand these fears and explore the influence of these fears on participants' sleep and mental health. To the best of our knowledge, this is the first qualitative study worldwide to investigate the relationship between fear of not being safe and sleep quality in adults. Key findings from this study suggest there are various attributes of this low SES area (gang activity, excessive alcohol consumption, drugs, darkness, lack of policing, high rate of unemployment and community level corruption) that create an environment characterised by frequent personal and community trauma, high crime and violence, sub-optimal living conditions and lack of community trust, fostering safety-related fears. Fears related to safety were linked to symptoms of hypervigilance, poor sleep and poor mental health, although poor mental health outcomes emerged as a separate theme (driven by multiple factors, not just fear). Many individuals have implemented adaptive strategies to try and minimise these fears related to not being safe including securing their homes, social strategies like community patrols, avoidance of certain areas or vigilance. Some of these strategies are detrimental to participant's sleep (e.g. purposefully trying to remain awake or waking up throughout the night to maintain vigilance) and/or quality of life and directly contradict common sleep advice. Given the very real danger and ongoing threat to both themselves and their families, however, these behaviours may still be considered adaptive. Changing behaviour at the individual-level doesn't address the root causes of this systemic issue and highlights the importance of addressing the safety of these communities at a policy level and prioritising initiatives for better housing, employment opportunities and more effective policing strategies among others.

Chapter 4

Both Chapters 2 and 3 highlighted fear as key factor in understanding sleep in this cohort but that the relationship between fear and sleep may manifest differently between men and women. Chapter 3 also suggested that individuals who experience fear also experience poorer mental health. This Chapter (Chapter 4) paints a picture of a community with long but disturbed actigraphy-derived sleep, fear of sleep and a high prevalence of moderate-severe symptoms of depression, anxiety and PTSD. Few of the expected relationships between sleep and mental health were observed, which seems to be due to the influence of adaptive behaviours such as those observed in the previous chapter. More fear of sleep came through strongly as a predictor of moderate-severe symptoms of depression and anxiety and likely presence of PTSD. Trauma and fear of sleep likely contributes to the high prevalence of depression, anxiety and PTSD symptoms in South African adults in urban neighbourhoods with high levels of violence and insecurity. More fear was related to poorer perceived sleep quality in men and more fragmented sleep in women, once again highlighting gender-based differences in the effect of fear on sleep as seen in Chapter 2. One could speculate that the roles of trauma and fear of sleep may be even stronger, or may have more widespread associations unobserved here, as these factors don't occur in isolation and there are other factors characteristic of low SES environments such as noise or poverty-related stress which may fragment sleep both independently or in tandem.

Chapter 5

Many participants described symptoms of nocturnal hypervigilance in Chapter 3. As such, we aimed to investigate this in a non-invasive manner through using HRV as an index of autonomic regulation. It is well-established that there is a strong relationship between sleep and mental health and many studies have shown HRV is altered in individuals with insomnia, depression, anxiety and PTSD. As such, we systematically reviewed the literature on HRV in healthy individuals, individuals with sleep disorders and individuals with mood- or anxiety-related disorders to try and determine whether HRV may explain part of the relationship between sleep and symptoms of mental health. We found that although the current evidence is too varied to conclusively state that ANS dysregulation plays a role in the relationship between disordered sleep and mood- and anxiety-related disorders, we did find that ANS dysregulation appears to be independently associated with both disordered sleep and mood-

and anxiety-related disorders. Lower sleep-related HRV, lower markers of sleep-related parasympathetic activity and altered sleep-related sympathovagal balance was largely observed in populations with sleep or mood- and anxiety-related disorders versus controls which could be a marker of hyperarousal in these populations. For the scope of this thesis, this provides common ground between sleep and psychiatric disorders and provides support for the hypothesis that sleep-related ANS dysregulation influences the observed bidirectional relationship between sleep and mood- and anxiety-related disorders.

Chapter 6

Previous chapters highlighted the prevalence of fear and hypervigilance symptoms in this community. This chapter demonstrates that residents of this high-crime, low SES area show markedly lower HRV values than previously reported norms, suggesting significant autonomic dysregulation in both men and women. The consistently low HRV values across the cohort are closer to those in clinical populations such as individuals with major depression and insomnia. Those showing higher HRV during wake than sleep (indicating nocturnal hyperarousal) may represent a particularly vulnerable subset of the population but this reversed diurnal variation cannot be explained by demographics, chronic disease or medication or sleep variables alone. Coupled with women exhibiting lower HRV specifically during sleep than men, more dampened diurnal variation and reporting more fear suggests that environmental stress and fear contribute to disrupting ANS regulation in this population. These findings build on previous chapters by demonstrating how environmental stressors, particularly fear and the need for hypervigilance, may impact sleep and health through autonomic dysregulation, with women showing greater vulnerability to these effects. This provides further evidence for the complex interplay between environmental stress, fear and sleep, observed throughout this thesis, while highlighting the importance of considering gender when examining these relationships in high-stress environments.

Chapter 7

Chapter 5 highlighted a few key gaps in the literature. Firstly, there was a notable lack of

research in individuals with generalised anxiety or symptoms of anxiety. Rather, studies looked at anxiety-related disorders which were almost uniformly PTSD and the symptoms thereof. Secondly, no studies investigated how sleep-related HRV may mediate the relationship between disordered sleep and mood- and anxiety-related disorders or more generally, how HRV, sleep and mental health variables may interact together. Most studies just looked at HRV as an outcome in populations diagnosed with or self-reporting disordered sleep or mood- and anxiety-related disorders. This chapter aimed to fill those gaps by i) having symptoms of anxiety as one of our primary outcomes and ii) using SEM to model the interactions between trauma exposure (and associated PTSD symptoms in the depression model), fear of sleep, sleep fragmentation, change in HRV between sleep and wake (specifically those measures most strongly reflecting parasympathetic input) and symptoms of depression and anxiety in women. Although these data are preliminary we established that fear responses contribute to more severe depressive and anxiety symptoms. Dampened HRV was also related to more sleep fragmentation in the anxiety model, which suggests that hyperarousal is implicated in disrupted sleep for these participants.

8.3. Vigilance-Sleep Trade-Off Theory

This thesis has documented significant physiological and psychological challenges in residents of a low SES community. These challenges are characterised by disrupted sleep patterns, blunted HRV, and a high prevalence of fear and clinically significant symptoms of depression, anxiety, and PTSD. However, many individuals demonstrate remarkable resilience, with the expected relationships between poor sleep quality and mental health largely being unobserved. The reason for this may lie in the adaptive behaviours individuals are implementing. These adaptive behaviours may be disturbing sleep quality (waking up multiple times a night which fragments sleep, etc.) but may help people feel safer therefore improving their mental health - eliminating the expected relationship. This suggests a complex interplay between environmental challenges and adaptive responses.

I would like to propose a theory to explain this named the **Vigilance-Sleep Trade-Off Theory.** In unsafe communities, individuals develop heightened vigilance as an adaptive response to perceived threats, leading them to engage in behaviours that further reinforce this

hypervigilant state. While this adaptive vigilance negatively impacts their physiological health through disrupted sleep patterns and reduced heart rate variability, it paradoxically provides psychological benefits as a coping mechanism, creating a complex trade-off between physical wellbeing and mental resilience. This framework would expand on the current theoretical understanding of stress responses in challenging environments and builds upon Brosschot et al.'s (2016) "*Generalized Unsafety Theory of Stress*" (GUTS), which posits that the stress response is our default state, which is typically inhibited by the vagal system when safety is perceived[364,370]. According to GUTS, in low SES environments, where safety concerns are persistent, this vagal inhibition may be chronically withdrawn, manifesting as reduced HRV and maintaining a state of physiological preparedness or perpetual activation. In the proposed framework emanating from this thesis, this perpetual activation creates a biological environment where achieving restorative sleep becomes increasingly challenging.

The **Vigilance-Sleep Trade-Off Theory** extends the "*Shift-and-persist*" model[389] proposed by Chen et al. (2015). This model suggests that individuals residing in low SES settings utilise coping mechanisms to accommodate uncontrollable stressors when resources are limited, while maintaining resilience through purpose and hope and that this cognitive reframing has anti-inflammatory effects. Chen et al. (2015) propose that lower perceived psychological stress through this adaptive cognitive reframing reduces the biological stress response, specifically via the ANS and hypothalamic-pituitary-adrenal axis to prevent glucocorticoid resistance. Glucocorticoid has anti-inflammatory properties but, under conditions of chronic stress, various hormone and cytokine cascades trigger down-regulation of the activity of glucocorticoid receptors[389]. While both models propose accommodations by low SES residents to endure the environments in which they live, the shift-and-persist model introduces the value of cognitive adaptations and the associated anti-inflammatory effects. Meanwhile, the proposed framework encompasses the physiological effect of the environment and behavioural, rather than cognitive, adaptations. Unfortunately, these behavioural shifts, while essential for immediate survival, may paradoxically reinforce the physiological dysregulation initiated by environmental stressors which may create a feedback loop.

One key feature of the proposed **Vigilance-Sleep Trade-Off Theory** is that low SES communities face a fundamental conflict between immediate safety and long-term health.

The adaptive behaviours that ensure survival in challenging environments may inadvertently perpetuate poor sleep and autonomic dysregulation. This represents more than individual choice - it reflects a systemic issue where environmental conditions force residents to prioritize vigilance over rest. The resulting physiological and psychological burden creates a public health imperative for intervention at the community level. This explains why traditional sleep interventions may have limited success in these communities - they often fail to address the underlying safety concerns driving vigilant behaviours. Additionally, it highlights the need for comprehensive environmental interventions that address both physical and perceived safety. Finally, it suggests that short-term interventions should focus on supporting adaptive behaviours while minimizing their physiological costs.

8.4. Recommendations for intervention

The findings of this thesis suggest the need for a multi-level intervention approach. Addressing the root of the sleep, autonomic and mental health issues in this community requires social and policy change, which while noble and critical, are not easily solved and may take decades before any effects are seen. In the meantime, more immediate interventions to support individuals are required. At the individual level, several relatively accessible interventions could be implemented, such as structured breathing exercises to act on the vagus nerve, combating physiological hyperarousal, improving HRV and facilitating better quality sleep. Even one session of deep breathing has been shown to improve indices of parasympathetic activity and feelings of anxiety in both younger and older adults, although older adults appear to experience greater benefits[366]. Throughout this thesis we observed that certain adaptive behaviours may be more destructive to sleep quality than others. Passive behaviours (such as leaving a light on) may be more sleep-compatible compared to active behaviours such as waking up to assess potential threats while still providing psychological comfort, minimizing sleep disruption. While digital health interventions for both sleep and mental disorders (such as insomnia and PTSD respectively) show promise[391–393], these feasibility for implementing these interventions in a low SES setting is still being investigated. Furthermore, it is crucial to recognize that these technological solutions alone are insufficient without addressing broader systemic issues. Home environment modifications, such as improved soundproofing or security features, could theoretically

benefit sleep quality, but the associated costs make these interventions unfeasible for many residents in low SES communities.

Overall, poverty drives many of the safety concerns and creates tangible barriers to quality sleep and both mental and physical health. This is, therefore, a social justice issue requiring urgent government action and policy-level interventions to create meaningful change. Interventions should target neighbourhood environmental factors that contribute to sleep disturbance and safety concerns. These may include prioritising government housing as suboptimal housing materials leave participants vulnerable to gunshots, break-ins, robbery, fire and other safety concerns as well as noise, inopportune light and high temperatures – known disruptors of sleep. Employment opportunities and economic investment into these communities is essential to deter people from entering gangs and crime for financial reasons. Changes to policing strategies may help combat the crime and violence in areas like Khayelitsha. Unfortunately, crime and violence are not unique to Khayelitsha, and populations living in other urban areas in South Africa, and even some rural areas, could be affected by the same cycle of insecurity and fear, disrupted sleep and mental health issues. Therefore, these proposed interventions and changes in policy could benefit many areas and populations across South Africa. These systemic changes, while more challenging to implement, are essential for creating sustainable improvements in sleep health security.

8.5. Methodological considerations and limitations

The studies in this thesis are subject to several methodological limitations. Firstly, the cross-sectional, observational study design across all chapters inherently limits causal inference. Additionally, the small sample size in the SEM analysis for Chapter 7, and limiting the analyses to women only, may limit the generalizability and statistical power of these findings.

Chapter 2 relied solely on self-report measures of sleep and limited, binary questions for fears related to sleep. Previous research has consistently demonstrated that self-reported total sleep time tends to overestimate actual sleep duration. This potential measurement bias may have influenced the study's results. Moreover, several potentially influential variables were not investigated, including childcare responsibilities, societal factors, length of community residence, sleep disorders, psychiatric conditions, and measures of psychological distress.

The language barrier was the predominant methodological challenge for the qualitative interviews (Chapter 3). As such, the researchers who analysed the data did not conduct the interviews. Efforts were made to mitigate this limitation, however, by using the same fieldworker for interviews and transcription/translation. Despite this, there is a chance some nuanced information may have been inadvertently lost in the process.

HRV, while a useful proxy for autonomic function, cannot comprehensively distinguish between sympathetic and parasympathetic contributions, especially in metrics like LF and ambulatory SDNN. Aggregated HRV and sleep measures may obscure dynamic, within-night variations including sleep stage-specific findings. Critical moderating factors were not investigated and/or statistically controlled for in Chapters 4, 5 and 7. These include individual differences in resilience and emotional regulation and external influences like social support systems, time since trauma occurrence, light exposure, physical activity, diet, napping, and medication use which are potential modulators of autonomic regulation and sleep.

8.6. Future research

While cross-sectional data have proved useful to identify associations between fear, sleep, HRV and mental health outcomes, future research should explore longitudinal and interventional strategies to understand the complex relationships between environmental factors, physiological responses, and mental health. This could involve:

- Interventional studies examining the direct manipulation of living environments to assess impacts on fear, HRV, sleep quality, and mental health outcomes would be valuable. This could involve assessing the same individuals perceived safety, HRV and sleep in different residential environments. Previous studies looking at neighbourhood interventions reported limited or mixed effects. This would help establish clearer causal relationships compared to previous neighbourhood-level interventions which have shown mixed results. As Kirkbridge et al (2024) described in their recent review: "The paucity of evidence for neighbourhood interventions reflects the complexity of delivering such interventions and their possible unintended consequences, despite evidence that neighbourhood social disadvantage, fragmentation and social capital are significantly associated with mental health". Thus, trying a more targeted intervention focused on sleep environment rather than the wider neighbourhood may help to

isolate the effects of perceived safety on HRV, sleep and symptoms of depression and anxiety.

- Comparative studies between different housing contexts within low SES settings (such as (informal housing compared to Reconstruction and Development Programme housing) could provide insights into how specific aspects of the built environment and perceived safety influence physiological and psychological outcomes. This could inform more targeted intervention strategies.
- Randomized controlled trials investigating specific HRV-focused interventions (such as structured breathing exercises) could help determine if directly modifying autonomic nervous system function impacts sleep and mental health outcomes in individuals living in low socioeconomic environments. Key outcomes would include measures of depression, anxiety, and PTSD symptoms.
- Longitudinal studies tracking changes in environmental conditions, autonomic nervous system function (through HRV monitoring), sleep patterns, and psychological well-being over time would be particularly valuable. Using multiple measurement timepoints could elucidate temporal relationships and potential causal pathways between environmental modifications and health outcomes.

Furthermore, conducting SEM analyses, such as in Chapter 7, with a larger sample size would improve the reliability of our results and would allow for more complex models to be investigated, potentially identifying additional pathways.

8.7. Conclusion

This thesis provides novel insights into the complex relationships between sleep, mental health, and autonomic regulation among residents of a high-crime, low SES community in South Africa. These findings emphasize the importance of examining sleep health comprehensively, moving beyond traditional focus on sleep duration to consider other aspects of sleep health as they relate to depression, anxiety, and autonomic dysfunction, with fragmented sleep emerging as a key factor in this thesis. The data revealed how the neighbourhood environment profoundly shapes sleep patterns and mental health outcomes in this population.

Furthermore, the data suggest that the challenging neighbourhood environment, potentially compounded by past trauma, may induce a state of nocturnal hypervigilance and fear associated with sleep itself. This psychological and physiological arousal appears to manifest in disturbed sleep patterns, characterized by insufficient sympathetic withdrawal during sleep and increased sleep fragmentation. Notably, we propose a "Vigilance-Sleep Trade-Off"; heightened vigilance as an adaptive response to perceived threats, which negatively impacts the physiological health of individuals through disrupted sleep patterns and reduced heart rate variability, but paradoxically provides psychological benefits as a coping mechanism. The bidirectional relationships between sleep disturbance, hyperarousal, and mood disorders appear particularly salient in this context, where environmental threats may activate both psychological and physiological stress responses that persist into the sleep period. This research underscores the systemic barriers to restorative sleep in this community which may create and perpetuate mental health disparities.

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APPENDIX 2.1: Customised questionnaire adapted from the Fear of Sleep Inventory used to asses fears related to safety during sleep.

Do you have any difficulty falling asleep or staying asleep for a long time normally?

☑ Yes ☑ No

If so, why? (tick where appropriate). You may tick more than one option.

		Tick
a)	Fear of not being safe while asleep	
b)	Fear of being attacked while asleep	
c)	Fear of falling asleep	
d)	Being awakened by strange noises out of sleep	
e)	Dreams about past traumatic experiences	
f)	Sleeping with the light on to feel safe	

APPENDIX 2.2: Univariate analyses between each of the potential covariates and self-reported excessive daytime sleepiness as measured by Epworth Sleepiness Scale, poor sleep quality as measured by Pittsburgh Sleep Quality Index, clinically significant symptoms of insomnia as measured by Insomnia Severity Index, sleep disturbances as measured by the Pittsburgh Sleep Quality Index and daytime dysfunction as measured by Pittsburgh Sleep Quality Index as well as self-reported time-in-bed and total sleep time in men (n=177).

	Excessive daytime sleepiness (ESS>10)	**Poor sleep quality (PSQI>5)**	**Clinically significant insomnia symptoms (ISI>14)**	**Disturbance**	**Daytime dysfunction**	**Time-in-bed**	**Total sleep time**
Age	0.94 (0.94-1.03), p=0.505	1.06 (1.02-1.12), **p-0.006**	1.03 (0.94-1.13), p=0.500	1.05 (1.01-1.09), **p=0.026**	1.01 (0.97-1.05), p=0.724	0.96 (0.92-1.00), **p=0.038**	0.96 (0.92-1.00), **p<0.031**
Body mass index	1.06 (0.98-1.15), p=0.115	1.03 (0.96-1.12), p=0.392	1.02 (0.88-1.19), p=0.769	1.06 (0.99-1.14), **p=0.118**	1.02 (0.95-1.09), p=0.587	0.96 (0.90-1.03), p=0.301	0.91 (0.84-0.98), p=0.013
Smoking	1.23 (0.78-1.94), p=0.369	0.88 (0.55-1.41), p=0.592	0.33 (0.09-1.13), p=0.078	1.44 (0.94-2.20), p=0.095	1.08 (0.72-1.63), p=0.714	1.23 (0.82-1.85), p=0.326	1.45 (0.96-2.19), p=0.075
Alcohol consumption	1.00 (0.99-1.01), p=0.964	1.00 (0.99-1.02), p=0.528	1.02 (1.00-1.03), p=0.065	1.01 (1.00-1.02), p=0.057	1.00 (0.99-1.01), p=0.925	1.01 (1.00-1.02), p=0.170	1.00 (0.99-1.01), p=0.428
Household density	0.98 (0.85-1.13), p=0.821	0.96 (0.84-1.11), p=0.606	0.65 (0.43-1.00), p=0.052	0.99 (0.88-1.13), p=0.931	1.01 (0.90-1.15), p=0.832	0.93 (0.82-1.04), p=0.209	0.96 (0.85-1.08), p=0.507
Presence of young children	0.83 (0.43-1.60), p=0.581	0.93 (0.49-1.78), p=0.830	0.11 (0.01-0.94), **p=0.044**	0.82 (0.45-1.49), p=0.512	0.86 (0.49-1.52), p=0.603	0.90 (0.51-1.60), p=0.724	0.99 (0.56-1.75), p=0.980

Work for pay	0.89 (0.46-1.72), p=0.726	1.22 (0.64-2.34), p=0.546	1.80 (0.43-7.42), p=0.419	1.26 (0.69-2.29), p=0.454	1.49 (0.84-2.65), p=0.172	0.49 (0.27-0.88), **p=0.017**	0.58 (0.32-1.03), p=0.064
Annual household income	1.06 (0.85-1.32), p=0.624	0.83 (0.66-1.05), p=0.122	0.87 (0.54-1.42), p=0.583	0.89 (0.73-1.09), p=0.256	1.06 (0.88-1.27), p=0.571	0.91 (0.75-1.11), p=0.356	0.93 (0.77-1.13), p=0.468
Level of education	1.04 (0.69-1.57), p=0.841	1.53 (1.02-2.32), **p=0.042**	1.10 (0.48-2.50), p=0.824	1.28 (0.88-1.87), p=0.194	1.24 (0.87-1.77), p=0.228	0.69 (0.48-0.99), **p=0.043**	0.70 (0.49-1.00), p=0.051

APPENDIX 2.3: Univariate analyses between each of the potential covariates and self-reported excessive daytime sleepiness as measured by Epworth Sleepiness Scale, poor sleep quality as measured by Pittsburgh Sleep Quality Index, clinically significant symptoms of insomnia as measured by Insomnia Severity Index, sleep disturbances as measured by the Pittsburgh Sleep Quality Index and daytime dysfunction as measured by Pittsburgh Sleep Quality Index as well as self-reported time-in-bed and total sleep time in women (n=234).

	Excessive daytime sleepiness (ESS>10)	**Poor sleep quality (PSQI>5)**	**Clinically significant insomnia symptoms (ISI>14)**	**Disturbance**	**Daytime dysfunction**	**Time-in-bed**	**Total sleep time**
Age	1.00 (0.97-1.04), p=0.895	1.05 (1.01-1.08), **p=0.014**	1.14 (1.06-1.24), **p=0.001**	1.03 (1.00-1.06), **p=0.071**	1.02 (0.99-1.05), p=0.152	0.96 (0.93-1.00), **p=0.025**	0.93 (0.90-0.96), **p<0.001**
Body mass index	1.01 (0.98-1.04), p=0.514	1.01 (0.97-1.04), p=0.720	1.01 (0.94-1.08), p=0.857	1.01 (0.98-1.04), **p=0.579**	1.01 (0.98-1.04), p=0.384	0.95 (0.92-0.98), **p=0.001**	0.96 (0.93-0.99), **p=0.010**
Smoking	1.73 (1.16-2.58), **p=0.008**	0.91 (0.56-1.40), p=0.666	0.83 (0.32-2.16), p=0.711	0.94 (0.65-1.35), p=0.725	0.92 (0.66-1.33), p=0.651	1.25 (0.85-1.83), p=0.257	1.07 (0.74-1.55), p=0.725
Alcohol consumption	1.02 (1.00-1.04), p=0.052	1.02 (1.00-1.03), p=0.123	1.01 (0.99-1.02), p=0.073	0.98 (0.92-1.034), p=0.435	1.01 (0.99-1.02), p=0.463	1.01 (0.99-1.02), p=0.392	1.01 (0.99-1.02), p=0.392
Household density	0.87 (0.75-1.00), p=0.051	0.96 (0.83-1.11), p=0.597	0.98 (0.74-1.30), p=0.882	0.98 (0.86-1.11), p=0.704	0.98 (0.87-1.11), p=0.769	0.83 (0.73-0.95), **p=0.007**	0.94 (0.82-1.06), p=0.301
Presence of young children	0.85 (0.44-1.64), p=0.622	0.60 (0.31-1.17), p=0.135	1.45 (0.31-6.79), p=0.634	0.87 (0.47-1.60), p=0.649	0.95 (0.52-1.74), p=0.879	0.47 (0.24-0.91), **p=0.025**	0.69 (0.37-1.29), p=0.242

Work for pay	0.96 (0.53-1.74), p=0.892	1.12 (0.61-2.08), p=0.713	1.06 (0.32-3.56), p=0.925	0.92 (0.53-1.58), p=0.751	1.44 (0.86-2.40), p=0.166	0.48 (0.27-0.85), **p=0.012**	0.55 (0.31-0.97), **p=0.038**
Annual household income	0.72 (0.59-0.87), **p=0.001**	1.02 (0.86-1.21), p=0.823	0.78 (0.52-1.17), p=0.231	0.91 (0.78-1.06), p=0.238	1.00 (0.86-1.15), p=0.961	1.01 (0.86-1.17), p=0.946	1.04 (0.90-1.21), p=0.583
Level of education	0.74 (0.51-1.08), p=0.114	0.64 (0.42-0.97), **p=0.036**	0.40 (0.17-0.93), **p=0.034**	0.81 (0.59-1.14), p=0.238	0.96 (0.70-1.30), p=0.771	0.82 (0.58-1.15), p=0.258	1.04 (0.75-1.44), p=0.821

APPENDIX 3.1: Semi-structured interview guide

1. Where is your home / where do you come from?
2. How long have you lived in Khayelitsha for?
3. What is your current state of employment - are you employed or unemployed? Part time or full time?

Topic Area 1: Physical sleep environment - home/sleep space

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 (I.e. light sheet, blanket, duvet, mattress on a base, mattress on the floor, blanket on the floor), 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*

Topic Area 2: Fear and safety at night

4. When you are trying to sleep at night, how safe do you personally feel? *Probes: How does physically feeling unsafe affect your sleep. Impact on 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? Characterising *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?

Topic Area 3: Neighbourhood environment

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? ***[If yes]:*** *please can you elaborate*
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? Characterising *Probes: Do you discuss the safety of your neighbourhood? Who can you rely on when you feel scared (facilitator or safety) i.e. the Police? Does the community leader know about this?*

Topic Area 4: Perceptions of sleep

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? *Probes: tell me more*
15. Has your sleep always been like this or has your sleep changed in the past few years? *Probes: tell me more*
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? barrier to good sleep
    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 spend time with family, do you get ready for the next day? What food, drinks (alcoholic on non-alcoholic, e.g. caffeine) are you consuming? Time of eating prior to going to bed?*
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?*

    *napping = light sleep during the day

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?

APPENDIX 4.1: Spearman rank order correlations between continuous sleep, mental health and fear of sleep variables in women (n=64).

	ESS		**PSQI**		**Time-in-bed (h)**		**Total sleep time (h)**		**Sleep efficiency (%)**		**SFI (%)**	
	rho	p-value	rho	p-value	rho	p-value	rho	p-value	rho	p-value	rho	p-value
BDI-II score	0.192	0.131	0.181	0.155	-0.028	0.829	-0.011	0.930	-0.045	0.726	0.121	0.367
BAI score	0.244	*0.055*	0.163	0.202	-0.197	0.118	-0.150	0.237	0.072	0.570	0.034	0.798
PC-PTSD score	0.167	0.191	0.073	0.571	0.095	0.454	0.071	0.580	0.065	0.611	0.051	0.705
Global fear of sleep score	0.076	0.578	-0.019	0.891	-0.061	0.652	-0.030	0.825	0.089	0.512	0.051	0.710
Fear of sleep subscale	0.066	0.632	-0.098	0.472	-0.087	0.523	-0.066	0.631	0.087	0.523	-0.042	0.758
Fear of loss of vigilance subscale	0.067	0.622	0.097	0.476	-0.158	0.244	-0.087	0.526	0.123	0.366	-0.008	0.952
Fear of trauma re-exposure subscale	0.143	0.293	0.033	0.811	-0.048	0.724	-0.064	0.640	-0.222	0.101	0.290	**0.030**
Vigilant behaviours subscale	0.262	*0.051*	0.019	0.891	0.041	0.764	0.026	0.851	0.076	0.576	0.032	0.813
Fear of the dark subscale	-0.135	0.321	0.030	0.828	-0.071	0.605	-0.032	0.814	0.153	0.259	-0.044	0.747

BAI: Beck Anxiety Inventory; BDI-II: Beck Depression Inventory; ESS: Epworth Sleepiness Scale; FoSI: Fear of Sleep Inventory; PSQI: Pittsburgh Sleep Quality Index; PC-PTSD: Primary Care post-traumatic stress disorder; SFI: sleep fragmentation index.

APPENDIX 4.2: Spearman rank order correlations between continuous sleep, mental health and fear of sleep variables in men (n=27).

	ESS		**PSQI**		**Time-in-bed (h)**		**Total sleep time (h)**		**Sleep efficiency (%)**		**SFI (%)**	
	rho	p-value	rho	p-value	rho	p-value	rho	p-value	rho	p-value	rho	p-value
BDI-II score	0.460	**0.021**	0.628	**0.001**	0.129	0.529	0.155	0.450	0.190	0.352	-0.083	0.695
BAI score	0.371	0.062	0.481	**0.015**	-0.245	0.218	-0.276	0.163	-0.077	0.704	0.066	0.748
PC-PTSD score	0.307	0.127	0.454	**0.023**	-0.137	0.495	-0.024	0.907	0.229	0.250	0.067	0.744
Global fear of sleep score	0.121	0.581	0.252	0.245	-0.211	0.333	-0.009	0.966	0.289	0.182	-0.226	0.299
Fear of sleep subscale	-0.036	0.871	0.489	**0.018**	-0.206	0.346	-0.173	0.430	-0.025	0.911	0.132	0.549
Fear of loss of vigilance subscale	0.047	0.830	0.157	0.475	-0.165	0.452	0.098	0.658	0.388	0.068	-0.418	**0.047**
Fear of trauma re-exposure subscale	0.102	0.642	0.403	*0.056*	-0.134	0.542	-0.206	0.346	-0.031	0.888	0.051	0.817
Vigilant behaviours subscale	0.207	0.344	-0.129	0.557	-0.054	0.805	0.265	0.221	0.403	*0.056*	-0.372	0.081
Fear of the dark subscale	0.022	0.920	0.267	0.218	-0.066	0.766	-0.076	0.730	0.058	0.792	0.238	0.273

BAI: Beck Anxiety Inventory; BDI-II: Beck Depression Inventory; ESS: Epworth Sleepiness Scale; FoSI: Fear of Sleep Inventory; PSQI: Pittsburgh Sleep Quality Index; PC-PTSD: Primary Care post-traumatic stress disorder; SFI: sleep fragmentation index.

APPENDIX 4.3: Logistic regressions exploring associations between sleep characteristics (independent variables) and moderate-severe symptoms of depression and anxiety or likely presence of PTSD (dependant variables) in women (n=64).

	ESS		**PSQI**		**Time-in-bed (h)**		**Total sleep time (h)**		**Sleep efficiency (%)**		**SFI (%)**	
	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
Moderate-severe depression	1.08 (0.96-1.22)	0.198	1.10 (0.89-1.35)	0.390	0.96 (0.87-1.37)	0.813	1.00 (0.68-1.46)	0.998	1.02 (0.94-1.10)	0.700	1.02 (0.96-1.09)	0.481
Moderate-severe anxiety	1.22 (1.06-1.41)	**0.007**	1.06 (0.85-1.31)	0.619	0.75 (0.49-1.13)	0.168	0.89 (0.59-1.36)	0.590	1.07 (0.98-1.18)	0.140	0.98 (0.92-1.04)	0.509
Likely presence of PTSD	1.07 (0.95-1.22)	0.265	1.04 (0.84-1.28)	0.716	1.09 (0.76-1.57)	0.635	1.11 (0.76-1.63)	0.595	1.00 (0.92-1.08)	0.944	1.01 (0.95-1.07)	0.779

CI: confidence interval; ESS: Epworth Sleepiness Scale; OR: odds ratio; PSQI: Pittsburgh Sleep Quality Index; PTSD: post-traumatic stress disorder; SFI: sleep fragmentation index.

APPENDIX 4.4: Logistic regressions exploring associations between sleep characteristics (independent variables) and moderate-severe symptoms of depression and anxiety or likely presence of PTSD (dependant variables) in men (n=27).

	ESS		**PSQI**		**Time-in-bed (h)**		**Total sleep time (h)**		**Sleep efficiency (%)**		**SFI (%)**	
	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
Moderate-severe depression	1.34 (0.99-1.82)	0.061	1.34 (0.82-2.19)	0.251	1.94 (0.78-4.81)	0.151	2.12 (0.82-5.47)	0.119	1.13 (0.93-1.37)	0.233	0.96 (0.85-1.10)	0.574

Moderate-severe anxiety	1.26 (0.94-1.69)	0.117	1.20 (0.75-1.94)	0.442	0.76 (0.33-1.77)	0.525	0.60 (0.23-1.54)	0.290	0.95 (0.82-1.10)	0.480	1.00 (0.89-1.11)	0.944
Likely presence of PTSD	1.08 (0.77-1.50)	0.658	6.92 (0.61-78.38)	0.118	1.66 (0.61-4.55)	0.323	1.10 (0.43-2.84)	0.842	0.96 (0.81-1.13)	0.616	1.03 (0.92-1.16)	0.576

CI: confidence interval; ESS: Epworth Sleepiness Scale; OR: odds ratio; PSQI: Pittsburgh Sleep Quality Index; PTSD: post-traumatic stress disorder; SFI: sleep fragmentation index.

APPENDIX 4.5: Spearman rank order correlations between mental health and fear of sleep variables in women (n=64).

	Global fear of sleep score		**Fear of sleep subscale**		**Fear of loss of vigilance subscale**		**Fear of trauma re-exposure subscale**		**Nighttime vigilant behaviours subscale**		**Fear of the dark subscale**	
	rho	p-value	rho	p-value	rho	p-value	rho	p-value	rho	p-value	rho	p-value
BDI-II score	0.435	**<0.001**	0.378	**0.002**	0.273	**0.029**	0.461	**<0.001**	0.180	0.177	0.241	*0.055*
BAI score	0.450	**<0.001**	0.456	**<0.001**	0.348	**0.005**	0.409	**<0.001**	0.207	0.119	0.256	**0.042**
PC-PTSD score	0.323	**0.009**	0.308	**0.013**	0.190	0.133	0.318	**0.010**	0.255	*0.054*	0.148	0.242

BAI: Beck Anxiety Inventory; BDI-II: Beck Depression Inventory; PC-PTSD: Primary Care post-traumatic stress disorder.

APPENDIX 4.6: Spearman rank order correlations between mental health and fear of sleep variables in men (n=27).

	Global fear of sleep		**Fear of sleep subscale**		**Loss of vigilance subscale**		**Trauma re-exposure subscale**		**Nighttime vigilant behaviours subscale**		**Fear of the dark subscale**	
	rho	p-value	rho	p-value	rho	p-value	rho	p-value	rho	p-value	rho	p-value
BDI-II score	0.599	**0.001**	0.453	**0.030**	0.384	0.070	0.516	**0.012**	0.229	0.293	0.256	0.239
BAI score	0.628	**0.001**	0.559	**0.006**	0.433	**0.039**	0.639	**0.001**	0.104	0.636	0.148	0.502
PC-PTSD score	0.434	**0.023**	0.482	0.020	0.349	0.103	0.481	**0.020**	0.157	0.474	0.096	0.662

BAI: Beck Anxiety Inventory; BDI-II: Beck Depression Inventory; PC-PTSD: Primary Care post-traumatic stress disorder.

APPENDIX 4.7: Sleep characteristics of participants grouped by trauma status.

	Women				Men			
	No trauma (n=7)	**Resilient (n=21)**	**Symptoms indicative of likely PTSD (n=37)**	**p-value**	**No trauma (n=16)**	**Resilient (n=8)**	**Symptoms indicative of likely PTSD (n=4)**	**p-value**
ESS	6 [2-9]	4 [2-5]	6 [3-8]	0.290	0 [0-2]	3 [1-7]	3 [1-5]	0.200
PSQI	3 [2-5]	4 [3-6]	4 [2-6]	0.493	3 [2-4][c]	3 [2-4][b]	6 [5-10][b,c]	**0.041**
Time-in-bed (h)	8.96±1.39	8.51±1.37	8.79±1.43	0.616	9.88±1.16	9.94±1.24	10.51±0.92	0.733
Total sleep time (h)	7.20±1.56	7.00±1.28	7.23±1.31	0.820	7.72±1.19	8.30±1.27	8.04±0.23	0.516
Sleep efficiency (%)	81 [76-88]	82 [80-87]	84 [80-88]	0.919	79 [73-82]	85 [80-87]	82 [75-82]	*0.052*
SFI (%)	30±10	25±8	27±9	0.560	35±10	27±4	34±3	0.099

Data are presented as mean ± standard deviation or median [interquartile range]. Trauma status is defined as either no exposure where individuals have experienced no trauma, "resilient" where individuals have experienced a trauma but exhibit sub-clinical PC-PTSD scores <4 or "likely PTSD" where individuals have experienced a trauma and show PC-PTSD scores of 4 or 5 indicating likely presence of clinical PTSD. ESS: Epworth Sleepiness Scale; PSQI: Pittsburgh Sleep Quality Index; PTSD: post-traumatic stress disorder; SFI: Sleep Fragmentation Index. P-values represent between group comparisons determined using Kruskal-Wallis ANOVA. Post hoc differences were assessed using Sidak post hoc. [a] indicates a significant post hoc difference between "no trauma" and "resilient", [b] indicates a post hoc difference between "resilient" and "symptoms indicative of likely PTSD" and [c] indicates a post hoc difference between "no trauma" and "symptoms indicative of likely PTSD".

APPENDIX 4.8: Mental health and fear of sleep characteristics of participants grouped by trauma status.

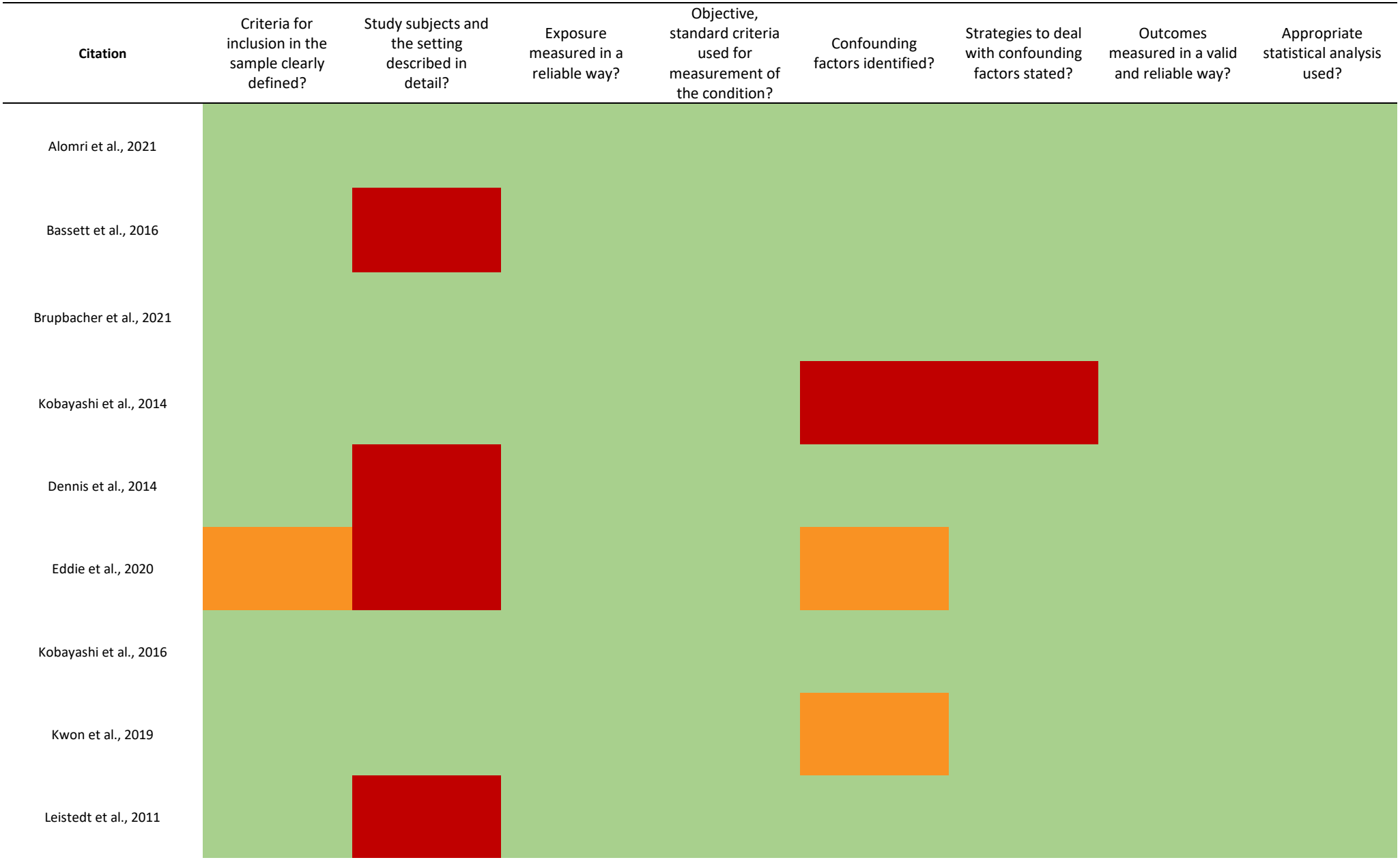
	Women				Men			
	No trauma	**Resilient**	**Symptoms indicative of likely PTSD**	**p-value**	**No trauma**	**Resilient**	**Symptoms indicative of likely PTSD**	**p-value**
BDI-II score	12 [8-15]	13 [10-21][b]	21 [14-31][b]	**0.009**	8 [3-12][c]	13 [10-21]	22 [18-28][c]	**0.005**
BAI score	7 [4-15]	7 [4-12][b]	14 [8-20][b]	**0.012**	7 [2-10]	10 [7-17]	15 [11-20]	**0.042**
PC-PTSD score	0 [0-0][a,c]	2 [2-3][a,b]	4 [4-5][b,c]	**<0.001**	0 [0-0] [a,c]	2 [0-3] [a,b]	5 [5-5] [b,c]	**<0.001**
Global fear of sleep score	14±11	16±11	21±9	0.084	11±6	16±11	21±9	0.071
Fear of sleep subscale	1 [0-5]	3 [0-5]	3 [2-5]	0.118	0 [0-2]	0 [0-2]	4 [3-5]	*0.056*
Fear of loss of vigilance subscale	2 [0-7]	4[2-5]	4 [3-6]	0.348	3 [2-4]	5 [3-10]	7 [4-9]	0.172
Fear of trauma re-exposure subscale	1 [0-3]	2 [1-3]	3 [2-5]	*0.057*	0 [0-2]	2 [1-2]	2 [2-3]	**0.048**
Vigilant behaviours subscale	7 [1-11]	4 [2-8]	8 [4-9]	0.065	6 [5-8]	8 [6-8]	8 [6-11]	0.281
Fear of the dark subscale	0 [0-1]	0 [0-4]	0 [0-6]	0.689	0 [0-0]	0 [0-0]	0 [0-2]	0.936

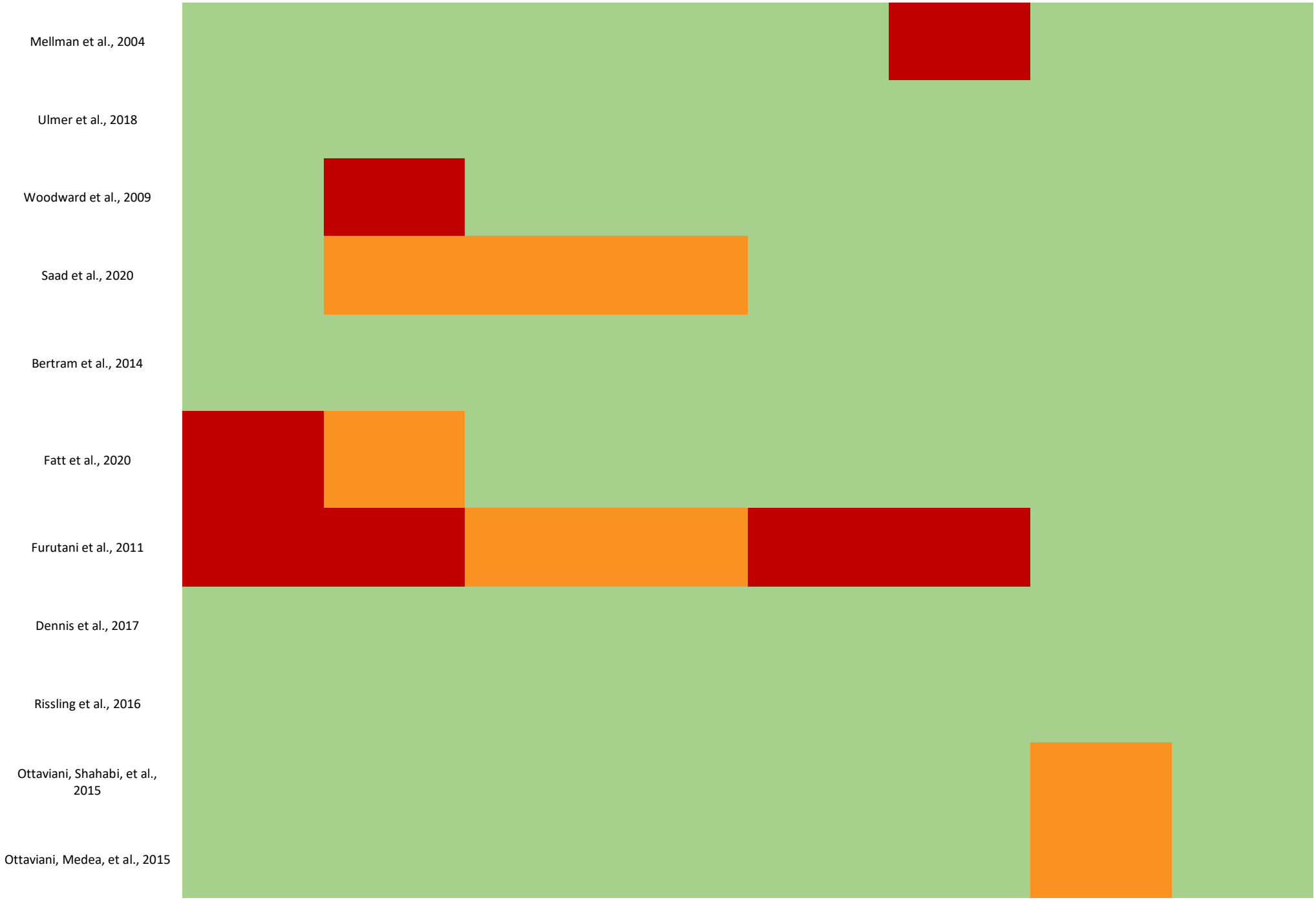
Data are presented as mean ± standard deviation or median [interquartile range]. Trauma status is defined as either no exposure where individuals have experienced no trauma, "resilient" where individuals have experienced a trauma but exhibit sub-clinical PC-PTSD scores <4 or "likely PTSD" where individuals have experienced a trauma and show PC-PTSD scores of 4 or 5 indicating likely presence of clinical PTSD. BAI: Beck Anxiety Inventory; BDI-II: Beck Depression Inventory; FoSI: Fear of Sleep Inventory; PC-PTSD: Primary Care post-traumatic stress disorder. P-values represent between group comparisons determined using Kruskal-Wallis ANOVA. Post hoc differences were assessed using Sidak post hoc. [a] indicates a significant post hoc difference between "no trauma" and "resilient", [b] indicates a post hoc difference between "resilient" and "symptoms indicative of likely PTSD" and [c] indicates a post hoc difference between "no trauma" and "symptoms indicative of likely PTSD".

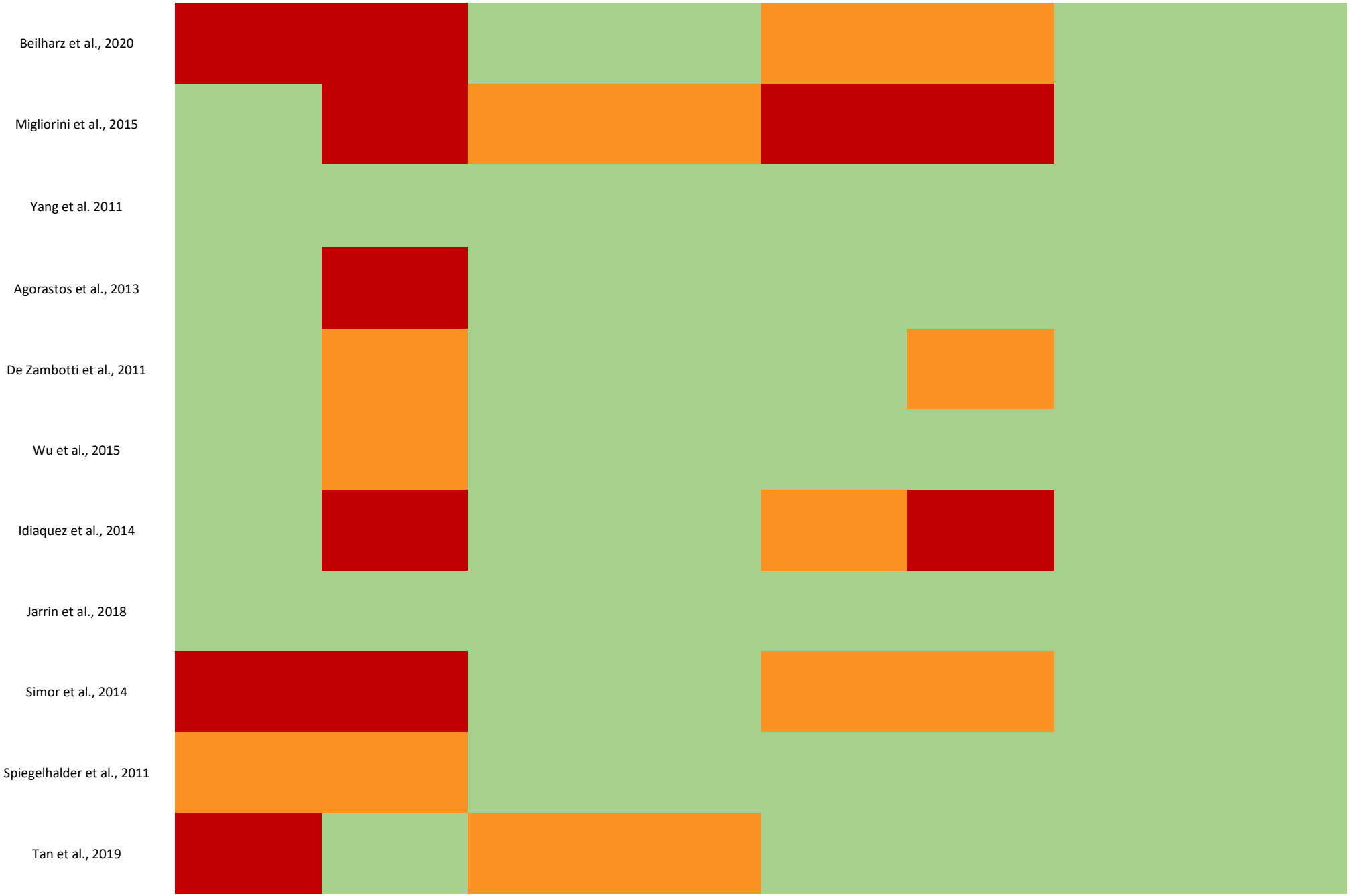
APPENDIX 5.1: Search terms used to search PubMed, Scopus and Web of Science databases.

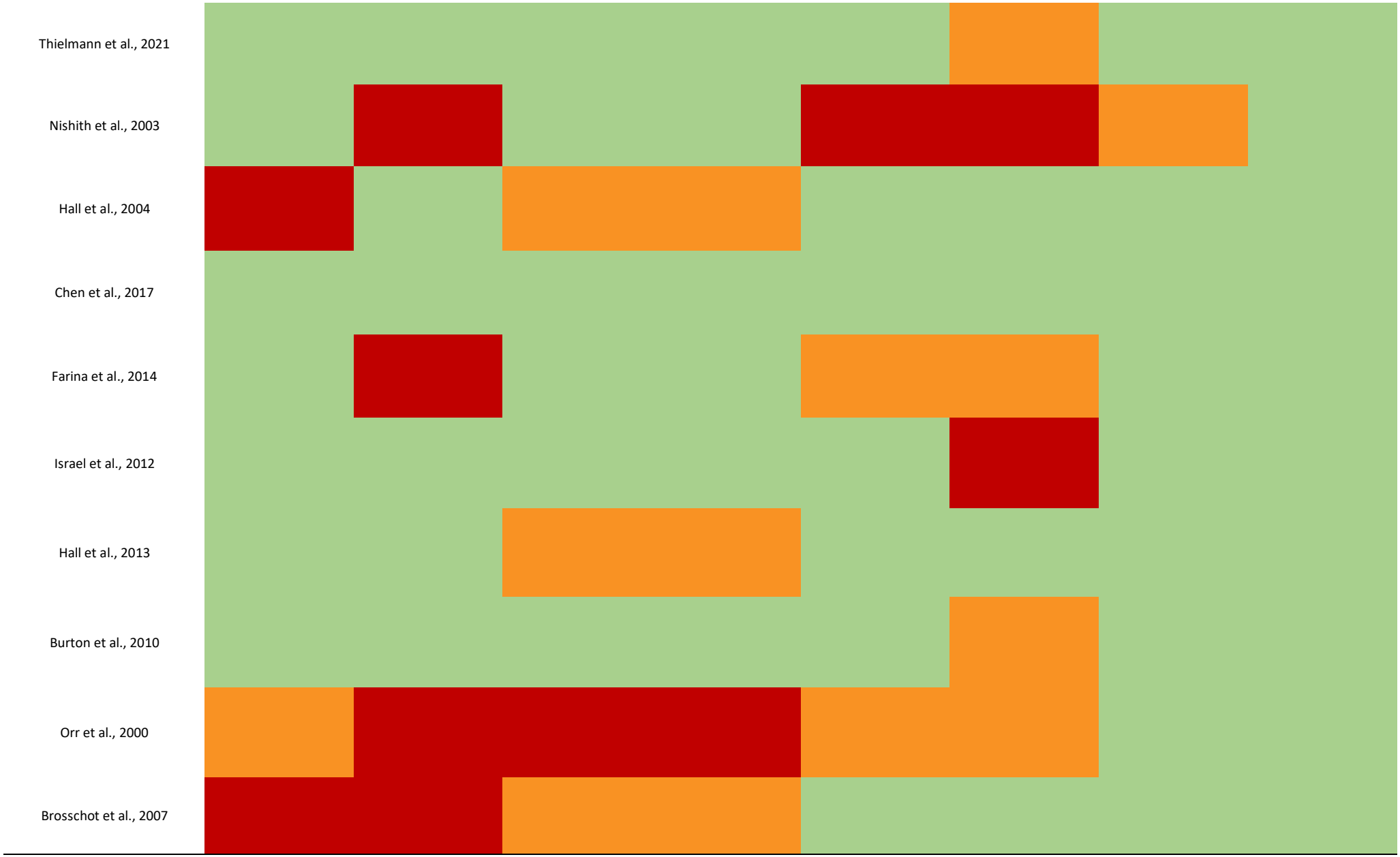
Database	Search terms
PubMed	(Sleep [MeSH] OR Sleep [tiab] OR insomnia [MeSH] OR insomnia [tiab]) AND (("nervous system" [MeSH] OR "nervous system" [tiab] OR "autonomic nervous system" [MeSH] OR "autonomic nervous system" [tiab] OR ANS [MeSH] OR ANS [tiab]) OR "parasympathetic nervous system" [MeSH] OR "parasympathetic nervous system" [tiab] OR PNS [MeSH] OR PNS [tiab] OR "sympathetic nervous system" [MeSH] OR "sympathetic nervous system" [tiab] OR SNS [MeSH] OR SNS [tiab] OR hyperarousal [MeSH] OR hyperarousal [tiab]) AND ("heart rate variability" [MeSH] OR "heart rate variability" [tiab] OR HRV [MeSH] OR HRV [tiab])) AND ("mental health" [tiab] OR "mental health" [MeSH] OR "mental illness"[tiab] OR "mental illness" [MeSH] OR "mental disease"[tiab] OR "mental disease"[MeSH] OR "mental disorder"[MeSH] OR "mental disorder"[tiab] OR depression [MeSH] OR depression [tiab] OR anxiety [MeSH] OR anxiety [tiab] OR "post-traumatic stress disorder" [MeSH] OR PTSD [MeSH] OR "posttraumatic stress disorder" [MeSH] OR "post traumatic stress disorder" [MeSH] OR PTSD [tiab] OR "post-traumatic stress disorder" [tiab] OR "posttraumatic stress disorder" [tiab] OR "post traumatic stress disorder" [tiab])
Scopus	(TITLE-ABS-KEY (sleep OR insomnia)) AND (TITLE-ABS-KEY (("autonomic nervous system" OR "nervous system" OR ans OR "sympathetic nervous system" OR sns OR "parasympathetic nervous system" OR pns OR hyperarousal) AND ("heart rate variability" OR hrv))) AND (TITLE-ABS-KEY ("mental illness" OR "mental health" OR "mental disorder" OR "mental disease" OR depression OR anxiety OR "posttraumatic stress disorder" OR "post traumatic stress disorder" OR "post-traumatic stress disorder" OR ptsd)) AND (LIMIT-TO (SRCTYPE , "j")) AND (LIMIT-TO (LANGUAGE , "English")) AND (LIMIT-TO (DOCTYPE , "ar"))
Web of Science	TS=(Sleep OR Insomnia) AND (("Nervous system" OR "autonomic nervous system" OR ANS OR "parasympathetic nervous system" OR PNS OR "sympathetic nervous system" OR SNS OR hyperarousal) AND ("heart rate variability" OR HRV)) AND ("Mental health" OR "mental illness" OR "mental disease" OR "mental disorder" OR depression OR anxiety OR "post traumatic stress disorder" OR PTSD OR "post-traumatic stress disorder" OR "posttraumatic stress disorder")

APPENDIX 5.2: Results of bias assessment using the Joanna Briggs Institute Critical Appraisal Checklist for Analytical Cross-Sectional Studies.




Mellman et al., 2004
Ulmer et al., 2018
Woodward et al., 2009
Saad et al., 2020
Bertram et al., 2014
Fatt et al., 2020
Furutani et al., 2011
Dennis et al., 2017
Rissling et al., 2016
Ottaviani, Shahabi, et al., 2015
Ottaviani, Medea, et al., 2015


Beilharz et al., 2020
Migliorini et al., 2015
Yang et al. 2011
Agorastos et al., 2013
De Zambotti et al., 2011
Wu et al., 2015
Idiaquez et al., 2014
Jarrin et al., 2018
Simor et al., 2014
Spiegelhalder et al., 2011
Tan et al., 2019



Key: Green - yes; Orange - unclear; Red - no.

APPENDIX 5.3: Sleep, mood- and anxiety-related outcomes and sleep-related HRV of studies conducted in apparently healthy participants.

Citation	Sleep method	Sleep data				Mood/anxiety symptom method	Mood/anxiety symptom data			HRV method	HRV data				
Burton et al., 2010	SPHERE		0.7±1.2			PSQ	61.1±10.3			Ambulatory ECG	Power spectral density derived: autoregressive modelling	RMSSD (ms)	53.6±40.8		
	Overall rating of sleep (from 1 to 10)		7.0±1.0			SPHERE	2.6±2.6					HF (%)	23.5±8.1		
						K10	12.9±3.1				Noise and artifact: manually removed	LF (%)	30.3±17.3		
Fatt et al., 2019	PSG	TST (h)	6.64±1.52			SPHERE	1.25±1.57			PSG	Measurement: 5 min epochs from homogenous sleep stages. Power spectral density derived: Lomb periodogram. Program used: LabChart Pro 8	Not reported numerically			
		SOL (min)	14.25±11.66												
		SE (%)	85.36±9.03												
		WASO (min)	53.87±38.09			K10	12.92±2.72								
		N1 (%)	8.08±3.50												
		N2 (%)	53.80±11.32			PHQ-9	1.92±1.77								
		N3 (%)	15.60±7.95												
		REM (%)	22.51±12.25			SF-36	82.06±8.86								
	ESS	4.75±3.05													
	PSQI	2.96±1.52													
Hall et al., 2013	PSG		European	African	Chinese		European	African	Chinese	PSG	Measurement: 2 min epochs from homogenous		European	African	Chinese

		N1 (%)	6.3±4.0*	7.9±5.8*	6.7±4.1*	IDS (without the sleep questions)	4.5±2.6***	5.3±3.4***	4.4±3.2***		sleep stages summing to a total of 15min of each.		N2	REM	N2
		N2 (%)	64.6±8.0	65.5±7.5	64.6±4.1							nHF (ms^2)	0.4±0.01***	0.2±0.01**	0.4±0.02***
		N3 (%)	4.2±4.9***	2.7±4.2***	2.7±4.0***	STAI	14.6±4.9	15.1±5.2	15.6±6.0		Power spectral density derived: FFT.	nLF (ms^2)	0.7±0.01***	0.8±0.01**	0.6±0.02***
		REM (%)	25.0±5.7*	23.7±6.5*	26.1±4.6*						Noise and artifact: removed using automated artifact detection algorithm and manual inspection	LF/HF (ms^2)	2.4±1.1***	5.1±1.1**	1.7±1.1***
Orr et al., 2000	PSG	TST (min)	385.4±9.0	TST (min)	385.4±9.0	BDI		2.8±0.8		PSG	Measurement: 15min epochs during homogenous sleep stages.	Not reported numerically			
		SOL (min)	18.5±4.7	SOL (min)	18.5±4.7										
		NREM (%)	76.9±1.5	NREM (%)	76.9±1.5										
		SWS (%)	28.4±2.2	SWS (%)	28.4±2.2										
		REM (%)	20.1±1.2	REM (%)	20.1±1.2										
		SE (%)	89.2±2.2	SE (%)	89.2±2.2										
		WASO (min)	23.5±5.1	WASO (min)	23.5±5.1						Program used: MATLAB signal processing toolbox.				
		No. arousals	12.1±2.0	No. arousals	12.1±2.0										
	PSQI	Not reported numerically													
Ottaviani, Medea, et al., 2015		Men		Women		Men		Women		Ambulatory ECG	Measurement: 1min and 5min epochs. For sleep analyses, the 1min epochs were further	Men		Women	

	Sleep duration (h)			PSWQ	43.9±12.7	46.9±15.1		averaged based on self-reports of bed and wake up times.	RMSSD wake (ms^2)		40.2±14.2	
	PROMIS Sleep Disturbance Form	16.9±4.6	14.3±4.6	Stress Reactive Rumination Scale	155.4±215.2	204.5±224.9		Noise and artifact detection: Kubios HRV software Program used: Kubios HRV software	RMSSD sleep (ms^2)		64.1±37.3	
		Younger	Older		Younger	Older		Measurement: HRV was extracted in 5min epochs.		Younger		Older
	PSQI	3.9±3.0	3.9±1.8	SPHERE	1.1±1.8	0.4±0.7			RMSSD (ln(ms))	3.2±0.6		3.2±0.8
Tan et al., 2019	ESS	4.7±3.0	6.2±3.7	SF-36	80.7±13.3	82.9±9.2	Ambulatory ECG	Power spectral density derived using: Lomb-Scargle periodogram.	Total spectral power ($ln(us^2)$)	7.1±0.9		6.9±1.1
				K10	13.3±5.0	12.8±3.1		Program used: LabChart 8.	HF spectral power ($ln(us^2)$)	5.4±1.3		5.2±1.4

Data are presented as mean ± SD. BDI: Becks depression inventory; ECG: Electrocardiogram; ESS: Epworth sleepiness scale; FFT: Fast Fourier transformation; HF: High frequency; HRV: Heart rate variability; IDS: Inventory of depressive symptomology; K10: Kessler-10; LF: Low frequency; N1: Non-rapid eye movement (NREM) sleep stage 1; N2: NREM sleep stage 2; N3: NREM sleep stage 3; nHF: normalized HF; nLF: normalized LF; PSG: Polysomnography; PSQ: Psychological stress questionnaire; PSQI: Pittsburgh sleep quality index; PSWQ: Penn state worry questionnaire; RMSSD: Root mean square of successive differences between R-R intervals; SE : sleep efficiency; SF-36: Health survey short form 36 (mental component); SOL: Sleep onset latency; SPHERE: Somatic and psychological health report; STAI: State-trait anxiety index; SWS: Slow-wave sleep; TST: Total sleep time; WASO: Wake after sleep onset.

**p<0.05, **p<0.01, ***p<0.001.*

Burton et al. (2010) used only the SPHERE sleep specific questions from 0 to 8 and Tan et al. (2019) used only the SPHERE PSYCH subscale.

APPENDIX 5.4: Sleep, mood- and anxiety-related outcomes and sleep-related HRV of studies conducted in participants with sleep disorders.

Citation	Sleep method	Sleep data					Mood/anxiety symptom method	Mood/anxiety symptom data				HRV method	HRV data				
			No OSA	Mild OSA	Moderate OSA	Severe OSA		No OSA	Mild OSA	Moderate OSA	Severe OSA				No OSA	Mild OSA	Moderate OSA	Severe OSA
Alomri et al., 2021	PSG	TST (min)	299±64*	248±65*	270±46*	230±60*	DASS-21 depression subscale	8.3±8.3	13±9.3	11.5±10.7	12.2±8.8	PSG	Measurement: 5-min epochs analysed. Frequency: 1 kHz. Power spectral density derived: FFT Noise and artifact: manually removed.	LF/HF	0.1±0.6*	0.04±0.8	0.04±0.8	0.6±0.7*
		SOL (min)	19±14	50±48	30±21	35±28												
		SE (%)	78.1±13.4*	63.7±14.8*	73.3±10.8*	63.2±15.5*												
		WASO (min)	63±51	73±48	68±38	99±47												
		N1 (%)	8±4*	11±8*	12±7*	22±13*												
		N2 (%)	49±10	45±12	55±16	40±13												
		N3 (%)	22±9	26±13	21±16	19±20												
		REM (%)	14±8*	9±7*	7±6*	6±7*												
	ESS		9.1±5.3	9.0±39	11±6.7	13.3±6.4												
Brupbacher et al., 2021	PSG	TST (min)	Intervention 439.0 (393.3-479.5)		Control 416.7 (382.3-463.1)		PHQ-15	Intervention 12.5 (8.3-15.8)		Control 12.5 (8.0-14.0)		PSG	Measurement: 5 min epochs Pre-processing and filtering:	RMSSD	Intervention 32.1 (20.7-49.0)		Control 34.4 (24.5-51.4)	

	SOL (min)	14.0 (5.5-23.3)	14.5 (6.8-27.2)				Pan-Tompkins algorithm, and bandpass filtering.		
	SE (%)	91.3 (84.4-93.5)	88.8 (82.5-94.0)						
	WASO (min)	30.8 (18.0-43.3)	37.8 (19.1-62.6)	PHQ-9	14.0 (12.0-17.0)	15.0 (12.0-17.0)	Noise and artifacts: identified using a validated algorithm and visually inspected.	SDNN	37.8 (27.2-55.0)	34.7 (29.5-52.6)
	No. of awakenings	17.0 (13.5-23.5)	15.8 (11.4-20.8)						
PSQI		10.0 (7.0-13.8)	9.5 (6.3-12.0)				Ectopic beats were replaced by phantom beats using cubic spline interpolated RR values.	LF (ms^2)	858 (474-1659)	780 (436-1852)
FIRST		27.0 (24.0-29.8)	27.5 (21.3-29.8)							
				HADS anxiety	11.0 (9.3-14.0)	11.5 (9.0- 14.0)	Power spectral density derived: Lomb–Scargle periodogram with a moving aver- age filter (width 0.02 Hz).	HF (ms^2)	382 (159-925)	410 (253-810)
DBAS		4.6 (3.6-5.7)	4.8 (3.8-5.4)							

										Program used: Kubios HRV			
			Poor sleepers	Good sleepers		Poor sleepers	Good sleepers						
Cosgrave et al., 2021	PSG	TST (h)	7.68±1.13	7.5±7	DASS depression score	14.0±9.9	4.0±5.1	PSG	Measurement: 5 min epochs from specific sleep stages. Sampling frequency: 256 Hz. Noise and artifacts: visually inspected.	Not reported numerically			
		SOL (h)	0.6±0.53	0.23±0.4									
		SE (%)	88.43±7.1*	94.55±4.2*									
		N1 (h)	0.35±0.25	0.38±0.23									
		N2 (h)	3.93±0.85	3.70±0.55									
		N3 (h)	0.5±0.15	0.4±0.17									
		N4 (h)	1.18±0.32	1.15±0.35									
		REM (h)	1.72±0.55	1.87±0.55									
		REM latency (h)	1.5±0.6	1.87 ±0.73									
		WASO (h)	1.03±0.67*	0.45±0.42*	DASS anxiety score	8.0±7.6	4.0±2.6						
		Arousal index	9.87±4.27	8.7±2.2									
	PSQI		10.1±2.2	2.3±0.9									
	ISI		14.4±3.3	1.5±1.5									
			Insomnia	Good sleepers		Insomnia	Good sleepers		Processing and filtering: amplified and band-pass filtered (1–100 Hz).	Baseline HF (n.u.)	Insomnia	Good sleepers	
De Zambotti et al., 2011	PSG	TST (min)	433.0±23.0*	458.0±12.0*	BDI	11.3±5.4***	2.6±2.1***	PSG			41.5±24.3	53.5±18.7	
		SOL (min)	19.0±14.0	10.0±6.0									
		SE (%)	90.0±4.0*	95.0±2.0*									
		N1 (min)	51.0±25.0	56.0±17.0	STAI-T	46.9±7.9**	34.1±5.6**			Pre-sleep onset HF (n.u.)	50.0±13.9	42.4±21.4	
		N2 (min)	216.0±32.0	216.0±24.0									

	N3 (min)	87.0±47.0	106.0±21.0					Noise and artifact: visually inspected.				
	REM (min)	18.2±5.8	17.5±2.2									
	WASO (min)	27.0±19.0	13.0±8.0									
	PSQI	9.6±1.3***	4.6±3.1***					Spectral power density derived: FFT	Post-sleep onset HF (n.u.)	57.0±18.4	57.2±13.2	
	ISI	13.4±3.3***	3.0±3.3***	STAI-S	50.1±2.1	52.3±2.6						
	ESS	5.9±4.2	4.5±2.9					Program used: Kubios HRV				
		Insomnia	Control		Insomnia	Control				Insomnia	Control	
Eddie et al., 2021	ISI	17.35±2.49***	1.63±1.64***	HAM-D		0.55±0.88***	PSG	Measurement: 5 min epochs from specific sleep stages	Wake SDNN (ms)	61.48±25.79	78.38±41.18	
									N2 SDNN (ms)	58.51±21.46	64.55±16.74	
									REM SDNN (ms)	69.08±17.29	79.36±26.47	
								Processing and filtering: amplified and band-pass filtered (1–100 Hz).	Wake RMSSD (ms)	39.70±17.91	48.82±27.23	
									N2 RMSSD (ms)	50.83±26.15	57.59±22.67	
									REM RMSSD (ms)	48.19±23.14	55.71±27.41	
								Noise and artifact: visually inspected.	Wake pNN50 (%)	18.95±15.79	24.00±19.23	
									N2 pNN50 (%)	27.41±19.62	33.53±18.03	

							Program used: Kubios HRV	REM pNN50 (%)	21.42±14.46	26.34±18.17
								Wake HF (ms^2)	572.34±489.03	951.17±997.39
								N2 HF (ms^2)	1210.33±1534.20	1374.25±892.13
				BDI-II	2.31±1.00****			REM HF (ms^2)	1087.13±1544.70	1204.13±1202.16
								Wake LF (ms^2)	999.06±1114.21	1564.12±1349.06
								N2 LF (ms^2)	1507.86±817.39	1507.86±817.39
								REM LF (ms^2)	1679.33±1003.04	1675.81±1000.82
								Wake SI	0.68±1.22	0.24±1.22
								N2 SI	-0.10±0.99	−0.65±0.88
								REM SI	0.14±0.83	−0.31±0.90
								Wake PI	-0.26±1.15	0.17±1.31
	PSG	Not reported numerically						N2 PI	0.55±1.22	1.10±1.24
								REM PI	0.10±1.07	0.68±1.25
				Perceived stress scale	18.63±1.53**			Wake approximate entropy	1.06±0.12	1.05 (0.09)
								N2 approximate entropy	1.29±0.04	1.25±0.07
								REM approximate entropy	1.19±0.11	1.21±0.13
Farina et al., 2014		Insomnia	Control		Insomnia	Control	Measurement:		Insomnia	Control

	TST (min)	388.3±91.8	387.2±66.0					5min epochs.	HR pre-sleep (bpm)	67.8±8.7***	59.0±7.3***
	SOL (min)	27.8±79.4***	26.0±22.9***					Processing and filtering: REMbrandt SleepView, Medcare software identified R-wave peaks and calculated intervals.	HR N2 early stage (bpm)	64.8±7.6***	49.0±5.4***
									HR N2 late stage (bpm)	60.9±8.0***	53.5±10.4***
									HR N3 (bpm)	63.5±8.5	57.1±21.6
	SE (%)	82.4±22.0***	86.9±14.2***	BDI	7.8±6.7	Not reported			HR REM (bpm)	64.7±9.0	67.5±9.3
								Noise and artifact: manually inspected.	RMSSD pre-sleep (ms)	31.8±15.9	28.9±13.6
PSG							PSG		RMSSD N2 early stage (ms)	35.9±17.5**	27.2±13.5**
	WASO (min)	178.5±125.0***	91.3±78.8***								
								Power spectral density derived: Parametric autoregressive model	RMSSD N2 late stage (ms)	41.1±25.5	36.8±24.6
	N1 (%)	8.1±4.5	9.7±7.1						RMSSD N3 (ms)	34.4±17.4	32.6±20.5
									RMSSD REM (ms)	32.3±18.5	34.4±19.6
	N2 (%)	37.2±11.8	38.6±11.9					Program used: Kubios HRV	HF pre-sleep (n.u.)	38.0±22.9	35.2±20.2
				SAS	49.5±9.7	Not reported numerically			HF N2 early stage (n.u.)	40.7±22.5	32.4±15.8
	N3 (%)	23.0±11.7	21.8±11.0						HF N2 late stage (n.u.)	46.8±25.1	42.6±24.6

										HF N3 (n.u.)	54.4±25.5	52.0±30.8
										HF REM (n.u.)	35.4±51.0	42.8±64.2
		REM (%)	15.5±5.9	17.0±7.5						LF/HF pre-sleep	3.7±3.3	2.9±2.9
	PSQI		12.5±3.6	Not reported						LF/HF N2 early stage	2.5±3.4*	1.5±2.3*
										LF/HF N2 late stage	1.5±1.8	1.3±1.7
	ESS		4.6±4.2	Not reported						LF/HF N3	1.0±1.4	0.8±1.0
										LF/HF REM	1.5±1.8	1.3±1.7
			Mild OSA	Severe OSA		Mild OSA	Severe OSA		Pre-processing: R-R wave detection performed using the maximum after threshold method.		Mild OSA	Severe OSA
		AHI	18.1±13.2	55.3±32.1						LF (n.u.)		68.1±3.0
	PSG											
Idiaquez et al., 2014		Micro awakenings	19.2±12.8 ***	50.3±31.0***						HF (n.u.)		27.7±3.0
					BDI	8.6±5.1	7.4±4.6	PSG	Noise and artifacts: manually removed		Not reported numerically	
	ESS		12.6±5.0	13.6±5.6					Power spectral density derived: FFT with a Hann window	LF/HF ratio		3.9±0.8

									with ½ overlap			
			Insomnia	Control		Insomnia	Control				Insomnia	Control
Israel et al., 2012	PSG	TST (min)	397.9±48.7	426.7±36.7	IDS	10.1±5.4***	3.1±5.3***		Noise and artifacts: manually edited by interpolating preceding successive beats.	HF NREM (ms^2/Hz)	0.5±0.1	0.5±0.1
		SOL (min)	26.1±18.3	19.9 ±14.4								
		SE (%)	85.6±8.0	90.5±5.5						HF REM (ms^2/Hz)	0.4±0.2	0.4±0.1
		WASO (min)	41.4±33.5	26.6±22.8								
		N1 (%)	5.6±3.7	4.5±2.1					Power spectral density derived: autoregressive models used on 2min IBI epochs for spectral power analysis.	LF/HF ratio NREM	1.9±1.4	1.3±0.7
		N2 (%)	61.2±6.5	57.3±5.7								
		N3 (%)	9.2±6.8	12.2±6.7						LF/HF ratio REM	3.4±2.5	2.2±1.6
			Objectively short sleep	Subjectively short sleep		Objectively short sleep	Subjectively short sleep				Objectively short sleep	Subjectively short sleep
Jarrin et al., 2018	PSG	TST (min)	321.8±34.6***	400.4±24.6***	BDI	9.0±5.1	9.5±7.1	PSG	Measurement: 2 min epochs from specific sleep stages	HF (n.u.)	35.1*	40.0*
		SOL (min)	16.9±16.9***	10.4±7.5***								
		SE (%)	73.7±8.9***	86.3±5.3***						lnHF	5.1*	5.5*
		WASO (min)	87.2±40.9	45.0±24.6								
	Sleep diaries	Subjective sleep quality	2.8±0.7	3.8±0.6					Noise and artifacts: manually removed	LF/HF ratio	1.2*	1.1*

	ISI		17.5±3.5	17.8±3.5					Processed using: Kubios HRV				
			Nightmare	Control		Nightmare	Control				Nightmare	Control	
Simor et al., 2014	Likert scale		1 or more nightmares per week						Noise and artifacts: automatically detected and manually inspected. Power spectral density derived: Hanning-tapered FFT Program used: Software for HRV toolkit for MATLAB developed by Kaplan and Staffin.	RMSSD pre-REM (ms)	52.3±10.2	99.5±9.6	
										LF pre-REM (ms^2/s)	1174.0±542.2	3661.0±506.5	
										HF pre-REM (ms^2/s)	775.0±716.2	4533.0±659.6	
										LF/HF pre-REM	1.7±0.2	1.1±0.2	
	DQQ		8.1±1.9	4.0±1.8	STAI-T	50.4±8.2	33.3±8.5			RMSSD post-REM (ms)	52.0±9.4	82.9±8.8	
										LF post-REM (ms^2/s)	1338.0±295.4	2060±276.0	
										HF post-REM (ms^2/s)	1061.0±665.7	3438.0±622.0	
	VDAS-H		20.6±7.5	0.2±0.6						LF/HF post-REM	1.4±0.2	1.1±0.2	
			Insomnia	Control		Insomnia	Control				Insomnia (short sleep)	Insomnia (not short sleep)	Control
Spiegelhalder et al., 2011	PSG	TST (min)	412.0±47.8	427.2±44.0	BDI	9.7±6.6***	2.0±3.0***	PSG	Measurement: 5 min epochs from specific	SDNN wake (ms)	50.5±3.8	64.1±4.7	63.5±4.8

		SOL (min)	17.3±18.8	17.0±15.0						sleep stages	SDNN NREM (ms)	44.6±4.4	56.4±3.9	62.2±4.9
		SE (%)	85.8±9.8	89.0±9.2							SDNN REM (ms)	61.9±6.8	66.3±3.9	75.0±6.0
		N1 (%)	7.5±3.3	6.7±3.7						Pre-processing: peak detection program used	RMSSD wake (ms)	34.4±4.1	48.8±4.7	51.1±6.1
		N2 (%)	56.3±8.2	54.7±8.7							RMSSD NREM (ms)	40.9±5.9	50.3±4.6	55.7±5.4
		N3 (%)	6.7±7.6	8.8±7.9							RMSSD REM (ms)	41.2±7.2	45.6±4.4	55.6±6.2
		REM (%)	19.7±5.0*	22.1±4.3*						Noise and artifacts: visually inspected and manually edited.	HF wake (ms^2)	545±185	640±105	1019±265
		WASO (min)	42.7±40.1	33.1±36.5							HF NREM (ms^2)	522±116	902±224	1054±179
	PSQI		11.2±2.8***	3.4±1.7***						Power spectral density derived: FFT	HF REM (ms^2)	497±121	684±169	1002±203
			Poor sleepers	Good sleepers		Poor sleepers	Good sleepers					Poor sleepers	Good sleepers	
Thielmann et al., 2021	PSQI		3.5±1.3***	9.0±2.6***	GHQ-12	9.1±3.7**	12.6.1**	Ambulatory ECG		Measurement: Six-hour night window was between 11:00 p.m. and 01:00 a.m.	HR (bpm)	68.53±26.14		62.74±6.49
											SDNN (ms)	98.53±26.14		110.17±37.72
											RMSSD (ms)	45.55±21.08		59.01±34.15
											pNN50 (%)	20.13±15.51		27.41±20.66
										Power spectral density	LFnu	66.04±13.34		63.31±15.03
											HFnu	33.96±13.34		36.70±15.03

										derived: FFT	LF/HF	2.50±1.67	2.34±1.88
											SD1	32.22±14.91	41.74±24.16
										Program used: Kubios HRV	SD2	135.24±35.13	149.48±49.55
											Alpha 1	1.18±0.19	1.14±0.22
											Alpha 22	1.00±0.10	0.98±0.07
Wu et al., 2011	PSG		PLMS OSA	Non-PLMS OSA	HDS	PLMS OSA	Non-PLMS OSA	PSG	Measurement: 5 min epochs from N2		PLMS OSA	Non-PLMS OSA
		SE (%)	81.1±12.4	81.4±14.3					R-waves detected: discrete wavelet transforms and a wavelet coefficient threshold.	RMSSD (ms)	35.1±21.9*	55.5±45.9*
		N1 (%)	19.0±13.4	19.9±11.2						SDNN (ms)	35.2±16.7*	48.6±28.0*
		N2 (%)	50.8±9.1	52.1±11.3						HF (ms^2)	467.9±495.4*	1391.4±2392.2*
		SWS (%)	14.1±10.9	12.3±10.9						LF (ms^2)	359.1±418.3	482.1± 534.9
		REM (%)	16.1±6.9	15.9±6.2						n-HF (%)	0.5±0.2*	0.6±0.1*
	PSQI		8.9±4.0	9.8±5.2						n-LF (%)	0.4±0.2*	0.3±0.1*
	ESS		10.9±5.0	10.3±5.1					Power spectral density: FFT	LF/HF ratio	1.1±1.2*	0.6±0.3*
Yang et al., 2011	PSQI		Insomnia 10.7±3.9***	Controls 4.3±2.2***	BDI	Insomnia 10.9±6.5***	Controls 4.5±4.7***	Ambulatory ECG	Processing: open-source HRV algorithms		Insomnia	Control
										Mean HR (bpm)	83.3±12.7	78.6±9.5
										SDNN (ms)	92.4±28.2 *	107.9±32.3*
									Program used:	RMSSD (ms)	26.9±12.7*	34.1±19.2*

							PhysioToolkit.	pNN50 (%)	7.0±7.7*	11.8±12.6*
								HF ln (ms^2/Hz)	6.1±1.0*	6.6±0.99*
								LF ln (ms^2/Hz)	7.0±0.7*	7.4±0.8*
ESS	9.1±5.4***	9.5±4.3***	HDS	5.8±5.0***	1.0±2.3***			LF/HF (n.u)	3.8±2.3	3.3±1.7
								Multiscale entropy	22.1±5.3	22.6±5.1

AHI: Apnoea hypopnea index; BDI: Becks depression inventory; DASS-21: Depression, anxiety and stress scale-21; DQQ: Dream quality questionnaire (negative dream affect scale); ECG: Electrocardiogram; ESS: Epworth sleepiness scale; FIRST: Ford insomnia response to stress test; FFT: Fast Fourier transformation; HDS: Hamilton depression rating scale; HF: High frequency; HRV: Heart rate variability; IBI: Interbeat intervals; IDS: Inventory of depressive symptomology; ISI: Insomnia severity index; K10: Kessler-10; LF: Low frequency; N1: NREM stage 1; N2: NREM stage 2; N3: NREM stage 3; n.u.: Normalized units; OSA: Obstructive sleep apnoea; PI: parasympathetic index; PLMS: Periodic limb movement syndrome; PSG: Polysomnography; PSQ: Psychological stress questionnaire, PSQI: Pittsburgh sleep quality index; RMSSD: Root mean square of successive differences between R-R intervals; SCID: Structured clinical interview for DSM-IV; SDNN: Standard deviation of the R-R intervals; SE : Sleep efficiency; SF-36: Health survey short form 36; SI: sympathetic index; SPHERE: Somatic and psychological health report; SOL: Sleep onset latency; STAI-S: State-trait anxiety index – state; STAI-T: State-trait anxiety index - trait; TST: Total sleep time, WASO: Wake after sleep onset; VDAS-H: Van dream anxiety scale.

**p<0.05, **p<0.01, ***p<0.001.*

APPENDIX 5.5: Methods and main findings of studies conducted in participants with depression-, anxiety- or stress-related disorders.

Citation	Sleep method	Sleep data			Mood/anxiety symptom method	Mood/anxiety symptom data		HRV method	HRV data			
			PTSD	No PTSD		PTSD	No PTSD				PTSD	No PTSD
Agorastos et al., 2013	Actigraphy	Sleep 24h (% of sleep per time period)	45.4±20.7	58.7±14.5	CAPS	66.0±7.8***	16.0±15.8***	Ambulatory ECG	Measurement: two 5-h sub-epochs for analysis of diurnal rhythmicity, daytime (10 a.m.–3 p.m.) and night-time (12 a.m.–5 a.m.).	HR day (bpm)	64.5±3.8	59.1±6.2
										HR night (bpm)	61.3±6.5*	51.8±7.5*
										RMSSD day (ms)	63.5±27.2	104.0±43.6
										RMSSD night (ms)	69.9±45.3	114.2±41.5
					HDS	7.7±3.9**	1.7±3.4**			SDNN 24hr (ms)	127.5±30.6	155.0±55.4
										pNN50 24hr (%)	32.2±18.8*	48.7±18.3*
		Sleep night (% of sleep per time period)	84.5±10.1	91.9±5.8	GAF	64.3±4.5**	74.4±7.3**		Noise and artifact: visually	LF/HF day	2.7±1.9	1.2±0.5
										LF/HF night	1.7±0.97*	0.8±0.4*
									Program used: LabChart	DFA alpha fast day	1.15±0.19*	0.93±0.15*
										DFA alpha fast night	1.07±0.22	0.87±0.17
					CTQ	38.2±9.5	32.8±6.6			DFA alpha slow day	0.96±0.10	1.00±0.05
										DFA alpha slow night	1.00±0.09	1.08±0.06
		Bipolar	MDD	Control							Bipolar	MDD	Control
Bassett et al., 2016	PSQI				SCID			Ambulatory ECG	Artifact and noise: visually inspected	RMSSD (ms)	30.9±14.7 ***	25.7±12.0 ***	48.8±25.3 ***

										Program used: Nevrokard aHRV	SDNN (ms)	88.7±31.8***	83.2±23.6***	109.1±29.1***
											pNN50 (%)	11.7±11.3***	7.5±8.4***	22.6±16.3***
		5.8±2.9***	7.0±4.5***		2.8±2.0***						HF (ms^2)	4.2±3.9***	2.6±2.4***	7.3±6.6***
											LF (ms^2)	7.3±5.9**	6.5±5.8**	10.2±5.3**
											LF/HF	0.7±0.1*	0.7±0.1*	0.6±0.1*
		Childhood trauma	Non childhood trauma			Childhood trauma	Non childhood trauma			Measurement: 5min epochs				
		7.4±3.1***	4.5±2.6***		PSQ	69.5±16.6**	52.9±14.2**							
					K 10	18.5±7.6***	12.9±4.5***			Power spectral density derived: Lomb–Scargle periodogram.				
Beilharz et al., 2020	PSQI				SPHERE	2.3±2.8***	0.8±1.6***		Ambulatory ECG		Not reported numerically			
					CTQ-SF	Not reported				Program used: LabChart 8				
		PTSD	Control			PTSD	Control			Pre-processing: high-pass filtering at 10Hz.		PTSD		Control
					BDI	22.2±11.4***	6.4±7.2***				HR wake (bpm)	82.9±9.8**		76.0±12.1**
	PSQI	12.1±3.7***	6.4±4.0***											
Bertram et al., 2014					CAPS total	74.5±21.8***	11.1±11.5***		Ambulatory ECG	Artifact and noise: automatic artifact rejecting algorithms discarded data where R-R-intervals were below or above physiological limits	HR sleep (bpm)	67.2±8.4***		59.1±9.8***
	PSQI-A	8.6±5.4***	0.6±1.0***		CAPS hyperarousal	25.5±6.4***	5.6±4.8***				RSA	3.9±3.4		3.5±2.8
Brosschot et al., 2007	Groningen Sleep	23.9±3.3			PSWQ	40.0±11.5			Ambulatory ECG	Program used: Ambulatory	RMSSD wake (ms)	29.1±13.5		

	Quality Scale			STAI		45.6±11.7		Monitoring System device	RMSSD sleep (ms)	51.6±35.5		
		PTSD	Non-PTSD			Combined participants			Measurement: sampling 125Hz.	RMSSD (ms)	PTSD	Non-PTSD
				DTS	DTS B	11.5±11.3						
					DTS Av	5.0±5.5						
Dennis et al., 2014	PSQI	9.6±3.4***	5.2±3.1***		DTS Numb	11.1±11.8	Ambulatory ECG		Noise and artifact: all intervals screened	SDNN (ms)	135.4±42.0*	150.1±49.5*
					DTS D	14.5±12.7						
				CAPS		Not reported			Program using: HRV Tools 1.72 software.	Log HF (ms^2/Hz)	5.7±1.1**	6.2±1.3**
										Log LF (ms^2/Hz)	6.8±0.9**	7.1±0.9**
		All participants (controls and PTSD patients)		CAPS		Not reported		Sampling was done at 125Hz.	All participants (controls and PTSD patients)			
								All		Mean EMA HR (bpm)	80.2±11.6	
Dennis et al., 2017	Sleep diary	Sleep duration (h)	8.3±2.1	DTS		Not reported	Ambulatory ECG	QRS intervals screened, and only beats showing normal sinus rhythm were retained for HRV analyses.		Mean EMA HF (ms)	27.1±14.2	
										Mean EMA LF (ms)	39.6±15.1	
								Analysis was done using HRV Tools 1.72 software.		Mean EMA SDNN (ms)	144.1±46.9	
		MDD	Control		MDD	Control					MDD	Control
Eddie et al., 2020	ISI	15.02±5.01***	1.63±1.64***	HAM-D	20.53±4.5***	0.55±0.88***	PSG	Measurement: 5min epoch from specific sleep stages		Wake SDNN (ms)	69.89±28.37	78.38±41.18

							N2 SDNN (ms)	62.33±19.76	64.55±16.74
						Noise and artifacts: visually inspected and manually edited	REM SDNN (ms)	80.49±28.28	79.36±26.47
							Wake RMSSD (ms)	46.72±24.72	48.82±27.23
						Program used: Kubios HRV	N2 RMSSD (ms)	59.81±31.57	57.59±22.67
							REM RMSSD (ms)	59.02±35.05	55.71±27.41
							Wake pNN50 (%)	23.57±20.22	24.00±19.23
							N2 pNN50 (%)	34.71±22.21	33.53±18.03
							REM pNN50 (%)	28.68±21.50	26.34±18.17
							Wake HF (ms^2)	862.50±872.22	951.17±997.39
							N2 HF (ms^2)	1576.81±1572.27	1374.25±892.13
			BDI-II	24.21±7.99***	2.31±1.00****		REM HF (ms^2)	1534.70±1824.28	1204.13±1202.16
							Wake LF (ms^2)	1101.05±1211.00	1564.12±1349.06
							N2 LF (ms^2)	1220.19±717.58	1507.86±817.39
PSG	Not reported numerically						REM LF (ms^2)	1776.92±1240.85	1675.81±1000.82
							Wake SI	0.52±1.33	0.24±1.22
				22.61±4.12**	18.63±1.53**		N2 SI	−0.60±0.97	−0.65±0.88

										REM SI	−0.26±1.03	−0.31±0.90
										Wake PI	0.01±1.31	0.17±1.31
										N2 PI	1.14±1.47	1.10±1.24
										REM PI	0.68±1.54	0.68±1.25
					Perceived stress scale					Wake approximate entropy	1.03±0.12	1.05 (0.09)
										N2 approximate entropy	1.26±0.08	1.25±0.07
										REM approximate entropy	1.21±0.13	1.21±0.13
			High chronic stress	Low chronic stress		High chronic stress	Low chronic stress				High chronic stress	Low chronic stress
Furutani et al., 2011	PSG	TST (min)	399.1±65.4	425.2±22.0	STAI	45.2±4.0**	35.6±4.1**	PSG	Measurement: sampling rate 1 kHz.	HF wake (ms^2)	733.0±407.8	647.4±539.4
		SOL (min)	15.8±5.3	17.8±8.0								
		SE (%)	94.1±2.7	93.9±2.8						HF sleep onset period (ms^2)	1 765.8±1 594.3	952.4±972.3
		WASO (min)	11.7±16.9	10.8±14.7								
		N1 (%)	8.8±5.9	7.0±3.7					Power spectral density derived: MemCalc method	HF sleep (ms^2)	2 155.8±2 263.8	996.1±710.8
		N2 (%)	59.0±8.0	61.2±9.6								
		N3 (%)	11.8±3.7	13.0±6.8						LF wake (ms^2)	1 363.1±706.0	829.2±781.6
		REM (%)	17.1±4.3	15.9±4.3								
	OSA Sleep Inventory	Falling asleep	10.0±3.6	13.6±2.3	Stress response questionnaire	Not reported			Program used: commercial software	LF sleep onset period (ms^2)	993.7±825.8	548.3±292.8
		Sleep maintenance	19.0±5.9	23.7±2.2						LF sleep (ms^2)	890.5±1 074.9	358.3±112.2

		Satisfaction with sleep	22.9±9.8	24.5±5.0							LF/HF wake	2.4±0.5	1.8±1.1
		Daytime sleepiness in morning	29.1±3.9	26.3±5.0							LF/HF sleep onset period	0.8±0.5	1.0±0.6
		Anxiety	27.8±4.3	31.4±2.3							LF/HF sleep	0.4±0.1	0.9±0.9
Hall et al., 2004	PSG		Stress	Control		Stress	Control	PSG	Measurement: 2min epochs.		Not reported numerically		
		TST (min)	412.8±44.2	381.8±56.7									
		SE (%)	97.0±2.5	95.1±4.7	PSWQ	44.2±12.2	50.5±15.8						
		WASO (min)	13.2±11.9	19.3±19.1									
		N1 (%)	4.3±2.7	4.9±3.2	Symptom checklist - 90R global distress	0.4±0.4	0.6±0.6		Noise and artifact: manually corrected.				
		N2(%)	60.0±9.1	60.0±5.8									
		SWS (%)	13.2±8.0	12.5±6.2									
		REM (%)	22.5±4.9	22.6±5.3	VAS ambient stress	7.4±4.9***	13.1±6.9***						
	PSQI		4.6±2.6	5.7±2.6									
Kobayashi et al., 2014	Actigraphy		PTSD	Resilient		PTSD	Resilient	Ambulatory ECG	Measurement: sampling rate 250Hz. Analysed 5min epochs		PTSD	Resilient	
		TST (min)	315.2±126.0	354.5±130.4									
		SOL (min)	37.8±47.4	38.7±35.7	CAPS	54.9±15.6***	5.6±6.7***		Noise and artifact: visually inspected	nHF (n.u)	0.5±0.01*	0.5±0.01*	
		SE (%)	74.2±13.3	77.2±15.9									
		WASO (min)	79.8±65.6	72.8±87.8	PHQ-9	13.0±5.8***	4.4±3.4***		Power spectral density derived: FFT	LF/HF ratio	1.0±0.02	1.0±0.02	

										Program used: CardioCard software			
			PTSD	Resilient		PTSD	Resilient		Measurement: sampling rate 256Hz. Analysed 5min epochs per sleep stage			
		TST (min)	385.9±60.2	372.4±67.9								
		SOL (min)	33.7±44.7	39.9±59.9								
		SE (%)	86.4±9.3	86.2±11.7								
		WASO (min)	31.4±28.7	25.3±31.9					Power spectral density derived: Lomb periodogram			
Kobayashi et al., 2016	PSG	N1 (%)	2.2±1.1	2.2±1.6							Not reported numerically		
		N2 (%)	52.0±8.5	50.7±7.8	CAPS	41.5±17.7***	8.2±7.7***	PSG					
		N3 (%)	25.1±9.1	23.4±8.9					Noise and artifact: visually inspected and manually corrected				
		REM (%)	20.8±5.7*	23.7±4.9*									
									Program used: LabChart				
			MDD	Control		MDD	Control				MDD	Control	
		TST (min)	390.7±63.1	410.8±70.4					Measurement: sampling rate 250Hz. Analysed 5min epochs	SDNN pre-sleep (ms)	41.2±19.3*	34.6±15.2*	
		SOL (min)	23.8±21.6	12.8±16.8									
		SE (%)	80.8±17.4	88.3±16.6						HF pre-sleep (%)	38.3±15.5*	31.7±12.8*	
		WASO (min)	57.6±61.5	42.9±42.8									
Kwon et al., 2019	PSG	N1 (%)	15.2±9.8	20.5±6.7	BDI	26.4±5.6***	8.6±4.1***	PSG	Power spectral density derived: FFT	LF/HF ratio pre-sleep	2.8±1.5*	3.6±2.3*	
		N2 (%)	53.4±13.2	52.3±12.9									
		N3 (%)	5.9±7.9	7.7±6.7									
		REM (%)	25.5±6.2*	19.5±3.2*						DFA alpha-1 during REM	1.3±0.2*	1.2±0.1*	
	PSQI			Not reported									

			MDD	Control		MDD	Control		Pre-processing: automated QRS detection algorithm was used to detect beats and annotate them as either normal sinus or ectopic		MDD	Control
		TST (min)	375 (204–485)***	487 (436–543)***						RMSSD (s)	0.04 (0.01–0.09)	0.05 (0.02–0.09)
		SOL (min)	48 (19–186)***	28 (7–40)***						SDNN (s)	0.10 (0.06–0.14)	0.10 (0.06–0.17)
		SE (%)	66.9 (35.8–89.3)***	85.6 (78.2–94.5)***						pNN50 (s)	0.15 (0.00–0.51)*	0.25 (0.02–0.54)*
Leistedt et al., 2011	PSG	WASO (min)	98 (38–204)*	58.5 (14–90)*					Noise and artifact: identified using a sliding window average filter. Intervals less than 0.4 s or greater than 2.0 s were excluded from the window average.	LF (s^2)	0.001 (0.000–0.003)*	0.002 (0.001–0.004)*
		N1 (%)	10 (2.9–61)**	7.9 (3.8–11)**								
		N2 (%)	58 (7.0–74.1)	58.3 (35.1–73.0)	HADS	32 (24-51)***	1 (0-3)***	PSG		HF (s^2)	0.001 (0.000–0.003)	0.001 (0.000–0.003)
		N3 (%)	3.8 (0–17)***	14.1 (7–25.9)***								
		REM (%)	20.5 (9.5–32.1)	21.3 (14.5–27.4)								
	PSQI		10 (7-20)***	1 (1-6)***						LF/HF	1.98 (0.43–11.18)	1.59 (0.65–4.076)
									Power spectral density derived: Lomb periodogram			
			PTSD	Non-PTSD		PTSD	Non-PTSD		Measurement: sampling rate		PTSD	Non-PTSD
Mellman et al., 2004	PSG	TST (min)	297.3±73.5	300.4±77.1	CAPS	54.4±24.2***	11.8±9.2***	PSG	128 Hz. Analysed 5min epochs from specific sleep stages	HR early REM (bpm)	80.1±15.5	74.2±13.8
										HR late REM (bpm)	72.4±18.8	69.1±11.6
									Pre-processing: antialiasing filter applied.	HR early NREM (bpm)	81.4±19.4	73.1±14.9

											HR late NREM (bpm)	71.9±19.3	68.4±11.1
										Noise, artifact and ectopic beats: manually corrected	LF/HF early REM	5.7±5.9	2.5±1.9
											LF/HF late REM	4.3±2.3	1.9±1.8
		REM (%)	17.7±6.5	18.5±7.8						Power spectral density derived: autoregression with a model order of 15	LF/HF early NREM	3.5±3.4	2.2±2.6
										Program used: signal-processing software for MATLAB.	LF/HF late NREM	2.4±1.7	2.1±2.3
			Depressive	Non-depressive								Depressive	Non-depressive
		TST (h)	5.7±2.5*	4.7±2.7*							SDNN (msec)	105.8±38.4*	129.3±46.0*
										Measurement: 5min epochs	pNN50 (%)	20.9±18.2*	36.2±22.1*
Migliorini et al., 2015	Sensitized T-shirt	SOL (min)	9.3±32.2	10.8±19.8	QUIDS-16				Sensitized T-shirt		HFn (n.u.)	0.5±0.1	0.5±0.1
										Power spectral density derived: autoregressive model	LFn (n.u.)	0.6±0.1	0.6 ±0.1
		SE (%)	67.4±27.2*	53.5±27.2*							LF/HF (Au)	153.4±415.4*	86.6±211.7*
											DFA alpha 1	0.8±0.1	0.9±0.1
		WASO (min)	6.8±2.6	6.6±2.4							SampEn	1.0±0.3*	1.2±0.4*
			PTSD Treatment-responders baseline	PTSD Treatment non-responder baseline		PTSD Treatment-responders baseline	PTSD Treatment non-responder baseline					PTSD Treatment-responders baseline	PTSD Treatment non-responder baseline
Nishith et al., 2003	PSG	TST (h)	7.0±1.3	4.4	BDI	25.6±12.2	19.0	PSG	Missing or noisy segments were replaced by linear interpolation	REM LF/HF		1.6±0.6	4.14
		SOL (min)	6.9±3.2	7.5									

		SE (%)	92.0±0.0	89.0					from the surrounding signal				
		NREM (%)	70.4±6.7	66.3									
		REM (%)	21.7±5.1	23.6									
	PSQI		11.6±3.6	13.0	PSS	35.2±9.5	27.0		Power spectral density derived: FFT				
			MDD	Control		MDD	Control				MDD	Control	
Ottaviani, Shahabi, et al., 2015	PROMIS Sleep Disturbance Form		10.4±3.1	12.0±4.3	STAI	59.5±8.8***	35.2±11.5***	Ambulatory ECG	Measurement: 1min epochs	Wake HR (bpm)	85.3±8.2*	77.6±7.9*	
	Sleep duration (h)		6.7±1.3	7.3±1.3	BDI	31.1±12.2***	6.7±8.6***		Program used: Kubios HRV software.	Wake RMSSD (ms^2)	34.9±16.9*	46.3±15.3*	
	Time to sleep (min)		25.2±23.9	15.3±14.4	PHQ-9	17.9±6.1***	2.4±3.2***			Sleep HR (bpm)	65.7±8.3	60.2±9.4	
					PSWQ	55.0±14.7	48.7±13.3			Sleep RMSSD (ms^2)	41.7±18.9*	62.8±33.5*	
						PTSD	Non-PTSD				PTSD	Non-PTSD	
Rissling et al., 2016	Actigraphy	Sleep duration (h)		7.5±2.0	DTS	71.5±30.7***	18.6±25.1***	Ambulatory ECG	Data digitized at 125Hz and 1-minute epochs were averaged.	Mean HF (ms)	26.6±14.1	30.7±16.1	
										Mean LF (ms)	37.8±15.1**	44.5±17.0**	
			MDD	Control		MDD	Control		Measurement: 30sec epoch from specific sleep stages		MDD	Control	
Saad et al., 2020	PSG	TST (min)	396.6±52.3	390.0±48.2	BDI	22.6±9.5***	7.0±4.3***	PSG	Noise and artifacts: visually inspected and manually edited	HR Wake (bpm)	67.5±9.2	62.5±7.9	
		SOL (min)	13.4±10.4	10.8±10.2						HR NREM (bpm)	65.3±8.4	60.2±7.4	
		SE (%)	88.2±10.0	85.9±9.2						HR REM (bpm)	67.6±7.9	62.3±7.7	
		WASO (min)	41.1±43.4	55.2±40.1						RMSSD Wake (ms)	41.1±20.3	42.8±18.2	

		N1 (%)	16.0±12.9	12.2±8.6					Program used: MATLAB. ARTiiFACT software and Kubios HRV	RMSSD NREM (ms)	39.5±18.1	51.0±23.6
		N2 (%)	49.5±10.5	58.0±9.1						RMSSD REM (ms)	33.7±18.4	41.4±19.3
		N3 (%)	15.3±10.9	12.8±8.2						SDNN Wake (ms)	47.2±15.4	48.7±16.0
		REM (%)	19.2±7.3	17.0±4.2						SDNN NREM (ms)	42.0±14.1*	52.1±17.6*
	Subjective rating (scale of 1 to 3)	Subjective sleep quality	1.6±0.6	1.8±0.6						SDNN REM (ms)	41.1±20.3*	49.9±16.6*
	ESS		9.0±4.6	9.8±4.5								
			PTSD	Non-PTSD		PTSD	Non-PTSD		Measurement: sampling rate 1024 Hz. Analysed 2min epochs from specific sleep stages	Parameter	Coefficient of fixed effects	
		TST (min)	377.6±68.2	396.7±55.7						Within-person predictors		
		SOL (min)	19.7±15.6	24.6±27.6						Intercept	8.3±0.6***	
		SE (%)	87.5±9.5	88.2±8.3	BDI	10.3±7.4**	5.0±5.2**			Sleep type (NREM vs REM)	0.3±0.1***	
	PSG	WASO (min)	35.3±37.5	28.6±26.3						Between-person predictors		
		N1 (%)	5.0±3.6	4.9±2.7					Noise and artifact: automatically detected using software and visually inspected.	Age	−0.06±0.02***	
Ulmer et al., 2018		N2 (%)	62.0±8.5**	61.9±5.7**				PSG		Sex	0.3±0.4	
		N3 (%)	9.3±7.8	6.8±6.2	BAI	7.5±6.9*	4.0±5.1*			AHI	0.02±0.04	
		REM (%)	23.6±5.4	26.3±5.1						BDI	0.01±0.02	
	PSQI		8.7±3.4	6.9±4.5					Power spectral density derived: FFT	PTSD status	−0.4±0.3	
	PSQI-A		4.6±2.5**	1.3±1.6**						PTSD x sleep type	−0.2±0.1	
					CAPS	58.8±13.5***	19.7±12.9***			Interindividual variation	0.9±0.2***	
	ISI		14.6±3.8**	10.6±6.9**					Program used: Mindware Heart Rate	Variability between sleep cycles	0.04±0.02*	

													Variability Scoring Module	Variability within sleep cycles			0.2±0.02***		
			PTSD	PD	PTSD + PD	Control		PTSD	PD	PTSD + PD	Control		Measurement: Signal extracted from sleep period (visually inspected)		PTSD	PD	PTSD + PD	Control	
		No. of nights	14.6±5.1*	12.0±4.4*	10.9±5.5*	6.7±4.3*	CAPS	Not reported											
	Mattress actigraphy	ISP (min)	504.6±68.1*	436.9±58.6*	435.1±83.5*	472.5±61.5*	BDI-II	14.2±10.9*	10.2±8.6*	20.4±10.8*	0.4±8.4*			HR (bpm)	66.6±9.2*	61.3±8.0*	69.8±10.0*	61.2±7.7*	
		KCG (min)	240.5±58.4*	240.5±58.4*	179.9±63.4*	224.4±49.1*							Pre-processing: signal rectified, peak frequency determined and band-filtered around peak frequency.						
Woodward et al., 2009	PSQI		11.5±2.9*	9.4±2.3*	11.4±2.9*	8.0±2.2*						Ambulatory ECG							
							BAI	10.8±12.8*	15.8±10.1*	26.7±12.7*	1.2±9.8*			RSA	0.21±0.1*	0.31±0.09*	0.21±0.11*	0.25±0.08*	
	PSQI-A		13.3±4.1*	9.9±3.3*	16.2±4.1*	7.5±3.2*							Method previously validated						
													.						
			MDD	Controls				MDD	Controls						MDD		Control		
														Mean HR (bpm)	83.0±11.3		78.6±9.5		
	PSQI		12.8±4.0***	4.3±2.2***			BDI	26.4±13.7***	4.5±4.7***				Processing: automatically processed and analyzed by open-source HRV algorithms	SDNN (ms)	93.1±27.5**		107.9±32.3**		
Yang et al., 2011														RMSSD (ms)	23.7±9.4***		34.1±19.2***		
												Ambulatory ECG		pNN50 (%)	5.2±5.7***		11.8±12.6***		
	ESS		10.7±6.2***	9.5±4.3***			HDS	16.8±7.5***	1.0±2.3***				Program used: PhysioToolkit.	HF ln (ms^2/Hz)	5.9±0.9***		6.6±0.99***		
														LF ln (ms^2/Hz)	6.8±0.9***		7.4±0.8***		
														LF/HF (n.u)	3.9±1.7		3.3±1.7		

		Multiscale entropy	21.2±5.1	22.6±5.1

All results presented as mean±SD or median (range). AHI: Apnoea-hypopnea index; BAI: Becks Anxiety Inventory; BDI: Becks Depression Inventory; CAPS: Clinician-administered PTSD Scale; CTQ-SF: Childhood Trauma Questionnaire Short Form; DFA: detrended fluctuation analysis; DTS: Davidson Trauma Scale; ECG: electrocardiogram; GAF: Global assessment of functioning scale; HADS: Hospital anxiety and depression scale; HDS: Hamilton depression rating scale; HF: high frequency (between 0.15 and 0.4 Hz); HR: heart rate; HRV: heart rate variability; IBI: interbeat interval; ISI: Insomnia Scale Index; ISP: intended sleep period; KCG: kinetocardiogram; LF: low frequency; MINI: Mini-international Neuropsychiatric Interview; NA: negative affect; N1: NREM stage 1; N2: NREM stage 2; N3: NREM stage 3; PHQ-9: Patient Health Questionnaire 9; pNN50: percent of differences of adjacent RR intervals greater than 50msec ; PSG: polysomnography; PSQ: Perceived Stress Questionnaire; PSQI: Pittsburgh Sleep Quality Index; PSWQ: Penn State Worry Inventory of Symptomology; RMSSD: root mean square of successive differences between R-R intervals; RSA: respiratory sinus arrhythmia; SampEn: Sample entropy; SDNN: standard deviation of R-R intervals; SE: sleep efficiency; SOL: Sleep onset latency; SWS: slow wave sleep; STAI: State-trait anxiety index; SCID: Structured clinical interview for DSM-IV; SPHERE: Somatic and psychological health report; SWS: slow-wave sleep, TST: total sleep time; VAS: Visual analogue scale; WASO: wake after sleep onset

Values reported for Furutani et al. (2011) paper are from the third night of monitoring.

**p<0.05, **p<0.01, ***p<0.00*

APPENDIX 6.1: HRV parameters in participants grouped by chronic disease status.

	All			Women			Men*		
	No chronic disease (n=19)	**Chronic disease (n=38)**	**p-value**	**No chronic disease (n=15)**	**Chronic disease (n=31)**	**p-value**	**No chronic disease (n=4)**	**Chronic disease (n=7)**	**p-value**
RMSSD wake (ms)	19.75 [14.69-25.92]	18.59 [14.50-26.57]	0.879	19.75 [14.69-25.69]	18.38 [13.97-23.98]	0.806	20.65 [14.88-34.80]	22.91 [16.28-45.32]	-
RMSSD sleep (ms)	30.55 [21.08-38.12]	27.51 [19.14-40.98]	0.652	26.51 [19.90-36.87]	27.03 [19.14-33.45]	0.836	51.30 [31.63-63.93]	55.45 [20.30-65.55]	-
RMSSD Δ (ms)	9.16 [0.87-17.65]	8.47 [0.05-17.09]	0.866	5.37 [-1.10-14.78]	7.59 [0.43-15.52]	0.717	16.50 [11.48-34.41]	17.16 [0.05-17.83]	-
SDNN wake (ms)	26.19 [23.40-31.84]	25.59 [18.31-33.29]	0.852	25.90 [20.86-28.48]	24.31 [18.16-33.29]	0.861	30.39 [24.81-42.41]	31.59 [24.42-44.19]	-
SDNN sleep (ms)	31.15 [23.20-37.34]	28.93 [20.35-37.70]	0.721	29.98 [23.05-36.09]	27.06 [18.98-35.85]	0.938	45.78 [33.28-59.65]	53.35 [26.47-62.78]	-
SDNN Δ (ms)	3.05 [-3.76-13.49]	2.88 [-1.17-12.48]	0.721	-0.47 [-5.28-10.56]	2.50 [-0.98-10.81]	0.407	10.32 [4.29-21.42]	12.36 [-3.47-17.35]	-
VLF wake (ms^2)	79.50 [54.94-115.54]	73.26 [34.02-127.47]	0.509	77.81 [39.28-92.14]	51.17 [32.58-89.29]	0.406	107.36 [83.23-212.62]	137.94 [89.70-150.41]	-
VLF sleep (ms^2)	117.97 [75.08-149.95]	84.60 [59.74-172.86]	0.836	108.39 [55.95-133.74]	79.52 [59.03-145.17]	0.897	185.56 [118.75-307.04]	201.80 [172.86-286.10]	-
VLF Δ (ms^2)	37.84 [-18.02-68.48]	34.65 [11.39-72.15]	0.487	15.09 [-18.02-57.58]	31.72 [11.39-55.88]	0.364	84.71 [11.38-118.56]	92.54 [22.45-129.78]	-

LF wake (ms^2)	433.59 [321.34-580.01]	407.63 [225.48-637.45]	0.600	411.88 [310.32-484.95]	376.54 [202.55-556.04]	0.535	691.17 [453.42-1147.46]	650.30 [468.69-944.95]	-
LF sleep (ms^2)	522.63 [316.49-686.99]	331.74 [204.41-616.77]	0.302	452.66 [186.45-591.08]	294.17 [195.62-532.78]	0.468	1297.80 [613.25-2147.28]	954.30 [431.36-1440.98]	-
LF Δ (ms^2)	6.40 [-256.40-263.82]	8.62 [-164.57-177.26]	0.910	134.60 [-261.56-218.87]	3.84 [-127.67-103.54]	0.756	553.03 [-10.74-1170.40]	349.22 [-218.94-684.42]	-
HF wake (ms^2)	171.95 [101.46-246.28]	157.32 [55.85-308.43]	0.787	171.95 [118.35-238.66]	148.17 [49.83-308.43]	0.898	188.59 [93.03-479.94]	202.26 [92.72-591.06]	-
HF sleep (ms^2)	303.55 [184.75-533.99]	287.51 [135.32-665.86]	0.693	270.49 [181.91-503.22]	228.68 [108.21-526.27]	0.796	760.27 [274.22-1223.85]	926.76 [203.67-1267.16]	-
HF Δ (ms^2)	120.66 [-5.08-374.01]	110.82 [11.52-390.57]	0.948	92.28 [-6.74-362.04]	92.95 [11.52-361.08]	0.907	353.42 [94.06-831.04]	413.59 [42.60-596.59]	-

Data are presented as median [interquartile range]. HF: high frequency; LF: low frequency; RMSSD: root mean square of successive differences between R-peak to R-peak (R-R) intervals; SDNN: standard deviation of differences between R-R intervals; *VLF: very low frequency. P-values represent comparisons between the no chronic disease and chronic disease groups determined using Mann-Whitney U tests. * Data for the men are presented for descriptive purposes only, since the small sample size precluded statistical analysis.*

APPENDIX 6.2: HRV parameters in participants grouped by chronic medication use status.

	All			**Women**			**Men***		
	No chronic medication (n=37)	**Chronic medication (n=20)**	**p-value**	**No chronic medication (n=28)**	**Chronic medication (n=18)**	**p-value**	**No chronic disease (n=9)**	**Chronic disease (n=2)**	**p-value**

RMSSD wake (ms)	19.00 [14.50-25.69]	22.30 [15.22-26.83]	0.581	19.02 [14.21-23.56]	20.03 [15.06-26.57]	0.653	17.94 [15.37-30.60]	34.12 [22.91-45.32]	-
RMSSD sleep (ms)	30.41 [19.75-40.04]	24.74 [19.35-38.51]	0.393	27.51 [18.38-36.87]	24.74 [19.25-34.74]	0.754	55.15 [31.63-65.43]	41.73 [20.30-63.16]	-
RMSSD Δ (ms)	9.48 [0.05-17.48]	5.97 [0.43-11.94]	0.388	7.13 [-1.10-16.20]	5.97 [0.59-10.65]	0.841	17.12 [11.48-34.41]	37.89 [31.59-44.19]	-
SDNN wake (ms)	26.19 [20.78-31.68]	27.19 [17.97-33.91]	0.867	25.84 [19.65-29.27]	24.46 [16.95-33.38]	0.875	29.95 [24.42-34.56]	31.59 [24.42-44.19]	-
SDNN sleep (ms)	30.29 [23.20-37.84]	26.99 [18.80-35.85]	0.302	29.12 [20.35-36.09]	26.99 [18.34-35.75]	0.651	52.47 [33.28-63.40]	40.61 [24.16-57.05]	-
SDNN Δ (ms)	5.08 [-3.61-13.76]	2.29 [-0.98-9.97]	0.464	2.88 [-5.28-12.48]	2.29 [-0.63-7.30]	0.980	12.81 [4.29-23.21]	2.72 [-7.43-12.86]	-
VLF wake (ms^2)	77.81 [46.15-115.54]	80.37 [32.41-119.70]	0.726	59.47 [39.84-81.13]	73.48 [31.83-107.04]	1.00	130.89 [83.83-141.68]	134.12 [111.993-156.31]	-
VLF sleep (ms^2)	123.42 [61.93-153.88]	78.71 [46.42-157.53]	0.338	99.44 [59.03-135.63]	78.71 [46.22-151.35]	0.782	201.62 [162.59-291.53]	176.90 [67.69-286.10]	-
VLF Δ (ms^2)	34.69 [-3.06-72.15]	26.46 [-8.42-55.88]	0.453	30.06 [-6.40-61.74]	26.46 [-6.66-53.75]	0.920	89.21 [45.47-121.90]	42.77 [-44.24-129.78]	-
LF wake (ms^2)	433.59 [310.32-580.01]	398.06 [214.02-666.89]	0.676	410.86 [278.87-503.41]	381.41 [202.41-651.07]	0.787	620.91 [468.69-861.74]	802.37 [659.79-944.95]	-
LF sleep (ms^2)	482.02 [217.86-686.99]	310.97 [195.62-533.16]	0.182	388.69 [186.45-591.08]	289.52 [163.42-521.35]	0.451	1013.40 [554.15-2147.28]	875.82 [310.65-1440.98]	-

LF Δ (ms^2)	94.53 [-248.72-263.82]	-10.82 [-164.57-79.24]	0.302	-76.01 [-261.56-209.31]	-10.82 [-146.12-45.99]	0.725	443.42 [-10.74-934.27]	73.44 [-349.14-496.03]	-
HF wake (ms^2)	157.37 [89.09-238.66]	205.22 [56.10-323.70]	0.514	158.41 [84.04-215.16]	199.15 [49.31-313.44]	0.589	101.79 [92.72-275.72]	396.66 [202.26-591.06]	-
HF sleep (ms^2)	328.20 [135.91-568.61]	258.10 [108.21-672.90]	0.707	262.08 [135.86-503.22]	258.10 [94.76-606.48]	0.900	929.10 [274.22-1261.26]	695.66 [203.66-1187.65]	-
HF Δ (ms^2)	133.84 [-5.08-391.19]	85.38 [11.52-267.58]	0.554	107.48 [-6.74-374.01]	85.38 [25.12-217.28]	0.910	413.59 [94.06-831.04]	299.00 [1.4-596.59]	-

Data are presented as median [interquartile range]. HF: high frequency; LF: low frequency; RMSSD: root mean square of successive differences between R-peak to R-peak (R-R) intervals; SDNN: standard deviation of differences between R-R intervals; *VLF: very low frequency. P-values represent comparisons between the no chronic disease and chronic disease groups determined using Mann-Whitney U tests. . * Data for the men are presented for descriptive purposes only, since the small sample size precluded statistical analysis.*

APPENDIX 6.3: Demographics and sleep characteristics of participants grouped by diurnal HRV pattern (n=53).

	Expected RMSSD Δ (n=41)	**Reverse RMMSD Δ (n=13)**	**p-value**	**Expected SDNN Δ (n=34)**	**Reverse SDNN Δ (n=19)**	**p-value**	**Expected VLF Δ (n=41)**	**Reverse VLF Δ (n=13)**	**p-value**	**Expected LF Δ (n=28)**	**Reverse LF Δ (n=26)**	**p-value**	**Expected HF Δ (n=42)**	**Reverse HF Δ (n=12)**	**p-value**
Age (y)	44 [38-50]	43 [38-45]	0.599	43 [38-50]	43 [36-50]	0.856	43 [38-50]	43 [33-51]	0.992	43 [36-49]	43 [38-50]	0.589	44 [39-50]	41 [36-45]	0.211
Presence of chronic disease	27 (66)	9 (69)	0.822	23 (68)	12 (63)	0.741	27 (71)	8 (53)	0.220	19 (68)	17 (65)	0.847	28 (68)	7 (58)	0.522
Chronic medication use	14 (34)	5 (38)	0.776	12 (35)	6 (32)	0.784	12 (32)	6 (40)	0.560	9 (32)	10 (38)	0.627	15 (37)	3 (35)	0.456

PSQI score	3 [2-5]	3 [2-5]	0.839	3 [2-5]	3 [2-5]	0.562	3 [2-5]	4 [2-5]	0.504	4 [2-5]	3 [2-5]	0.449	3 [2-5]	3 [2-5]	0.438
ESS score	5 [2-8]	2 [1-4]	0.199	5 [1-9]	3 [1-6]	0.317	5 [1-9]	2 [1-5]	0.197	6 [2-9]	3 [1-6]	0.229	4 [2-8]	3 [1-6]	0.331
Total sleep time (h)	7.47 [6.98-7.94]	7.48 [6.43-7.95]	0.808	7.60 [7.18-8.08]	7.10 [6.30-7.86]	0.085	7.54 [6.98-8.08]	7.43 [6.30-7.86]	0.269	7.60 [7.16-8.04]	7.34 [6.43-7.91]	0.268	7.43 [6.98-7.94]	7.61 [6.37-7.97]	0.975
Sleep efficiency (%)	81 [78-86]	82 [81-86]	0.498	81 [78-86]	82 [80-86]	0.335	81 [78-86]	85 [80-86]	0.214	80 [77-87]	82 [80-86]	0.194	82 [79-86]	82 [77-86]	1.00
SFI (%)	32 [23-36]	32 [31-37]	0.595	33 [22-38]	32 [29-36]	0.853	33 [22-37]	32 [29-33]	0.765	31 [22-38]	32 [29-34]	1.00	32 [23-36]	32 [31-38]	0.243

Data are presented as median [interquartile range] or count (percentage). ESS: Epworth Sleepiness Scale; HF: high frequency; LF: low frequency; PSQI: Pittsburgh Sleep Quality Index; RMSSD: root mean square of successive differences between R-peak to R-peak (R-R) intervals; SDNN: standard deviation of differences between R-R intervals; SFI: Sleep Fragmentation Index; *VLF: very low frequency. P-values represent between-group comparisons determined using Mann-Whitney U tests.*

APPENDIX 6.4: Heart rate variability characteristics of three researchers of lab to ensure device and methodical validity.

	Researcher 1	**Researcher 2**
Heart rate (bpm)	55 ()	68 ()
RMSSD wake (ms)	94.99 (81.30-108.90)	67.98 (59.13-75.91)
RMSSD sleep (ms)	142.53 (127.85-153.41)	44.34 (38.85-51.49)
RMSSD Δ (ms)	47.54	-23.65
SDNN wake (ms)	88.79 (80.01-97.35)	55.54 (49.26-61.07)
SDNN sleep (ms)	107.98 (94.43-113.86)	47.10 (42.18-52.92)
SDNN Δ (ms)	19.18	-8.44
VLF wake (ms^2)	317.78 (236.62-384.71)	183.77 (127.88-214.41)
VLF sleep (ms^2)	336.35 (234.58-430.53)	251.40 (204.24-320.49)
VLF Δ (ms^2)	18.58	67.63
LF wake (ms^2)	3710.67 (2886.56-4502.37)	1085.00 (817.53-1298.59)
LF sleep (ms^2)	3979.29 (3160.79-4805.16)	1071.15 (815.70-1332.39)
LF Δ (ms^2)	268.62	-13.85

HF wake (ms^2)	3042.38 (2339.49-3509.26)	888.70 (622.53-1005.30)
HF sleep (ms^2)	5911.37 (4651.55-7195.32)	745.80 (540.17-890.46)
HF Δ (ms^2)	2868.99	-142.90

Data are presented as median (interquartile range). Change variables were calculated as the difference between median sleep and wake values such that a negative indicates higher values during wake than sleep. Bpm: beats per minute; HF: high frequency; LF: low frequency; RMSSD: root mean square of successive differences between R-peak to R-peak (R-R) intervals; SDNN: standard deviation of differences between R-R intervals; *VLF: very low frequency. P-values represent comparisons between the men and women determined using Mann-Whitney U tests.*

APPENDIX 7.1: Descriptive characteristics of participants.

	All (n=110)	**Women (n=83)**	**Men (n=27)**	**p-value**
Age (y)	41 [35-48]	42 [35-49]	41 [36-48]	0.866
BMI ($kg.m^{-2}$)	28.5 [23.3-35.7]	32.8 [25.7-38.0]	22.0 [19.1-24.2]	**<0.001**
Chronic disease (count, %)	59 (54)	45 (55)	14 (52)	0.784
Employed (count, %)	33 (30)	25 (30)	8 (30)	0.990
Highest degree of formal education (count, %)				**0.001**
None	2 (2)	1 (1)	1 (4)	
Primary	72 (66)	4 (5)	0 (0)	
Secondary	28 (26)	77 (93) *	19 (73) *	
Tertiary	7 (6)	1 (1) *	6 (23) *	
Smoking status (count, %)				**<0.001**
Non-smoker	63 (57)	58 (69)*	5 (19)*	
Smoker	42 (38)	22 (26)*	20 (74)*	
Ex-smoker	6 (5)	4 (5)	2 (7)	
Alcohol consumption (standard drinks/ week)	0 [0-9]	0 [0-5]	8 [0-16]	**0.001**

*Data are presented as median [interquartile range] or count (percentage). BMI: body mass index. Presence of chronic disease was classified as anyone having a history of cardiovascular disease (heart attack, rheumatic heart disease, stroke, etc.) cancer, high cholesterol, diabetes mellitus, osteoarthritis, rheumatoid arthritis, kidney failure, a diagnosed mental disorder or any other chronic disease. P-values represent comparisons between the men and women determined using Mann-Whitney U, Chi-squared and Fisher's exact tests. * indicates significant post hoc differences (p<0.05) between groups as determined using Fisher's exact tests.*

APPENDIX 7.2: Actigraphy and self-reported sleep characteristics.

	All (n=110)	**Women (n=83)**	**Men (n=27)**	**p-value**
Bedtime (hh:mm)	22:06 [21:35-22:40]	22:07 [21:38-22:54]	22:04 [21:23-22:35]	0.311
Wake-up time (hh:mm)	7:16 [6:23-7:56]	7:00 [6:09-7:45]	7:34 [7:16-8:34]	**0.002**
Time-in-bed (h)	8.94 [8.11-10.08]	8.78 [8.03-9.93]	10.00 [8.83-10.56]	**0.002**
TIB >9h	53 (49)	35 (42)	18 (69)	**0.016**
Total sleep time (h)	7.36 [6.59-8.05]	7.19 [6.29-7.95]	7.65 [7.02-8.50]	**0.029**
TST <7h	42 (39)	36 (43)	6 (23)	0.179
TST 7-9h	57 (52)	40 (48)	17 (65)	
TST >9h	10 (9)	7 (8)	3 (12)	
Sleep efficiency (%)	81.67 [77.45-85.76]	82.11 [77.53-86.50]	79.29 [76.2-83.61]	0.165
Low sleep efficiency (<85%)	77 (69)	55 (65)	22 (81)	0.117
Wake after sleep onset (min)	82.6 ± 41.2	77.5 ± 39.8	98.2 ± 42.1	**0.022**
Arousal index (number.h^{-1})	7 [6-9]	7 [5-8]	9 [7-10]	**0.008**
SFI (%)	29.24±9.21	29.31±9.95	29.07±7.27	0.883
PSQI score	3 [2-5]	4 [2-5]	2 [2-4]	0.070

Poor sleep quality (PSQI >5)	21 (19)	18 (22)	3 (11)	0.206
ESS score	4 [1-8]	5 [2-8]	1 [0-4]	**<0.001**
Excessive daytime sleepiness (ESS >10)	11 (10)	11 (13)	0 (0)	**0.045**
ISI score	1 [0-4]	1 [0-4]	0 [0-2]	**0.042**
Clinically significant insomnia symptoms (ISI >14)	5 (5)	3 (4)	2 (7)	0.419

*Data are presented as mean ± standard deviation, median [interquartile range] or count (percentage). ESS: Epworth Sleepiness Scale; ISI: Insomnia Severity Index; PSQI: Pittsburgh Sleep Quality Index; SFI: Sleep Fragmentation Index; TIB: time-in-bed; TST: total sleep time. P-values represent comparisons between the men and women determined using independent t-tests, Mann-Whitney U, Chi-squared and Fisher's exact tests. * indicates significant post hoc differences (p<0.05) between groups as determined using Fisher's exact tests.*

APPENDIX 7.3: Symptoms of depression, anxiety, post-traumatic stress disorder, trauma and fear of sleep among participants.

	All (n=110)	**Women (n=83)**	**Men (n=27)**	**p-value**
BDI-II score	14 [8-22]	15 [9-24]	12 [8-14]	0.053
Moderate-severe depression symptoms (BDI-II >19)	36 (33)	31 (37)	5 (19)	0.093
BAI score	9 [4-15]	10 [4-15]	9 [4-13]	0.918
Moderate-severe anxiety symptoms (BAI >15)	25 (23)	19 (23)	6 (22)	0.966
Trauma status				**0.001**

No trauma	37 (35)	20 (25)*	17 (63)*	
Yes, resilient	32 (30)	25 (31)	7 (26)	
Yes, symptoms indicative of PTSD	38 (35)	35 (44)*	3 (11)*	
PC-PTSD score	2 [0-4]	3 [0-4]	0 [0-2]	**<0.001**
Likely presence of PTSD	37 (34)	34 (42)	3 (11)	**0.003**
FoSI score	14 [9-24]	14 [8-25]	13 [9-17]	0.324
Fear of sleep subscale	1 [0-4]	2 [0-5]	0 [0-3]	**0.010**
Fear of loss of vigilance subscale	4 [2-6]	4 [2-6]	3 [2-5]	0.521
Fear of trauma re-exposure subscale	2 [0-3]	2 [1-3]	1 [0-2]	**0.040**
Nighttime vigilant behaviour subscale	6 [3-8]	6 [3-8]	6 [5-8]	0.710
Fear of the dark subscale	0 [0-2]	0 [0-3]	0 [0-0]	0.076

*Data are presented as median [interquartile range] or count (percentage). Likely presence of PTSD is defined as having PC-PTSD scores >3. BAI: Beck Anxiety Inventory; BDI-II: Beck Depression (II) Inventory; FoSI: Fear of Sleep Inventory; PC-PTSD: Primary Care Post-traumatic Stress Disorder. P-values represent comparisons between the men and women determined using Mann-Whitney U, Chi-squared and Fisher's exact tests. *indicates significant post hoc differences (p<0.05) between male and female groups as determined using Fisher's exact test.*

APPENDIX 7.4: Spearman rank order correlations between fear, mental health outcomes and HRV measures in men (n=27).

	Global fear of sleep		**Fear of sleep subscale**		**Fear of loss of vigilance at night subscale**		**Fear of trauma re-exposure subscale**		**Nighttime vigilant behaviours subscale**		**Fear of the dark subscale**	
	rho	p-value	rho	p-value	rho	p-value	rho	p-value	rho	p-value	rho	p-value
BDI-II score	0.524	**0.006**	0.482	**0.013**	0.291	0.150	0.692	**<0.001**	0.273	0.177	0.134	0.514
BAI score	0.651	**<0.001**	0.573	**0.002**	0.421	**0.029**	0.696	**<0.001**	0.240	0.227	0.141	0.484
PC-PTSD score	0.512	**0.006**	0.431	**0.025**	0.395	**0.041**	0.530	**0.005**	0.223	0.263	0.026	0.898
RMSSD wake (ms)	-0.259	0.500	0.410	0.273	-0.338	0.374	0.105	0.787	-0.272	0.478	-0.251	0.515
RMSSD sleep (ms)	-0.156	0.713	0.399	0.328	-0.099	0.816	0.265	0.527	-0.171	0.686	-0.083	0.846
RMSSD Δ (ms)	-0.180	0.670	0.206	0.624	-0.124	0.771	0.000	1.000	-0.024	0.954	-0.083	0.846
HF power wake (ms^2)	-0.285	0.458	0.298	0.436	-0.381	0.311	0.158	0.685	-0.230	0.552	-0.251	0.515
HF power sleep (ms^2)	-0.192	0.649	0.261	0.532	-0.16a;1	0.704	0.340	0.410	-0.122	0.774	-0.083	0.846
HF power Δ (ms^2)	-0.311	0.453	0.247	0.555	-0.185	0.660	-0.151	0.721	-0.122	0.774	-0.247	0.555

The subscale variables are subscales of the Fear of Sleep Inventory (FoSI). Δ delta *ESS: Epworth Sleepiness Scale; HF: high frequency; PSQI: Pittsburgh Sleep Quality Index; PTSD: post-traumatic stress disorder; RMSSD: root mean square of successive differences between R-R intervals; SFI: sleep fragmentation index.*

APPENDIX 7.5. Spearman rank order correlations between continuous mental health variables including FoSI-derived sleep variables and sleep variables in men (n=27).

	ESS score		**PSQI score**		**Time-in-bed (h)**		**Total sleep time (h)**		**Sleep efficiency (%)**		**SFI (%)**	
	rho	p-value	rho	p-value	rho	p-value	rho	p-value	rho	p-value	rho	p-value
BDI-II score	0.401	**0.042**	0.534	**0.005**	0.178	0.395	0.107	0.395	-0.109	0.597	-0.068	0.760
BAI score	0.325	0.098	0.387	**0.046**	-0.159	0.439	-0.225	0.270	-0.177	0.377	0.007	0.974
PC-PTSD score	0.483	**0.011**	0.291	0.141	-0.024	0.906	0.025	0.905	0.216	0.280	-0.024	0.910
Global fear of sleep score	0.293	0.138	0.245	0.219	-0.025	0.903	0.035	0.864	0.113	0.576	-0.151	0.481
Fear of sleep subscale	0.218	0.274	0.311	0.114	-0.018	0.932	-0.042	0.839	-0.013	0.948	0.029	0.891
Fear of loss of vigilance subscale	0.113	0.575	0.136	0.500	-0.032	0.878	0.099	0.632	0.278	0.160	-0.342	0.102
Fear of trauma re-exposure subscale	0.210	0.294	0.340	0.083	0.049	0.811	-0.095	0.645	-0.112	0.579	0.046	0.831
Nighttime vigilant behaviours subscale	0.293	0.139	-0.007	0.973	0.076	0.711	0.245	0.229	0.202	0.312	-0.232	0.275
Fear of the dark subscale	0.159	0.427	0.161	0.423	-0.091	0.660	-0.114	0.578	0.092	0.650	0.083	0.699

RMSSD wake (ms)	0.542	0.132	0.785	**0.012**	0.250	0.517	-0.100	0.798	-0.467	0.205	0.333	0.420
RMSSD sleep (ms)	0.307	0.460	0.355	0.389	0.405	0.320	0.119	0.779	0.000	1.000	-0.250	0.589
RMSSD delta (ms)	0.025	0.954	0.300	0.470	0.238	0.570	0.167	0.693	0.143	0.736	-0.250	0.589
HF power wake (ms^2)	0.428	0.250	0.858	**0.003**	0.233	0.546	-0.117	0.765	-0.400	0.286	0.333	0.420
HF power sleep (ms^2)	0.160	0.706	0.464	0.247	0.381	0.352	0.095	0.823	0.095	0.823	-0.250	0.589
HF power Δ (ms^2)	0.172	0.684	0.109	0.797	0.286	0.493	0.214	0.610	0.024	0.955	-0.214	0.645

BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory; ESS: Epworth Sleepiness Scale; FoSI: Fear of Sleep Inventory; HF: high frequency; PSQI: Pittsburgh Sleep Quality Index; PC-PTSD: Primary Care post-traumatic stress disorder; RMSSD: root mean square of successive differences between R-R intervals; SFI: sleep fragmentation index.

APPENDIX 7.6. Spearman rank order correlations between heart rate variability and mental health measures in men (n=27).

	RMSSD wake (ms)		**RMSSD sleep (ms)**		**RMSSD delta (ms)**		**HF power wake (ms^2)**		**HF power sleep (ms^2)**		**HF power delta (ms^2)**	
	rho	p-value	rho	p-value	rho	p-value	rho	p-value	rho	p-value	rho	p-value
BDI-II score	0.819	**0.007**	0.386	0.317	0.241	0.565	0.869	**0.002**	0.458	0.254	0.072	0.865
BAI score	0.780	**0.013**	0.317	0.444	0.122	0.774	0.814	**0.008**	0.366	0.373	-0.049	0.909
PC-PTSD score	0.456	0.217	0.078	0.855	-0.312	0.452	0.456	0.217	0.078	0.855	-0.312	0.452

BDI: Beck Depression Inventory; BAI: Beck Anxiety Inventory; HF: high frequency; PC-PTSD: Primary care post-traumatic stress disorder; RMSSD: root mean square of successive differences between R-peak to R-peak (R-R) intervals.

APPENDIX 7.7. Measurement model for depression symptoms.

				95% CI	
Factor	**Item**	**Composite Reliability**	**Standardised factor loading**	**Lower limit**	**Upper limit**
PTSD symptom severity		0.874			
	PC-PTSD item 1		0.680*	0.544	0.816
	PC-PTSD item 2		0.912*	0.841	0.983
	PC-PTSD item 3		0.760*	0.646	0.873
	PC-PTSD item 4		0.698*	0.563	0.833
	PC-PTSD item 5		0.744*	0.627	0.861
Fear		0.716			
	Fear of sleep subscale		0.763*	0.630	0.896
	Fear of loss of vigilance subscale		0.538*	0.356	0.720

	Fear of trauma re-exposure subscale		0.791*	0.669	0.913
Change in parasympathetic activity		0.939			
	Delta HF power		0.784*	0.463	1.105
	Delta RMSSD		1.129*	0.694	1.565
Depressive symptoms		0.796			
	Cognitive domain		0.834*	0.719	0.948
	Affective domain		0.759*	0.631	0.887
	Somatic domain		0.659*	0.507	0.810

*Although fear of sleep showed a relatively low composite reliability, the items provide the best available measure of the hypothesised latent variable and, since error variance is accounted for when using a structural equation model, we continued with our analysis. BDI-II: Beck Depression Inventory; CI: confidence interval; HF: high frequency; PC-PTSD: post-traumatic stress disorder; RMSSD: root mean square of successive R-R intervals; * indicates p<0.050.*

APPENDIX 7.8. Measurement model for anxiety symptoms.

Factor	Item	Composite Reliability	Standardised factor loading	95% CI	
				Lower limit	Upper limit
Fear		0.727			
	Fear of sleep subscale		0.805*	0.681	0.929
	Fear of loss of vigilance subscale		0.579*	0.403	0.755
	Fear of trauma re-exposure subscale		0.716*	0.577	0.855
	Nighttime vigilant behaviours subscale		0.550*	0.366	0.734
Change in parasympathetic activity		0.938			
	Delta HF power		0.690*	0.109	1.271
	Delta RMSSD		1.281*	0.235	2.327
Anxiety symptoms					
	BAI global score		1.00	1.00	1.00

*Despite the relatively poor composite reliability for fear of sleep, the items provide the best available measure of the hypothesised latent variable and, since error variance is accounted for when using a structured equation model, we continued with our analysis. BAI: Beck Anxiety Inventory; CI: confidence interval; HF: high frequency; RMSSD: root mean square of successive R-R intervals. * indicates p<0.050.*