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Reddy, Tracy. (2024). The association between poor sleep quality and cardiometabolic risk in HIV+ individuals and the general population living in a rural area of South Africa [Master`s dissertation, University of the Witwatersrand, Johannesburg]. WIReDSpace. Value Lang Edit https://hdl.handle.net/10539/47074

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The association between poor sleep quality and cardiometabolic risk in HIV+ individuals and the general population living in a rural area of South Africa

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A Dissertation submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in fulfilment of the requirements for the degree of Master of Science in Medicine (Research)

Johannesburg, 2023

Declaration

I, Tracy Reddy, declare that this Dissertation is my own, unaided work. It is being submitted for the Degree of Master of Science in Medicine (Research) at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.



(Signature of candidate)

26th day of April 2023 in Sandton, Johannesburg

Dedication

To my family,

for their unending support

Publications and presentations

I presented my findings at the Brain Functions Group (BFG) Research Day at the University of the Witwatersrand on 14 Septempber 2022

Abstract

Studies show that both poor sleep quality and HIV infection independently increase cardiometabolic risk (CMR). Additionally, poor sleep quality is common with HIV infection. Our study investigated whether HIV infection interacts with poor sleep quality to affect CMR in people living with HIV (PLWH) in a rural area of South Africa. We recruited 200 HIV+ participants and 200 controls from Qwa Qwa in Free State in South Africa and assessed their CMR, sleep quality, daytime sleepiness, risk of obstructive sleep apnoea and degree of depressive symptoms. Sleep quality ($p = 0.15$), daytime sleepiness ($p = 0.31$) and the cardiometabolic risk score (MetScore) ($p = 0.93$) were similar between HIV+ and control participants. Fewer HIV+ participants had a high risk of sleep apnoea ($p = 0.019$) but more HIV+ participants had symptoms of clinical depression ($p = 0.0007$). Poorer sleep quality in the HIV+ participants was associated with pain ($p = 0.0006$), more severe depressive symptoms ($p<0.0001$) and longer HIV duration ($p = 0.011$). However, HIV infection was not associated with a higher MetScore ($p = 0.18$) once age, sex and sleep and depression markers were adjusted for. Additionally, HIV infection increased the risk of hypertension ($p = 0.016$). HIV status did not interact with sleep quality ($p = 0.32$) to affect CMR. Our findings indicate that healthcare facilities should consider monitoring CMR factors in HIV+ individuals.

Acknowledgements

I would like to thank my family for their support, motivation and always encouraging me to never give up.

I would also like to thank my supervisors, Prof. Karine Scheuermaier and Dr Alan Karstaedt, for giving me the opportunity to be part of their research and for all their assistance and support.

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Abbreviations

ABC = abacavir

ACTH = adrenocorticotropin hormone

AHI = apnoea-hypopnoea index

ART = anti-retroviral treatment

BDI = Beck’s Depression Inventory I

BMI = body mass index

BQ = Berlin Questionnaire

cARTs = combination anti-retroviral treatment

CMDs = cardiometabolic disease

CMR = cardiometabolic risk

CMV = cytomegalovirus

CRF = corticotropin-releasing factors

CRP = C-reactive protein

CVD = cardiovascular disease

EBV = Epstein-Barr virus

EFV = efavirenz

ESS = Epworth Sleepiness Scale

FDC = fixed-dose combination

FTC = emtricitabine

GALT = gut association lymphoid tissue

HAART = Highly Active Anti-retroviral Therapy

HDL = high density lipoprotein

HICs = high-income countries

HIV = human immunodeficiency disease

ICAM-1 = intercellular adhesion molecule-1

IL-1ß = interleukin-1ß

IL-6 = interleukin-6

LDL = low density lipoprotein

MetScore = metabolic score

NCDs = non-communicable diseases

NREM = non-rapid eye movement

OPN = osteopontin

OSA = obstructive sleep apnoea

PLWH = people living with HIV

PSQI = Pittsburgh Sleep Quality Index

SBP = systolic blood pressure

sCD14 = soluble cluster of differentiation 14

SSA = sub-Saharan Africa

T2DM = type 2 diabetes mellitus

TDF = tenofovir

TGF-ß = transforming growth factor-ß

TNF-α = tumour necrosis factor –α

VCAM-1 = vascular cell adhesion molecule-1

WHO = World Health Organisation

Chapter 1: Introduction

1.1 General Introduction

In South Africa (SA), cardiometabolic diseases (CMDs) are increasing in prevalence (Statistics South Africa, 2017). Indeed, lifestyle habits are a major contributor to the prevalence of CMDs and the associated risk factors such as hypertension and obesity. While urban lifestyles definitely promote CMDs, the effects of modernisation and economic development has also trickled down to rural areas. A study conducted using over 4362 rural dwellers in northeastern South Africa found that 46% of the sample had a high waist circumference, 30% were obese, 45% had an increased low density lipoprotein (LDL) - cholesterol and 44% had a decreased high density lipoprotein (HDL) - cholesterol (Clark et al, 2015). Surprisingly, van Zyl et al (2012) showed that rural dwellers in the Free State had a similar or an even greater cardiometabolic risk (CMR) than peri-urban areas in SA and cohorts in high-income countries (van Zyl et al, 2012). It appears that despite being in the early stages of the epidemiological transitions, rural lifestyles are beginning to increase the risk of CMD.

There is limited recent data that compares CMR in urban and rural areas of SA. Nevertheless, it has been found that urban dwellers in South Africa have a high prevalence of diabetes (Erasmus et al, 2012; Peer et al, 2012) compared to rural and urban dwellers in Congo (Katchunga et al, 2012) and Kenya (Ploubidis et al, 2013).

It is well established that traditional risk factors such as a poor diet and lack of exercise promote CMDs (WHO, 2021); however, a lesser-known risk factor is poor sleep quality. Sleep quality includes aspects of sleep, such as sleep quality, daytime sleepiness, sleep duration but also sleep disorders, in particular risk of sleep apnoea. In fact, a randomised controlled trial (n = 123) found a causal relationship between poor sleep quality and cardiovascular diseases (CVDs) (Irwin et al, 2014). Additionally, meta-analytic data found that difficulty in falling asleep, maintaining sleep and non-restorative sleep are all associated with an increase in CMR (He et al, 2017).

In people living with HIV (PLWH), poor sleep quality is common (Allavena et al,, 2016; Redman et al,, 2018; Gómez-Olivé et al,, 2018; O'Brien et al, 2022). Additionally, studies outside sub-Saharan Africa (SSA) have found that PLWH have an increased CMR as defined by the Framingham Risk Score (Fedele et al, 2011), the risk of a myocardial infarction (Freiberg et al, 2013; Paisible et al, 2015) and the risk of stroke (Mayer et al, 2018). Since 7.5 million people are HIV+ in South Africa itself, HIV is a major burden to the healthcare system. Undoubtedly, there are significantly fewer studies conducted in SSA that investigate the relationship between HIV and CMD. In South Africa, two large, cross-sectional, studies found increased CMR in PLWH (Schoffelen et al, 2015; Clark et al, 2015). However, these studies did not include an appropriate HIV negative control group. Additionally, meta-analytic data from PLWH in SSA found a lower CMR in PLWH than the controls (Dillon et al, 2013). This was confirmed in a more recent study where people with HIV were older but had lower traditional CMR factors than HIV negative counterparts (Vos et al, 2020). Finally studies on sleep health in PLWH have focused on sleep quality but aspects such as excessive daytime sleepiness or risk of sleep apnoea have not yet been investigated collectively together with sleep quality

Another common challenge facing PLWH is depression (Nanni et al,, 2015), which has been associated with poor sleep quality (Redman et al, 2018; Oh et al, 2019) and increased CMR (Charlson et al, 2011).

A greater number of studies examining the association between HIV and poor sleep quality have been conducted in high-income countries (Crum-Cianflone et al, 2012; Taibi, 2013; Allavena et al, 2016; Chaponda, 2018; Gutierrez et al, 2019) than in SSA (Redman et al, 2018; Gómez-Olivé 2018; Roche et al, 2021). However, the characteristics of PLWH in SSA and high-income countries differ greatly. For example, the majority of PLWH in high-income countries are men of European ancestry- whereas in SSA, the majority are women between the ages of 15-49 years who are of African ancestry (UNAIDS, 2017; StatsSA, 2022).

With the exception of Gómez-Olivé et al, (2018), no other study has investigated sleep quality in PLWH in rural areas of South Africa. Gómez-Olivé et al (2018) found that in their aging population, PLWH have poorer sleep quality, as assessd by self-reported awakenings during the night, compared to the general population. Additionally, only a single South African study has investigated the combined effect of sleep quality and HIV status on CMR (Roche et al, 2021). Roche et al, (2021)

suggested that shift workers who work nights had higher inflammation and thus CVD risk when they were HIV+ vs. HIV-. To the best of our knowledge, no study has been conducted among PLWH in a rural South African area that investigated the effect of several markers of sleep health (sleep quality, daytime sleepiness and risk of sleep apnoea) and HIV status on CMR. To try and fill the knowledge gap, we set our study in the Thabo Mofutsanyana district in Qwa Qwa in the Free State province. We measured several aspects of sleep health (sleep quality, daytime sleepiness and risk of sleep apnoea) and CMR in HIV+ and control participants in order to assess whether poor sleep health and HIV status independently and collectively affects CMR.

1.2 Literature Review

1.2.1. Human Immunodeficiency Virus (HIV) and Cardiometabolic Disease (CMD)

1.2.1.1 CMD in Africa

CMDs are responsible for the highest number of annual deaths worldwide (Cardiovascular diseases, 2016; Global burden of disease 2020). CMD includes CVD, insulin resistance, diabetes mellitus, non-alcoholic fatty liver disease and chronic renal failure (de Waard et al, 2018; Tufts Health and Nutrition Letter 2021).

Indeed, rapid population growth, epidemiological transitions (Omran, 1971) and longer life expectancies together potentiate the rise in CMDs in Africa. This is especially true in SSA where the percentage of urban dwellers has almost than doubled from 1980 to 2020, therefore, increasing the risk of CMDs (Figure 1). The risk of CMDs are higher in urban dwellers compred to rural dwellers since urban lifestyles are often associated with unhealthier diets and more sedentary lifestyles.

Urbanisation is the main reason why many countries in SSA are transitioning into the later stages of the epidemiological transition. SSA describes all African countries, excluding Tunisia, Djibouti, Morocco, Libya, Egypt, Sudan, Somalia and Algeria. Additionally, the term epidemiological transition was coined in 1971 and as part of this transition, the main cause of mortality moves from communicable diseases in younger individuals to non-communicable diseases (NCDs), such as CMDs, in older individuals (Omran, 1971). For example, the number of deaths from CVD increased by 81% in SSA from 1990 to 2013 (Mensah et al, 2013). Consequently, CVD has moved from being the fourth highest cause of death in 1990 to being the top cause of death in 2017 in SSA (Figure 2 and Figure 3). Due to increasing burden of CMDs (such as CVD), more resources will have to be allocated and therefore, placing a strain on the limited medical resources in many areas of SSA (Mbanya et al, 2006; Beaglehole and Yach, 2003; Maher et al, 2011).

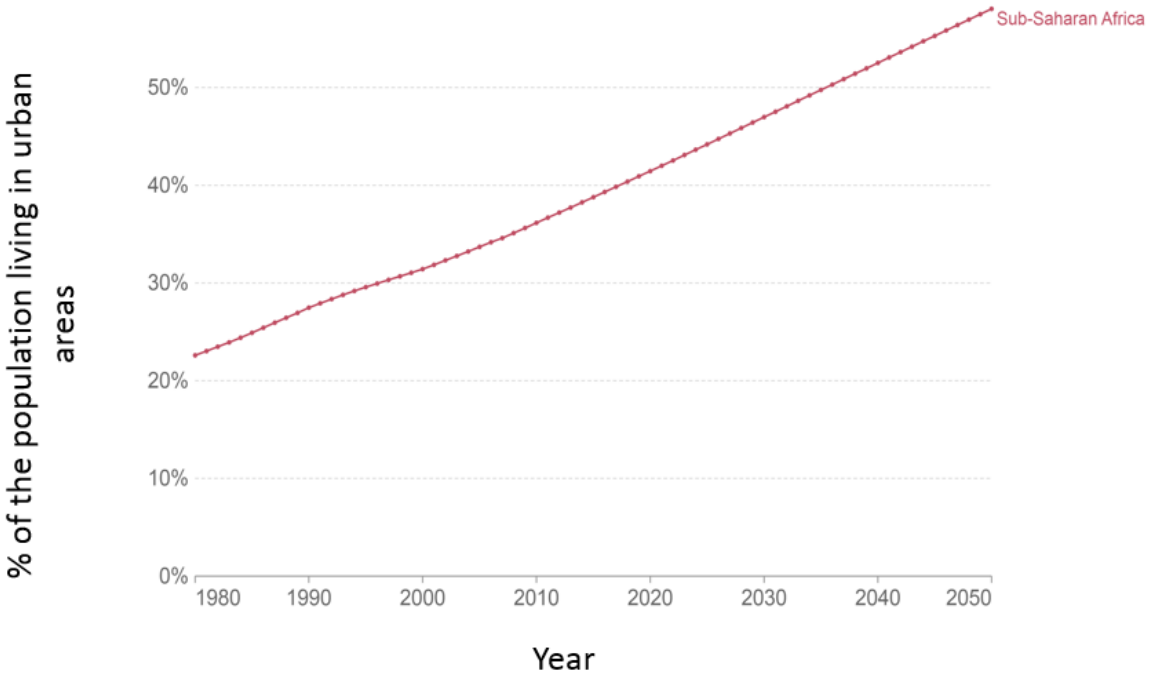


Figure 1. Graph showing the percentage of the population in Sub-Saharan Africa that live in urban areas and the projected percentage. ourworldindata.org

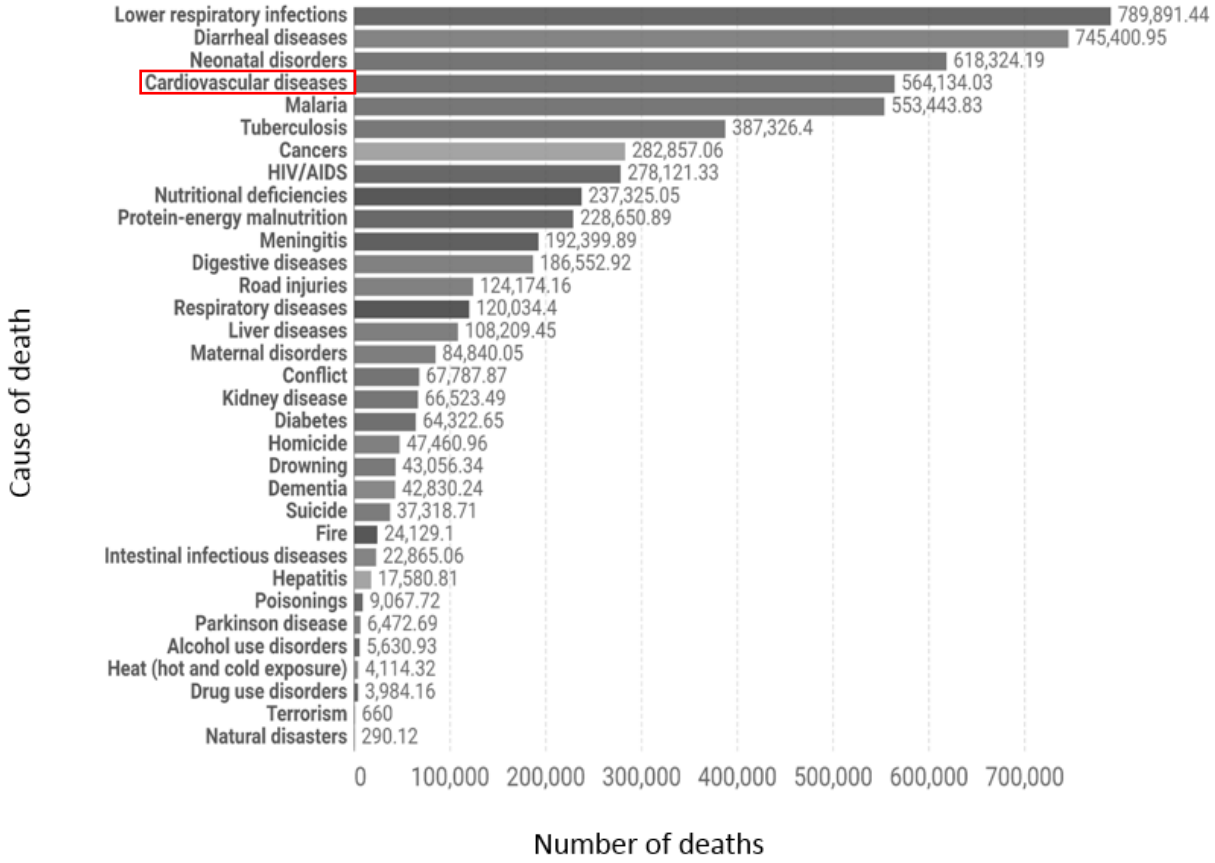


Figure 2. The annual number of deaths by cause in 1990 in Sub-Saharan Africa

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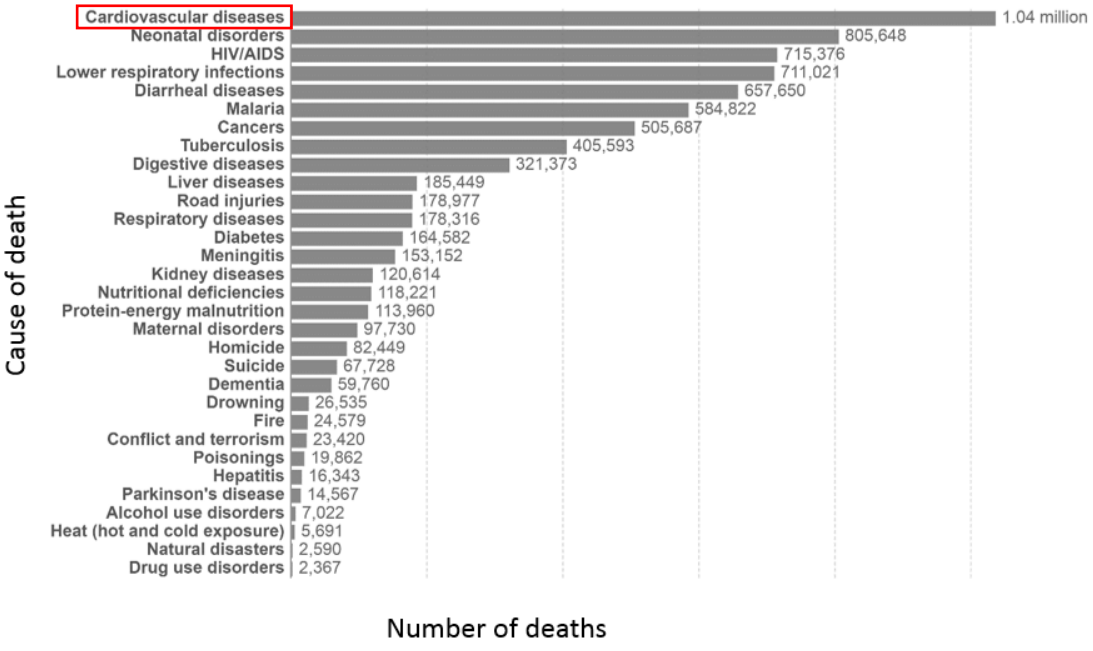


Figure 3. The annual number of deaths by cause in 2017 in Sub-Saharan Africa

Ourworldindata.org

The main risk factors for CMDs include obesity, high triglyceride levels, suboptimal levels of HDL cholesterol, hypertension and high blood sugar levels (Adebamowo et al, 2017). An individual is diagnosed with metabolic syndrome (MetS) when they have at least three of the aforementioned risk factors (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001). Individuals with MetS have a five times greater risk for type 2 diabetes mellitus (T2DM), a two to three times greater risk of having a stroke and are twice as likely to develop CVD within the next 5 to 10 years compared to people who do not have MetS (Alberti et al, 2005; Alberti et al, 2009). Other CMD risk factors include insufficient exercise (McDonnell et al, 2013), smoking (Goldstein et al, 2011), urbanisation (Sliwa et al, 2016), western diets (Aljefree and Ahmed, 2015), sleep apnoea (Redline et al, 2010) and genetics (Marcadenti, 2016). Indeed, the several lifestyle risk factors together with genetic susceptibility contribute to the development of CMDs.

In SSA specifically, hypertension was the third greatest risk factor and high blood sugar was the sixth greatest risk factor that caused the most deaths in 2017 (Roser and Ritchie, 2021). In facts, it is estimated that by 2025, SSA will have approximately 125.5 million people with hypertension (Poulter 2011). Additionally, 18.7 million people in SSA are expected to have T2DM by 2030, which is a 161% increase compared to the year 2000 (Wild et al, 2004). It has been shown that people of African ancestry have an increased risk of hypertension compared to other ancestries. One study that showed this finding was Carson et al (2011) who found that in people of African ancestry living in the USA, they had a greater genetic predisposition to hypertension compared to other ancestries. This finding was confirmed by Africans living in Africa, where it was suggested that SBP is up to 68% and DBP is up to 65% the result of genetics, with the other variable being lifestyle risk factors (Adeyemo et al, 2002; Rotimi et al, 1999; Gu et al, 1998).

In SSA, the number of deaths attributed to obesity increased by almost 110% from 1995 to 2017 (Ritchie and Roser, 2021). Additionally, the average body mass index (BMI) in SSA was 24.15 kg/m^2 in 2016, which is close to the world average of 24.75 kg/m^2 for the same year (Ritchie and Roser 2021). In South Africa, Ng et al (2014) found that the prevalence of obesity for was 13.5% for males older than 20 years and 42.0% for females older than 20 years, thus this burden of obesity and thus higher risk of mortality falls predominantly on women in South Africa. It is suggested that insufficient exercise and the consumption of high-calorie food promotes obesity in

SSA (Akarolo-Anthony and Adebamowo 2014; Rguibi and Belahsen 2004; Akarolo-Anthony et al, 2013).

1.*2.1.2 HIV in Africa*

HIV is transmitted through blood, breast milk, vaginal fluid, semen and anal mucus from an HIV-infected individual. The most common methods of transmission are through penetrative sex and sharing of needles among drug users. HIV can cause morbidity by destroying CD4 positive (CD4+) T cells, which are an important part of the immune system (Alimonti et al, 2003). Since CD4+ T cells fight off infection, a shortage means that PLWH are susceptible to opportunistic infections, which are illnesses that are more common in people with compromised immune systems (Stein et al, 1992).

The World Health Organisation (WHO) uses a 4-stage system to classify PLWH according to the severity of the disease (The WHO Clinical Staging System for HIV/AIDS 2010).

- Stage 1 patients are those who are asymptomatic or have constant swollen lymph nodes (The WHO Clinical Staging System for HIV/AIDS 2010).
- Stage 2 patients are those who have mild symptoms such as slight unintentional weight loss, recurring respiratory infections and/ or dermatological conditions (WHO, 2005).
- Stage 3 patients are those with moderate symptoms such as unexplained loss of more than 10% of body weight and pulmonary tuberculosis, chronic diarrhoea (with no known cause) and severe systemic bacterial infections. Additionally, mucocutanous conditions may also be present (WHO, 2005).
- Stage 4 patients are those with severe symptoms that are classified with acquired immunodeficiency virus (AIDS) if they have a CD4 count of less than 200 cells/mm^3 and/or AIDS-defining illnesses such as HIV wasting syndrome, central nervous system toxoplasmosis, extrapulmonary cryptococcosis, extrapulmonary tuberculosis and HIV-associated cardiomyopathy (WHO, 2005; NIH, 2021).

PLWH are treated using anti-retroviral therapy (ART). ART prevents the virus from making copies of itself and consequently, immune function is retained (or

reconstituted if advanced). Additionally, ART lowers the amount of HIV in the individual's body (viral load) to undetectable levels and therefore, they cannot transmit the virus (Attia et al, 2009).

More than 70% of the global HIV+ population reside in SSA (UNAIDS: The Gap Report 2014). Furthermore, the second greatest cause of mortality in SSA is HIV/AIDS (Roser and Ritchie, 2021). While there are many reasons for the high prevalence of HIV in Africa, it is suggested that poor living conditions, lack of education and substandard health care all increase the spread of HIV (Van Niekerk and Kopelman 2005). Significantly fewer studies have been done in PLWH in SSA compared to high-income countries (HIC). We cannot necessarily extrapolate data from HIC to SSA since the HIV+ populations (and general populations) differ greatly in terms of socioeconomic backgrounds, lifestyles and ethnicity (Vos et al, 2019). For example, the majority of PLWH in HIC are white men and whereas in SSA, the majority of PLWH are black women (UNAIDS, 2017). South Africa has the highest number of people living with HIV/AIDS in the world (Mayosi et al, 2012) and as of 2020, has approximately 7.8 million people living with HIV (13% of the population) (Statistics South Africa, 2021). As mentioned earlier, the majority of these people are female (60%) and of African ancestry (97%) (Statistics South Africa, 2016).

1.2.1.3 Aging and CMDs

In PLWH, the increased availability of ART has resulted in longer life expectancies (WHO, 2015; Deeks et al, 2013). When ART is started soon after diagnosis, there is a high likelihood that the individual will live past the age of 50 years (Negin et al, 2012). However, their longer life expectancy increases the likelihood of developing NCDs, such as CVD (Vos et al, 2017).

It is well established that the risk of having a CVD increases with older age (North and Sinclair, 2012). Lloyd-Jones et al (2009) found that the prevalence of CVD is approximately 40% in people between the ages of 40-59 years whereas it is between 70-75% in people between the ages of 60-79 years. Additionally, CVD is the leading cause of mortality among people older than 65 years with 40% of deaths being due to CVD (North and Sinclair, 2012).

Numerous studies highlight how aging impacts the heart and blood vessels. As large arteries lose elasticity with age, the left ventricle works harder, increasing afterload

(Vaitkevicius et al, 1993; Cheitlin, 2003). This speeds up the pulse wave in arteries, raising SBP and lowering DBP (Cheitlin, 2003). Additionally, age-related myocyte loss and increased afterload lead to left ventricular hypertrophy (Yin et al, 1982), further reducing DBP and causing heart ischemia and fibrosis (Cheitlin, 2003). Finally, aging also results in the loss of sinoatrial node cells and reduced responsiveness to certain stimuli (Cheitlin and Zipes, 2001). These changes collectively raise the risk of CVD in the elderly.

1.2.1.4 CMD and HIV

A group that is particularly susceptible to CVD is the 35 million PLWH worldwide (UNAIDS: The Gap Report, 2014). Indeed, PLWH are twice as likely to develop CVD compared to the general population, such that CVD is a main cause of mortality among PLWH internationally (Polanka et al, 2021; Rodger et al, 2013; Trickey et al, 2016; Palella et al, 2006).

Similarly, CVD risk factors are common among PLWH. Several studies show that hypertension is common among PLWH with up to 57% of PLWH being hypertensive (Armah et al, 2012; Bergersen et al, 2003). Additionally, the prevalence of MetS in SSA has been shown to be almost 80% greater in PLWH than the general population (Todowede et al, 2018). Studies also suggest that PLWH have greater arterial stiffness than the general population (van Vonderen et al, 2009; Seaberg et al, 2010), which suggests greater CVD risk.

The relationship between HIV and CMD (such as CVD) is not well understood and is believed to be multifactorial. Some PLWH may be more genetically predisposed to immune system and metabolic dysregulation than other PLWH (Zanni et al, 2014). Additionally, HIV infection is associated with immune activation and inflammation that has the ability to cause organ damage, which can increase CMR (Vos et al, 2020; Roche et al, 2021, Wolf and Ley 2019; Feinstein et al, 2019). Figure 4 summarises these mechanisms further.

Conversely, certain ARTs have been shown to affect cardiovascular risk. Studies show that EFV promotes increases in LDL cholesterol, hyperlipidaemia and the adhesion of leukocytes to endothelial cells, which all potentiate cardiovascular risk (Bavinger et al, 2013; Feeney and Mallon, 2011). Additionally, abacavir (ABC) has

been associated with an increased risk of myocardial infarction and integrase strand inhibitors, such as dolutegravir, have been associated with weight gain in PLWH (Sabin et al, 2016; Venter et al, 2019).

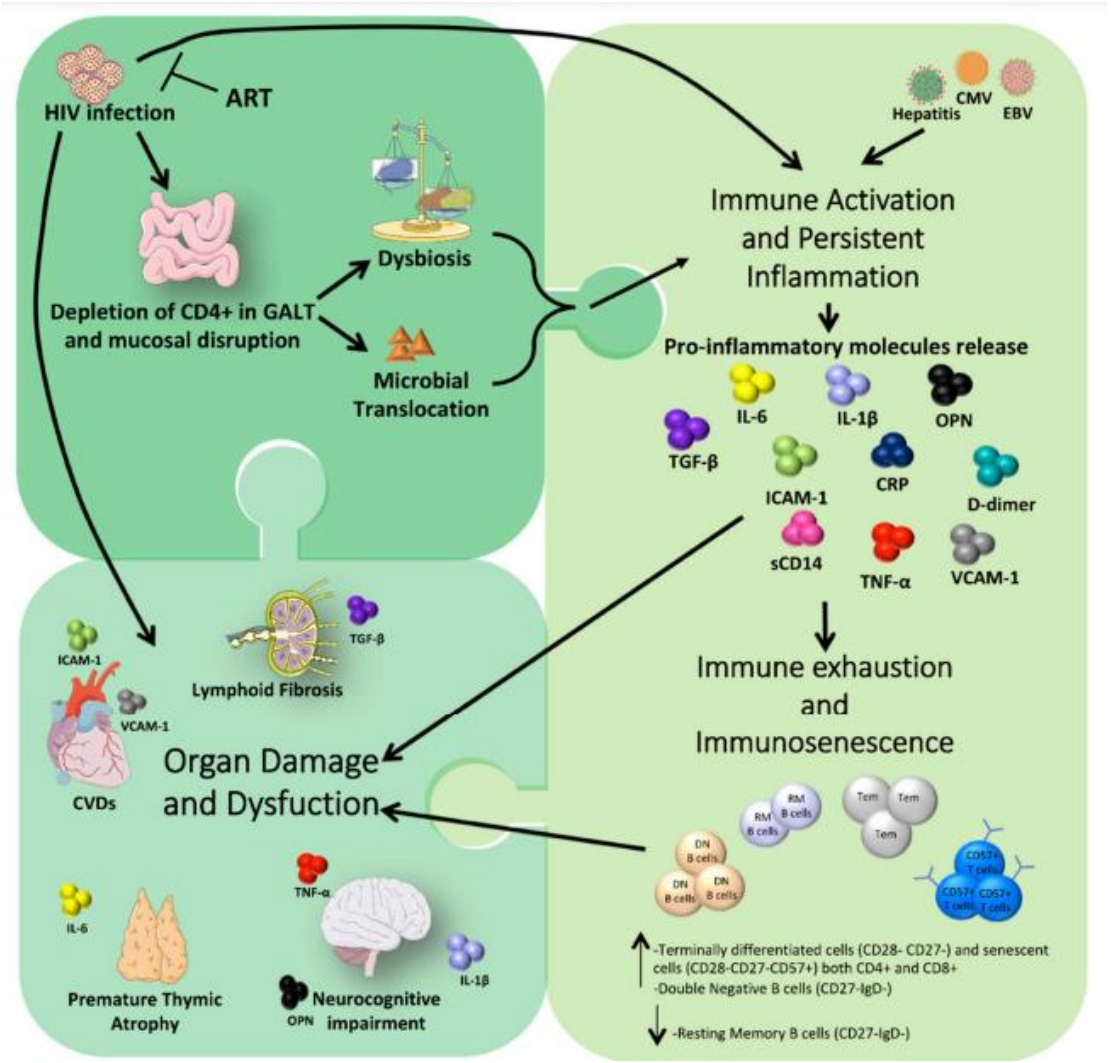


Figure 4. Possible mechanisms of the relationship between HIV infection and an increased cardiometabolic risk. Images were adapted from Servier Medical Art images (http://smart.servier.com/); HIV infection causes both mucosal disruption and depletion of CD4+ T cells in gut association lymphoid tissue (GALT), altering the microbial composition (dysbiosis) and allowing microbial product to enter the circulatory system. Even with the introduction of anti-retroviral therapy (ART), these two mechanisms lead to chronic immune activation and persistence inflammation that could be enhanced by opportunistic co-infections. In turn, chronic activation and persistent inflammation result in (i) immune exhaustion and pre-mature immune senescence, and (ii) a direct damage to organs, through the release of pro-inflammatory cytokines; CVDs = cardiovascular diseases, CMV = cytomegalovirus, EBV = Epstein-Barr virus, TGF-ß = transforming growth factor-ß, IL-6 = interleukin-6, IL-1ß = interleukin-1ß, OPN = osteopontin, ICAM-1 = intercellular adhesion molecule-1, CRP = C-reactive protein, sCD14 = soluble cluster of differentiation 14, TNF-α = tumour necrosis factor –α, VCAM-1 = vascular cell adhesion molecule-1.

However, several studies suggest that the increased CVD risk in PLWH is independent of HIV per se, ARTs and common CVD risk factors (Freiberg et al, 2013; Paisable et al, 2015; Womack et al, 2014). Even PLWH who have ideal CVD risk profiles still have a high risk of CVD (Paisible et al, 2015). Therefore, the effect of non-traditional risk factors on cardiovascular risk in PLWH needs to be investigated.

In people of European ancestry, it is suggested that HIV increases the risk of developing CMDs (de Wit et al, 2008; Brown et al, 2005; Tsiodras et al, 2000). However, the risk of CMD differs between people of European and African ancestry, with people of African ancestry generally having a high risk of CMDs (Triant et al, 2007; Schuster et al, 2007; Goedecke et al, 2010; Schutte et al, 2010). Additionally, it has also been found that a different strain of HIV is predominant in Africa compared to North America and Europe which may in turn impact differently CVD risk (Peeters 2001; Gaschen et al, 2002).

Undoubtedly, there are significantly fewer studies conducted in SSA (especially longitudinal studies) than in high-income countries that investigate the relationship between HIV and CMD. The few studies that have investigated this relationship had relatively small sample sizes, were retrospective studies, focused primarily on CVD risk factors and not the disease itself and/ or did not investigate the independent effect of HIV-related factors on CVD (Vos et al, 2019; Dillon et al, 2013; Schoffelen et al, 2015; Clark et al, 2015). The results of the studies conducted in SSA have found that PLWH do not have an increased CMR (Vos et al, 2019; Schoffelen et al, 2015; Clark et al, 2015) or may even have a lower CMR (Dillon et al, 2013) than the general population when using traditional risk factors. However, as indicated before, PLWH have higher CVD mortality than the general population. This discrepancy between lower traditaionl CMD risk factors in PLWH yet higher CVD mortality may thus indicate that non-traditional risk factors (such as higher inflammation) may play an important role in the pathophysiology of CVD in PLWH.

1.2.2 HIV and sleep

1.2.2.1 Importance of sleep and healthy sleeping habits

Sleep is vital to our survival and maintaining homeostasis in our body (Mukherjee et al, 2015). The amount of sleep each person needs depends on several factors such

as age, sex, genetics and environment (Mukherjee et al, 2015). However, it is believed that the majority of people require 7-8 hours of sleep to function optimally (Mukherjee et al, 2015). Yet, many people often overestimate the amount of time they sleep each night and consequently, they are unknowingly sleep deprived (Bonnet and Arand 1995). Additionally, with aging come changes in sleeping patterns (Li et al, 2018). For the most part, it is common for elderly individuals to have frequent nocturnal awakenings, more frequent daytime naps and decreased slow wave sleep (Li et al, 2018).

Sleeping for too few hours (≤ 6 hours) or too many hours per night (> 9-10 hours) both are associated with higher CVD risk, obesity, hypertension and T2DM (Gangwisch et al, 2007; Cappuccio et al, 2010; Liu et al, 2013). During sleep, metabolic functions slow down, with a lower respiratory rate, slower heart rate, lower blood pressure than during wake (this is referred to blood pressure dipping, which should be 10% lower than the daytime wake values) (Sherwood et al, 2002). Poor sleep quality (multiple awakenings, lower deep sleep) result in excitatory inputs and an absence of dipping. In addition, poor sleep quality has been associated with lower leptin (satiety hormone) and higher ghrelin (hunger hormone) production which could induce weight gain (Loredo et al, 2004; Harvard Health Publishing, 2015; Sleep Foundation, 2024).

In PLWH, sleep may be disrupted due to changes in circadian rhythms regulation or due to undetected sleep disorders such as obstructive sleep apnoea

1.2.2.2 Sleep architecture and sleep disorders and CMD

Sleep cycles consist of four stages: Stage 1, 2, and 3 (N1, N2, and N3) are non-rapid eye movement (NREM) sleep stages, while the last stage is rapid eye movement (REM) sleep (Carskadon and Dement, 2005). Each cycle lasts about 70-120 minutes (Carskadon and Dement, 2005). During N1, the person begins to fall asleep. N2 involves a decrease in temperature, muscle relaxation, and slowed breathing and heart rate (Patel et al, 2022). N3, or deep sleep, further decreases bodily functions and supports restorative processes, including immune system strengthening (Patel et al, 2022). REM sleep is characterized by increased brain activity and is associated with creativity and learning (Patel et al, 2022).

All four stages are essential for optimal sleep. Sleep disorders like obstructive sleep apnea (OSA) disrupt sleep architecture, making it challenging to reach deep sleep (Gugger et al, 1989). Studying how sleep disorders affect these stages can help assess their impact on health and well-being.

1.2.2.3 Sleep measurements

Sleep can be assessed using subjective or objective measures. The most commonly used subjective sleep assessments are the Pittsburgh Sleep Quality Index (PSQI), the Epworth Sleepiness Scale (ESS) and the Berlin Questionnaire (BQ) (Buysse et al, 1989; Johns 1991; Netzer et al, 1999). The PSQI measures self-reported sleep quality by asking ten questions that assess usual sleeping habits during the preceding month (Buysse et al, 1989). Next, the ESS questionnaire assesses the self-reported likelihood of falling asleep during eight day-to-day situations. Lastly, the BQ assesses the risk of sleep apnoea by posing 10 questions relating to snoring and breathing during sleep, daytime sleepiness, blood pressure and BMI (Netzer et al, 1999).

The most commonly used objective measures of sleep assessment are polysomnography and actigraphy. With polysomnography and actigraphy, sensors are used to measure sleep parameters objectively (Sadeh et al, 1995; Douglas et al, 1992). Polysomnography is usually done overnight in a sleep centre/clinic whereas with actigraphy, a device is worn around the wrist for days/weeks to assess sleep at home over a longer period (Sadeh et al, 1995; Douglas et al, 1992).

After reviewing the importance of sleep in CMD, the basic composition of sleep architecture and the measuremenet of sleep, the next sections will focus on how changes in circadian rhythms, one of the two processes that regulate sleep, may be associated with both poor sleep and increased risk of CMD, independently. I will also show how OSA, a common sleep disorder is associated with higher CMD.- I will then overview what is known on the causes of poor quality sleep in PLWH.

1.2.2.4 Circadian rhythm

The suprachiasmatic nucleus (found in the brain) receives information about the levels of light entering our eyes (Klein et al, 1991). The suprachiasmatic nucleus

generates 24-hour cycles, known as our circadian rhythm, which controls different processes (Klein et al, 1991). One of the effects of our circadian rhythm at work is we feel sleepy when light levels are low i.e. at night (Klein et al, 1991). The main 'zeitgeber' or resetter of the timing of circadian rhyhms is light with light exposure in the morning leading to phase advances and light exposure at night leading to phase delays (Khalsa et al, 2003). Thus, external factors such as working night shifts or using light-emitting electronic devices at night can disrupt our circadian rhythm (Bedrosian and Nelson 2017; Roche et al, 2021).

Disruptions in our circadian rhythm, such as by sleeping at the wrong time, have been shown to increase the risk of cardiometabolic risk factors (Akerstedt 2003; Van Dongen and Dinges 2005; Ijaz et al, 2013). Therefore, by investigating factors that alter our circadian rhythm, we may improve sleep and reduce the prevalence of CMDs through both a sleep and circadian effect.

1.2.2.5 Obstructive sleep apnoea (OSA) and the effect on the cardiovascular system (CVS)

With OSA, the pharyngeal muscles that keep the upper airway open lose their muscle tone during sleep and consequently, breathing is disrupted because the pharynx collapses (Bradley and Floras, 2009). The diagnosis of OSA is done using objective sleep monitoring to measure the apnoea-hypopnoea index (AHI) (Kapur et al, 2017). The AHI is calculated by dividing the total number of apnoeas (complete cessation of airflow) and hypopnoeas (partial obstruction to airflow) per night by the total number of hours slept per night (Kapur et al, 217). A person is diagnosed with OSA if their AHI is five or more (Kapur et al, 2017).

It is well established that OSA is associated with CVD. This occurs through three main mechanisms namely: 1) arousal 2) hypoxia and hypercapnia and 3) the decrease in intrathoracic pressure. Firstly, arousals increase the risk of CVD by increasing sympathetic nervous system (SNS) activity and catecholamine levels, which together increase the heart rate and blood pressure (Horner et al, 1995). Secondly, hypoxia and hypercapnia promote CVD by causing arousals, independently increasing SNS activity and catecholamine levels, decreasing myocardial oxygen delivery and promoting oxidative stress, inflammation and endothelial dysfunction (Kusuoka et al, 1986; Cargill et al, 1995; Somers et al, 1995;

Dyugovskaya et al, 2002; Ryan et al, 2005). Finally, the decrease in intrathoracic pressure contributes to the development of CVD by increasing left ventricular wall tension and cardiac oxygen demand (Tkacova et al, 1988; Stoohs 1992).

Thus both changes in circadian timing and a common sleep disorder, sleep apnoea, may induce poor sleep quality and increase CMD risk. We will now examine sleep quality in PLWH and the hypothesized mechanisms thereof.

1.2.2.6 Poor sleep quality in people living with HIV (PLWH)

It is well established that PLWH have significantly lower sleep quality compared to the general population (Rubinstein and Selwyn 1998; Nokes and Kendrew 2001). As early as the 1980s and 1990s, it was observed that poor sleep quality is common among PLWH (Norman et al, 1988; White et al, 1995).

Specifically, PLWH have greater sleep latency, awaken more frequently, have insufficient total sleep and/ or wake up earlier (Crum-Cianflone et al, 2012; Wheatley and Smith 1994; Wiegand et al, 1991). However, Crum-Cianflone et al (2012) found no significant difference in sleep quality between the HIV+ and the control group (Crum-Cianflone et al, 2012). Since Crum-Cianflone et al (2012) used participants who were treated early, it is suggested that early treatment may attenuate the deterioration of sleep quality. While poor sleep quality is reported in all stages of HIV, it has been shown that sleep quality deteriorates with advancing of the disease (O'Brien 2022).

It has been suggested that HIV may in itself change circadian rhythms. Clark (2005) showed that injecting Tat, an HIV protein, led to phase delays of the activity of mice; Wang (2014) found and association between higher Tat and higher melatonin at 9 am in PLWH, suggesting that HIV< through tat may result also in circadian phase delays in humans. Finally Redman et al (2023) found that PLWH had a 1 hour delay in their dim light melatonin onset.

The majority of studies investigating sleep in PLWH have been conducted in high-income countries where access to healthcare may be easier than in low and middle-income countries, such as South Africa, especially rural South Africa. Additionally, the majority of participants in those studies were Caucasian and male (Allavena et al, 2016; Wibbeler et al, 2012; Salahuddin et al, 2009). There is also a "sleep disparity"

in that poor sleep quality has been found to affect women more than men (Davidson et al, 2010; Gutierrez et al, 2019) and African Americans and Latinos more than other race groups in the general population of America (Patel et al, 2010). This is relevant since, as previously mentioned, the majority of the HIV+ population in South Africa are black women. Another factor to consider is that many PLWH in South Africa only start ART treatment late after seroconversion. This is partly due to lower access to healthcare, the stigma of having HIV and up to 2013, due to previous ART treatment guidelines, whereby ART were started only when CD4 counts were below a certain threshold (Dos Santos et al, 2014; Redman et al, 2018). Due to this delay in treatment, even once ART treatment has restored CD4 counts, there may still be spontaneous activation of the immune system (Okulicz et al, 2015).

To the best of our knowledge, Redman et al (2018) (urban dwellers), Gómez-Olivé (2018) (rural dwellers) and Redman et al (2023) (older HIV+ participants) are the only studies that examined sleep quality in PLWH in South Africa. All studies found that PLWH have poor sleep quality (Redman et al, 2018; Gómez-Olivé 2018; Redman et al, 2023). Additionally, untreated PLWH had poorer sleep quality than treated PLWH and the general population (Gómez-Olivé 2018). Furthermore, poor sleep quality in treated PLWH was associated with daytime sleepiness and pain (Redman et al, 2018). Indeed, 55% of treated PLWH were currently experiencing moderate levels of pain (Redman et al, 2018). In summary, there is limited information on sleep quality in PLWH and how it compares to HIV negative people in the South African population

Interestingly, higher CD4 counts were associated with poor sleep quality in treated PLWH when pain and depression were adjusted for. While this is inconsistent with many studies, two older studies have suggested a similar relationship (Darko et al, 1992; Henderson et al, 2005). Furthermore, in the Redman et al (2018) study, there was a higher change in CD4 counts from baseline to current. The low CD4 counts at baseline were due to the participants waiting for the CD4 count to be greater than or equal to 350 cells/$mm^{3\ to}$ start treatment (WHO 2010) and consequently, patients may have a higher number of spontaneously activated effector CD4 T lymphocytes. This inverse relationship may suggest an underlying mechanism involving immune system activation that may be specific to South African HIV population.

1.2.2.7 Mechanisms of poor sleep quality in PLWH

It is suggested that the relationship between HIV and poor sleep quality is multifactorial with the exact physiological mechanisms remaining unclear. These factors include, i) the effect of the virus on the CNS, in particular the circadian pacemaker (Norman et al, 1990; Wang et al, 2014; Redman et al, 2023), ii) increased immune activation (Moeller et al, 1998; Cruess et al, 2003), iii) certain ARTs (such as Efavirenz and Dolutegravir) (Gaida et al, 2016; Elliot et al, 2019) and iv) psychosocial factors such as psychiatric disorders, stress and substance abuse (Gamaldo et al, 2013; Low et al, 2011) and v) OSA.

i) Effect of the virus on the CNS and th circadian pacemaker

Studies prior to highly active anti-retroviral therapy (HAART) suggested that poor sleep quality is an early indicator that the HIV has infected the brain (White et al, 1995). It has been shown that the virus is able to cross the blood brain barrier and enter the CNS where it infects macrophages, microglia and astrocytes (Kaul et al, 2001; Kaul and Lipton 2006). However, there is still uncertainty regarding the exact mechanism of how viral proteins affect the circadian rhythm (Wang et al, 2014). More recent studies show that due to the limited ability of ARTs to reach the CNS, the viral load accumulates in the CNS over prolonged periods and consequently, infects more cells, which may further attenuate sleep quality further (Low et al, 2014; Brew et al, 2009; Bell 2004; Kaul et al, 2001). This may be why poor sleep quality is associated with longer disease duration.

ii) Immune activation

Immune activation may be the greatest contributor to poor sleep quality in PLWH. In both HIV + rats and humans, immune activation has been associated with poor sleep quality (Opp et al, 1996; Darko et al, 1992). For example, increased immune activation in PLWH promotes elevated levels of interleukin-6 (IL-6), IL-1-β and tumour-necrosis factor alpha (TNF-α) (Phillips 1999). Elevated levels of these cytokines have been associated with shorter NREM and REM sleep (Besedovsky et al, 2019).

An indirect approach to studying the impact of immune activation on sleep in PLWH has also involved investigating the association between CD4 counts and sleep quality in PLWH. Studies show disagreement in the association between CD4 counts

and poor sleep quality. As expected, low CD4 counts have been associated with poor sleep quality whereas higher CD4 counts have been associated with higher sleep quality in PLWH (Seay et al, 2013; Lee et al, 1999). Conversely, several studies suggest that sleep quality is independent of CD4 (Vosvick et al, 2004; Robbins et al, 2004; Lee et al, 2001) or that higher CD4 counts are associated with worse sleep quality (Redman et al, 2018). This is unexpected since lower CD4 counts generally indicate greater disease progression and consequently, lower sleep quality.

A hypothesis has emerged that in populations who are treated early in the disease, CD4 counts reconstitute fully and recover normal functionality. Conversely, Okulicz et al (2015) have shown that PLWH treated more than 12 months after serovconversion (late in the disease) were less likely to reconstitute higher CD4 and those CD4 had higher markers of spontaneous activation (HLA -DR, CD38) than those who had been treated early. It is possible thus that in populations who are /were treated late in the disease (such as those in the Redman 2018 study) had higher levels of immune activation, which then would have led to more disrupted sleep. Conversely, in populations treated earlier in the disease (such as in the study by Seay et al, 2013), those reconstituted CD4 did not lead to higher immune activation.

iii) Antiretroviral therapy agents (efavirenz, integrase strand inhibitors)

It is suggested that some ARTs are able to penetrate the CNS and attenuate the sleep-reducing effects of HIV (Crum-Cianflone et al, 2012). However, some ARTs, such as efavirenz, raltegravir and dolutegravir may attenuate sleep quality, especially when used in higher doses (Núñez et al, 2001; Eiden et al, 2011; Elliot et al, 2019). The ART efavirenz has been shown to disrupt sleep and increase the risk of insomnia (especially when treatment has begun recently) (Gallego et al, 2004; Núñez et al, 2001). However, South Africa mainly used uses tenofovir disoproxil fumarate-lamivudine-dolutegravir (TLD) as a first-line treatment (Republic of South Africa National Department of Health, 2023). Nevertheless, efavirenz is still prescribed to some PLWH in South Africa (Republic of South Africa Department of Health 2015). Recording of brain activity confirmed that patients taking efavirenz have a greater sleep latency and have reduced REM sleep whereas at elevated plasma concentrations, insomnia may occur (Gallego et al, 2004; Koppel and Bharel 2005). However, studies show that the side effects of efavirenz are temporary and only last for approximately a month after starting treatment (Lochet et al, 2003; Kenedi and

Goforth 2011). Gómez-Olivé et al (2018) suggested that the effect of efavirenz on sleep quality may be minimal or non-existent in older people.

iv) Psychosocial aspects in HIV which may lead to poor sleep quality

Additionally, social support may improve or reduce sleep quality in PLWH. For example, social support in the form of assistance by friends was associated with an increase in sleep disturbance (Vosvick et al, 2004). However, it was speculated that this may be because participants who needed their friends' support had more debilitating health that resulted in sleep disturbance (Vosvick et al, 2004). Instead, participants who had social support in the form of friends who acknowledged their stress, attenuated sleep disturbances (Vosvick et al, 2004).

HIV-related symptoms and daytime sleepiness are all associated with sleep quality in PLWH. Markedly, greater pain, coughing, cramps and fever promotes poor sleep quality in PLWH (Redman et al 2018; Robbins et al, 2004). It has been suggested that treating HIV-related symptoms may improve sleep quality (Phillips 1999). Similarly, daytime sleepiness is present from the early stages of the disease and has been associated with poor sleep quality in PLWH (Aldrich et al, 1988; Darko et al, 1995; Nokes and Kendrew 2001). Approximately 30% of PLWH experienced daytime sleepiness, which is a major issue since it results in limitations in basic daily activities (Cleary et al, 1993; Crum-Cianflone et al, 2012). However, Crum-Cianflone et al (2012) found no significant difference in daytime sleepiness between the HIV+ participants and the controls. As mentioned earlier, this study used participants who were treated early and therefore, early treatment may attenuate daytime sleepiness.

As expected, mental disturbances and substance abuse are both associated with sleep quality in PLWH. A study using 115 PLWH found that 55% had anxiety and 32% of participants had depression, both of which have been associated with poor sleep quality in PLWH (Rubinstein and Selwyn 1998; Dabaghzadeh et al, 2013; Cruess et al, 2003). Specifically, anxiety is associated with less time spent in SWS and more shifts into non-REM sleep (Fuller et al, 1997). While the manifestations of depression are similar in PLWH and the general population, poor sleep quality is more commonly a side effect of depression in PLWH (Penzak et al, 2000).

It is suggested that poor sleep quality is associated with substance abuse (Low et al, 2014). Rubinstein and Selwyn (1998) found that approximately 25% of participants used intravenous drugs within the last 6 months. Amongst these drug users, 86%

reported poor sleep quality whereas among non-drug users, the prevalence was 69% (Rubinstein and Selwyn 1998). However, there was no significant difference, which may be due to the small sample size (Rubinstein and Selwyn 1998).

v) OSA

Finally, OSA reduces sleep quality but is underdiagnosed in PLWH (Kunisaki et al, 2015; Owens et al, 2018). Among 176 PLWH, Gutierrez et al, (2019) found that more than half had a moderate to high risk of OSA. This risk was associated with adverse cardiometabolic outcomes such as a higher BMI, hypertension and diabetes (Gutierrez et al, 2019).

1.2.3 Sleep and CMDs

1.2.3.1 Sleep and CMDs in the general population

In the general population, several studies have demonstrated a relationship between poor sleep quality and CMDs. Indeed, a large randomised controlled trial (n =123) found a causal relationship between poor sleep quality and CVD (Irwin et al, 2014). Additionally, meta-analytic data found that difficulty in falling asleep, maintaining sleep and non-restorative sleep were all associated with an increase in CVD risk (He et al, 2017).

Additionally, the timing of sleep and amount of hours slept has an effect on cardiometabolic health. Prospective cohort studies showed that sleeping for less than 6 hours and sleeping for more than 9 hours both increase the risk for CVD (Chien et al, 2010; Magee et al, 2013; Li et al, 2014; Yeo et al, 2013). Lucassen et al (2012) also showed that sleeping at a suboptimal time could increase the risk of obesity, CVD and T2DM (Lucassen et al, 2012).

1.2.3.2 Sleep and CMDs: mechanisms

Sleep deprivation causes imbalances in the hormones that cause hunger (ghrelin) and satiety (leptin) (Spiegel et al, 2004; Chaput et al 2007). Consequently, they may feel hungry quicker, which can lead to the consumption of calorie-rich foods (Spiegel

et al, 2004). Additionally, since these people are awake for longer hours, they are likely to consume more food. Furthermore, sleep deprived individuals usually experience daytime sleepiness and as a result are reluctant to participant in physical activity (Spiegel et al, 2009). The consumption of more food together with sedentary behaviour can cause weight gain.

It has also been suggested that sleep deprivation impairs the handling of glucose (Spiegel et al 2009). In the long term, this can lead to the development of T2DM. In fact, it has been shown that consistently sleeping fewer hours increases independently the risk of T2DM with the same effect as someone who is overweight or lives a sedentary lifestyle (Anothaisintawee et al, 2016).

Sleep deprivation also increases the risk of developing hypertension (Gangwisch et al, 2006; Knutson et al, 2009). During sleep (a parsympathetic dominant state with low heart rate, low respiratory rate and low metabolism), blood pressure decreases. Poor sleep quality or low sleep duration have both been associated with a lack of blood pressure dipping during sleep (Sayk et al, 2010). In turn, lack of blood pressure dipping has been associated with a higher risk of hypertension during the wake period (Knutson et al, 2009).

Furthermore, it has been suggested that a short sleep duration independently increases all-cause mortality by approximately 12% (Cappuccio et al, 2010). A British study found that the increased risk of mortality in short sleepers is mainly attributed to cardiovascular-related deaths rather than other causes (Ferrie et al, 2007). Studies also shown that sleeping more than 9 hours promotes adverse health outcomes (Cappuccio et al, 2010; Cappuccio et al, 2007). However, further studies are needed to assess whether longer sleep is the cause or outcome of poor health.

Poor sleep quality

There is controversy whether sleep quality is associated with cardiovascular risk. Studies have shown an inverse relationship between sleep quality (as measured by PSQI) and coronary artery calcium (Kim et al, 2015), carotid-intima media thickness (actigraphy) (Nakazaki et al, 2012) and endothelial function (Cooper et al, 2014) and arterial stiffness (Osonoi et al, 2015). However, other studies show no relationship between sleep quality and coronary artery calcium (as measured by actigraphy) (King et al, 2008), carotid-intima media thickness (self-reported) (Abe et al, 2011) or endothelial function (self-reported) (Strand et al, 2012). The relationship between

poor sleep quality and CMR has not been studied as extensively as the relationship between short sleep durations and CMR. Some studies show that poor sleep quality is associated with an increased risk of mortality (all-causes) (Dew et al, 2003) while others show no relationship (Suzuki et al, 2009).

Among people with CVDs, poor sleep quality is prevalent (as assessed by PSQI) (Matsuda et al, 2017). Although poor sleep quality per se has not been identified as one of the main contributors to CVD, there is increasing studies which suggest that poor sleep quality potentiates CVD (Redline and Foody 2011; Cappuccio et al, 2011). However, there is a lot of heterogeneity in diagnosis methods and study methodology.

1.2.3.3 Sleep and CMDs in PLWH gap in knowledge

A large prospective longitudinal study in the USA using over 3000 PLWH (and equal number of controls) found that after a 10.8-year follow-up period, HIV+ participants with insomnia had a higher risk of cardiovascular events than those without insomnia or HIV negative controls with and without insomnia (Polanka et al, 2019). However, only PLWH who have severe insomnia have a greater cardiovascular risk. Interestingly, once depressive symptoms were adjusted for, the aforementioned 66% greater risk of having a CVD event in PLWH with poor sleep quality became non-significant (Polanka et al, 2019).

Similarly, a large, cross-sectional study among 1542 HIV+ veterans found that there was no association between insomnia and the biological mechanisms that promote the relationship between HIV and CVD (immune system activation, coagulation and inflammation) (Polanka et al, 2021). However, the study used a single indicator that assessed only a few insomnia symptoms while not assessing other aspects of sleep health such as poor sleep quality, daytime sleepiness or risk of sleep apnoea.

Only a single South African study has investigated the combined effect of sleep quality and HIV status on cardiometabolic risk (Roche et al, 2021). Roche et al (2021) suggested that shift workers who worked day and night shifts and thus, we likely sleeping at a non-optimal circadian time chronologically had higher inflammation and thus CVD risk when they were HIV+ vs. HIV-. This suggests that circadian misalignment (and not only poor sleep quality) is a risk factor for CVD. To

the best of our knowledge, no study has been conducted among PLWH in a rural South African area that investigated the effect of poor sleep quality and HIV status on cardiometabolic risk.

1.2.4 Association of depression with HIV, CMD and sleep

1.2.4.1 Depression and CMDs

Studies have shown that depression is associated with an increased risk of developing hypertension in the future (even when adjusting for other risk factors), which suggests a direct connection between depression and hypertension (Jonas and Lando 2000, Davidson et al, 2000). The connection between depression and cardiovascular disease (CVD) is not well understood. It is suggested that depressed individuals perhaps have a sense of indifference regarding their health and this could manifest as behavioural changes such as not following medical advice and not taking their chronic medication (Joynt et al, 2013). Consequently, this behaviour could increase CMR by promoting risk factors like hypertension, obesity, diabetes, and smoking.

Depressed individuals also tend to have overactivity in their autonomic nervous system and increased activity in the hypothalamic-pituitary-adrenal axis, which may accelerate the development of CVD (Ehlert et al, 2001; Maas et al, 1994; Troxler et al, 1977; Colao et al, 1999).

1.2.4.2 Literature on depression and HIV

Several studies confirm as association between depression and sleep quality in PLWH (Rubinstein and Selwyn 1998; Junqueira et al, 2008; Oshinaike et al, 2014). Since depression and poor sleep quality has a bidirectional relationship, by treating one of these conditions, we can improve the other condition (Fang et al, 2019).

Depressed patients have been associated with sleep changes such as greater sleep latency, awakenings that are more frequent and waking up earlier in the morning (Steiger & Pawlowski 2019). While the precise interactions may be unclear, it is suggested that sleep deficiency increases SNS activity and ß-adrenergic signalling

that increase nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) (Fang et al, 2019). Consequently, inflammation levels increase, which can promote depression (Fang et al, 2019). Conversely, depression can increase inflammation, which can cause sleep deficiency (Fang et al, 2019).

In PLWH, the prevalence of depression is much higher than in the general population (Rubin et al, 2019). Despite being aware of the consequences of depression, few PLWH receive treatment since healthcare workers often overlook depression in PLWH (Abas et al, 2014; Choi 2013). Surprisingly, it is estimated that over a quarter of PLWH in the United States who experienced depression, were not formally diagnosed (Beer et al, 2024). Perhaps depression could be difficult to diagnose in PLWH because HIV per se may promote physiological symptoms that mirror those seen in depressed individuals, for example, lethargy, poor sleep quality, decreased appetite and psychomotor impairment (Simoni et al, 2011; Nanni et al, 2015; Kalichman et al, 2000). When depression is diagnosed and managed in PLWH, they adhere better to ARTs, have stronger immune systems (higher CD4 counts) and more patients have undetectable viral loads (Watkins and Treisman 2012; Psaros et al, 2009; Schuster et al, 2012; Nakimuli-Mpungu et al, 2012; Arseniou et al, 2014; Mills et al, 2017).

SSA has a high prevalence of PLWH who are depressed. Meta-analytic data from PLWH across 16 countries in SSA found that 17% had depression, 26% had symptoms of depression and 33% had stress (Lofgren et al, 2019). In low and middle-income countries, the rate of diagnosis of depression is even lower than in high-income countries. This finding is confirmed by a Nigerian study that found none of the PLWH who were depressed, were diagnosed with depression (Olisah et al, 2011). The reason for the poor diagnosis rate in low and middle-income countries may be due to these countries not having the necessary resources to diagnose depression and where resources are available, there may be discrepancies in the symptoms of depression in PLWH (Abas et al, 2014; Rodkjaer et al, 2010; Marando et al, 2016). Since countries in SSA fall under the low, lower middle or upper middle - income category, there has to be a significant amount of data suggesting that depression is a major burden in PLWH in order for funds to be allocated to mental health care (Abas et al, 2014).

Depression greatly affects population health and may even result in mortality. Indeed, Lofgren et al (2019) found that approximately 1.57 million DALYs is lost in people living in SSA who are both HIV+ and depressed.

Few studies have investigated depression in PLWH in South Africa and none have investigated how depression may be a mediating factor in the association between sleep and CMD. It is suggested that approximately 29.1% of PLWH in South Africa are depressed (Lofgren et al, 2019). Additionally, Redman et al, (2018) found that 41% of PLWH had moderate to severe depression. In South Africa, it has been shown that poor sleep quality is associated with depression in PLWH (Redman et al, 2018).

1.2.4.3 Depression and HIV mechanisms

It is suggested that the virus itself and/ or stress could increase the risk of depression in PLWH (Medeiros et al, 2020). Firstly, the virus itself may have adverse effects in the central nervous system and the immune system (Del Guerra et al, 2013). Consequently, several neurobiological changes may occur which can contribute to the development of mental illnesses such as depression (Medeiros et al, 2020). Next, living with a life-threatening condition like HIV can be induce overwhelming stress and fear. Additionally, PLWH might also face socioeconomic challenges such as unemployment and poverty, which exacerbates their stress Simoni et al, 2011; Leserman 2008; Pellowski et al, 2013; Williams et al, 2017). This highly stressful lifestyle can lead to depression (Medeiros et al, 2020).

Other additional factors that have been associated with depression in PLWH is stigma and/ or external factors (Medeiros et al, 2020). PLWH often face stigma from the community or in some cases, the anticipation of stigma is sufficient to induce symptoms of depression (Earnshaw and Chaudoir 2009; Nachega et al, 2012). Finally, external factors could also contribute to the development of depression. This is because PLWH may feel a sense of hopelessness and therefore, may resort to drug and alcohol abuse, which has been associated with symptoms of depression (Hartzler et al, 2017; Berger-Greenstein et al, 2007). Furthermore, the ART regime and other drugs that PLWH might be using could increase the risk of symptoms of depression as a side effect (Poupard et al, 2007; Treisman and Soudry 2016; Udina et al, 2012).

1.2.5 South Africa (SA)

1.2.5.1 Epidemiological transition

South Africa has a quadruple burden of disease. Namely, communicable diseases, NCDs, perinatal and maternal diseases and injury-related disorders are among the main burdens placed on the healthcare system (Mayosi et al 2009). Infectious diseases such as HIV were the highest priority in South Africa in previous years (Chopra et al, 2009). However, as previously mentioned, life expectancies of PLWH have increased and consequently, decreased HIV-related mortality.

Additionally, South Africa is undergoing epidemiological and demographic transitions, similar to many countries in SSA. As part of these transitions, communicable diseases in young individuals are no longer the main contributor of mortality rates, but rather NCDs in older individuals (Omran 1971; Gómez-Olivé et al, 2018). This is confirmed by Stats SA (2018) who found that 54.7% of deaths in South Africa were attributed to NCDs. Additionally, cerebrovascular disease and ischaemic heart disease were among the top five conditions that caused the most years of life lost in South Africa in 2015 (Stats SA 2018; Massyn et al, 2017). Interestingly, diabetes ranked second in the top causes of mortality in South Africa in 2016 (Stats SA 2018; Massyn et al, 2017). Due to the aforementioned statistics, CMD has become a main priority to healthcare professionals in South Africa.

Lifestyle changes are the major contributor to the prevalence of CMD and the associated risk factors. Additionally, modernisation and economic developments have promoted lifestyles that potentiate the risk of CMDs (Kabudula et al, 2007). In fact, the percentage of people living in rural areas in South Africa has decreased from approximately 48% in 1990 to approximately 33% in 2020 (The World Bank 2021). One of the effects of modernisation is urbanisation that is generally followed by more sedentary lifestyles and access to high-calorie foods, which consequently increases the risk of CMDs (Collinson et al, 2014).

The incidence of CVD risk factors and CVD is increasing in rural areas. For example, the prevalence of hypertension and obesity in some rural areas is higher than the national prevalence of 35% for hypertension and 27% for obesity (Gomez-Olive et al, 2018; Roche et al, 2020; Berry et al, 2017; WHO 2021). Additionally, the diabetes

prevalence in some rural areas is similar to the national prevalence of 10% (Gomez-Olive et al, 2018; Roche et al, 2020; WHO 2021). Correspondingly, a study conducted using over 2000 rural dwellers found that 32.1% of men and 18.9% of women had at least a 20% chance of having a cardiovascular event in the next decade (Alberts et al, 2005). Furthermore, Houle et al (2021) found that the incidence of hypertension in a rural South African area to be 8.374 per 100 person-years. These studies suggest that despite being in the early stages of the aforementioned transitions, the effects of modernisation and economic development have trickled down to rural areas.

1.2.5.2 Sleeping habits in people of black ancestry

Compared to high-income countries, significantly fewer studies investigating sleeping pattern have been conducted in Africa. The epidemiological transition may cause changes in sleeping patterns (Pilz et al, 2018) and hence, sleeping patterns in countries of different phases of urbanisation is of interest.

Of the few sleep studies conducted in Africa, most suggest that race and urbanisation affects sleep. Objective and subjective sleep measures show that black, rural participants sleep between 8.2 to 10.5 hours per night, longer than the global average (Pretorius et al, 2015; Sani et al, 2015; Beale et al, 2017; Gómez-Olivé et al, 2018). Additionally, Peltzer et al, (2017) suggested that black South Africans sleep longer than white South Africans once the necessary variables were adjusted for. Similarly, Peltzer et al (2012) found that a greater percentage of rural dwellers slept more than 10 hours per night (self-reported sleep) compared to urban dwellers. This is confirmed by other studies in South Africa and Norway that confirmed rural dwellers report longer sleep than urban dwellers (Ursin et al, 2005; Peltzer 2012). Furthermore, a South African observational study found that in the 4044 rural participants, 30.2% of participants reported that they had significant sleep problems and 17.2% of participants felt that their sleep problems had a significant effect of their daytime activities (Gómez-Olivé et al, 2014). However, further studies are required using objective measures of sleep quality.

Conversely, a study using eight low and middle-income countries in Africa and Asia found that variations in the prevalence of self-reported sleep issues among different countries cannot be solely accounted for by economic status (Stranges et al, 2012).

1.2.5.3 Spread of HIV in rural areas

There are several reasons for the spread of HIV in rural areas. Many children (especially females) do not complete their schooling and therefore, are uneducated regarding the spread of HIV (Hargreaves et al, 2009; Linganiso & Gwegweni 2016). Additionally, many of these young women that left school may engage in relationships with much older men for financial gain (Pettifor et al, 2008). The power dynamics in these types of relationships means that men are often the sole decider on condom use (Hargreaves et al, 2009; Pettifor et al, 2008). Polygamous relationships, which are common in rural areas of SSA, have also been shown to potentiate the spread of the virus (Tanser et al, 2011).

Poor health care is a major contributor to the spread of HIV in rural areas. One of the consequences of poor health care is that there is often mother-to-child-transmission of the virus. Additionally, in rural areas, the stigma associated with HIV might result in PLWH not receiving proper healthcare. For example, men who have sex with men (MSM) that are HIV+ are often stigmatised and mistreated at healthcare facilities (Imrie et al, 2013). Consequently, they are reluctant to seek medical treatment and risk spreading the virus.

Studies show that the temporary movements between rural and urban areas potentiate the spread of HIV. For example, men who are long haul truck drivers or who go to urban areas to look for employment may engage in unplanned, casual sexual relationships (often without protection) (Zuma et al, 2005; Delany-Moretlwe et al, 2014). Consequently, they spread the virus to their sexual partners when they return home (Zuma et al, 2005; Delany-Moretlwe et al, 2014).

Common cultural practices also increase the spread of HIV in rural areas. Furthermore, 92% of rural participants believed that circumcision prevents against contracting HIV (Nyembezi et al, 2014). However, circumcision may lead to the spread of HIV. Additionally, the subordinate position of women in many cultures means that women are not able to insist on condom usage and are often victims of violence, such as rape, where they may contract HIV (Ackermann 2002; Jewkes et al, 2006).

It is also suggested that poverty and diets potentiate the spread of HIV in rural areas. Magadi (2013) suggested that because many people live in poverty, they may believe that they have minimal chance of a better future and therefore, may engage

in risky behaviour such as unprotected sex with several partners. Additionally, people living in poverty often eat what is available and do not have the option to choose healthy food, which can lead to nutritional deficiencies. It has been shown that those with nutritional deficiencies have a higher viral load and therefore, can transmit the virus easier through sex (Lourie et al, 2000).

As a province in South Africa, the Free State is of particular interest as life expectancy has been consistently the lowest amongst the nation in the past 20 years (currently 56 years in the males and 62 years in the females vs 72 years in the males and 71 years in the females in the Western Cape) (StatsSA 2022) while ranking third in the country in terms of HIV prevalence (14.6 %). In the Thabo Mofutsanyana district of the Free State, almost 13% of the population is HIV+ and HIV is the leading cause of death in the district for people between the ages of 5 and 64 years (Corporate governance and traditional affairs, 2020).

1.3 Aims and Objectives

The aims of our study were to investigate in a rural South African population:

- the prevalence of poor sleep quality in people living with HIV (PLWH) compared to the general population
- the correlates of poor sleep quality in PLWH
- whether poor sleep quality/symptoms of depression are associated with cardiometabolic risk
- whether HIV status interacts with sleep quality and consequently, modifies cardiometabolic risk.
- variables that affect the risk of hypertension

The objectives of our study were:

1. To measure the prevalence of poor sleep quality, daytime sleepiness, clinical depression symptoms and risk of sleep apnoea using validated questionnaires in 200 HIV+ participants and 200 controls selected from the general population living in the same rural area.
2. To investigate the correlates of sleep quality in the HIV+ participants using multivariable analyses.
3. To describe the following cardiometabolic outcome variables: systolic blood pressure (SBP), diastolic blood pressure (DBP), body mass index (BMI), neck circumference (a clinical marker of the risk of sleep apnoea) and the prevalence of hypertension and overweight/obesity in the HIV+ participants and the controls.
4. To investigate the association between poor sleep quality, daytime sleepiness, high risk of sleep apnoea and symptoms of depression (independent variables) and cardiometabolic risk (dependent variable, using SBP, DBP, BMI, neck

circumference and a metabolic score (MetScore)) using multivariable analyses for the HIV+ participants and the controls.

5. To investigate the variables that affect the risk of hypertension in our rural population using a logistic regression.

Chapter 2: Methods and Materials

2.1 Study location and participants

Ethics clearance was obtained for the original study (Appendix A and B) and for the sub-study (Appendix C).

From June 2016 to March 2017, a cross-sectional study was conducted in Qwa Qwa in the Free State province in South Africa. In total, 400 participants that were 18 years and older were recruited, 200 of whom were HIV+ and the remaining 200 served as controls. The HIV+ participants were recruited from the Tseki, Namahadi (Phuthaditjhaba) and Tshiame (Harrismith) clinics and the controls were recruited from the aforementioned clinics and the surrounding neighbourhood. All HIV+ participants received ART treatment in primary health care facilities. Informed consent (Appendix D) was obtained from the HIV+ participants (Appendix E) and the control participants (Appendix F).

We chose the Thabo Mofutsanyana district in Qwa Qwa in the Free State province since almost 13% of the population is HIV+ and HIV is the leading cause of death in the district for people between the ages of 5 and 64 (Corporate governance and traditional affairs 2020). Additionally, 95% of the population is of African ancestry and approximately 58% of the population is younger than 45 years old (Corporate governance and traditional affairs 2020).

2.2 Translation of Questionnaires

As our participants were generally not fluent in English and spoke Sesotho as a first language, we went through a formal translation process of the questionnaires used in this study.

Firstly, we first asked a formal translator (Mr Motsamai Motsapi, Sesiu sa Sesotho National Lexicography Unit, University of the Free State) and an informal translator (Mr Mohlalefi Makara) to translate the questionnaires from English to Sesotho. Thereafter, the informal and formal translators met and reconciled their versions. Next, another formal translator (a translation company, The Translation World,

http://translationworld.co.za/) and informal translator (Ms Mosilo Machere) back translated this reconciled version from Sesotho into English. Further corrections were then made to refine the translation into Sesotho. This final version was used for the study. All questionnaires and their translation are shown in Appendices G to K.

2.3 Data collection

Two experienced field workers, Ms Mampho Machere and Ms Mosilo Machere, who were fluent in Sesotho collected the data from HIV participants in the three clinics mentioned above from June 2016 to March 2017. They worked with a nurse from each clinic to identify eligible households in the general population living near the clinics to enrol the 200 controls from the general population. For the controls, we purposefully did not enquire about or test their HIV status due to the stigma of being HIV+. We took clinical measurements in all participants and asked them to answer a general questionnaire, three sleep questionnaires and a depression questionnaire (see below).

2.3.1 Clinical measurements

The following cardiometabolic markers were collected from each participant: SBP, DBP, height, weight and neck circumference. DBP and SBP were measured after patients were seated for at least 5 minutes using the Rossmax, a validated automated blood pressure measuring device (Torres et al, 2020). Blood pressure was measured after allowing each participant to sit down for five minutes and then blood pressure was taken three times with the average of the last two times being recorded. Their weight was measured using a calibrated scale and their height was measured using a stadiometer. Finally, their neck circumference was measured using a standard tape measure. Neck circumference was measured in a sitting position based on a point perpendicular to the long axis of the neck at the height of the cricothryoid ligament (see Figure 3 below).

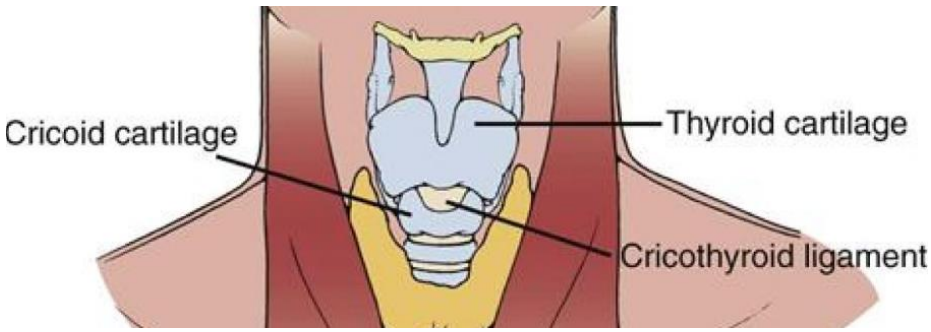


Figure 3: Position of the cricothyroid ligament where the measure of the neck circumference was performed

The participants' neck circumferences were of interest since a larger neck is one of the risk factors for sleep apnoea (Kim et al, 2015). To ensure the accuracy of the measurements, the field workers were trained on how to correctly obtain measurements from each participant. The principal investigator (Prof. Karine Scheuermaier) of the study went to the field and ensured field workers applied this measurement technique.

2.3.2 General Questionnaire (Appendix G)

Each participant filled in a general information questionnaire (Appendix G). The questionnaire included standard demographic information such as age, sex and employment. All participants were asked about their sleep environment such as whether they slept alone and what causes them to wake up during sleep. Those questions were used to verify information from the Pittsburgh Sleep Quality Index. All participants were asked about whether they had pain currently and in the past month. If they had pain, they were asked what their degree of pain (currently and in the past month) was on an 11-point Likert scale of going from 0 to 10 (0 = no pain and 10 = worst pain ever felt) and on what part of their body they felt it (by indicating on a picture). All participants were also asked about their caffeine, and drug use. They were also asked to list their habitual medications. If ART was listed as one of the medications for the controls, then we would have assumed this person was HIV+. The medications also helped us determine whether participants were treated for hypertension and helped us classify their hypertensive status (used as one of the outcome variables in one of the models). For the PLWH enrolled in the clinics, the following information was also obtained from the clinic records: date of diagnosis,

WHO staging, commencement of treatment, type of ARTs, their most recent viral load and CD4 count, other medical conditions and their current treatment. The information was confirmed with the clinic record.

2.3.3 Sleep and Depression Questionnaires (Appendices H-K)

Self-reported sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al, 1989). The PSQI makes use of 18 self-rated questions to calculate seven scores that each assess the following self-reported sleep measures: overall quality, latency, duration, efficiency, disturbances, sleep medications and daytime function (Buysse et al, 1989). Overall self-reported sleep quality and self-reported daytime function was assessed based on a subjective analysis from the participant, self-reported latency was assessed based on how long the participant takes to fall asleep and self-reported efficiency was calculated by dividing the time spent sleeping by the time spent in bed. Subsequently, the seven scores was added together to give a final PSQI score ranging from 0-21 (Buysse et al, 1989). As mentioned earlier, a score of zero indicated a high sleep quality whereas a score of 21 indicated severely poor sleep quality (Buysse et al, 1989). A PSQI score of more than five indicated poor sleep quality (Buysse et al, 1989).

Self-reported daytime sleepiness was assessed using the Epworth Sleepiness Scale (ESS) (Johns, 1991). The ESS questionnaire assesses the self-reported likelihood of falling asleep during eight day-to-day situations. For each situation, the self-reported likelihood of falling asleep is assessed on a scale of zero to three. Zero indicates they would “never doze” whereas three indicates a “high chance of dozing”. The ESS scores for all eight situations was captured and added together, with a score greater than 10 indicating excessive daytime sleepiness compatible with an underlying sleep disorder (as mentioned earlier) (Johns 1991).

The risk of sleep apnoea was assessed using the Berlin Questionnaire (BQ) (Netzer et al, 1999). The BQ questionnaire assesses the self-reported risk of sleep apnoea by posing 10 questions that have been divided into 3 categories. The first category comprises of questions relating to snoring and breathing during sleep, the second category comprises of questions relating to daytime sleepiness and the third category assesses blood pressure and BMI. A participant is scored as having a high risk of sleep apnoea if two or more of the three categories are “positive” (Netzer et al, 1999).

Depression symptoms were assessed using Beck Depression Inventory I (BDI) (Beck et al, 1961). The BDI questionnaire comprises of 21 questions that assess the degree of depressive symptoms. Each question is assessed on intensity of the depressive symptom on a 4-point Likert scale going from 0 to 3. The scores from all 21 questions are added together with the minimum score is zero and the maximum is 63. A participant is classified as having clinical depression symptoms if their total BDI score is 17 or higher. A total score of between 1-10 indicated “these ups and downs are normal”, a total score between 11-16 indicated “mild mood disturbance”, a total score between 17-20 indicated “symtoms of borderline clinical depression”, a total score between 21-30 indicated “symptoms of moderate depression”, a total score between 31-40 indicated “symptoms of severe depression” and a total score of over 40 indicated “symptoms of extreme depression” (Beck et al, 1961).

2.4 Data capturing and calculations

Firstly, all data was captured regarding demographics, HIV-associated characteristics, pain and medications (we were particularly interested in antihypertensive medications for classification of hypertensive status) for all 400 participants on an Excel spreadsheet. A participant was classified as hypertensive if they had at least one of the following: a SBP that was greater than or equal to 140 mmHg on the day of the study, a DBP that was greater than or equal to 90 mmHg on the day of the study or the use of anti-hypertensive medications. Each participant’s body mass index (BMI) was calculated by dividing their weight (kg) by their height (metres) squared. A participant was classified as overweight if their BMI was between 25-29 kg/m^2 and was classified as obese if their BMI was $\geq$ 30 kg/m^2.

Next, each participant’s metabolic score (MetScore) was calculated by adding together the z-scores for the SBP, DBP, BMI and neck circumference of each participant and dividing this number by four. The z-score is calculated using the following formula: (participant’s value – mean of the full sample studied)/standard deviation; the z-score indicates how far away each value is from the mean. Roche et al (2020) and Roche et al (2021) had used a laboratory version of the MetScore in paediatric and adult populations, respectively. The Roche et al (2021) study showed that people with metabolic syndrome had significantly higher MetScore than those who did not have metabolic syndrome. Gaziano et al (2016) showed that for

cardiovascular risk scores such as ASCVD or Framnigham Risk Score, there was a high correlation between a non-laboratory based score and the laboratory based score. Thus we extrapolated that the non-laboratory MetScore may reflect similarly cardiometabolic profiles with more power than by using each cardiovascular variable separately.

For all 400 participants, the individual components of the PSQI, ESS, BQ and BDI questionnaire was captured and used to calculate the final scores. Based on the final scores, each participant was assessed for poor sleep quality, excessive daytime sleepiness, a high risk of sleep apnoea and symptoms of depression.

2.5 Questionnaire validation and factor analysis

The questionnaires were validated for use in English as a second language (Redman et al, 2018) but the validation steps for these same questionnaires when administered in Sesotho was completed in the present study. In order to complete the validation and factor analysis of the PSQI, ESS and BDI questionnaires, SAS 9.4 was used. Cronbach's alpha was used as a measure of questionnaire validity (PROC CORR Alpha). Alpha values were interpreted as follows: 0.9 - 1 = excellent reliability, 0.81 - 0.89 = good reliability, 0.7 – 0.79: acceptable reliability, 0.6 – 0.69: questionable reliability, 0.5 – 0.59: poor reliability and less than 0.5 = unacceptable (StatisticsHowTo 2021). For the PSQI, ESS and BDI questionnaires, construct validity was tested using factor analysis (PROC FACTOR).

2.6 Data analysis

Graphpad Prism was used to do all bivariate and multivariable analyses. All continuous variables were tested for normality; normality was assumed if the skewness and kurtosis was between -1 and 1 and if the mean and median were similar. Before including any variable in a multivariable model, we tested for collinearity and if two variables were collinear, one of the variables were removed. We also tested for comfounding effects by looking at the beta estimates of the variable of interest. If it moved away from 0 by more than 10% when adding another variable into the model, this was positive confounding while if it moved closer to 0 this was negative confounding

2.6.1 The prevalence of poor sleep quality, daytime sleepiness, clinical depression symptoms and risk of sleep apnoea

The prevalence of individuals with self-reported poor sleep quality (defined as PSQI > 5), self-reported excessive daytime sleepiness (ESS > 10), clinical depression symptoms (BDI score >16) and a high risk of sleep apnoea (defined as a positive score for two or more categories) in both groups was calculated. Since PSQI and ESS scores were normally distributed, an unpaired t-test was used to test for a significant difference between the HIV+ and control participants. Since BDI scores were non-normally distributed, a Mann-Whitney U-test was used. A Fisher's exact test was used to compare the frequency of high risk of sleep apnoea in the HIV+ and control participants.

2.6.2 The correlates of sleep quality in the HIV+ participants

Bivariate analyses was done using PSQI as the outcome variable with each of the following independent variables: age, sex, duration since participant tested HIV+, ART duration, current CD4 count, current viral load, presence of pain currently, ESS, BQ and BDI.

For the multivariable analysis, to parallel the Redman et al, (2018) paper done in urban people living with HIV, PSQI was the outcome variable. An independent variable was included in the multivariable model if the p-value was less than 0.2 in a bivariate analyses of the variable with PSQI (Redman et al, 2018). Despite having a p-value of 0.075, current CD4 count was not included in the multivariable model since it was collinear with HIV duration. We used HIV duration in the model since was of greater interest than current CD4 count. Thereafter, the following interactions were tested separately: HIV duration*sex, HIV duration*presence of pain currently, HIV duration*ESS, HIV duration*BQ and HIV duration*BDI (while including all the independent variables).

2.6.3 Description of cardiometabolic variables and the prevalence of hypertension and overweight/obesity

Since the cardiometabolic variables (SBP, DBP, BMI, neck circumference and MetScore) were normally distributed, the mean ± SD was recorded for the HIV+ and control participants. To test for a significant difference in SBP, DBP, BMI and neck circumference between the HIV+ and controls, an unpaired t-test was used. The percentage of individuals in the HIV+ and controls with hypertension and obesity was also calculated and recorded.

2.6.4 The association between sleep/depression and cardiometabolic risk

Bivariate and multivariable analyses were done for the population as a whole (n = 400) and for the HIV+ participants only (n = 200).

Bivariate analyses were done using SBP, DBP, neck circumference and MetScore as the outcome variables. For the population as a whole, the following independent variables were tested with each outcome variable: age, sex, HIV status, BMI (BMI was not tested with MetScore since we used BMI as part of the MetScore calculation), PSQI, ESS, BQ and BDI. For the HIV+ participants, the following independent variables were tested with each outcome variable: age, sex, HIV status, BMI (for SBP, DBP, neck circumference and MetScore), HIV duration, ART duration, current CD4 count, current viral load, presence of pain currently, PSQI, ESS, BQ and BDI.

Two types of multiple linear regressions were used. For the first type of model, SBP, DBP, BMI, neck circumference and MetScore were the outcome variables with PSQI/ ESS/ BQ/ BDI individually. Other independent variables were included if the variable had a p-value of less than 0.2 in the bivariate analyses. For the second multiple linear regression, five models were run using SBP/ DBP/ BMI/ neck circumference/ MetScore as the outcome variable with PSQI, ESS, BQ and BDI in the model together. Other independent variables were included if the variable had a p-value of less than 0.2 in the bivariate analyses (Redman et al, 2018). For the multivariable models in the HIV+ participants, HIV duration and ART duration were both variables

of interest (even though their p-value were >0.2 for some outcome variables in the bivariate analyses). However, HIV duration and ART duration were collinear and we removed HIV duration since its p-values in the bivariate analyses were higher than that of ART duration.

In the multivariable analyses (first and second type of model) of the population as a whole (n = 400), the following interactions were tested separately: HIV status*PSQI, HIV status*ESS, HIV status*BQ and HIV status*BDI (while including all the independent variables).

2.6.5 Variables that affect the risk of hypertension

Bivariate analyses were done using hypertension status (0 = normal blood pressure; 1 = hypertensive) as the outcome variable. For the following independent variables, an unpaired t-test was used: age, BMI, PSQI, ESS and BDI. For the following dependent variable, a Fisher's exact test was used: sex, BQ, HIV status and the presence of pain currently.

For the logistic regression analysis, hypertension status was the outcome variable. An independent variable was included in the logistic regression model if the p-value was less than 0.2 (Redman et al, 2018). Despite having p-values of > 0.2 in the bivariate analyses, PSQI and ESS were added to the logistic regression model since they were variables of interest. Thereafter, the following interactions were tested separately: HIV status*PSQI, HIV status*ESS, HIV status*BQ and HIV status*BDI (while including all the independent variables).

CHAPTER 3: RESULTS

3.1 Questionnaire validation and factor analysis

3.1.1 Pittsburgh Sleep Quality Index (PSQI)

Figure 5 shows the presentation of the seven PSQI components that have been loaded onto the two major factors in the rotated matrix of the factor analysis.

The Cronbach's alpha for the PSQI was 0.7 (raw variable) among all 400 participants. Using factor analysis, we found that the PSQI questionnaire had a three-factor structure. The two factors plotted on the graph represent 92.86% of the variance.

Factor 1 comprised of the sleep quantity components: Component 3 (self-reported sleep duration) and Component 4 (self-reported sleep efficiency).

Factor 2 comprised of sleep quality components: Component 1 (self-reported sleep quality) and Component 5 (self-reported sleep disruption). Component 2 (self-reported sleep latency) loaded slightly onto Factor 2.

Component 6 (sleep medication) loaded onto Factor 3 and Component 7 (self-reported daytime consequences) loaded slightly onto Factor 3 (are not represented on the figure).

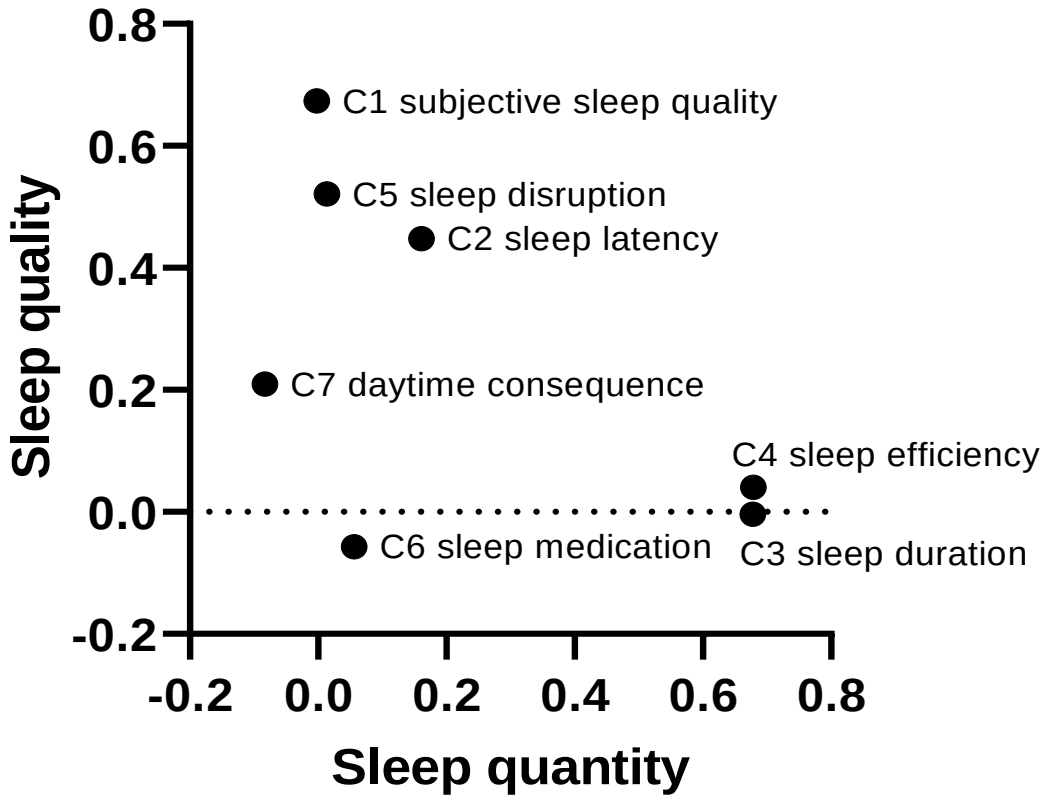


Figure 5. Presentation of the seven Pittsburgh Sleep Quality Index (PSQI) components that have been loaded onto the two major factors in the rotated matrix of the factor analysis. The two factors represented on the graph explained 92.86% of the variance

3.1.2 Epworth Sleepiness Scale (ESS)

Figure 6 shows the presentation of the eight ESS components that have been loaded onto the two major factors in the rotated matrix of the factor analysis.

The Cronbach's alpha for the ESS was 0.9 (raw variable) among all 400 participants. Using factor analysis, we found that the ESS questionnaire had a two-factor structure. The two factors plotted on the graph represent 92.96% of the variance.

Factor 1 comprised of the periods of inactivity components: Component 3 (sitting inactive in public), Component 4 (lying down in the afternoon), Component 6 (sitting quietly after lunch without alcohol) and Component 8 (in a car while stopped in traffic). Component 7 (passenger in a car for an hour) loaded slightly onto factor 1.

Factor 2 comprised of the moving/participating in an activity components: Component 1 (sitting and reading), Component 2 (watching television) and Component 5 (sitting and talking to someone).

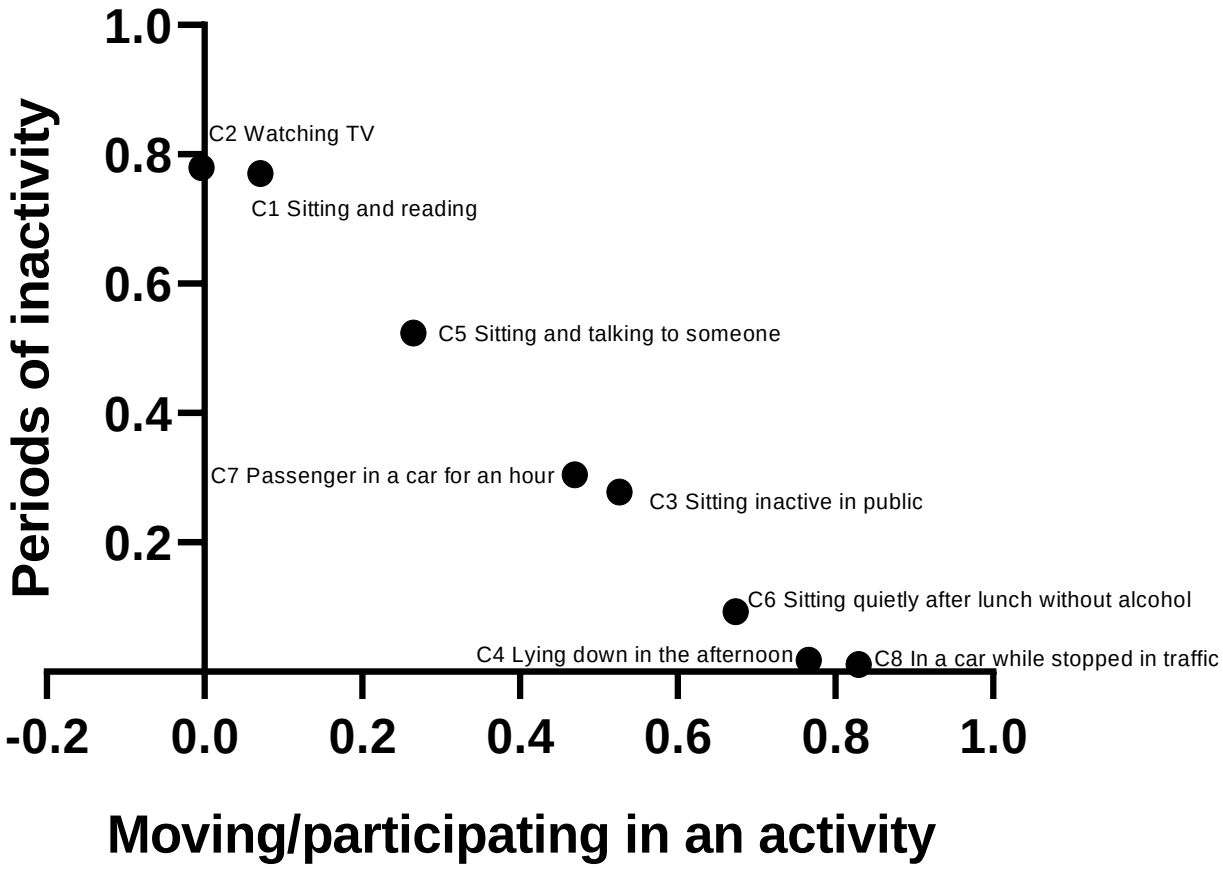


Figure 6. Presentation of the eight Epworth Sleepiness Scale (ESS) components that have been loaded onto the two major factors in the rotated matrix of the factor analysis. The two factors presented in the graph explained 92.96% of the variance

3.1.3 Beck's Depression Inventory (BDI)

Figure 7 shows the presentation of the 21 BDI components that have been loaded onto the two major factors in the rotated matrix of the factor analysis.

The Cronbach's alpha for the BDI was 0.92 (raw) among all 400 participants. Using the factor analysis, we found the BDI questionnaire had a three-factor structure. The two factors plotted on the graph explained 94.25% of the variance.

Factor 1 comprised of the cognitive components: Component 1 (sadness), Component 2 (future hopes), Component 3 (feeling of failure) and Component 4 (life satisfaction. The following components loaded slightly onto Factor 1: Component 5 (guilt), Component 6 (feeling of being punished), Component 11 (feeling irritated), Component 12 (loss of interest in people) and Component 13 (decision-making).

Factor 2 comprised of the somatic components: Component 15 (motivation to work), Component 16 (sleeping habits) and Component 17 (feeling tired). The following components loaded slightly onto Factor 2: Component 19 (weight loss), Component 20 (worries about health) and Component 21 (interest in sex).

Factor 3 comprised of Component 7 (disappointment), Component 8 (self-critical) and Component 9 (thoughts of suicide). The following components loaded slightly onto Factor 3: Component 10 (crying), Component 14 (physical appearance) and Component 18 (appetite).

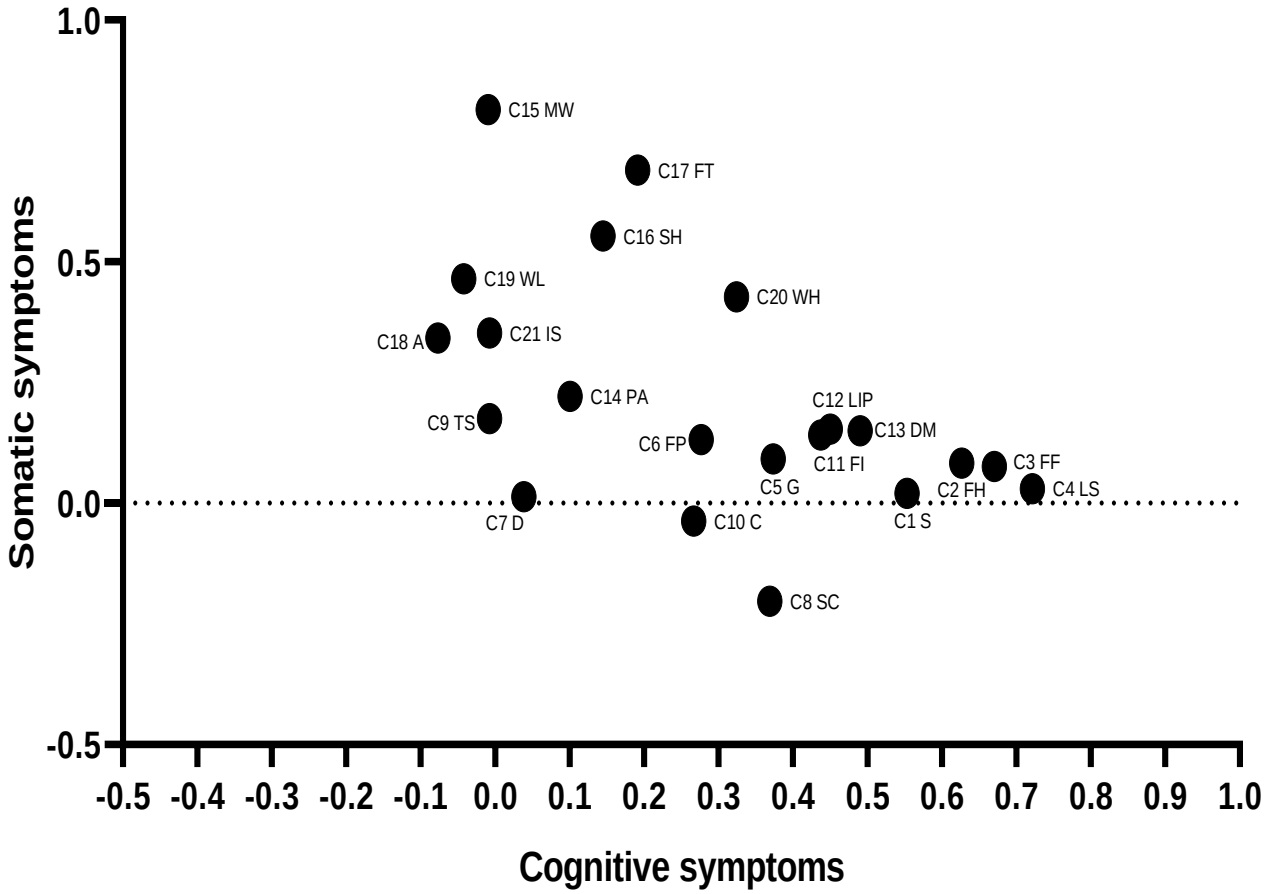


Figure 7. Presentation of the 21 Beck's Depression Inventory I (BDI) components that have been loaded onto the two major factors in the rotated matrix of the factor analysis. The two factors present in the graph explained 94.25% of the variance

C1 S = sadness; C2 FH = future hopes; C3 FF = feeling of failure; C4 LS = life satisfaction; C5 G = guilt; C6 FP = feeling of being punished; C7 D = disappointment; C8 SC = self-critical; C9 TS = thoughts of suicide; C10 C = crying; C11 FI = feeling irritated; C12 LIP = loss of interest in people; C13 DM = decision-making; C14 PA = physical appearance; C15 MW = motivation to work; C16 SH = sleeping habits; C17 FT = feeling tired; C18 A = appetite; C19 WL = weight loss; C20 WH = worries about health; C21 IS = interest in sex.

3.2 Demographic and cardiometabolic characteristics

3.2.1 All participants (n = 400)

Table 1 shows the demographic and cardiometabolic characteristics of all participants in our study.

The majority of our cohort were female and on average, were 43.53 years old. Only 20.3% of participants were employed and 4% of participants were shift workers. A large majority of participants were formally educated (86.5%) and 70% of participants had done some/completed secondary school.

On average, our cohort was overweight, pre-hypertensive and had a high prevalence of obesity (25.3%) and hypertension (45.7%). Only 44.63% of those with hypertension were treated. The average neck circumference was 33.92 cm and the prevalence of cigarette smokers was 35%.

3.2.2 HIV+ participant's vs control participants

Table 1 shows the comparison of demographic and cardiometabolic markers between the HIV+ and control participants.

The HIV+ and control groups were similar in terms of sex, age, employment and education. The HIV+ participants had lower BMIs ($p<0.0001$), a lower prevalence of obesity ($p= 0.0027$) and a lower percentage of treated hypertensives ($p<0.0001$) compared to the control group. The HIV+ and control participants were similar in terms of the number of overweight individuals ($25 < BMI < 30$) ($p = 0.33$), neck circumference ($p = 0.21$), SBP ($p = 0.69$), DBP ($p = 0.79$), the percentage of hypertensives ($p = 0.84$), MetScore ($p = 0.93$) and the prevalence of cigarette smokers ($p = 0.92$).

Table 1. Demographics and cardiometabolic information in the sample as a whole (n = 400), HIV+ participants (n = 200) and the control participants (n = 200) and the comparison between the HIV+ and control participants.

	All (n = 400)	***HIV+ (n = 200)***	***Control (n = 200)***	***P-value***
Demographics				
Females	283 (70.8)	143 (71.5)	140 (70)	0.83
Age (years) (range: 18-91 years), mean (SD)	43.53 (15)	43.24 (11.3)	43.83 (18)	0.7
Employed	81 (20.3)	44 (22)	37 (18.5)	0.45
Shift workers	16 (4)	11 (5.5)	5 (2.5)	0.2
Formally educated	346 (86.5)	169 (84.5)	177 (88.5)	0.31
Attended/ completed primary school	62 (15.5)	29 (14.5)	33 (16.5)	0.55
Attended/completed secondary school	280 (70)	137 (68.5)	143 (71.5)	
Post-secondary school	4 (1)	3 (1.5)	1 (0.5)	
Cardiometabolic information				
BMI (kg/m^2), mean (SD)	**26.11 (6.4)**	**24.84* (6)**	**27.38* (6.58)**	**< 0.0001**
Overweight	122 (30.5)	56 (28)	66 (33)	0.33
Obese	**101 (25.3)**	**37* (18.5)**	**64* (32)**	**0.0027**
Neck circumference (cm), mean (SD)	33.92 (3.3)	33.72 (3.41)	34.13 (3.26)	0.21
SBP (mmHg), mean (SD)	133.5 (24.6)	132.9 (23.3)	133.9 (25.75)	0.69
DBP (mmHg), mean (SD)	84.68 (16.6)	84.42 (17.6)	84.9 (15.7)	0.79
Hypertension	177 (45.7)	85 (45)	92 (46)	0.84
Treated hypertensives, n (% of hypertensives)	**79 (44.63)**	**23* (27.06)**	**56* (60.87)**	**< 0.0001**
MetScore, mean (SD)	-0.13 (2.7)	-0.12 (2.7)	-0.14 (2.8)	0.93
Cigarette smokers	140 (35)	71 (35.5)	69 (34.5)	0.92

Unless otherwise stated, data is presented as number of participants (% of column i.e. All/HIV+/Control); SD = standard deviation, BMI = body mass index, SBP = =systolic blood pressure, DBP = diastolic blood pressure, MetScore = metabolic score, n = number of participants; when data is presented as mean (SD), an unpaired t-test was used. When data is presented as a %, a Fisher's test was used. * indicates a significant difference between the HIV+ and control participants

3.3 Sleep and depression characteristics

3.3.1 All participants (n = 400)

Table 2 shows the sleep and depression characteristics of all participants.

The cohort had normal self-reported sleep quality (average PSQI score was 4.2) and 33.8% of participants reported poor sleep quality (i.e. PSQI>5). The average wake-time time was 06:29 and the bedtime was 21:08. On average, participants reportedly slept for 8 hours per night. The median reported sleep efficiency was 99% and the reported time to fall asleep was 30 minutes. The cohort had an average ESS score of 9.4 with 40.5% of participants reporting excessive daytime sleepiness (an ESS score > 10). Over 20% of participants had a high risk of sleep apnoea. The most common reported cause for waking up during the night was having to use the bathroom. 19.8% of participants consumed more than 2 cups of caffeinated drinks per day.

The cohort did not have symtoms of clinical depression (median BDI score was 4) and 15.3% of participants had symptoms of clinical depression. Almost 29% of participants had pain on the day of the study with their average pain being at 7.3 out of 10. Almost 32% of participants had pain in the month preceding the study with their average pain being at 7.4 out of 10.

Table 2. Sleep, depression and pain characteristics in the sample as a whole (n = 400), HIV+ participants (n = 200) and the control participants (n = 200) and the comparison between the HIV+ and control participants.

	All (n = 400)	***HIV+ (n = 200)***	***Control (n = 200)***	***P-value***
Sleep characteristics				
PSQI score (between 0-21), mean (SD)	4.2 (3.2)	3.96 (3.16)	4.4 (3.21)	0.15
Poor sleep quality/ PSQI>5	135 (33.8)	63 (31.5)	72 (36)	0.4
Time to fall asleep (min), median [IQR]	30 [10-45]	30 [10-60]	30 [10-45]	0.73
Actual sleep hours, mean (SD)	8.0 (1.8)	7.8* (1.6)	8.3 (1.9)	**0.0064**
Sleep efficiency %, median [IQR]	99 [82-100]	94* [80-100]	100 [86-100]	**0.009**
ESS score (between 0-24), mean (SD)	9.4 (7.8)	9.8 (8.23)	9.0 (7.42)	0.31
Excessive daytime sleepiness/ ESS > 10	162 (40.5)	82 (41)	80 (40)	0.92
High risk of sleep apnoea	82 (20.5)	32* (16)	52* (26)	**0.019**
Reasons for waking up during the night:				
Bathroom	334 (83.5)	169 (84.5)	165 (82.5)	0.69
Noise	98 (24.5)	35* (17.5)	63 (31.5)	**0.0016**
Sleeping in a room that was too hot or too cold	148 (37)	60 (30)	88 (44)	**0.0051**
Pain	100 (25)	35* (17.5)	65* (32.5)	**0.0008**
Bad dreams)	102 (25.5)	49 (24.5)	53 (26.5)	0.73
Consumption of more than 2 cups of caffeinated drinks/day	79 (19.8)	40 (20)	39 (19.5)	>0.99
Depression characteristics				
BDI score (between 0-63), median [IQR]	4 [1-11]	4.5 [1-13.5]	4 [1-9]	0.14
Symptoms of clinical depression/ BDI score > 16 (%)	61 (15.3)	43* (21.5)	18* (9)	0.0007
Pain				
Pain on the study day	115 (28.8)	52 (26)	63 (31.5)	0.19
Pain rating on the study day (1-10), mean (SD)	7.3 (2.3)	7.8* (2.2)	6.9 (2.2)	0.035
Pain in the month preceding the study	127 (31.8)	56 (28)	71 (35.5)	0.086
Pain rating in the month preceding the study (1-10), mean (SD)	7.4 (2.2)	7.8 (2.2)	7.1 (2.1)	0.054

Unless otherwise stated, data is presented as number of participants (% of column i.e. All/HIV+/Control); SD = standard deviation, PSQI = Pittsburgh Sleep Qual,ity Index, IQR = interquartile range, ESS = Epworth Sleepiness Scale, BDI-I = Beck's Depression Inventory I. For mean (SD), an unpaired t-test. For median [IQR], a Mann Whitney U-test was used. For a %, a Fisher's test was used

3.3.2 HIV+ participants vs control participants

Table 2 shows the comparison of sleep and depression characteristics between the HIV+ and control participants.

The HIV+ and control groups were similar in terms of PSQI ($p = 0.15$), the prevalence of reported poor sleep quality ($p = 0.40$) and reported time to fall asleep ($p = 0.73$). The control group reportedly slept 0.5 hours longer ($p = 0.0064$) and had a 6% higher slef-reported sleep efficiency ($p = 0.009$) than the HIV+ group. ESS scores ($p = 0.31$) and the prevalence of reported excessive daytime sleepiness ($p = 0.92$) were similar between groups. The control group had significantly more people with a high risk of sleep apnoea than the HIV+ group (52 vs 32; $p = 0.019$). More control participants reported waking up during the night due to noise (63 vs 35; $p = 0.0016$), heat/cold (88 vs 60; $p = 0.0051$) and pain (65 vs 35; $p = 0.0008$) than the HIV+ participants.

Although BDI scores were similar between groups ($p = 0.14$), the prevalence of clinical depression symptoms in the HIV+ group was more than double than in the control group ($p = 0.0007$).

Both groups had a similar percentage of participants who were in pain on the present day ($p = 0.19$) and in the past month ($p = 0.086$). Pain ratings were similar in those who had pain on the day in the past month ($p = 0.054$). Pain ratings in the HIV+ participants on the day of the study were greater than in the controls ($p = 0.035$).

3.4 HIV-related characteristics of the HIV+ participants

Table 3 shows the HIV-related characteristics of the HIV+ participants.

On average, HIV+ participants had been diagnosed with the disease for 2013.8 days and were on ARTs for 1709 days. The median time between diagnosis and the start of ART treatment was 270.8 days and 13.5% of participants had been hospitalised for HIV-related complications. The median baseline CD4 count was 213.5 cells/mm^3 and current CD4 count was 479.5 cells/mm^3. The majority of participants (80.1%) had

undetectable viral loads. Only two HIV+ participants were currently on TB treatment and two participants were currently on chemotherapy.

Almost 60% of HIV+ participants were classified as Stage 1, 19% were Stage 2, 18% were Stage 3 and 3% were Stage 4. All but 10 participants used the ART called Fixed Dose Combination (FDC) with tenofovir, emtricitabine and efavirenz. Cancer, cryptococcal meningitis and cerebral toxoplasmosis are three common conditions that are associated with the latter stages (stage 3 and 4) of HIV infection. Only three participants had cancer presently or in the past, no participants had cryptococcal meningitis or cerebral toxoplasmosis and only one participant had Reiter's syndrome presently or in the past.

Table 3. HIV-related characteristics in the 200 HIV+ participants

	HIV+ participants (n = 200)
General characteristics	
HIV duration (days), mean (SD)	2013.8 (1171.42)
Duration of ART treatment duration (days), mean (SD)	1709 (1068.61)
Days from diagnosis to start of ART treatment, median [IQR]	270.8 [15-305.5]
Hospitalised for disease	27 (13.5)
Baseline CD4 count (cells/m^3), median [IQR]	213.5 [122.8-340.3]
Current CD4 count (cells/m^3), median [IQR]	479.5 (352.5-672)
"Lower than detectable" current viral load, n (% out of 186)	149 (80.1)
Currently on tuberculosis (TB) treatment	2
Currently on chemotherapy	2
WHO stage:	
Stage 1	119 (59.5)
Stage 2	38 (19)
Stage 3	36 (18)
Stage 4	6 (3)
ART treatment	
NRTIs	
Tenofovir (TDF)	195 (97.5)
Emtricitabine (FTC)	193 (96.5)
Lamivudine (3TC), Abacavir (ABC) or Zidovudine (AZT)	8 (4)
NNRTIs	
Efavirenz (EFV)	193 (96.5)
Nevirapine (NVP)	2 (1)
PI	
Lopinavir (LPV)	3 (1.5)
HIV-related conditions (past/present)	
Cancer	3
Crytococcal meningitis	0
Reiter's syndrome	1

Unless otherwise stated, data is presented as number of participants (% of column i.e. All/HIV+/Control); ART = anti-retroviral treatment, SD = standard deviation, IQR = interquartile range, WHO = World Health Organisation, NRTI = non-reverse transcriptase inhibitor, NNRTI = non-nucleoside reverse transcriptase inhibitors, PI = protease inhibitor, n = number of HIV+ participants

3.5 Correlates of sleep quality in HIV+ participants (n = 200)

3.5.1 Bivariate analyses

Table 4 shows the bivariate analyses (simple linear regression) of the correlates of reported sleep quality in HIV+ participants.

The presence of pain currently was associated with a 2.84-point higher PSQI ($p < 0.0001$). An increase in BDI by 10 points was associated with a 1.3-point higher PSQI ($p < 0.0001$). PSQI was not associated with age ($p = 0.78$), sex ($p = 0.18$), HIV duration ($p = 0.1$), ART duration ($p = 0.27$), current CD4 count ($p = 0.075$), current viral load ($p = 0.33$), ESS ($p = 0.051$) or BQ ($p = 0.35$).

Table 4. Bivariate analyses of the correlates of reported sleep quality as assessed by the Pittsburgh Sleep Quality Index (PSQI) in the HIV+ participants

	PSQI		
	ß	*SE*	*P*
Age (years)	0.0057	0.02	0.78
Sex	0.67	0.49	0.18
HIV duration (days)	-0.00042	0.00025	0.10
ART duration (days)	-0.00025	0.00022	0.27
Current CD4 count (cells/m^3)	-0.0016	0.00089	0.075
Current viral load	0.57	0.59	0.33
Presence of pain currently	**2.84**	**0.47**	**<0.0001**
ESS	0.053	0.027	0.051
BQ	0.57	0.61	0.35
BDI	**0.13**	**0.017**	<**0.0001**

PSQI was the outcome variable in all bivariate analyses; PSQI = Pittsburgh Sleep Quality Index, ART = anti-retroviral treatment, ESS = Epworth Sleepiness Scale, BQ = Berlin Questionnaire, BDI = Beck's Depression Inventory; for sex, 0 = male and 1 = female; for current viral, load, 0 = undetectable viral load and 1 = detectable viral load; for presence of pain currently, 0 = no pain and 1 = presence of pain

3.5.2 Multivariable analyses

Table 5 shows the multivariable analyses of the correlates of reported poor sleep quality.

Age, ART duration and current viral load were not included in this multivariable model since in the bivariate analyses (Table 4), the p-value was greater than 0.2 (Redman et al, 2018). PSQI was positively associated with the presence of pain currently when sex, HIV duration, ESS, BQ and BDI were adjusted for ($p = 0.0006$). The presence of pain currently was associated with a 2.2-point higher PSQI. PSQI was positively associated with BDI when sex, the presence of pain currently, HIV duration, ESS and BQ were adjusted for ($p<0.0001$). An increase in BDI by 10 points was associated with a 1.1-point higher PSQI. PSQI was negatively associated with HIV duration when sex, presence of pain currently, ESS, BQ and BDI were adjusted for ($p = 0.011$). An increase in HIV duration by 1000 days (approximately 2.7 years) was associated with a 0.57-point lower PSQI. PSQI was not associated with sex, ESS or BQ. HIV duration did not interact with sex ($p = 0.92$), the presence of pain currently ($p = 0.58$), ESS ($p = 0.4$), BQ ($p = 0.71$) or BDI ($p = 0.11$) to affect PSQI.

Table 5. Multivariable analyses of the correlates of reported poor sleep quality as assessed by the Pittsburgh Sleep Quality Index (PSQI) in HIV+ participants (n = 200)

	PSQI		
	ß	*SE*	*P*
Main effects *			
Sex	0.044	0.59	0.94
HIV duration (days)	**-0.00057**	**0.00022**	**0.011**
Presence of pain currently	**2.20**	**0.62**	**0.0006**
ESS	0.017	0.034	0.61
BQ	0.067	0.72	0.93
BDI	**0.11**	**0.025**	**<0.0001**
Interactions **			
*HIV duration*sex*	0.000043	0.00045	0.92
*HIV duration*presence of pain currently*	0.00028	0.00051	0.58
*HIV duration*ESS*	0.000023	0.000027	0.40
*HIV duration*BQ*	-0.0002	0.00055	0.71
*HIV duration*BDI*	-0.000029	0.000018	0.11

PSQI was the outcome variable in all multivariable analyses; PSQI = Pittsburgh Sleep Quality Index, ESS = Epworth Sleepiness Scale, BQ = Berlin Questionnaire, BDI = Beck's Depression Inventory; for sex, 0 = male and 1 = female; for presence of pain currently, 0 = no pain and 1 = presence of pain

* main effects without interactions; ** interactions were tested separately in 4 different models while including all main effects shown above (the effect of the interaction on the beta of each main effect did not change meaningfully)

3.6 Association between cardiometabolic markers and sleep and depression indicators

3.6.1 Bivariate

3.6.1.1 All participants (n = 400)

Table 6 shows the bivariate analyses of the association between cardiometabolic markers and sleep and depression indicators in all participants.

Table 6. Bivariate analyses of the correlates of cardiometabolic markers all participants (n = 400) and the HIV+ participants (n = 200)

All participants (n = 400)

Outcome variables

	SBP			DBP			BMI			Neck circumference			MetScore		
	ß	*SE*	*P*	*ß*	*SE*	*P*	*ß*	*SE*	*P*	*ß*	*SE*	*P*	*ß*	*SE*	*P*
Age (years)	**0.66**	**0.077**	**<0.0001**	**0.24**	**0.055**	**<0.0001**	**0.073**	**0.021**	**0.0006**	**0.043**	**0.011**	**<0.0001**	**0.015**	**0.0022**	**<0.0001**
Sex	-1.87	2.822	0.51	-1.49	1.9	0.43	**3.20**	**0.69**	**<0.0001**	**-2.44**	**0.35**	**<0.0001**	**-0.17**	**0.073**	**0.022**
HIV status	-1.01	2.56	0.69	-0.47	1.73	0.79	**-2.54**	**0.63**	**<0.0001**	-0.42	0.33	0.21	0.09	0.067	0.18
BMI (kg/m^2)	**0.86**	**0.2**	**<0.0001**	**0.42**	**0.13**	**0.0019**				**0.19**	**0.024**	**<0.0001**			
PSQI	0.43	0.42	0.31	0.066	0.28	0.82	-0.10	0.10	0.31	0.069	0.052	0.19	0.008	0.012	0.50
ESS	-0.028	0.16	0.87	0.11	0.11	0.33	-0.022	0.041	0.6	-0.032	0.021	0.13	0.0016	0.0044	0.71
BQ	**9.12**	**3.05**	**0.003**	**6.34**	**2.05**	**0.0021**	**3.72**	**0.77**	**<0.0001**	0.64	0.41	0.12	**0.37**	**0.081**	**<0.0001**
BDI	-0.15	0.13	0.25	-0.14	0.086	0.11	-0.059	0.031	0.061	**-0.047**	**0.016**	**0.0037**	**-0.011**	**0.0037**	**0.0031**

HIV+ participants (n = 200)

Outcome variables

	SBP			DBP			BMI			Neck circumference			MetScore		
	ß	*SE*	*P*	*ß*	*SE*	*P*	*ß*	*SE*	*P*	*ß*	*SE*	*P*	*ß*	*SE*	*P*
Age (years)	**0.75**	**0.15**	**<0.0001**	**0.31**	**0.12**	**0.01**	0.0026	0.038	0.95	0.016	0.021	0.45	0.041	0.029	0.17
Sex	-6.06	3.97	0.13	-3.95	3.01	0.19	**2.84**	**0.92**	**0.0023**	**-2.34**	**0.51**	**<0.0001**	-0.43	0.78	0.58
BMI (kg/m^2)	**1.02**	**0.29**	**0.0006**	**0.55**	**0.23**	**0.016**				**0.18**	**0.038**	**<0.0001**			
HIV duration (days)	0.0031	0.0021	0.15	0.0025	0.0016	0.12	-0.00052	0.00048	0.29	-0.00013	0.00028	0.64	−0.000024	0.00061	0.97
ART duration (days)	0.0035	0.0018	0.052	0.0025	0.0014	0.071	-0.00081	0.00043	0.064	-0.00022	0.00025	0.37	0.00016	0.00069	0.81
Current CD4 count (cells/mm^3)	-0.0018	0.0070	0.8	-0.0016	0.0053	0.76	0.0011	0.0017	0.50	0.00001	0.00093	0.91	-0.00035	0.0011	0.75
Current viral load	-7.21	4.75	0.13	-1.79	3.59	0.62	0.42	1.1	0.7	**1.77**	**0.61**	**0.004**	0.71	0.73	0.34
Presence of pain currently	5.06	4.24	0.23	-1.58	3.21	0.62	-0.54	0.97	0.58	0.59	0.55	0.28	**1.93**	**0.85**	**0.026**
PSQI	-0.35	0.66	0.6	-0.36	0.5	0.47	-0.25	0.13	0.065	-0.0088	0.077	0.91	-0.089	0.13	0.48
ESS	-0.18	0.22	0.41	0.02	0.17	0.9	-0.0092	0.052	0.86	-0.045	0.029	0.13	-0.0084	0.042	0.84
BQ	8.19	4.65	0.08	**7.00**	**3.51**	**0.048**	**2.57**	**1.15**	**0.026**	-0.52	0.66	0.43	**2.25**	**0.85**	**0.010**
BDI	-0.26	0.15	0.092	-0.19	0.12	0.10	-0.063	0.036	0.086	**-0.056**	**0.02**	**0.0062**	**-0.078**	**0.034**	**0.024**

SBP = systolic blood pressure, DBP = diastolic blood pressure, BMI = body mass index, ART = anti-retroviral, PSQI = Pittsburgh Sleep Quality Index, ESS = Epworth Sleep Quality Index, BQ = Berlin Questionnaire, BDI = Beck's Depression Inventory; for sex, 0 = male and 1 = female; for HIV status, 0 = controls and 1 = HIV+; for current viral load, 0 = undetectable and 1 = detectable; for presence of pain currently, 0 = no pain and 1 = presence of pain

Age, BMI and BQ were all positively associated with SBP. Every increase in age by 1 year was associated with a 0.66 mmHg higher SBP (p<0.0001). Every increase in BMI by 1 kg/m^2 was associated with a 0.86 mmHg higher SBP (p<0.0001). A high risk of sleep apnoea was associated with a 9.12 mmHg higher SBP (p = 0.003).

Age, BMI and BQ were all positively associated with DBP. Every increase in age by 1 year was associated with a 0.24 mmHg higher DBP (p<0.0001). Every increase in BMI by 1 kg/m^2 was associated with a 0.42 mmHg higher DBP (p = 0.0019). A high risk of sleep apnoea was associated with a 6.34 mmHg higher DBP (p = 0.0021).

Age, sex and BQ were all positively associated with BMI. Every increase in age by 1 year was associated with a 0.073 kg/m^2 higher BMI (p = 0.0006). Being female was associated with a 3.2 kg/m^2 higher BMI (p<0.0001). A high risk of sleep apnoea was associated with a 3.73 kg/m^2 higher BMI (p<0.0001). HIV status was negatively associated with BMI. Being HIV+ was associated with a 2.54 kg/m^2 lower BMI (p<0.0001).

Age and BMI were positively associated with neck circumference. Every increase in age by 10 years was associated with a 0.43 cm higher neck circumference (p<0.0001). Every increase in BMI by 1 kg/m^2 was associated with a 0.19 cm higher neck circumference (p<0.0001). Sex and BDI were negatively associated with neck circumference. Being female was associated with 2.44 cm lower neck circumference (p<0.0001). An increase in BDI by 10 points was associated with a 0.47 cm lower neck circumference (p = 0.0037). High risk of sleep apnoea was not associated with neck circumference (ß (SE) = 0.64 (0.41), p = 0.12).

The presence of pain currently and BQ were positively associated with MetScore. The presence of pain was associated with a 1.63-point higher MetScore (p = 0.026). A high risk of OSA was associated with a 2.25-point higher MetScore (p < 0.0001). BDI was negatively associated with MetScore. An increase in BDI scores by 10 points was associated with a 0.78-point lower MetScore (p = 0.0024).

3.6.1.2 HIV+ participants (n = 200)

Table 6 shows the bivariate analyses of the association between cardiometabolic markers and sleep and depression indicators in the HIV+ participants.

Age and BMI were positively associated with SBP. An increase in age by 1 year was associated with a 0.75 mmHg higher SBP (p<0.0001). An increase in BMI by 1 kg/m^2 was associated with a 1.02 mmHg higher SBP (p = 0.0006).

Age, BMI and BQ were all positively associated with DBP. An increase in age by 1 year was associated with a 0.31 mmHg higher DBP (p = 0.01). An increase in BMI by 1 kg/m^2 was associated with a 0.55 mmHg higher DBP (p = 0.016). A high risk of sleep apnoea was associated with a 7 mmHg higher DBP (p = 0.048).

Sex and BQ were both positively associated with BMI. Being female was associated with a 2.84 kg/m^2 higher BMI (p = 0.0023). Having a high risk of sleep apnoea was associated with a 2.57 kg/m^2 higher BMI (p = 0.026).

BMI and current viral load were both positively associated with neck circumference. An increase in BMI by 1 kg/m^2 was associated with a 0.18 cm higher neck circumference (p<0.0001). A detectable viral load was associated with a 1.77 cm higher neck circumference (p = 0.004). Sex and BDI were both negatively associated with neck circumference. Being female was associated with a 2.34 cm lower neck circumference (p<0.0001). An increase in BDI by 10 points was associated with a 0.56 cm lower neck circumference (p = 0.0062).

Age was positively associated with MetScore. An increase in age by 10 years was associated with a 0.43-point higher MetScore (p = 0.019). BDI was negatively associated with MetScore. An increase in BDI score by 10 points was associated with a 0.48-point lower MetScore (p = 0.0059).

Neither HIV duration nor ART duration were associated with any cardiometabolic marker (Table 6).

3.6.2 Multivariable Model 1

3.6.2.1 All participants (n = 400)

Table 7 shows the multivariable analyses investigating the association between cardiometabolic markers and sleep and depression markers individually, in all

participants. Sex was not included in the model for SBP and DBP since in the bivariate analyses (Table 6), the p-value was greater than 0.2 (Redman et al, 2018).

Table 7. Multivariable analyses in a rural cohort (n = 400) of the association between cardiometabolic markers and each sleep and depression marker individually and the effect of the interaction between PSQI/ESS/BQ/BDI and HIV status on the cardiometabolic markers

	PSQI /ESS/ BQ/ BDI			***Age (years)***			***Sex***			***BMI (kg/m^2)***			***HIV status***			***Interaction of PSQI/ESS/BQ/BDI with HIV status*** **		
SBP (mmHg) *	*ß*	*SE*	*P*	*ß*	*SE*	*P*	*ß*	*SE*	*P*	*ß*	*SE*	*P*	*ß*	*SE*	*P*	*ß*	*SE*	*P*
PSQI	0.19	0.39	0.62	**0.61**	**0.078**	**<0.0001**				**0.63**	**0.19**	**0.0008**	1.56	2.40	0.52	-0.49	0.80	0.54
ESS	0.051	0.15	0.73	**0.61**	**0.077**	**<0.0001**				**0.63**	**0.19**	**0.0009**	1.33	2.37	0.58	-0.35	0.3	0.24
BQ	**6.01**	**2.85**	**0.036**	**0.61**	**0.077**	**<0.0001**				**0.54**	**0.19**	**0.0045**	1.65	2.35	0.48	3.55	5.74	0.54
BDI	-0.075	0.12	0.52	**0.61**	**0.077**	**<0.0001**				**0.62**	**0.19**	**0.001**	1.50	2.37	0.53	-0.33	0.24	0.17
DBP (mmHg) *																		
PSQI	-0.012	0.28	0.97	**0.21**	**0.056**	**0.0002**				**0.34**	**0.14**	**0.013**	0.65	1.74	0.71	-0.38	0.58	0.51
ESS	0.14	0.11	0.20	**0.22**	**0.056**	**0.0001**				**0.34**	**0.14**	**0.012**	0.59	1.71	0.73	-0.19	0.22	0.37
BQ	**5.03**	**2.06**	**0.015**	**0.21**	**0.055**	**0.0002**				0.27	0.14	0.051	0.91	1.70	0.59	2.95	4.15	0.48
BDI	-0.11	0.084	0.2	**0.21**	**0.056**	**0.0002**				**0.33**	**0.14**	**0.015**	0.87	1.71	0.61	-0.14	0.17	0.41
BMI (kg/m$^{2)}$ *																		
PSQI	-0.16	0.095	0.086	**0.073**	**0.020**	**0.0003**	**3.2**	**0.66**	**<0.0001**				**-2.62**	**0.60**	**<0.0001**	-0.27	0.19	0.16
ESS	-0.043	0.039	0.27	**0.069**	**0.020**	**0.0007**	**3.3**	**0.68**	**<0.0001**				**-2.52**	**0.61**	**<0.0001**	-0.035	0.078	0.66
BQ	**2.86**	**0.74**	**0.0001**	**0.067**	**0.020**	**0.0008**	**2.87**	**0.66**	**<0.0001**				**-2.26**	**0.60**	**0.0002**	-1.09	1.50	0.47
BDI	-0.057	0.030	0.061	**0.068**	**0.020**	**0.0008**	**3.35**	**0.67**	**<0.0001**				**-2.40**	**0.61**	**<0.0001**	-0.061	0.063	0.33
Neck circum (cm) *																		
PSQI	0.082	0.043	0.059	**0.026**	**0.0094**	**0.0055**	**-3.21**	**0.31**	**<0.0001**	**0.23**	**0.023**	**<0.0001**	0.28	0.28	0.32	0.019	0.087	0.83
ESS	0.0075	0.018	0.68	**0.028**	**0.0093**	**0.0027**	**-3.2**	**0.32**	**<0.0001**	**0.23**	**0.023**	**<0.0001**	0.23	0.28	0.41	-0.0019	0.036	0.96
BQ	0.25	0.35	0.47	**0.028**	**0.0093**	**0.0028**	**-3.2**	**0.31**	**<0.0001**	**0.23**	**0.023**	**<0.0001**	0.25	0.28	0.37	-1.13	0.69	0.10
BDI	-0.017	0.014	0.23	**0.028**	**0.0093**	**0.0031**	**-3.15**	**0.31**	**<0.0001**	**0.23**	**0.023**	**<0.0001**	0.27	0.28	0.33	-0.025	0.029	0.38
MetScore *																		
PSQI	-0.0047	0.011	0.67	**0.016**	**0.0022**	**<0.0001**	**-0.15**	**0.073**	**0.039**				0.024	0.068	0.72	-0.029	0.023	0.21
ESS	0.0012	0.0044	0.79	**-0.016**	**0.0022**	**<0.0001**	**-0.16**	**0.075**	**0.037**				0.028	0.067	0.67	-0.0070	0.0086	0.42
BQ	**0.32**	**0.080**	**<0.0001**	**0.015**	**0.0021**	**<0.0001**	**-0.19**	**0.072**	**0.0094**				0.057	0.066	0.39	-0.074	0.16	0.65
BDI	-0.0068	0.0034	0.4	**0.015**	**0.0022**	**<0.0001**	**-0.13**	**0.074**	**0.072**				0.043	0.067	0.52	-0.010	0.0069	0.14

The outcome variable was SBP/DBP/BMI/Neck circumference /MetScore while adding a single sleep/depression indicator at a time (PSQI/ESS/BQ/BDI) while adjusting for the necessary variables such as age, sex, BMI and HIV status. SBP = systolic blood pressure, DBP = diastolic blood pressure, BMI = body mass index, Neck circum = neck circumference, MetScore = metabolic score, PSQI = Pittsburgh Sleep Quality Index, ESS = Epworth Sleepiness Scale, BQ = Berlin Questionnaire, BDI = Beck's Depression Inventory; for sex: 0 = males and 1 = females; HIV status: 0 = controls and 1 = HIV+ * main effects without interactions; ** interactions were tested separately in different models for each outcome variable while including all main effects shown above (the effect of the interaction on the beta of each main effect did not change meaningfully)

SBP was positively associated with BQ when age, BMI and HIV status were adjusted for (Table 7). A high risk of sleep apnoea was associated with a 6.01 mmHg higher SBP (p =0.036). HIV status did not interact significantly with PSQI (p = 0.54), ESS (p = 0.24), BQ (p = 0.54) or BDI (p = 0.17) to affect SBP

DBP was positively associated with BQ when age, BMI and HIV status were adjusted for. (Table 7) A high risk of sleep apnoea was associated with a 5.03 mmHg higher DBP (p = 0.015). HIV status did not interact significantly with PSQI (p = 0.51), ESS (p = 0.37), BQ (p = 0.48) or BDI (p = 0.41) to affect DBP

BMI was positively associated with BQ after adjsuting for age, sex and HIV status (Table 7). A high risk of sleep apnoea was associated with a 2.86 kg/m^2 higher BMI (p = 0.0001). HIV status did not interact significantly with PSQI (p = 0.16), ESS (p = 0.66), BQ (p = 0.47) or BDI (p = 0.33) to affect BMI.

Neck circumference was not associated with PSQI (p = 0.059), ESS (p = 0.68), BQ (p = 0.47) or BDI (p = 0.23) after adjusting for age, sex, BMI and HIV status (Table 7). HIV status did not interact significantly with PSQI (p = 0.83), ESS (p = 0.96), BQ (p = 0.1) or BDI (p = 0.38) to affect neck circumference.

MetScore was positively associated with BQ after adjusting for age, sex, and HIV status (Table 7). A high risk of sleep apnoea was associated with a 0.32-point increase in MetScore (p < 0.0001). HIV status did not interact significantly with PSQI (p = 0.21), ESS (p = 0.42), BQ (p = 0.65) or BDI (p = 0.14) to affect MetScore.

3.6.2.2 HIV+ participants (n = 200)

Table 8 shows the association between cardiometabolic markers and sleep and depression markers individually, in the HIV+ participants. Age was not included in the model for BMI and neck circumference since in the bivariate analyses (Table 6), the p-values were greater than 0.2 (Redman et al, 2018).

Table 8. Multivariable analyses in 200 HIV+ rural participants of the association between cardiometabolic markers and each sleep and depression marker individually

	PSQI /ESS/ BQ/ BDI			***Age (years)***			***sex***			***BMI (kg/m^2)***			***ART duration (days)***			***Current viral load***		
	ß	*SE*	*P*	*ß*	*SE*	*P*	*ß*	*SE*	*P*	*ß*	*SE*	*P*	*ß*	*SE*	*P*	*ß*	*SE*	*P*
SBP (mmHg)																		
PSQI	0.60	0.68	0.38	**0.74**	**0.16**	**<0.0001**	-5.87	4.49	0.19	**1.33**	**0.31**	**<0.0001**	**0.0039**	**0.0018**	**0.032**	-6.74	4.46	0.13
ESS	0.057	0.23	0.8	**0.74**	**0.16**	**<0.0001**	-5.53	4.57	0.23	**1.28**	**0.31**	**<0.0001**	**0.0037**	**0.0018**	**0.04**	-6.25	4.44	0.16
BQ	8.35	5.09	0.10	**0.75**	**0.16**	**<0.0001**	-6.58	4.48	0.14	**1.18**	**0.31**	**0.0002**	0.0032	0.0018	0.075	-5.88	4.40	0.18
BDI	-0.13	0.17	0.43	**0.74**	**0.16**	**<0.0001**	-4.96	4.46	0.27	**1.25**	**0.31**	**<0.0001**	**0.0039**	**0.0018**	**0.032**	-6.28	4.43	0.16
DBP (mmHg)																		
PSQI	0.068	0.55	0.90	0.26	0.13	0.052	-4.99	3.66	0.18	**0.79**	**0.26**	**0.0025**	**0.0030**	**0.0015**	**0.038**	-1.63	3.63	0.65
ESS	0.16	0.19	0.38	0.26	0.13	0.051	-5.64	3.70	0.13	**0.8**	**0.25**	**0.0019**	**0.0031**	**0.0014**	**0.035**	-1.56	3.6	0.67
BQ	5.31	4.15	0.20	**0.26**	**0.13**	**0.046**	-5.75	3.66	0.12	**0.72**	**0.25**	**0.0051**	0.0027	0.0015	0.064	-1.34	3.59	0.71
BDI	-0.12	0.13	0.36	0.25	0.13	0.059	-4.63	3.62	0.20	**0.76**	**0.25**	**0.0031**	**0.0032**	**0.0015**	**0.029**	-1.60	3.6	0.66
BMI (kg/m^2)																		
PSQI	-0.33	0.14	0.023				**2.78**	**1.08**	**0.011**				**-0.0010**	**0.0004**	**0.022**	0.63	1.14	0.58
ESS	-0.047	0.058	0.43				**2.77**	**1.11**	**0.014**				**-0.001**	**0.0004**	**0.028**	0.41	1.15	0.72
BQ	**3.01**	**1.35**	**0.027**				2.09	1.1	0.059				**-0.001**	**0.0004**	**0.016**	0.56	1.13	0.62
BDI	**-0.085**	**0.043**	**0.048**				**2.79**	**1.08**	**0.011**				**-0.0009**	**0.0004**	**0.052**	0.4	1.14	0.73
Neck circum (cm)																		
PSQI	0.063	0.075	0.40				**-2.79**	**0.56**	**<0.0001**	**0.22**	**0.040**	**<0.0001**	0.00002	0.0002	0.92	**1.82**	**0.58**	**0.002**
ESS	0.0001	0.029	0.99				**-2.74**	**0.57**	**<0.0001**	**0.21**	**0.04**	**<0.0001**	0.00008	0.0002	0.97	**1.86**	**0.58**	**0.0017**
BQ	-0.43	0.70	0.54				**-2.68**	**0.57**	**<0.0001**	**0.22**	**0.040**	**<0.0001**	0.00003	0.0002	0.91	**1.84**	**0.58**	**0.0018**
BDI	-0.032	0.022	0.14				**-2.65**	**0.56**	**<0.0001**	**0.21**	**0.04**	**<0.0001**	0.00004	0.0002	0.87	**1.84**	**0.58**	**0.0017**
MetScore																		
PSQI	-0.0077	0.064	0.9	**0.043**	**0.015**	**0.0051**	**-1.18**	**0.43**	**0.0067**	**0.31**	**0.03**	**<0.0001**	0.00029	0.00017	0.092	0.28	0.42	0.5
ESS	0.0091	0.022	0.68	**0.043**	**0.015**	**0.005**	**-1.22**	**0.43**	**0.0054**	**0.31**	**0.029**	**<0.0001**	0.00029	0.00017	0.084	0.28	0.42	0.51
BQ	0.43	0.49	0.38	**0.044**	**0.015**	**0.0046**	**-1.25**	**0.43**	**0.0041**	**0.31**	**0.03**	**<0.0001**	0.00027	0.00017	0.12	0.3	0.42	0.48
BDI	-0.026	0.016	0.097	**0.042**	**0.015**	**0.0065**	**-1.12**	**0.42**	**0.0085**	**0.31**	**0.029**	**<0.0001**	0.00033	0.00017	0.052	0.27	0.42	0.51

The outcome variable was SBP/DBP/BMI/Neck circumference while adding a single sleep/depression indicator at a time (PSQI/ESS/BQ/BDI) while adjusting for the necessary variables such as age, sex, BMI, ART duration and current viral load. SBP = systolic blood pressure, DBP = diastolic blood pressure, BMI = body mass index, Neck circum = neck circumference, MetScore = metabolic score, PSQI = Pittsburgh Sleep Quality Index, ESS = Epworth Sleepiness Scale, BQ = Berlin Questionnaire, BDI = Beck's Depression Inventory, ART = anti-retroviral; for sex, 0 = male and 1 = female; for current viral load, 0 =undetectable and 1 = detectable

SBP was not associated with PSQI (p = 0.38), ESS (p = 0.8), BQ (p = 0.1) or BDI (p = 0.43) after adjusting for age, sex, BMI, ART duration and current viral load.

DBP was not associated with PSQI (p = 0.9), ESS (p = 0.38), BQ (p = 0.2) or BDI (p = 0.36) after adjusting for age, sex, BMI, ART duration and current viral load.

BMI was positively associated with BQ after adjusting for sex, ART duration and current viral load. A high risk of sleep apnoea was associated with a 3.01 kg/m^2 higher BMI (p = 0.027). BMI was negatively associated with PSQI and BDI after adjusting for sex, ART duration and current viral load. An increase in PSQI by 1 was associated with a 0.33 kg/m^2 lower BMI (p 0.023). An increase in BDI by 10 was associated with a 0.85 kg/m^2 lower BMI (p = 0.048).

Neck circumference was not associated with PSQI (p = 0.4), ESS (p = 0.99), BQ (p = 0.54) or BDI (p = 0.14) after adjusting for sex, BMI, ART duration and current viral load.

MetScore was not associated with PSQI (p = 0.68), ESS (p = 0.38), BQ (p = 0.097) or BDI after adjusting for age, sex, BMI, ART duration and current viral load.

3.6.3 Multivariable Model 2

3.6.3.1 All participants (n = 400)

Table 9 shows the multivariable analyses of the association between cardiometabolic markers and sleep and depression indicators collectively, in all participants. All sleep/depression independent variables were included in one model for each outcome variable.

Table 9. Multivariable analyses in 400 rural participants of the association between cardiometabolic markers and sleep and depression markers collectively and the effect of the interaction between PSQI/ESS/BQ/BDI and HIV status on the cardiometabolic markers

	SBP (mmHg)			***DBP (mmHg)***			***BMI (kg/m^2)***			***Neck circumference (cm)***			***MetScore***		
Main effects*	ß	*SE*	*P*	ß	*SE*	*P*	ß	*SE*	*P*	ß	*SE*	*P*	ß	*SE*	*P*
Age (years)	**0.6**	**0.078**	**<0.0001**	**0.21**	**0.056**	**0.0002**	**0.065**	**0.020**	**0.0012**	**0.024**	**0.0094**	**0.0097**	**0.015**	**0.0022**	**<0.0001**
Sex							**3.12**	**0.67**	**<0.0001**	**-3.15**	**0.32**	**<0.0001**	**-0.17**	**0.07**	**0.022**
BMI (kg/m^2)	**0.71**	**0.19**	**0.0003**	**0.39**	**0.14**	**0.0055**				**0.23**	**0.023**	**<0.0001**			
HIV status	2.11	2.44	0.39	1.12	1.76	0.52	**-2.054**	**0.61**	**0.0008**	0.41	0.29	0.15	0.090	0.067	0.18
PSQI	0.29	0.42	0.49	0.09	0.31	0.77	-0.071	0.10	0.49	**0.12**	**0.047**	**0.0088**	0.0079	0.011	0.50
ESS	0.11	0.16	0.48	0.21	0.11	0.077	-0.038	0.039	0.34	0.0075	0.018	0.68	0.0016	0.0044	0.71
BQ	**6.85**	**2.94**	**0.021**	**5.72**	**2.12**	**0.0072**	**3.22**	**0.75**	**<0.0001**	0.40	0.36	0.26	**0.17**	**0.066**	**0.0099**
BDI	-0.1	0.13	0.44	-0.14	0.093	0.14	-0.065	0.033	0.052	**-0.037**	**0.015**	**0.018**	**-0.011**	**0.0037**	**0.0031**
Interactions*															
*HIV status*PSQI*	-0.18	0.83	0.83	-0.21	0.60	0.72	-0.25	0.19	0.19	0.050	0.088	0.57	-0.022	0.023	0.32
*HIV status*ESS*	-0.28	0.30	0.36	-0.16	0.22	0.46	-0.011	0.077	0.89	0.0062	0.035	0.86	-0.0036	0.0084	0.67
*HIV status*BQ*							-1.08	1.50	0.47	-1.29	0.69	0.063	-0.087	0.16	0.59
*HIV status*BDI*	-0.34	0.24	0.16	-0.020	0.022	0.36	-0.030	0.063	0.64	-0.025	0.029	0.39	-0.0073	0.0068	0.28

The outcome variable was SBP/DBP/BMI/Neck circumference/MetScore with all sleep/depression indicators in the model (PSQI, ESS, BQ and BDI) while adjusting for the necessary variables such as age, sex, BMI and HIV status. SBP = systolic blood pressure, DBP = diastolic blood pressure, BMI = body mass index, MetScore = metabolic score, PSQI = Pittsburgh Sleep Quality Index, ESS = Epworth Sleepiness Scale, BQ = Berlin Questionnaire, BDI = Beck's Depression Inventory; for sex: 0 = males and 1 = females; HIV status: 0 = controls and 1 = HIV+ * main effects without interactions; ** interactions were tested separately in 4 different models for each outcome variable while including all main effects shown above (the effect of the interaction on the beta of each main effect did not change meaningfully)

SBP was positively associated with BQ when age, BMI, HIV status, PSQI, ESS and BDI were adjusted for. A high risk of sleep apnoea was associated with a 6.85 mmHg higher SBP ($p = 0.021$). HIV status did not interact significantly with PSQI ($p = 0.6$), ESS ($p = 0.32$), BQ ($p = 0.6$) or BDI ($p = 0.24$) to affect SBP

DBP was positively associated with BQ when age, BMI, HIV status, PSQI, ESS and BDI were adjusted for. A high risk of sleep apnoea was associated with a 5.72 mmHg higher DBP ($p = 0.0072$). DBP was negatively associated with BDI when age, BMI, HIV status, PSQI, ESS and BQ were adjusted for. An increase in BDI by 1 point was associated with a 0.21 mmHg lower DBP ($p = 0.029$). HIV status did not interact significantly with PSQI ($p = 0.63$), ESS ($p = 0.53$), BQ ($p = 0.52$) or BDI ($p = 0.53$) to affect DBP

BMI was positively associated with BQ when age, sex, HIV status, PSQI, ESS and BDI were adjusted for. A high risk of sleep apnoea was associated with a 3.22 kg/m^2 higher BMI ($p<0.0001$). BMI was negatively associated with HIV status when age, sex, PSQI, ESS, BQ and BDI were adjusted for ($p = 0.0008$) . Being HIV+ was associated with a 2.054kg/m^2 lower BMI. HIV status did not interact significantly with PSQI ($p = 0.19$), ESS ($p = 0.89$), BQ ($p = 0.47$) or BDI ($p = 0.64$) to affect BMI.

Neck circumference was positively associated with PSQI when age, sex, BMI, HIV status, ESS, BQ and BDI were adjusted for. An increase in PSQI by 1 point was associated with a 0.12 cm higher neck circumference ($p = 0.0088$). Neck circumference was negatively associated with BDI when age, sex, BMI, HIV status, PSQI, ESS and BDI were adjusted for. An increase in BDI by 10 points was associated with a 0.37 cm lower neck circumference ($p = 0.018$). HIV status did not interact significantly with PSQI ($p = 0.57$), ESS ($p = 0.86$), BQ ($p = 0.063$) or BDI ($p = 0.39$) to affect neck circumference.

MetScore was positively associated with BQ and negatively associated with BDI when age, sex and HIV status were adjusted for. A high risk of sleep apnoea was associated with a 0.37-point higher MetScore ($p < 0.0001$). An increase in BDI scores by 10 was associated with a 0.11-point lower MetScore ($p = 0.031$). Being HIV+ was not associated with MetScore ($p = 0.18$). HIV status did not interact significantly with PSQI ($p = 0.32$), ESS ($p = 0.67$), BQ ($p = 0.59$) or BDI ($p = 0.28$) to affect BMI.

3.6.3.2 HIV+ participants (n = 200)

Table 10 shows the multivariable analyses of the association between cardiometabolic markers and sleep and depression markers collectively, in the HIV+ participants.

Table 10. Multivariable analyses in 200 HIV+ rural participants of the association between cardiometabolic markers with sleep and depression markers collectively

	SBP (mmHg)			***DBP (mmHg)***			***BMI (kg/m^2)***			***Neck circumference (cm)***			***MetScore***		
	ß	*SE*	*P*	*ß*	*SE*	*P*	*ß*	*SE*	*P*	*ß*	*SE*	*P*	*ß*	*SE*	*P*
Age (years)	**0.73**	**0.16**	**<0.0001**	0.24	0.13	0.062							**0.041**	**0.015**	**0.0074**
Sex	-7.23	4.59	0.12	-6.45	3.75	0.088	**2.39**	**1.1**	**0.031**	**-2.69**	**0.57**	**<0.0001**	**-1.30**	**0.44**	**0.0034**
BMI (kg/m^2)	**1.22**	**0.32**	**0.0002**	**0.73**	**0.26**	**0.0063**				**0.22**	**0.041**	**<0.0001**	**0.31**	**0.03**	**<0.0001**
ART duration (days)	**0.0041**	**0.0019**	**0.029**	**0.0033**	**0.0015**	**0.033**	**-0.0011**	**0.00044**	**0.016**	0.00011	0.00023	0.63	0.00035	0.00018	0.051
Current viral load	-6.83	4.45	0.13	-1.68	3.63	0.65	0.66	1.12	0.56	**1.74**	**0.58**	**0.0031**	0.25	0.42	0.56
PSQI	1.14	0.79	0.15	0.41	0.65	0.53	-0.26	0.16	0.12	0.15	0.085	0.078	0.062	0.075	0.41
ESS	0.065	0.24	0.12	0.19	0.19	0.33	-0.032	0.058	0.58	0.01	0.03	0.74	0.016	0.022	0.47
BQ	8.76	5.22	0.096	5.58	4.27	0.19	**3.53**	**1.34**	**0.0095**	-0.34	0.71	0.64	0.53	0.5	0.29
BDI	-0.34	0.2	0.087	-0.25	0.16	0.13	-0.058	0.049	0.24	**-0.053**	**0.025**	**0.039**	**-0.04**	**0.019**	**0.035**

The outcome variable was SBP/DBP/BMI/Neck circumference while including all sleep and depression indicators (PSQI, ESS, BQ and BDI) in the model while adjusting for the necessary variables such as age, sex, BMI, ART duration and current viral load. SBP = systolic blood pressure, DBP = diastolic blood pressure, BMI = body mass index, MetScore = metabolic score, PSQI = Pittsburgh Sleep Quality Index, ESS = Epworth Sleepiness Scale, BQ = Berlin Questionnaire, BDI = Beck's Depression Inventory, ART = anti-retroviral; for sex, 0 = male and 1 = female; for current viral load, 0 =undetectable and 1 = detectable

SBP was not associated with PSQI (p = 0.15), ESS (p = 0.12), BQ (p = 0.096) or BDI (p = 0.087) when age, sex, BMI, ART duration, current viral load and the respective sleep/depression indicators were adjusted for. SBP was positively associated with ART duration when age, sex, BMI, current viral load, PSQI, ESS, BQ and BDI were adjusted for. An increase in ART duration by 1000 days (approximately 2.7 years) was associated with a 4.1 mmHg higher SBP (p = 0.029).

DBP was not associated with PSQI (p = 0.53), ESS (p = 0.33), BQ (p =0.19) or BDI (p = 0.13) when age, sex, BMI, ART duration, current vira, load and sleep/depression indicators were adjusted for. DBP was positively associated with ART duration when age, sex, BMI, current viral load, PSQI, ESS, BQ and BDI were adjusted for. An increase in ART duration by 1000 days (approximately 2.7 years) was associated with a 3.3 mmHg higher DBP (p = 0.033).

BMI was not associated with PSQI (p = 0.12), ESS (p = 0.58) or BDI (p = 0.24) when sex, ART duration, current viral load and sleep/depression indicators were adjusted for. BMI was positively associated with BQ when sex, ART duration, current viral load, PSQI, ESS and BDI were adjusted for. Having a high risk of sleep apnoea was associated with 3.53 kg/m^2 higher BMI (p = 0.0095). BMI was negatively associated with ART duration when sex, current viral load, PSQI, ESS, BQ and BDI were adjusted for. An increase in ART duration by 1000 days (approximately 2.7 years) was associated with a 1.1 kg/m^2 lower BMI (p = 0.016).

Neck circumference was not associated with PSQI (p = 0.078), ESS (p = 0.74) or BQ (p = 0.64) when sex, BMI, ART duration, current viral load and sleep/depression indicators were adjusted for. Neck circumference was negatively associated with BDI when sex, BMI, ART duration, current viral load, PSQI, ESS and BQ were adjusted for. An increase in BDI by 10 points was associated with a 0.53 cm lower neck circumference (p = 0.039). Neck circumference was positively associated with current viral load when sex, BMI, ART duration, PSQI, ESS, BQ and BDI were adjusted for. A detectable viral load was associated with 1.74 cm higher neck circumference (p = 0.0031).

MetScore was negatively associated with BDI when age, sex, BMI, ART duration, CD4 duration, PSQI, ESS and BQ were adjusted for. An increase in BDI by 10 points was associated with a 0.4-point lower MetScore (p = 0.035). MetScore was not associated with PSQI (p = 0.41), ESS (p = 0.47) or BQ (p = 0.29).

3.7 Risk of hypertension in all participants (n = 400)

3.7.1 Bivariate analyses

Table 11 shows the bivariate analysis of hypertension status.

There was a significant difference in age, BMI, and BDI scores between the hypertensive participants and non-hypertensive participants. The hypertensive participants were older ($p<0.0001$), had higher BMIs ($p = 0.0021$) and lower BDI scores ($p = 0.0014$) than the non-hypertensive participants. The hypertensive group also had a higher prevalence of a “high risk of OSA” classification compared to the non-hypertensive group ($p = 0.0012$). There was no significant difference between the hypertensive and non-hypertensive group in terms of sex ($p = 0.22$), PSQI scores ($p = 0.95$), ESS scores ($p = 0.18$), the number of HIV+ participants ($p = 0.19$) and the number of participants with the presence of pain currently ($p = 0.50$).

Table 11. Bivariate analyses of the correlates of hypertension in 400 rural participants

	Hypertensive participants	***Non-hypertensive participants***	***t value (df)***	***P-value***
*Age (years), mean (SD)**	**48.5 (15.4)**	**39.9 (13.6)**	**t (398) = 5.84**	**<0.0001**
*Males (%)***	32.5	26.8	-	0.22
*BMI (kg/m^2), mean (SD)**	**27.25 (5.97)**	**25.26 (6.60)**	**t (399) = 3.10**	**0.0021**
*PSQI score, mean (SD) **	4.19 (3.19)	4.17 (3.2)	t (398) = 0.063	0.95
*ESS, mean (SD)**	8.79 (7.58)	9.87 (8)	t (398) = 1.35	0.18
*High risk of sleep apnoea (%)***	**28.8**	**15.2**	**-**	**0.0012**
*BDI**	**6.15 (7.82)**	**9.43 (11.44)**	**t (398) = 3.22**	**0.0014**
*HIV+ (%)***	45.8	53.0	-	0.19
*Presence of pain currently (%)***	26.9	30.6	-	0.50

SD = standard deviation, PSQI = Pittsburgh Sleep Quality Index, ESS = Epworth Sleepiness Scale, BQ = Berlin Questionnaire, BDI = Beck's Depression Inventory; * an unpaired t-test was used; ** a Fisher's exact test was used

3.7.2 Multivariable analysis

Table 12 shows the predictive analysis of hypertension in all participants.

Being older ($p<0.0001$) and having a high risk of sleep apnoea ($p = 0.0022$) were risk factors for hypertension. For every one year of age, the odds of being hypertensive increased by 4%. Participants with a high risk of sleep apnoea had a 2.45 times higher odds of being hypertensive than participants with a low risk of sleep apnoea. Higher BDI scores had a protective effect against hypertension ($p = 0.0003$). For every 1-point increase in BDI scores, the odds of being hypertensive is reduced by 5%.

There was a significant interaction between PSQI and HIV status on the odds of being hypertensive ($p = 0.015$). In the general population, for every 1-point increase in PSQI, the odds of being hypertensive increases by 13%. In the HIV+ participants, for every 1-point increase in PSQI, the odds of being hypertensive reduces by 5%. However, when the interaction between PSQI and HIV status was added to the model, HIV status became significant in a positive direction (for HIV+ participants: estimate = 0.9, $p = 0.016$).

Table 12. Multivariable analyses investigating the odds of being hypertensive in 400 rural participants

	Odds ratio	***95% Wald confidence interval***	***P-value***
Main effects*			
Age (years)	**1.04**	**1.03 -1.06**	**<.0001**
BMI (kg/m^2)	1.03	0.99- 1.07	0.1
PSQI	1.04	0.97-1.13	0.26
ESS	0.99	0.97 -1.02	0.67
BQ	**2.45**	**1.38- 4.36**	**0.0022**
BDI	**0.95**	**0.92- 0.98**	**0.0003**
HIV status	1.2	0.77- 1.87	0.43
Interactions			
*PSQI*HIV status*	**At HIV status = 0: 1.13** At HIV status = 1: 0.95	**At HIV status = 0: 1.03- 1.25** At HIV status = 1: 0.85- 1.06	**0.015**
*ESS*HIV status*	At HIV status = 0: 1.01 At HIV status = 1: 0.99	At HIV status = 0: 0.96 -1.05 At HIV status = 1: 0.95- 1.02	0.51
*BQ*HIV status*	At HIV status = 0: 1.95 At HIV status = 1: 3.34	At HIV status = 0: 0.93- 4.08 At HIV status = 1: 1.41- 7.9	0.34
*BDI*HIV status*	At HIV status = 0: 0.97 At HIV status = 1: 0.94	At HIV status = 0: 0.93- 1.01 At HIV status = 1: 0.91- 0.97	0.29

BMI = body mass index, PSQI = Pittsburgh Sleep Quality Index, ESS = Epworth Sleepiness Scale, BQ = Berlin Questionnaire, BDI = Beck's Depression Inventory; For HIV status, 0 = controls and 1 = HIV+; * main effects without interactions; ** interactions were tested separately in 4 different models for each outcome variable while including all main effects shown above (the effect of the interaction on the beta of each main effect did not change meaningfully)

CHAPTER 4: DISCUSSION AND CONCLUSION

The prevalence of self-reported poor sleep quality was similar between the HIV+ participants and the controls (Table 2). In the HIV+ participants, higher PSQI scores was associated with shorter HIV duration, the presence of pain currently and greater BDI scores (Table 5). In our 400 participants, a higher SBP, DBP, BMI and MetScore were all associated with a higher risk of sleep apnoea (Table 7). HIV status did not interact with any sleep/depression variable to affect cardiometabolic risk (Table 7). Older age and having a high risk of sleep apnoea were risk factors for hypertension (Table 12). However, higher BDI scores reduced the risk of hypertension (Table 12). In the HIV+ and control participants as a whole, higher PSQI scores was associated with a higher risk of hypertension. In the HIV+ participants, higher PSQI scores was associated with a lower risk of hypertension. However, when the interaction between PSQI and HIV status was added to the model, HIV status became significant.

4.1 Questionnaire Validation and Factor Analysis

Since our study relied on questionnaires that were translated for the first time into Sesotho, it was necessary to first validate the questionnaires and also run factor analysis.

The Pittsburgh Sleep Quality Index (PSQI) had an acceptable internal consistency of 0.7. The Epworth Sleepiness Scale (ESS) and Beck's Depression Inventory I (BDI) both had excellent internal consistencies of 0.9 for the ESS and 0.92 for the BDI. The PSQI, ESS and BDI all had construct validity. Other studies confirm that the PSQI (Spira et al, 2012; Qiu et al, 2016, Redman et al, 2018), ESS (Redman et al, 2018; Roche et al, 2021) and BDI (Schotte et al, 1997; Redman et al, 2018) have acceptable or excellent internal consistency and construct validity.

4.2 Sleeping patterns

4.2.1 All participants (n = 400)

Sleep characteristics in the present study were consistent with other rural areas in South Africa. Firstly, our self-reported average sleep duration of 8 hours is similar to the 8.23 hours (Gómez-Olivé et al, 2018) and 8.28 hours (Peltzer & Pengpid, 2018) observed in other South African rural participants. Additionally, the prevalence of self-reported poor sleep quality in our sample (33.8%) was similar to Kahn et al, (2012) who reported a 30.2% prevalence of poor sleep quality among 4044 rural, South African participants. Studies in Norway and South Africa suggest that rural dwellers have longer sleep durations than urban dwellers (self-reporting) (Ursin et al, 2005; Peltzer 2012). Rural dwellers often have fewer screens, less artificial light and less night-time entertainment (for example, night clubs and cinemas) than non-rural dwelling South Africans and consequently, rural dwellers may sleep earlier and for longer hours.

4.2.2 HIV+ participants

Our study adds to a recent study investigating sleep in HIV+ and HIV- participants in a rural region of Mpumalanga, which, similar to our study, found HIV+ participants slept for a shorter time per night (Redman et al, 2023). However, despite sleeping 0.5 hours less than the controls, the participants of our study had normal sleep quality (PSQI = 3.96) whereas Redman et al (2018) found an average PSQI of 7.7 among the 139 South African urban HIV+ participants of their study, indicating poor sleep quality. However, as mentioned earlier, rural dwellers generally have better sleep quality than urban dwellers (Ursin et al, 2005; Peltzer 2012). Additionally, Redman et al (2018) found that poor sleep quality in their participants was associated with daytime sleepiness and pain. Conversely, in the Redman et al (2018) study, the prevalence pain in the last month (73%) was higher than in the present study. This suggests that the high prevalence of pain in Redman et al (2018) study may have contributed to the poor sleep quality. The results of our study may suggest that when

participants have less pain, they have better sleep quality. However, further studies are required to investigate sleep quality in PLWH in rural areas of South Africa.

4.2.3 HIV+ participants vs controls

There is limited research on Africans living in Africa that compares sleep quality in PLWH and the general population. To the best of our knowledge, only a single South African study has compared sleep quality in PLWH and the general population (Gómez-Olivé et al, 2018). Indeed, Gómez-Olivé et al (2018) found that HIV+ participants who had a high viral load reported more sleep disturbances than HIV- participants. However, 80.1% of our HIV+ participants had a “lower than detectable” viral load. Hence, to the best of our knowledge, our study is the first South African study to do an in-depth comparison between self-reported sleep quality between PLWH and the general population.

Outside of SSA, newer research may challenge previous findings that suggest PLWH have poorer sleep quality than the general population. Unquestionably, several studies show that PLWH have overall poorer sleep quality, sleep fewer hours, have a greater sleep latency, lower sleep efficiency and more sleep disturbances than HIV- participants (Junqueira et al, 2008; Abdu et al, 2020; Wu et al, 2015). However, Polanka et al (2019) found that while insomnia symptoms were significantly different between HIV+ veterans and their controls, the difference was only minimal. Specifically, 43.9% of the controls reported no insomnia symptoms whereas 40.7% of the HIV+ veterans reported no insomnia symptoms (Polanka et al, 2019). Additionally, Crum-Cianflone et al (2012) found no difference in sleep quality between HIV+ participants and the controls. Granted, the majority of studies that found poorer sleep quality in PLWH were conducted prior to the use of HAART, which describes the use of a combination of ART drugs. As Crum-Cianflone et al (2012) postulated, when PLWH are treated early and with HAART they may in fact have similar sleep quality as the general population. While the participants in the present study were treated fairly late (approximately 9 months after diagnosis), they were on HAART, which may have attenuated poor sleep quality associated with HIV infection.

4.3 Depression

Our finding of 21.5% of our HIV+ participants having symptoms of clinical depression is within the range of 14.8 – 41% prevalence found in other HIV+ rural populations in South Africa (Nyirenda et al, 2013; Rochat et al, 2006). It should be noted that the aforementioned populations used the Composite International Diagnostic Interview (Nyirenda et al, 2013) and the Edinburgh Postnatal Depression Scale (Rochat et al, 2006) to assess the degree of depressive symptoms. However, the prevalence of depression in South African urban HIV+ populations has been shown to be in the range of 30-55% (Simbayi et al, 2007; Ramirez-Avila et al, 2012; Redman et al, 2018). The higher prevalence of depression in PLWH in urban areas is expected since urban dwellers have been associated with more stressful lifestyles that increase the risk of depression (Gruebner et al, 2017).

Similar to the present study, several other studies show that there is a greater prevalence of depression among PLWH than the general population (Nakasujja et al, 2010; Norman et al, 1992; Wibbeler et al, 2012; Junqueira et al, 2008).

4.4 Cardiometabolic Risk

4.4.1 All participants (n = 400)

Cardiometabolic markers in the rural population of our study are broadly consistent to other studies conducted in rural areas of South Africa. Firstly, the average BMI of 26 kg/m^2 is within the 22.7 kg/m^2 to 27.5 kg/m^2 range that was found in other rural South African populations in Mpumalanga (Gómez-Olivé et al, 2018; Gaziano et al, 2017) and Limpopo (Godijk et al, 2020). Additionally, our obesity prevalence of 25% is within the 17 to 45% range that was found in other rural South African populations (Clark et al, 2015; Gómez-Olivé et al, 2018; Roche et al, 2020). The average blood pressure was in the pre-hypertensive range, which is similar to the average blood pressure that was found by Roche et al (2020) (138 mmHg/82 mmHg) and Gaziano et al (2017) (139 mmHg/81mmHg).

However, the hypertension prevalence of approximately 45.7% was lower than other studies conducted in rural areas of South Africa that reported a prevalence of 58.4% (Gaziano et al, 2017; Gómez-Olivé et al, 2018) and 61% (Roche et al, 2020). This may be because the participants in the aforementioned studies were older and on average, in their 60s. Nevertheless, the prevalence of hypertension in the present study is similar to the average prevalence of 46.7% for non-urban areas in South Africa (StatsSA 2016). Taken together, the high hypertension prevalence in the present study and other rural areas of South Africa (Gaziano et al, 2017; Gómez-Olivé et al, 2018; Roche et al, 2020) confirms that hypertension is an extensive problem in rural areas.

The low prevalence of treated hypertensives in the present study was concerning. Indeed, only 44.63% of hypertensives in the present study were treated. However, it may be that some individuals who appeared to have hypertension on the day were in fact, not hypertensive but simply had raised blood pressures due to the “white coat hypertension”. Nevertheless, Roche et al (2020) also reported a low hypertension treatment rate of only 30% in the rural South African population. This suggests that hypertension screening and treatment needs to be prioritised in rural areas of South Africa.

4.4.2 HIV+ participants

The cardiometabolic measurements in the HIV+ participants of our study were similar to other South African rural HIV+ participants. Indeed, the average BMI, SBP, DBP, obesity prevalence and hypertension prevalence were all similar to other South African rural HIV+ participants (Godijk et al, 2020; Schoffelen et al, 2015; Clark et al, 2015; Manne-Goehler et al, 2017). This is important because since it suggests that the study participants are a good representation of other South African rural communities and therefore, it would be easier to extrapolate our results to other South African rural communites

4.4.3 HIV+ participants vs controls

Our finding of similar cardiometabolic risk (besides BMI) between HIV+ participants and the controls is consistent with studies in South Africa (Clark et al, 2015; Godijk et al, 2020) but contrasts the findings globally and in high-income countries (HICs). Indeed, a global review found that the risk of incident CVD was twice as high in PLWH than the general population (Shah et al, 2018). However, traditional CVD risk factors such as smoking, hypertension and diabetes are more prevalent in PLWH compared to the general population in HICs (Triant et al, 2007; Vidrine 2009; Mdodo et al, 2015). Additionally, the majority of PLWH in HICs are white men whereas in SSA, the majority of PLWH are black women (UNAIDS 2017). Finally, a different strain of HIV (serotype C) is predominant in Africa compared to North America and Europe (Serotype B) (Avert, 2019). Consequently, because of the aforementioned differences, differences in cardiometabolic risk occur between South Africa and the rest of the world.

Our finding of lower BMIs in the HIV+ participants is expected since lower BMIs have been associated with advanced stages of the disease (Grunfeld et al, 2007; Maas et al, 1998). Furthermore, 40% of our HIV+ participants were at least at a WHO Stage 2 classification and from Stage 2 onwards, unintentional weight loss is common (WHO 2005). However, since on average our participants had been on ART for more than four years, the ART should have reversed the effects of unexplained weight loss. Perhaps the psychological distress of being HIV+ may have caused reduced appetite and therefore, a lower BMI than the controls.

4.5 Correlates of poor sleep quality in the HIV+ participants

Poorer self-reported sleep quality was associated with the presence of pain currently, a higher severity of depressive symptoms and shorter time since HIV+ diganosis. Several other studies have similar findings that pain is associated with poor sleep quality in PLWH (Redman et al, 2018; Vosvick et al, 2004; Crum-Cianflone et al, 2012). Indeed, pain is common among PLWH (Mphahlele et al, 2012; Namisango et

al, 2012; Barroso et al, 2015). PLWH experience pain due to the effect of the virus on the nervous system, due to opportunistic infection and/ or ART treatment side effects (Parker et al, 2014).

Our finding of poor self-reported sleep quality being associated with greater depression scores in PLWH is consistent with other studies (Junqueira et al, 2008; Oshinaike et al, 2014; Redman et al, 2018). Depression and poor sleep quality have a bidirectional relationship, whereby treating one of these conditions, we can improve the other condition (Ford and Kamerow 1989).

Our finding of poorer self-reported sleep quality being associated with longer HIV duration is inconsistent with other studies (Allavena et al, 2016; Milinkovic et al, 2020). However, the HIV duration in those studies were 12.4 years (Allavena et al, 2016) and 8 years (Milinkovic et al, 2020), which is longer than in the present study (5.5 years). In the present study, the increase in CD4 counts from baseline to current may contribute to the aforementioned association since studies show an increase in CD4 count is associated with better sleep quality in PLWH (Oshinaike et al, 2013; Seay et al, 2013). Therefore, in the present study, once participants began ART treatment, their CD4 counts improved and this improvement may have contributed to improved sleep quality in the HIV+ participants. Perhaps if our HIV duration was longer, we might have observed the decline in sleep quality that has been associated with longer HIV duration.

4.6 Association between cardiometabolic markers and sleep and depression indicators: all participants (n = 400)

4.6.1 No association between sleep quality and HIV status on cardiometabolic risk (CMR)

We found no association between sleep quality and cardiometabolic risk in this study, even when testing an interaction with HIV status. While very few studies have

investigated the interaction between HIV and sleep quality on CMR, the findings are controversial. Interestingly, Roche et al (2020) found that sleeping at the incorrect time increased inflammatory markers in HIV+ truck drivers but not in HIV- truck drivers. Since circadian misalignment might be a greater contributor to CMR in PLWH, it would confirm our finding of a lack of association between sleep quality and HIV status on CMR.

Polanka et al (2019) found that only those with the most severe insomnia symptoms were associated with an increased CVD risk in PLWH. This suggests that insomnia and not the subclinical symptoms promote CVD in PLWH (Polanka et al, 2019). However, the relationship between insomnia and CVD became non-significant once antidepressant use was adjusted for (Polanka et al, 2019). Additionally, it has been shown that cytokine levels are similar between PLWH who had sleep onset insomnia and those who did not (Gay et al, 2015). This suggests that insomnia might not affect inflammation levels in PLWH. Nevertheless, further research is needed to investigate if HIV infection interacts with poor sleep quality to potentiate CMR. Even though we investigated self-reported poor sleep quality (and not insomnia), the non-significant relationship found by Polanka et al (2019) and Gay et al (2015) suggests that perhaps, as mentioned, sleeping at unusual times may be a greater contributor to CMR in PLWH compared to poor sleep quality or insomnia.

4.6.2 No association between MetScore and HIV

In the present study, being HIV was not associated with CMR. This is in contrast to studies conducted in people of European ancestry which suggest being HIV+ increases CMR (de Wit et al, 2008; Brown et al, 2005; Tsiodras et al, 2000). However, the finding of the present study is confirmed by other studies conducted in SSA which also found no association between being HIV+ and CMR (Vos et al, 2020; Schoffelen et al, 2015; Clark et al, 2015). Interestingly, Dillon et al, 2013 found that PLWH in SSA have a lower CMR than the general population.

This difference in CMR between people of European ancestry and those living in SSA may be due to differences in the HIV+ population. For example, the majority of HIV+ people in HICs are white men whereas in SSA, it is black women (UNAIDS

2017). Additionally, there could be a different HIV strain that is predominant in SSA compared to other parts of the world ((Peeters 2001; Gaschen et al, 2002).

4.6.3 Association between the risk of OSA and blood pressures

In our population, a high risk of OSA was associated with a higher SBP and DBP. This finding is consistent with meta-analytic data using over 6000 participants (Xia et al, 2018) as well as several, other studies (Sánchez-de-la-Torre et al, 2013; Franklin et al, 2013; Bouloukaki et al, 2020; Jun et al, 2016) that found sleep apnoea increases the risk of hypertension.

OSA promotes hypertension by disrupting non-REM sleep, which may have severe consequences (Narkiewicz & Somers 1997). During non-REM sleep bodily functions slow down and sympathetic nervous system (SNS) activity decreases such that blood pressure and heart rate decrease (Narkiewicz & Somers 1997). However, OSA causes bouts of hypoxia and hypercapnia that promotes an increase in SNS activity (Narkiewicz & Somers 1997). Consequently, peripheral, vasoconstriction occurs that raises blood pressure (Narkiewicz & Somers 1997). Additionally, arousals cause a sudden increase in SNS activity that increases blood pressure and heart rate further (Narkiewicz & Somers 1997). Assuredly, these acute effects can continue following consciousness and cause hypertension (Narkiewicz & Somers 1997).

4.6.4 Association between neck circumference and poor sleep quality

We found that a larger neck circumference was associated with poorer self-reported sleep quality. Additionally, a larger neck circumference has been positively associated with a larger waist circumference (Ben-Noun et al, 2006; Onat et al, 2009; Zhang et al, 2020). Additionally, waist circumference (and not BMI) has been associated with poor sleep quality (Peltzer and Pengpid 2017). As mentioned earlier, poor sleep quality promotes weight gain through tiredness the next day, a more sedentary lifestyle, increased appetite, decreased satiety and having more time to consume food (Ryu et al, 2016; van Cauter et al, 2008; Qin et al, 2003). Therefore, the link between a larger neck circumference and poor sleep quality may be mediated through a higher waist circumference.

4.6.5 Association between neck circumference and severity of depression symptoms

A larger neck circumference was associated with a lower severity of depressive symptoms. As previously mentioned, neck circumference has been positively associated with waist circumference (Ben-Noun et al, 2006; Onat et al, 2009; Zhang et al, 2020), which is an indicator of central obesity (Barzin et al, 2015). Individuals with central obesity have been shown to have greater activation of the SNS, and consequently higher plasma norepinephrine levels, compared to individuals with general obesity (Grassi et al, 2004). Studies show that low norepinephrine levels are associated with depression (Klimek et al, 1997; Moret et al, 2011). Therefore, it is possible that the presence of central obesity in this study participants promoted elevated plasma norepinephrine levels that attenuated depressive symptoms.

4.6.6 Association between MetScore and depression symptoms

Our finding of a lower CMR being associated with greater severity of depression symptoms is inconsistent with other findings. Additionally, our finding of a greater severity of depressive symptoms being associated with a reduced odds of hypertension is also contrary to other findings. Depression has been associated with an increased CMR as indicated by platelet activation (Serebruany et al, 2003), endothelial dysfunction (van Dooren et al, 2016), hypertension (Meng et al, 2012) and higher levels of inflammation (Beurel et al, 2020). Furtermore, studies show that depression is associated with a higher risk of incident coronary artery disease (Brown et al, 2011), strokes (Pan et al, 2011) and peripheral artery disease (Grenon et al, 2012).

We suggest that in the present study, perhaps participants with symptoms of depression had poor appetite (Patkel 1977; Simmons et al, 2016) and therefore ate less, which lowered their intake of unhealthy food. Additionally, the participants with symptoms of depression may have spent more time at home (Choi et al, 2015) and thus, consumed less unhealthy “street food” or fast foods.

4.6.7 No association between neck circumference and the risk of sleep apnoea

Our finding of a lack of association between neck circumference and the risk of sleep apnoea is surprising since several studies have confirmed this relationship (Nukton et al, 2014; Senaratna et al, 2017). Perhaps in the present study, neck circumference was altered due to the presence of lipodystrophy in the HIV+ participants and this may have resulted in a lack of association between neck circumference and the risk of sleep apnoea (Alencastro et al, 2017).

4.7 Association between cardiometabolic markers and sleep and depression indicators: HIV+ participants (n = 200)

4.7.1 Association between blood pressures and ART duration

SBP and DBP were positively associated with ART duration. Our finding of increased ART duration being associated with increased blood pressure is consistent with studies that found that longer ART duration was independently associated with hypertension (Manner et al, 2013; Baekken et al, 2013; Seaberg et al, 2005). Additionally, HIV duration and ART duration were strongly associated in the present study ($r = 0.92$; $p < 0.0001$). Therefore, our results may suggest that longer HIV duration is associated with higher blood pressures. This is consistent with Medina-Torne et al (2012) and Manner et al (2012) who found that longer HIV duration increased the odds of being hypertensive.

In the present study, the HIV+ participants were not hypertensive. However, in the present study, ART duration was only 4.7 years and average HIV duration was only 5.5 years. We found that an increase in ART duration by 1000 days (approximately 2.7 years) was associated with a 4.1 mmHg higher SBP and 3.3 mmHg DBP. This

means that an ART duration of 4.7 years is associated with an increase in SBP by only 7 mmHg and DBP by only 5.6 mmHg. Therefore, the ART and HIV duration might not have been long enough to observe the presence of hypertension.

4.7.2 Association between BMI and ART duration

We found that a lower BMI was associated with a longer ART duration. As previously mentioned, there is a strong positive correlation between ART duration and HIV duration in the present study ($r = 0.92$; $p < 0.0001$). Hence, a higher BMI may be associated with a shorter HIV duration.

This is an unexpected finding since weight loss has been associated with efavirenz-based ART (Lake et al, 2017). The mechanism behind weight loss in HIV+ individuals is not well understood but there are several possible explanations. Firstly, HIV+ individuals may consume less calories due to mental disturbances, financial problems, opportunistic infections or medication toxicities (Mangili et al, 2006; Mankal et al, 2014). Additionally, metabolic changes in PLWH may cause weight loss through hormonal changes, cytokine dysregulation and/ or altered metabolic demands (Grinspoon and Mulligan 2003). Indeed, studies show that resting metabolic rate was significantly greater in HIV+ individuals than the general population (Mittelsteadt et al, 2013; Kosmiski 2001). Furthermore, hypogonadism promotes weight loss in up to 50% of HIV+ males and females (Badowski et al, 2016). Low testosterone in hypogonadism is associated with reduced protein synthesis, which reduces lean body mass (Badowski et al, 2016). Finally, acute infections in PLWH has been shown to increase cytokine production, which was associated with weight loss (Mangili et al, 2006). Therefore, in the present study, a longer HIV duration may suggest that the participant is in the advanced stages of the disease, which is associated with weight loss/ a lower BMI.

4.7.3 Association between neck circumference and viral load

The present study found that a larger neck circumference was associated with a detectable current viral load. It has been shown that neck circumference is an

important predictor of metabolic syndrome (MetS) (Stabe et al, 2013). Furthermore, PLWH who have a detectable viral load have higher odds of having MetS than those with an undetectable viral load (Mangili et al, 2007; Squillace et al, 2009; Sobieszczyk et al, 2008). Therefore, in the present study, a higher neck circumference may suggest the presence of MetS, which is also associated with a detectable viral load. The “virological goal” for ART treatment is to achieve an undetectable viral load. The results of our study and the aforementioned studies suggest that when ARTs are taken consistently and correctly, it can not only control the disease (and consequently achieve an undetectable viral load) but also attenuate the risk of MetS.

4.8 Correlates of hypertension: all participants

4.8.1 Age and odds of hypertension

Being older was a risk factor for hypertension. Our finding is consistent with well-established knowledge (McEniery et al, 2007; Sun 2015; Buford 2016). Aging is accompanied by the thickening and loss of elasticity in the walls of large arteries, especially of the aorta (Sun 2015). Consequently, these arteries stiffen and have a reduced buffering ability, which increases SBP (Sun 2015). DBP remains unchanged or may even decrease (Sun 2015).

4.8.2 Depression symptoms and odds of hypertension

Greater severity of depressive symptoms had a protective effect against hypertension. The association between depression and hypertension is controversial. Meta-analytic data found that the 26.7% of depressed individuals are hypertensive (Li et al, 2015). Several studies have supported an association between depression and hypertension (Ganatra et al, 2008; Almas et al, 2014; Mahmood et al, 2017; Kretchy et al, 2014). It is suggested that since depression may promote hypertension due to the increased adrenergic activity that is present in depressed individuals (Siever and Davis 1985). Additionally, people with hypertension may be susceptible to psychological distress, such as depression, due to physical symptoms,

antihypertensive medication side-effects and a possible lower quality of life due to ill-health (Krijnen et al, 2005; Middeke et al, 2008; Reibis et al, 2012; Almas et al, 2014; Kretchy et al, 2014; Li et al, 2015).

On the contrary, a large longitudinal study using over 17 000 participants found that after a 22-year follow-up, depression was associated with lower SBP and lower DBP (Hildrum et al, 2011). Additionally, other studies have also found that depression was associated with lower blood pressure (Paterniti et al, 2000; Licht et al, 2009).

It has been found that depressed individuals often eat less, which may lower their BMI and consequently, attenuate the risk of hypertension (Patkel 1977; Simmons et al, 2016). As mentioned earlier, increased nitric oxide levels in depressed individuals may promote vasodilation, which decreases DBP (Kim et al, 2006; Zhou et al, 2007; Dhir and Kulkarni 2011; Inserra et al, 2019; Ignarro 1989; Siddiqui 2011).

4.8.3 Interaction between HIV status and sleep quality on the odds of hypertension

For the controls, poorer self-reported sleep quality was a risk factor for hypertension. Our finding is consistent with several studies (Fiorentini et al, 2007; Bruno et al, 2013; Bansil et al, 2011; Lu et al, 2015) and meta-analytic data (Lo et al, 2018; Li et al, 2020) that found poor sleep quality is an independent predictor of hypertension in the general population. For the HIV+ participants, poorer self-reported sleep quality had a protective effect against hypertension. However, when the interaction between HIV status and PSQI was added to the model, HIV status was a risk factor for hypertension.

4.9 Study Limitations

Firstly, since our study was cross-sectional in design, we have the usual limitations that accompany this type of study design such as being unable to observe differences temporally and being unable to determine cause and effect relationships. We also cannot be sure as to whether some of our controls were HIV+. Given the stigma associated with being HIV+ in rural areas of South Africa, we did not enquire

directly whether the control participants were HIV+. However, we did enquire about any medications they were on in an attempt to check for ART use. Since the HIV prevalence is approximately 13% in the Thabo Mofutsanyana district (Corporate governance and traditional affairs, 2020), we can estimate the prevalence of HIV to be approximately 13% among the controls. Granted, 13% is a low enough prevalence to reduce the bias towards the null. Additionally, we did not measure waist circumference, which could have been very useful is establishing a greater understanding of CMR. Instead of objective sleep measurements, we used the PSQI (a subjective measure of sleep quality) that may alter reliability, even though it did meet reasonable criteria for validity using the Cornbach's alpha and factor analysis.. Finally, we did investigate the association between BQ with SBP and DBP in the bivariate and multivariable analyses since hypertension status (and not SBP and DBP individually) was used to calculate BQ. However, hypertension status was half of one of the three components used to calculate BQ. There may thus have been some overlap between the BQ and the blood pressure outcome variables, which may limit the generalizability of our findings.

Conclusion

We conclude in our rural South African population, HIV+ participants showed a greater risk of hypertension. However, self-reported sleep quality was similar between the HIV+ participants and the controls. As expected, there was a greater prevalence of clinical depression symptoms in the HIV+ participants compared to the controls.

In the HIV+ participants, poorer self-reported sleep quality was associated with the presence of pain currently, a greater severity of depressive symptoms and shorter HIV duration. HIV status did not interact with self-reported sleep quality to affect CMR. Our study highlights the importance of monitoring and treating cardiometabolic risk factors in PLWH as well as general public health education. In particular, these findings suggest healthcare facilities, especially in rural areas, need to allocate more resources to assessing the blood pressure and mental health of PLWH since it appears to be a notable concern. Additionally, due to there being only a few studies that have studied sleep quality in PLWH in a rural South African area, we suggest

that further studies be conducted to confirm our finding of similar sleep quality between the general population and PLWH.

CHAPTER 5: REFERENCES

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Appendix A: Ethics clearance for original study (4 May 2012)

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr Karine Scheuermaier

CLEARANCE CERTIFICATE	**M120411**
PROJECT	Sleep, Mood and Morningness-Eveningness Preference in Treated and Untreated HIV Patients
INVESTIGATORS	Dr Karine Scheuermaier.
DEPARTMENT	School of Physiology
DATE CONSIDERED	04/05/2012
+DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 17/05/2012 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor :

DECLARATION OF INVESTIGATOR(S)
To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

Appendix B: Renewed ethics clearnace for original study (2 August 2022)

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG	HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research and Innovation)

TO:	Professor K Scheuermaier School of Physiology Medical School University E-mail: Karine.Scheuermaier@wits.ac.za
CC:	Supervisor: Not applicable <> and <HREC-Medical Research Office@wits.ac.za>
FROM:	Mr Iain Burns Human Research Ethics Committee (Medical) Tel: 011 717 1252 E-mail: Iain.Burns@wits.ac.za
DATE:	2022/08/02
REF:	R14/49
PROTOCOL NO:	**M220767** (This is your ethics application reference number. Please quote it in all enquiries, oral or written, relating to this study.)
PROJECT TITLE:	*Sleep, mood and morningness-eveningness preference in treated and untreated HIV-positive patients*

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to Government funding of the University.



MSWorks2000/Iain0007/Clearscan.wps

Appendix C: Ethics clearance for sub-study

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Miss Tracy Reddy et al

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M220887

NAME: (Principal Investigator)	Miss Tracy Reddy et al
DEPARTMENT:	School of Physiology
PROJECT TITLE:	The association between poor sleep quality and cardiometabolic risk in HIV+ individuals and the general population living in a rural area of South Africa
DATE CONSIDERED:	Ad hoc
DECISION:	Approved unconditionally
CONDITIONS:	Sub-study under M120411
SUPERVISOR:	Prof K. Scheuermaier
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	19/09/2022

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

Appendix D: Consent form for participants

UNIVERSITY OF THE WITWATERSRAND

School of Physiology

CONSENT TO ACT AS A STUDY PARTICIPANT IN RESEARCH

I, _____, being 18 years or older,
Consent to participating in a research project entitled : "**Sleep, mood and morningness-eveningness preference in treated and untreated HIV positive patients"**

The questionnaires have been explained to me and I understand and appreciate their purpose, any risks involved, and the extent of my involvement, I have read and understand the attached information leaflet.

I understand that the procedures form part of a research project and may not provide any direct benefit to me.

I understand that all experimental procedures have been sanctioned by the Human Research Ethics Committee, University of the Witwatersrand, Johannesburg.

I understand that my participation is voluntary and that I am free to withdraw from the project at any time without prejudice.

_____
_____
Subject NAME and SIGNATURE DATE

_____
_____
Investigator NAME and SIGNATURE DATE

OPTIONAL ACTIGRAPHY AND SLEEP DIARY RECORDING

I agree to participate in the actigraphy and sleep diary recording part of the study:
YES ☐ **NO** ☐
SIGNATURE: …….

OPTIONAL SLEEP RECORDING

I agree to participate in the part of the study which involves sleep recording two nights at the Wits Sleep Laboratory:
YES ☐ **NO** ☐
SIGNATURE: …….

Appendix E: Information document and informed consent (HIV+ participants)

INFORMATION DOCUMENT

Study title: Sleep, mood and morningness-eveningness in HIV positive patients, treated and untreated

Greeting:

Introduction: We, Dr Karine Scheuermaier and Dr Alan Karstaedt and Dr Katinka de Wet, are doing research on how HIV infection and its treatment affect your sleep, your mood and your activities during the day. Research is just the process to learn the answer to a question. In this study we want to learn if HIV itself, the impact it has on your CD4 counts, and the treatment of HIV have an effect on your sleep and your mood.

Invitation to participate: We are inviting you to take part in this research study because you attend the (name of clinic) today.

What is involved in the study

In this study, we would like you to please fill out the questionnaires which we will give to you. These questionnaires will ask you detailed questions about your sleep and your general motivation to get things done during the day. They will also ask you when you feel at your best during the day and if you get sleepy during the day. Because the following can have an effect on your sleep and mood, we will also ask you how long you have been taking your treatment (if you are treated for HIV), if you are taking other treatments, what is your last CD4 count, what is your last viral load and if you have another infection (like tuberculosis) or condition (like cancer) that you are treated for. Because pain may influence your sleep and mood, we will also ask you if you have any regular pain and how intense it is. We also ask you to please allow us to check in your file if there is information that you don't remember (for example: when did you start your treatment? – when were you diagnosed for the first time with HIV? - your last CD4 count - your last viral load). We will only look for the information that we need to complete your questionnaire. Since you may come back to the (name of clinic) clinic several times during the time we run the study, we may ask you to fill in the questionnaires at each of your visits. This will give us an idea of how HIV or your treatment may affect your sleep, mood and activities during the day over a period of time. However your participation in this study is completely voluntary and if you don't wish to fill in these questionnaires, you can say so at any time. Filling in these questionnaires should typically

take 30 minutes but can take up to one hour. A person from the study is here and you can ask them to help you understand the questions if they are not clear.

Risks of being involved in the study**:** there should not be any risk. You may not want to answer these questions because you may find the questionnaires too long or not interesting. At any point, you can decide not to participate in the study and stop filling in the questionnaires. You may also feel uncomfortable when answering sensitive, personal questions about you. You can choose to skip these questions and not answer them. You can also decide not to participate in the study.

Benefits of being in the study: we are hoping to learn on how HIV and its treatment influence sleep quality, your mood and your daily activities. If you feel your sleep is not good enough, we may be able to find solutions for improving it through this study. You may also attend the information sessions about sleep that we will organize throughout this study.

There are no alternatives to this study but you may withdraw from the study at any time. There is no particular way of withdrawing: just tell us at any time you would rather not be part of the study.

As soon as we have results from this study, we will post in the waiting room a copy of these results and of any discovery we have made that could help with your sleep or mood.

Participation is voluntary: it is your right to refuse to participate in this study. If you have started the study, you can withdraw from the study at any time. This will not change the way your doctors take care of you or your access to treatment in this hospital or any other hospital you decide to go to.

Reimbursements for “out of pocket” expenses: there should not be any cost to you since you will fill in the questionnaires while waiting at the clinic.

Confidentiality: Efforts will be made to keep personal information confidential. Absolute confidentiality cannot be guaranteed. Personal information may be disclosed if required by law. Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the Research Ethics Committee and the Medicines Control Council. If results are published, we will use a code that we only know how to identify. Therefore, your results will stay anonymous.

Contact details of researcher/s – for further information / reporting of study related adverse events, you can contact Dr Karine Scheuermaier on 011 717 2453 or by email Karine.scheuermaier@wits.ac.za or Dr Katinka de Wet on 051 401 2918 or by email dewetk@ufs.ac.za.

Contact details of REC administrator and chair – for reporting of complaints / problems with this study, you may contact Professor Cleaton-Jones through the Wits Human Research Ethics Committee administrators zanele.ndlovu@wits.ac.za or Langutani.Masingi@wits.ac.z

Appendix F: Information document and informed consent (control participants)

INFORMATION DOCUMENT

Study title: Sleep, mood and morningness-eveningness in HIV positive patients, treated and untreated

Greeting:

Introduction: We, Dr Karine Scheuermaier and Dr Alan Karstaedt and Dr Katinka de Wet, are doing research on how people who live with HIV sleep, how their mood and activities during the day are compared to the general population. Research is just the process to learn the answer to a question.

Invitation to participate: We are inviting you to take part in this research study because you live in the Thabo Mofutsanyana district.

What is involved in the study

In this study, we would like you to please fill out the questionnaires which we will give to you. These questionnaires will ask you detailed questions about your sleep and your general motivation to get things done during the day. They will also ask you when you feel at your best during the day and if you get sleepy during the day. Because it can have an effect on your sleep and mood, we will also ask you if you are taking any treatment. Because pain may influence your sleep and mood, we will also ask you if you have any regular pain and how intense it is. Your participation in this study is completely voluntary and if you don't wish to fill in these questionnaires, you can say so at any time. Filling in these questionnaires should typically take 30 minutes but can take up to one hour. A person from the study is here and you can ask them to help you understand the questions if they are not clear.

Risks of being involved in the study: there should not be any risk. You may not want to answer these questions because you may find the questionnaires too long or not interesting. At any point, you can decide not to participate in the study and stop filling in the questionnaires. You may also feel uncomfortable when answering sensitive, personal questions about you. You can choose to skip these questions and not answer them. You can also decide not to participate in the study.

Benefits of being in the study: we are hoping to learn on how HIV and its treatment influence sleep quality, mood and daily activities in people living with HIV. You may also attend the information sessions about sleep that we will organize throughout this study.

There are no alternatives to this study but you may withdraw from the study at any time. There is no particular way of withdrawing: just tell us at any time you would rather not be part of the study.

Participation is voluntary: it is your right to refuse to participate in this study. If you have started the study, you can withdraw from the study at any time.

Confidentiality: Efforts will be made to keep personal information confidential. Absolute confidentiality cannot be guaranteed. Personal information may be disclosed if required by law. Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the Research Ethics Committee and the Medicines Control Council. If results are published, we will use a code that we only know how to identify. Therefore, your results will stay anonymous.

Contact details of researcher/s – for further information / reporting of study related adverse events, you can contact Dr Karine Scheuermaier on 011 717 2453 or by email Karine.scheuermaier@wits.ac.za or Dr Katinka de Wet on 051 401 2918 or by email dewetk@ufs.ac.za.

Contact details of REC administrator and chair – for reporting of complaints / problems with this study, you may contact Professor Cleaton-Jones through the Wits Human Research Ethics Committee administrators zanele.ndlovu@wits.ac.za or Langutani.Masingi@wits.ac.za

Appendix G: General Questionnaire

Name:

Lebitso: _____

Surname:

Sefane: _____

Date of birth:

*Letsatsi la tswalo:*_____

GENERALINFORMATION ABOUT YOU AND YOUR SLEEP

Age:

*Dilemo:*_____

Gender: Female ☐ Male ☐

Bong: *Mosadi* ☐ *Monna* ☐

Do you work?: YES ☐ NO ☐

Na wa sebetsa?: *EYA* ☐ *TJHEE* ☐

If YES, what do you do?

Haeba EYA, o sebetsa eng?

If YES: do you ever work at night (shiftwork)?

Haeba EYA: na o ke o sebetse bosiu (mosebetsi wa shifti)?

Do you sleep alone in your room?

YES ☐ NO ☐

Na o robala o le mong ka kamoreng ya hao?

EYA ☐ *TJHEE* ☐

If No, do you have a bed partner?

Haeba TJHEE, na o na le motho eo o robalang le yena?

If No, how many people in addition to you sleep in the same room?

Haeba TJHEE, ke batho ba ba kae ha o ikenyeletsa ba robalang ka kamoreng yona eo?

If you wake up during sleep, what is likely to wake you up?

Haeba o tsoha hara boroko, ke eng se ka etsang hore o tsohe?

Having to go to the bathroom	☐	*Ho tlameha ho ya ntlwaneng*	☐
Noise	☐	*Lerata*	☐
Too hot	☐	*Ho thjesa haholo*	☐
Too cold	☐	*Ho bata haholo*	☐
Pain	☐	*Ho opelwa*	☐
Bad dreams	☐	*Ditoro tse mpe*	☐
Other	☐	*Ho hong*	☐

WHO stage (will be filled out by researcher)_____

INFORMATION ABOUT YOUR DISEASE:

When did you find out you were HIV positive?_____(month/year)

O fumane neng hore o HIV positive? _____(kgwedi/selemo)

When did you start taking HIV treatment?_____

O qadile neng ho nka tritmente ya HIV? _____

Have you ever been admitted to the hospital due to a complication of HIV? YES ☐ NO ☐

Na o kile wa amohelwa sepetlele ka baka la mathata a HIV? EYA ☐ *TJHEE*☐

If YES, when was your last hospitalization? _____ (month/year)

Haeba EYA, o qetetse neng ho robala sepetlele? _____ (kgwedi/selemo)

Current treatment (please give a list of ALL medications you take):

Tritmente ya jwale (ka kopo fana ka lenane la meriana KAOFELA eo o enkang):

Are you on tuberculosis (TB) treatment? YES ☐ NO☐

Na o tritmenteng ya TB? EYA ☐ *TJHEE*☐

If YES, please list your medication:

Haeba EYA, ka kopo bolela meriana ya hao:

Are you on Chemotherapy? YES ☐ NO☐

Na o Khemotheraping? EYA ☐ *TJHEE*☐

If YES, for which type of cancer?		*Haeba EYA, bakeng sa mofuta ofeng wa kankere?*	
Kaposi	☐	*Kaposi*	☐
Lymphoma	☐	*Lymphoma*	☐
Other	☐_____	*Tse ding*	☐_____

Have you had **<u>in the past</u>** or do you **<u>presently</u>** have any of the following diseases?

(if you cannot fill in this information, we can check your medical file)

*Na o kile wa ba le mahloko a latelang **<u>kgale</u>** kapa **<u>ha na jwale?</u>***

(haeba o sa kgone ho araba, re ka lekola faele ya hao)

	past YEAR? SELEMONG se fetileng?		Current Ha jwale
cryptococcal meningitis/	☐	_____	☐
cerebral toxoplasmosis/	☐	_____	☐
pneumocystis carinii/	☐	_____	☐
cancer/*kankere*	☐	_____	☐
other/*a mang*	☐	_____	☐

Baseline CD4 (when first put on antiretroviral therapy)_____

Baseline viral load:_____

Current CD4 count:_____

Current viral load:_____

<u>INFORMATION ABOUT ANY PAIN YOU MAY FEEL NOW</u>

Do you have pain **<u>now</u>**? YES ☐ NO ☐

*Na wa opelwa **<u>hona jwale</u>***? EYA ☐ TJHEE ☐

If YES:

Haeba EYA:

Can you please rate your pain level by picking **<u>one</u>** number that best describes your pain **<u>now</u>**?

*Ka kopo bontsha boemo ba hao ba bohloko ka ho kgetha nomoro **<u>e le nngwe</u>** eo e hlalosang ka botlalo bohloko ba hao **<u>hona jwale</u>**?*

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

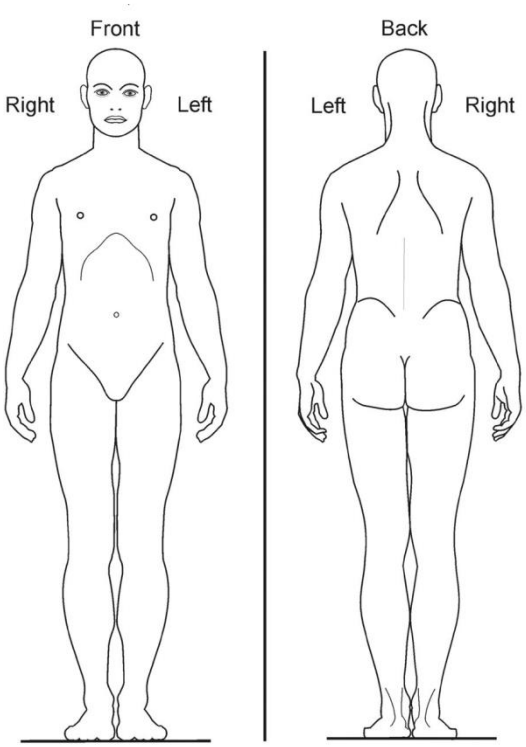
1 2 3 4 5 6 7 8 9 10

No pain — mild pain — moderate pain — severe pain — worst pain ever felt

Ha ho bohloko ho bohlokonyana ho bohloko hantle ho bohloko haholo ho bohloko bo fetisisang

Can you please show on this picture **where** it hurts? (colour the areas where it hurts)

*Ka kopo bontsha setshwantsong sena **moo** ho leng bohloko? (khalara moo ho leng bohloko)*



INFORMATION ABOUT ANY PAIN YOU HAVE FELT IN THE PAST MONTH

Did you have pain **in the past month**? YES ☐ NO ☐

*Na o ne o opelwa **kgweding e fetileng?*** *EYA* ☐ *TJHEE* ☐

If YES: what was your **highest pain level** in the **past month**?

*Haeba EYA: maemo a hao a **bohloko bo fetisisang** e ne ele afe **kgweding e fetileng?***

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

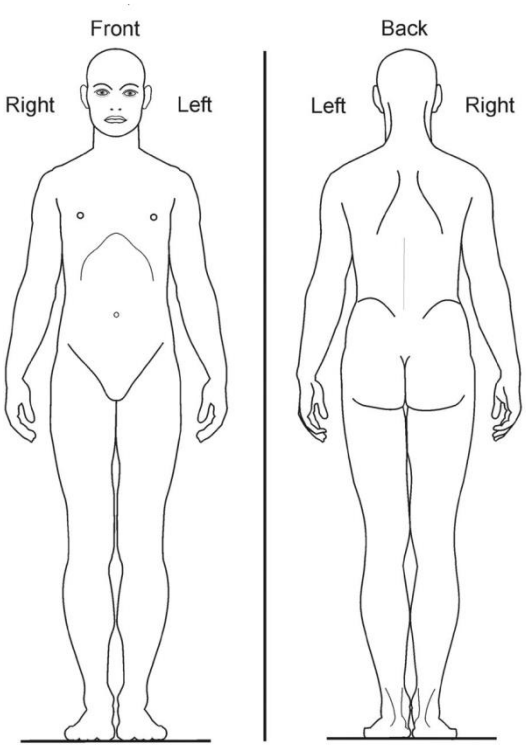
1 2 3 4 5 6 7 8 9 10

No pain — mild pain — moderate pain — severe pain — worst pain ever felt

Ha ho bohloko ho bohlokonyana ho bohloko hantle ho bohloko haholo ho bohloko bo fetisisang

Can you please show on this picture **where** it was hurting when you felt this highest pain level? (colour the areas where you felt your worst pain)

*Ka kopo bontsha setshwantsong sena **moo** ho neng ho le bohloko ha o ne o utlwa maemo ana a bohloko bo fetisisang? (khalara moo o utlwileng bohloko ba hao be fetisisang)*



During the past week how much did the state of your health, including any pain, interfere with the following things: choose the **one** number, from 0 to 4 below, that best describes your state.

*Bekeng e fetileng, maemo a hao a bophelo bo botle, le bohloko bofe kapa bofe, di ile tsa sitisa dintho tse latelang ha kakang: kgetha nomoro **e le nngwe** ho tloha ho 0 ho fihlela ho 4 ka fatshe, tse hlalosang ka botlalo maemo a hao.*

0=Not at all 1=A little bit 2=Moderately 3=Quite a bit 4=Extremely

0=Le letho 1=Hanyane feela 2=Mahareng 3=Haholonyana 4=Haholoholo

Your rating (from 0 to 4)

_____ MOOD

MOYA

_____ RELATIONS WITH OTHER PEOPLE

DIKAMANO LE BATHO BA BANG

_____ WALKING ABILITY

BOKGONI BA HO TSAMAYA

_____ SLEEP

BOROKO

_____ NORMAL WORK (includes both work outside the home and housework)

MOSEBETSI O TLWALEHILENG (o kenyeletsa mosebetsi wa kantle le wa ka tlung)

_____ ENJOYMENT OF LIFE

BOITHABISO BA BOPHELO

_____ OTHER

TSE DING

Appendix H: Pittsburgh Sleep Quality Index (PSQI) Questionnaire

CODE (leave blank)_____ Date_____ Score_____

INSTRUCTIONS: *The following questions relate to your usual sleep habits during the past month only. answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions.*

During the past month,

Kgweding e fetileng,

1. When have you usualy gone to bed? _____

   O ne o atisa ho ya dikobong neng? _____

2. How long (in minutes) has it taken you to fall asleep each night? _____

   Ho o kukile nako e kae (ka metsotso) ho kgaleha bosiu bo bong le bo bong? _____

3. When have you usually gotten up in the morning? _____

   O ne o atisa ho tsoha neng hoseng? _____

4. How many hours of actual sleep did you get that night? (This may be different than the number of hours you spend in bed.) _____

   O kgalehile dihora tse kae bosiung boo? (Sena se ka fapana le dihora tseo o dinkileng dikobong.) _____

5. During the past month, how often have you had trouble sleeping because you . . *Kgweding e fetileng, ke hangata ha kae o bileng le bothata ba ho robala hobane o ne o….*	Not during the past month *Eseng kgweding e fetileng*	Less than once a week *Ka tlase ho hangwe ka beke*	Once or twice a week *Hangwee kapa habedi ka beke*	Three or more times a week *Hararo kapa ho feta ka beke*
a. Cannot get to sleep within 30 minutes *sa kgone ho kgaleha metsotsong e 30*				
b. Wake up in the middle of the night or early morning				

tsoha hara bosiu kapa hoseng haholo				
c. Have to get up to use the bathroom *tlamehile ho tsoha ho sebedisa ntlwana*				
d. Cannot breathe comfortably *sa kgone ho hema hantle*				
e. Cough or snore loudly *kgohlola kapa o kgona haholo*				
f. Feel too cold *hatsetse haholo*				
g. Feel too hot *tjhesa haholo*				
h. Had bad dreams *na le ditoro tse mpe*				
i. Have pain *opelwa*				
j. Other reason(s), please describe, including how often you have had trouble sleeping because of this reason(s): *mabaka a mang, hlalosa hle, le hore na o ne o atisa ha kae ho ba le bothata ba ho robala ka baka la mabaka ana:*				
6. During the past month, how often have you taken medicine (prescribed or "over the counter") to help you sleep? *Kgweding e fetileng, o ile wa atisa ha kae ho nka meriana (ya lengolo la ngaka kapa "ya kantle ho lengolo la ngaka") ya ho o thusa ho robala?*				
7. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity? *Kgweding e fetileng o ile wa atisa ha kae ho ba le bothata ba ho dula o shebile ha o kganna, o ja kapa o le hara batho?*				
8. During the past month, how much of a problem has it been for you to keep up enthusiasm to get things done? *Kgweding e fetileng, ho bile thata ha kae hore o dule o na le thahasello ya ho etsa dintho?*				

	Very good *Hantle haholo*	Fairly good *Hantle feela*	Fairly bad *Hampe feela*	Very bad *Hampe haholo*
9. During the past month, how would you rate your sleep quality overall? *Kgweding e fetileng, o ka reita maemo a boroko ba hao jwang ka kakaretso?*				

Reprinted from: Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ: Journal of Psychiatry Research, 28:193-213, 1989.

Appendix I: Epworth Sleepiness Scale (ESS) questionnaire

In the last 30 days, how likely are you to dose off or fall asleep in the following situations (in contrast to feeling just tired)? *Matsatsing a 30 a fetileng, ho etsahetse hakae hore o otsele kapa o robale maemong a latelang (kantle le ho ikutlwa o kgathetse feela)?*	**HIGH CHANCE** ***HAHOLO***	**MODERATE CHANCE** ***HANTLE FEELA***	**SLIGHT CHANCE** ***HANYANE FEELA***	**NEVER DOZE** ***LEKGALE KE OTSELA***
• Sitting and reading. *O ituletse o ipalla.*	☐	☐	☐	☐
• Watching TV. *O shebelletse TV.*	☐	☐	☐	☐
• Sitting inactive in a public place (e.g. theater, Church) *O ituletse o sa etse letho tulung ya batho bohle (e.g. baeskopong, Kerekeng)*	☐	☐	☐	☐
• As a passenger in a car for an hour without a break. *O le mopalami wa koloi horeng e le nngwe ntle le phomolo.*	☐	☐	☐	☐
• Lying down to rest in the afternoon when circumstances permit. *O ipaqametse ho phomola hara motsheare ha maemo a dumela.*	☐	☐	☐	☐
• Sitting and talking to someone *O ituletse o ntse o buwa le motho e mong.*	☐	☐	☐	☐
• Sitting quietly after lunch without alcohol. *O ituletse ka kgutso kamora dijo tsa motsheare ntle le bojwala.*	☐	☐	☐	☐
• In a car while stopped for a few minutes in traffic. *Ka koloing ha o emisitse metsotso e se mekae sephethephetheng*	☐	☐	☐	☐

Appendix J: Berlin Questionnaire (BQ)

Scoring the Berlin questionnaire

Adapted from: Table 2 from Netzer, et al,., 1999. (Netzer NC, Stoohs RA, Netzer CM, Clark K, Strohl KP. Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. Ann Intern Med. 1999 Oct 5;131(7):485-91).

The questionnaire consists of 3 categories related to the risk of having sleep apnea. Patients can be classified into High Risk or Low Risk based on their responses to the individual items and their overall scores in the symptom categories.

Categories and scoring:

Category 1: items 1, 2, 3, 4, 5.

Item 1: if '**Yes**', assign **1 point**

Item 2: if '**c**' or '**d**' is the response, assign **1 point** Item 3: if '**a**' or '**b**' is the response, assign **1 point** Item 4: if '**a**' is the response, assign **1 point**

Item 5: if '**a**' or '**b**' is the response, assign **2 points**

Add points. Category 1 is positive if the total score is 2 or more points

Category 2: items 6, 7, 8 (item 9 should be noted separately).

Item 6: if '**a**' or '**b**' is the response, assign **1 point** Item 7: if '**a**' or '**b**' is the response, assign **1 point** Item 8: if '**a**' is the response, assign **1 point**

Add points. Category 2 is positive if the total score is 2 or more points

Category 3 is positive if the answer to item 10 is 'Yes' OR if the BMI of the patient is greater than 30kg/m^2.

(BMI must be calculated. BMI is defined as weight (kg) divided by height (m) squared, i.e., kg/m^2).

High Risk: if there are 2 or more Categories where the score is positive

Low risk: if there are only 1 or no categories where the score is positive

Height (m)_____ Weight (kg) _____ Age _____ Male / Female

Botelele *Boima* *Dilemo* *Monna/Mosadi*

Please choose the correct response to each question.

Ka kopa kgetha karabo e nepahetseng potsong engwee le engwee

CATEGORY 1

1. **Do you snore? *Na wa kgona?***

a. Yes *Eya*

b. No *Tjhee*

c. Don't know *Ha ke tsebe*

If you snore: Haeba o kgona:

2. **Your snoring is: *Ho kgona ha hao ho:***

a. Slightly louder than breathing *Ho hodimo hanyane ho feta ho hema*

b. As loud as talking *Ho hodimo jwalo ka ho buwa*

c. Louder than talking *Ho hodimo ho feta ho buwa*

d. Very loud – can be heard in adjacent rooms *Ho hodimo haholo – ho ka utlwahala ka kamoreng tse mabapi*

3. **How often do you snore? *O kgona hangata hakae?***

a. Nearly every day *E batlile eba tsatsi le leng le le leng*

b. 3-4 times a week *makgetlo a 3-4 ka beke*

c. 1-2 times a week *makgetlo a 1-2 ka beke*

d. 1-2 times a month *makgetlo a 1-2 ka kgwedi*

e. Never or nearly never *Lekgale kapa e batlile eba lekgale*

4. **Has your snoring ever bothered other people? *Na ho kgona ha hao hokile ha tshwenya batho ba bang?***

a. Yes *Eya*

b. No *Tjhee*

c. Don't Know *Ha ke tsebe*

5. **Has anyone noticed that you quit breathing during your sleep? *Na ho na le motho ya lemohetseng hore o tlohela ho hema ha o robetse?***

a. Nearly every day *E batlile eba tsatsi le leng le le leng*

b. 3-4 times a week *makgetlo a 3-4 ka beke*

c. 1-2 times a week *makgetlo a 1-2 ka beke*

d. 1-2 times a month *makgetlo a 1-2 ka kgwedi*

e. Never or nearly never *Lekgale kapa e batlile eba lekgale*

CATEGORY 2

6. **How often do you feel tired or fatigued after your sleep?** ***Ke ha ngata hakae o ikutlwa o kgathetse kapa o na le mokgathala kamora boroko ba hao?***

a. Nearly every day *E batlile eba tsatsi le leng le le leng*

b. 3-4 times a week *makgetlo a 3-4 ka beke*

c. 1-2 times a week *makgetlo a 1-2 ka beke*

d. 1-2 times a month *makgetlo a 1-2 ka kgwedi*

e. Never or nearly never *Lekgale kapa e batlile eba lekgale*

7. **During your waking time, do you feel tired, fatigued or not up to par?** ***Nakong ya hao ya ho tsoha, na o ikutlwa o kgathetse, o na le mokgathala kapa o se maemong a matle?***

a. Nearly every day *E batlile eba tsatsi le leng le le leng*

b. 3-4 times a week *makgetlo a 3-4 ka beke*

c. 1-2 times a week *makgetlo a 1-2 ka beke*

d. 1-2 times a month *makgetlo a 1-2 ka kgwedi*

e. Never or nearly never *Lekgale kapa e batlile eba lekgale*

8. **Have you ever nodded off or fallen asleep while driving a vehicle?** ***Na okile wa otsela kapa wa kgaleha o ntse o kganna koloi?***

a. Yes *Eya*

b. No *Tjhee*

If yes: Haeba eya:

9. **How often does this occur?** ***Se se etsahala hangata hakae?***

a. Nearly every day *E batlile eba tsatsi le leng le le leng*

b. 3-4 times a week *makgetlo a 3-4 ka beke*

c. 1-2 times a week *makgetlo a 1-2 ka beke*

d. 1-2 times a month *makgetlo a 1-2 ka kgwedi*

e. Never or nearly never *Lekgale kapa e batlile eba lekgale*

CATEGORY 3

10. **Do you have high blood pressure?** ***Na o na le high blood?***

Yes *Eya*

No *Tjhee*

Don’t know *Ha ke tsebe*

Appendix K: Beck's Depression Indventory I (BDI) questionnaire

STUDY CODE(leave blank): _____ DATE:

1. 0 I do not feel sad.

   Ha ke ikutlwi ke hlomohile.

   1 I feel sad.

   Ke ikutlwa ke hlomohile

   2 I am sad all the time and I can't snap out of it.

   Ke dula ke hlomohile ka nako tsohle ebile ha ke kgone ho tswa maemong ao.

   3 I am so sad and unhappy that I can't stand it.

   Ke hlomohile haholo ebile ha ke ya thaba hoo ke sa kgoneng ho o emela.

2.

   0 I am not particularly discouraged about the future.

   Ha ke nyahamiswe hakaalo ke bokamoso.

   1 I feel discouraged about the future.

   Ke ikutlwa ke nyahamiswa ke bokamoso.

   2 I feel I have nothing to look forward to.

   Ke ikutlwa ekare ha ken a letho leo ke le shebelletseng pele.

   3 I feel the future is hopeless and that things cannot improve.

   Ke ikutlwa ekare bokamoso ha bona tshepo ebile dintho ha dina ho loka.

3.

   0 I do not feel like a failure.

   Ha ke ikutlwi ke le ya hlolehileng.

   1 I feel I have failed more than the average person.

   Ke ikutlwa ke hlolehile ho feta motho ya tlwalehileng.

   2 As I look back on my life, all I can see is a lot of failures.

   Ha ke sheba morao bophelong b aka, sohle seo ke se bonang ke

   3 I feel I am a complete failure as a person.

   Ke ikutlwa ke le motho ya hlolehileng ka ho phethahala.

4.

   0 I get as much satisfaction out of things as I used to.

   Ke kgotsofatswa ke dintho tseo ke neng ke tlwaetse ho di etsa.

   1 I don't enjoy things the way I used to.

   Ha ke thabele dintho jwale ka ha ke ne ke tlwaetse.

   2 I don't get real satisfaction out of anything anymore.

   Ha ke sa kgotsofatswa ka nnete ke eng kapa eng.

3 I am dissatisfied or bored with everything.

Ha ke kgotsofatswe kapa ke tenwa ke dintho tsohle.

5.

0 I don't feel particularly guilty

Ha ke ikutlwi ke le molato ho hang.

1 I feel guilty a good part of the time.

Ke ikutlwa ke le molato ka nako e kgolo.

2 I feel quite guilty most of the time.

Ke ikutlwa ke le molatonyna nako e kgolo.

3 1 feel guilty all of the time.

Ke ikutlwa ke le molato ka nako tsohle.

6.

0 I don't feel I am being punished.

Ha ke ikutlwi ekare key a otlwa.

1 I feel I may be punished.

Ke ikutlwa ekare nka otlwa.

2 I expect to be punished.

Ke lebelletse ho otlwa.

3 I feel I am being punished.

Ke ikutlwa ekare key a otlwa.

7.

0 I don't feel disappointed in myself.

Ha ke ikutlwi ke itshwabela.

1 I am disappointed in myself.

Ke ya itshwabela.

2 I am disgusted with myself.

Ke ya inyonya.

3 I hate myself.

Ke ithloile.

0 I don't feel I am any worse than anybody else.

Ha ke ikutlwi ekare ke fetelletse ho feta mang kapa mang.

1 I am critical of myself for my weaknesses or mistakes.

Key a ipimetsa ka bofokodi le diphoso tsa ka.

2 I blame myself all the time for my faults.

Ke inyatsa ka nako tsohle ka baka la diphoso tsa ka.

3 I blame myself for everything bad that happens.

Ke inyatsa ka ntho tsohle tse mpe tse etsahalang.

9.

0 I don't have any thoughts of killing myself.

Ha ke na menahano ya ho ipolaya.

1 I have thoughts of killing myself, but I would not carry them out.

Ke na le menahano ya ho ipolaya empa ha ke na ho e phetha.

2 I would like to kill myself.

Ke batla ho ipolaya.

3 I would kill myself if I had the chance.

Nka ipolaya ha nkaba le monyetla.

10.

0 I don't cry any more than usual.

Ha ke lle ho feta tlwaelo.

1 I cry more now than I used to.

Ke lla ho feta kamoo ke tlwaetseng ka teng.

2 I cry all the time now.

Ke lla ka nako tsohle.

3 I used to be able to cry, but now I can't cry even though I want to.

Ke ne ke kgona ho lla empa ha ke sa kgona ho lla le ha ke batla.

11.

0 I am no more irritated by things than I ever was.

Ke tenwa ke dintho ho feta pele.

1 I am slightly more irritated now than usual

Ke teneha hanyane ho feta mehleng.

2 I am quite annoyed or irritated a good deal of the time.

Ke dula ke tenehile boholo ba nako.

3 I feel irritated all the time.

Ke ikutlwa ke tenehile ka nako tsohle.

12.

0 I have not lost interest in other people.

Ha keya lahlehelwa ke kgahleho bathong ba bang.

1 I am less interested in other people than I used to be.

Ha ke san a kgahleho bathong ba bang jwalo ka pele.

2 I have lost most of my interest in other people.

Ke lahlehetswe ke boholo ba kgahleho bathong ba bang.

3 I have lost all of my interest in other people.

Ke lahlehetswe ke kgahleho yohle bathong ba bang.

13.

0 I make decisions about as well as I ever could.

Ke etsa diqeto hantle ho ya kamoo nka kgonang kateng.

1 I put off making decisions more than I used to.

Ke behela ka thoko ho etsa diqeto ho feta kamoo ke neng ke tlwaetse kateng.

2 I have greater difficulty in making decisions more than I used to.

Ke na le bothata bo boholo ba honka diqeto ho feta kamoo ke neng ke etsa ka teng.

3 I can't make decisions at all anymore.

Ha ke kgone ho hang ho etsa diqeto.

14.

0 I don't feel that I look any worse than I used to.

Ha ke ikutlwi ekare ke shebeha hamper ho feta kamoo ke neng ke le kateng.

1 I am worried that I am looking old or unattractive.

Ke tshwenywa ke hore ke shebeha ke le moholo kapa ke sa kgahlisi.

2 I feel there are permanent changes in my appearance that make me look unattractive

3 I believe that I look ugly.

Ke kgolwa hore ke mobe.

15.

0 I can work about as well as before.

Ke kgona ho sebetsa hantle jwale ka pele.

1 It takes an extra effort to get started at doing something.

Ho nka boikgathatso bo eketsehileng ho qala ho etsa ntho e itseng.

2 I have to push myself very hard to do anything.

Ke tlameha ho itshutsumetsa ka thata haholo ho etsa ntho efe kappa efe.

3 I can't do any work at all.

Ha ke kgone hohang ho sebetsa.

16.

0 I can sleep as well as usual.

Nka robala hantle jwale ka tlwaelo.

1 I don't sleep as well as I used to.

Ha ke robale jwale ka ha ke ne ke tlwaetse.

2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.

Ke tsoha hora 1-2 pele ho tlwaelo ebile ke fumana ho le boima ho kgutlela borokong.

3 I wake up several hours earlier than I used to and cannot get back to sleep.

Ke tsoha dihora di se kae pele le kamoo ke neng ke tlwaetse ebile ha ke kgone ho kgutlela borokong.

17.

0 I don't get more tired than usual.

Ha ke kgathale jwale ka tlwaelo.

1 I get tired more easily than I used to.

Ke kgathala ha bobebe ho feta

2 I get tired from doing almost anything.

Ke batla ke kgathatswa ke ho etsa eng kapa eng.

3 I am too tired to do anything.

Ke kgathetse haholo ho etsa eng kapa eng.

18.

0 My appetite is no worse than usual

Takatso ya ka ya dijo ha e fokole ho feta tlwaelo.

1 My appetite is not as good as it used to be.

Takatso ya ka ya dijo ha e ntle jwale ka ha e ne e le kateng.

2 My appetite is much worse now.

Takatso ya ka ya dijo e fokola haholo ho feta jwale.

3 I have no appetite at all anymore.

Hakesana takatso ya dijo hohang.

19.

0 I haven't lost much weight, if any, lately.

Ha ke ya fokola mmele haholo, le haeba, ha jwale.

1 I have lost more than five pounds.

Ke fokotse ka diponto tse hlano.

2 I have lost more than ten pounds.

Ke fokotse ka diponto tse fetang leshome.

3 I have lost more than fifteen pounds.

Ke fokotse ka diponto tse fetang tse 15.

20.

0 I am no more worried about my health than usual.

Ha keya kgathatseha ka bophelo b aka bo bottle ho feta tlwaelo.

1 I am worried about physical problems like aches, pains, upset stomach, or constipation.

Ke kgathatsehile ka mathata a mmele jwale ka mahlaba, bohloko, mala a bohloko kapa ho soka

2 I am very worried about physical problems and it's hard to think of much else.

Ke kgathatsehile haholo ka mathata a mmele ebile ho boima ho nahana ka ho hong.

3 I am so worried about my physical problems that I cannot think of anything else.

Ke kgathatsehile ka mathata a mmele kahoo ke sa kgoneng ho nahana ka eng kapa eng.

21.

0 I have not noticed any recent change in my interest in sex.

Ha ke so lemohe phetoho ya jwale takatsong yaka ya thobalano.

1 I am less interested in sex than I used to be.

Ha kena takatso ya thobalano ho feta kamoo ke neng ke tlwaetse ka teng.

2 I have almost no interest in sex.

Ke batla ke sena takatso ya thobalano.

3 I have lost interest in sex completely.

Ke lahlehetswe hohang ke takatso ya thobalano.