THE IMPACT OF THE INDICES OF ADIPOSITY ON CARDIOVASCULAR TARGET ORGAN DAMAGE IN PEOPLE OF AFRICAN ANCESTRY

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Declaration

I, Kgothatso Freddy Nkoana, declare that this dissertation, except where acknowledged on and referenced accordingly, is my own work. It is being submitted for the degree of Master of Science in Medicine at the University of the Witwatersrand, Johannesburg. It has not been previously submitted for any degree to the current or any other institution.

I certify that the assessments contained in this dissertation have the approval of the Committee for Research in Human Subjects (Medical) of the University of the Witwatersrand, Johannesburg. The ethics approval number is **M190649**.

Nkoana Kgothatso Freddy

Signed on the 14th June 2021

I certify that the above statement is correct:

Prof Muzi Maseko

(Supervisor)

Signed on the 14th June 2021

Dedication

This dissertation is dedicated to my father Piet Nkoana, my mother Thabitha Nkoana and my siblings. Thank you for your unending love and support.

Abstract

The excess body fat in overweight/obese people has serious health implications including cardiovascular health. Historically, body mass index has been the preferred for the assessment of adiposity; however, a number of studies have shown that this method has limitations because it does not distinguish between visceral and subcutaneous fat. Consequently, waist circumference (WC) is regarded as a more representative index of obesity. Proper assessment of overweight/obesity is essential especially in populations with a high incidence of obesity as was the case in the current study our study population which has a 65% incidence of obesity. Previous studies conducted in this population have mainly used BMI as an index of obesity and therefore the impact of obesity on cardiovascular target organ changes may not be well understood. Therefore, in this study we used both indices (BMI and WC) to assess the impact of increased adiposity on preclinical cardiovascular target organ changes. We recruited 551 individuals of African ancestry and took anthropometric measurements. Both conventional and 24-hour blood pressure (BP) were measured. Echocardiography and pulse wave velocity were performed to measure cardiac and vascular changes, respectively. Additionally, we collected blood samples to measure serum lipid and hormone (renin, aldosterone, insulin, and leptin) concentrations and 24-hour urine samples to assess urinary sodium excretion. When participants were stratified according to BMI status, total cholesterol (TCHOL), triglycerides (TRGL) and LDL-cholesterol (LDL) were significantly higher in the overweight/obese group compared to the normal BMI individuals. On the other hand, HDL-cholesterol (HDL) was significantly higher in the normal weight individuals compared to the overweight/obese group. When WC was used to classify the participants, TCHOL, TRGL and LDL were significantly higher in the high WC women, while no significant differences were observed in men. Similar to women, HDL was significantly higher in the normal WC group compared to the increased WC group. After correcting for covariates, both BMI and WC were significantly associated with all the lipid profiles in men, while only TRGL and HDL were associated with the two indices. Overweight/obese participants had significantly high insulin and leptin levels compared to normal BMI participants. There was no significant difference in renin and aldosterone concentrations between participants with increased WC and those with normal WC. When participants were stratified according to BMI, blood pressure was significantly higher in the total population, men, and women in the overweight/obese group compared to the normal weight participants. However, when stratification was done according to WC, gender differences were observed. Significant differences in blood pressure were only observed in women but not in men. Only night-time blood pressure was significantly different between the

two male groups. Differences were also observed in the PWV and LVMI between the groups. Individuals with high BMI and WC had a significantly higher PWV and LVMI compared to the normal weight group. We then assessed the combined effects of BMI and WC on target organs. Individuals with a normal BMI and normal WC had the lowest PWV and LVMI, followed by individuals with a normal WC and an increased BMI. Then individuals with increased BMI and increased WC had the highest PWV and LVMI. None of the participants with normal BMI had increased WC. These findings indicate that an increase in BMI and WC is associated with an increase in circulating plasma lipids in women but not in men. Since a raised BP and plasma lipids is associated with cardiovascular pathology, increased adiposity is more detrimental to women than men in this population. Furthermore, our results show an independent relationship between the indices of adiposity (BMI and WC) and preclinical cardiovascular pathology (increased PWV and LVMI). Even though general adiposity (BMI) occurs independent of visceral adiposity (WC), visceral adiposity does not develop independent of general adiposity. Therefore, a reduction of BMI does not necessarily translate into WC reduction, but WC reduction always results in BMI reduction. This means reduction of WC is more beneficial than the reduction of BMI in this population.

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Table of Contents

List of tables

List of figures

List of abbreviations

ACE	Angiotensin-converting enzyme
AGE	Advanced glycation end products
AGT	Angiotensinogen
Ang II	Angiotensin II
APWV	Aortic Arch Pulse Wave Velocity
BMI	Body mass index
BP	Blood pressure
C_DBP	Conventional diastolic blood pressure
C_SBP	Conventional systolic blood pressure
CETP	Cholesteryl ester -transfer-protein; HL
CHD	Coronary heart disease
CI	Confidence interval
CLS	Clinical Laboratory Services
CRP	C- reactive protein
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DBPC	Conventional diastolic blood pressure
DBPD	Daytime diastolic blood pressure
DBPN	Night-time diastolic blood pressure
DBP24	24-Hour diastolic blood pressure
EC	Endothelial cell
ENaC	Epithelial Na+ channel
FFA	Free fatty acids
GSIS	Glucose stimulated insulin secretion

HDL-C	High-density lipoprotein cholesterol
HDL	High density lipoproteins
HL	Hepatic lipase
HT	Hypertension
IBMI	Increased body mass index
IL	Interleukin
IR	Insulin resistance
IWC	Increase waist circumference
LDL	Low density lipoproteins cholesterol
LVH	Left ventricular hypertrophy
LVMI	Left ventricular mass index
MAP	Mean arterial pressure
MAPK	Mitogen-activated protein kinase
MCP-1	Monocyte chemotactic protein-1
Mg/Dl	Milligrams per decilitre
mm Hg	Millimetre mercury
mmol/d	Millimoles per day
mmol/l	Millimoles per litre
MMPs	Matrix metalloproteinase
MR	Mineralocortorticoid receptors
NBMI	Normal body mass index
NEFA	Non-esterified fatty acids (NEFA)
ng/mL	Nanogram per millilitre
NO	Nitric Oxide

NWC	Normal waist circumference
pg/mL	Picogram per millilitre
PI3K	Phosphatidylinositol 3-kinase
PP	Pulse pressure
PWV	Pulse wave velocity
R^2	Coefficient of determination.
RAS	Renin-angiotensin system
RSNS	Renal sympathetic nervous system
SA	South Africa
SA	Sinoatrial
SAHDS	South African Hypertension and Diet Study
SBP	Systolic blood pressure
SBPC	Conventional systolic blood pressure
SBPD	Daytime systolic blood pressure
SBPN	Night-time systolic blood pressure
SBP24	24-Hour systolic blood pressure
SNS	Sympathetic nervous system
TCHOL	Total cholesterol
TG2	Tissue transglutaminase
TGF-β	Transforming growth factor- β
TNF	Tumour necrosis factor
TRGL	Triglycerides
TxA2	Thromboxane A2
VLDL	Very low-density lipoproteins

VSMC	Vascular smooth muscle cell
WC	Waist circumference
WHO	World Health Organisation

Preface

Overweight or Obesity is defined as excess body fat. Categorisation of individuals into different weight groups is generally by body mass index (BMI). However, there are some BMI-related errors that must be taken into consideration. For instance, self-reported weight and height is mostly inaccurate as men tend to overestimate their height while women underestimate their weight. For this reason, clinically measured weight and height are more accurate. Excess body weight is commonly a result of excess fat. However, excess weight can be a result of muscle mass rather than fat. A classic example being body builders. Therefore, BMI should be used in consideration of these limitations. Nonetheless, BMI continues to be a relatively easy way to assess general obesity. However, BMI does not distinguish between visceral and subcutaneous fat.

Waist circumference (WC) is a measure of abdominal obesity. Findings from the Rotterdam study suggested that WC may be a better predictor of overweight than BMI. Furthermore, high quintiles of WC, but not BMI were related to increased mortality among non-smoking men. Studies have suggested that WC is a better predictor of cardiovascular disease (CVD) risk. However, they did not disregard BMI as they suggested that combining measures of general obesity with those of abdominal obesity may improve their discriminatory ability. Most studies use these measures independently. Consequently, little is known about the combined impact of these two indices on cardiovascular risk.

The prevalence of overweight/obesity is high in South Africa and currently there is no data on how the combined effects of BMI and WC contribute to the increasing surge of cardiovascular diseases. There is therefore a need to investigate the combined effects of these two indices on the cardiovascular system. In addition, currently there is no evidence on the gender differences in relation to the impact of these two indices on plasma lipid profiles, BP, and preclinical target organ changes. Therefore, the investigations in this current study sought to close some of the gaps in the current literature. Chapter one gives background on the available literature on the topic. In chapter two the methods and materials used in this study are explained. Chapter three gives results of the statistical analysis of the data collected during this study. Chapter four is a discussion of the findings of the current study contrasted with available literature. Lastly, chapter five is the conclusion and possible limitations of the study. This study will add to the existing body of knowledge regarding the impact of adiposity of cardiovascular target organ damage as well as provide information on how to better utilise indices of obesity to assess cardiac changes and vascular damage.

CHAPTER 1

Introduction

1.1 Introduction

Overweight or Obesity is generally defined as excess body fat (Al-Ghamdi *et al.* 2018). However, it is difficult to measure body fat directly therefore a definition of obesity/overweight as excess body weight is more precise (Ogden *et al*. 2007). Hence, the use of BMI and WC as indices of adiposity has been widely accepted. Based on BMI, individuals can be divided into four categories: underweight, normal weight, overweight and obese. Though these categories are generally accepted, there are some BMI-related errors that must be taken into consideration. Self-reported weight and height are mostly inaccurate as men tend to overestimate their height, while women tend to underestimate their weight (Ogden *et al*. 2007). For this reason, clinically measured weight and height are more accurate. Excess body weight is commonly a result of excess fat; however, it can also be due to increased muscle mass. Body builders are a classic example (Rothman, 2008). These limitations should always be considered when BMI is used. Nonetheless, BMI continues to be a relatively easy way to assess general obesity. However, BMI does not account for abdominal obesity.

Despite its usefulness, BMI does not account adequately for abdominal obesity. Hence, waist circumference (WC) has been accepted as a more accurate a measure of abdominal obesity (Lean *et al.* 1995). Unlike BMI which does not distinguish between the genders, thresholds for WC differ according to gender. Therefore, WC may be more accurate than BMI in predicting cardiovascular risk. This is confirmed by several studies including the Rotterdam study which suggested that WC may be a better predictor of overweight than BMI. Furthermore, high quintiles of WC, but not BMI were shown to be more related to increased mortality among non-smoking men (Visscher *et al.* 2001). Huxley *et al* (2010) also concluded that WC is a better predictor of cardiovascular disease (CVD) risk. Most studies still use these measures independently, consequently, the advantages of using both indices (BMI and WC) in the same study are not well understood.

1.2. The association between overweight/obesity and cardiovascular disease.

1.2.1. Overweight/obesity and blood pressure.

Studies have shown a positive association between overweight/obesity and blood pressure (BP) (Bravo *et al*. 2006; Koolhaas *et al*. 2017; Kotsis *et al*. 2010; Senbanjo and Oshikoya, 2012). These studies show that overweight/obese individuals are more likely to have higher BP as

opposed to normal weight individuals of the same age group. The association between BP and body weight is dependent on adiposity. Furthermore, the position of body fat storage will determine its effect on BP. Visceral fat is an important risk factor for hypertension (HT) (Wolk *et al.* 2003; Rahmouni *et al.* 2005). It is estimated that 60-70% of HT in adults is related to increased body fat (Kotchen 2010). This highlights the need for the accurate measurement of adiposity. Hence, if using both BMI and WC gives a more accurate assessment of obesity, there is an urgent need for studies that will provide evidence for the importance of using both indices concurrently, taking into consideration the mechanisms involved in the relationship between BP and adiposity.

There are several mechanisms involved in the relationship between overweight/obesity and BP. Activation of the sympathetic nervous system (SNS) is one of the key determinants of adiposity related BP increases. Fat cells in adipose tissue release leptin, a peptide hormone positively associated with the degree of obesity. Leptin binds to its receptors in the brain stem and hypothalamus, activating neural pathways that increase energy expenditure and SNS activity (Hall *et al*. 2010). Therefore, serum leptin levels should be carefully considered when stating potential mechanisms involved in cardiac and vascular alternations observed in overweight/obese individuals.

Sympathetic nerves control cardiac pace and contractility. Stimulation of the SNS results in positive chronotropic effects whereby the main pacemaker of the heart, the sinoatrial (SA) node no longer maintains a normal sinus rhythm because of overstimulation by the SNS, consequently sinus tachycardia (faster heart rate) occurs (Gordan *et al.* 2015). Furthermore, stimulation by the SNS causes increases in intracellular calcium (Ca^{2+}) concentration which will result in increased contractility. Sympathetic stimulation also cause vasoconstriction which will increase the total peripheral resistance resulting in an increase in BP. The chronic increase in BP will ultimately result in HT. Besides the rise in total peripheral resistance, BP is further increased through renal mechanisms. Renal sympathetic nervous system (RSNS) is comprised of efferent and afferent nerve fibres (Sata *et al.* 2018). These fibres are near the adventitial layer of the renal arteries. The activation of efferent sympathetic nerve fibres leads to increased renal tubular sodium absorption, decreased renal blood flow and increased renin secretion. Consequently, fluid retention is increased, and vascular HT is sustained (Kannan, 2014).

Overweight/obesity is characterised by glomerular injury and consequently nephron damage. Before these events can occur, there is an increase renal tubular reabsorption which leads to primary sodium retention (Kotsis *et al.* 2010). The resultant increase of extracellular-fluid volume will result in a resetting of the kidney-fluid apparatus due to the hypertensive adjustment of the pressure natriuresis (Wolk *et al.* 2003; Kotsis *et al.* 2010). Pressure natriuresis, a process whereby surges in renal perfusion pressure lead to increased sodium excretion, is a key factor of the feedback system that normally stabilises body-fluid volumes and BP. Overweight/obesity impairs pressure natriuresis, resulting in BP increases (Hall *et al.* 2010; Kotsis *et al.* 2010). An increased BP will likely lead to arterial damage. Hence, the need to assess the impact of adiposity on arterial compliance in this population.

1.2.2. The impact of adiposity on arterial compliance

Pulse wave velocity (PWV), which is the speed at which pressure waves move along a blood vessel, is used to assess arterial stiffness (Mitchell, 2014). Arterial stiffness describes the rigidity/non-compliance of the arterial walls (Mackenzie *et al.* 2002). An increased PWV is an indication of arterial stiffness (Safar *et al.* 2006). Therefore, PWV is an important tool that can be utilised to evaluate CVD risk as well as assess target organ damage. Furthermore, the non-invasive nature of the procedure makes it ideal for clinician research. There is extensive data linking PWV to the risk incidence of cardiovascular events (Shiburi *et al.* 2006; de Lima Santos *et al.* 2011; Pierce *et al.* 2013; DuPont *et al.* 2019) Hence, PWV is regarded as the "gold standard" for the assessment of arterial stiffness (Chirinos, 2012).

Overweight/obesity is associated with arterial stiffness (Nordstrand *et al.* 2011; Aroor *et al.* 2018). Therefore, overweight/obese individuals will have stiffer arteries compared to normal weight individuals and increased arterial stiffness has been shown to be an independent predictor of cardiovascular morbidity and mortality (Nordstrand *et al.* 2011). As shown in figure 1.1, overweight/obesity induced arterial stiffness can occur because of decreased nitric oxide (NO) bioavailability, insulin resistance (IR), menopause, impaired smooth muscle cell function, as well as elevated serum cholesterol and hyperleptinemia (Seifalian *et al.* 2010).

Nitric oxide, principally produced in the vascular endothelium by L-arginine (Pal and Radavelli-Bagatini, 2013) stimulates guanylyl cyclase to form 3′,5′-cyclic guanosine monophosphate, which promotes vasodilation of vascular smooth muscle cells, anti-inflammatory effects on endothelial cells, leukocytes, and vascular smooth muscle cells

(Hermann *et al.* 2006). Decreased NO bioavailability is the main factor involved in endothelial dysfunction (Chen *et al.* 2018) which is characterised by reduced widening of arteries (Seifalian *et al.* 2010).

The mechanisms underlying the relationship between insulin resistance and arterial stiffness are well established. Endothelium-mediated vasodilation may be impaired in individuals with IR (Strazhesko *et al.* 2015). This could be an important link between IR and arterial stiffness. Insulin has both vascular protective and deleterious effects. Deleterious effects consist of the initiation of vascular smooth muscle cell proliferation, vasoconstriction, proinflammatory and proliferation activity through mitogen-activated protein kinase (MAPK) pathway. Furthermore, IR leads to impairment of insulin-stimulated NO pathway, resulting in vasoconstriction and high BP (Zhou *et al.* 2014). Insulin resistance is associated with endothelial dysfunction. In IR, phosphatidylinositol 3-kinase-dependent (PI3K) signalling is impaired, causing an imbalance in the secretion of endothelin-1 and production of NO, resulting in endothelial dysfunction (Muniyappa and Sowers, 2013). The association between overweight/obesity, IR and arterial stiffness is further explained in figure 1.1 below.

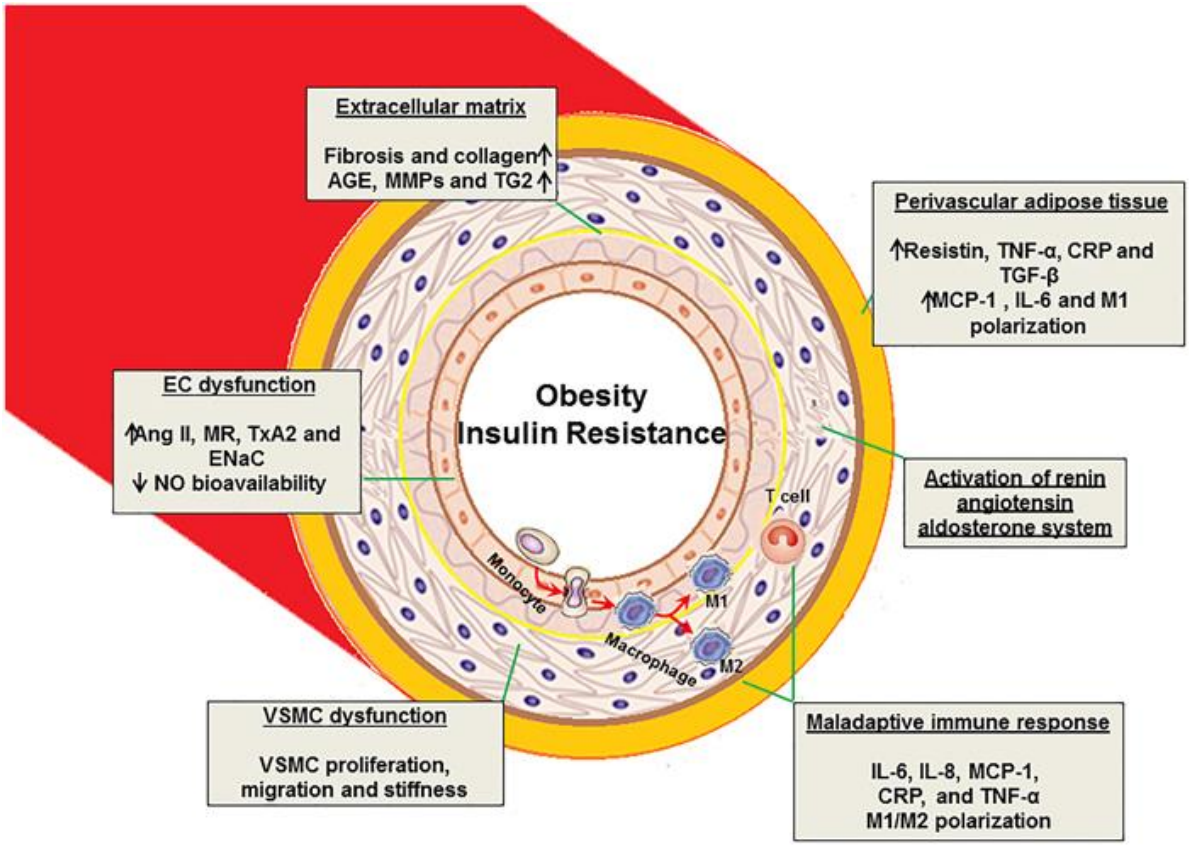


Figure 1. 1: Diagram showing possible mechanisms of arterial stiffness in overweight/obesity. IR, insulin resistance; VSMC, vascular smooth muscle cell; EC, endothelial cell; MMPs, matrix metalloproteinase; AGE, advanced glycation end products; TG2, tissue transglutaminase; MR, mineralocorticoid receptor; Ang II, angiotensin II; TxA2, thromboxane A2; IL, interleukin; ENaC, epithelial Na+ channel; TNF, tumour necrosis factor; TGF-β, transforming growth factor- β; MCP-1, monocyte chemotactic protein-1; CRP, C- reactive protein; NO, nitric oxide; ⬆, increase;⬇, decrease (Jia et al. 2015).

1.2.2.2 Sex and ethnic differences in arterial stiffness.

The impact of overweight/obesity on cardiovascular health is dependent on gender (Snijder *et al.* 2015; Aroor *et al.* 2018; Schutte *et al.* 2020). To add to the observed gender disparities, women have higher incidence of overweight/obesity than men (DuPont *et al.* 2019). Therefore, the impact of overweight/obesity on CVD progression is not only dependent on sex hormones but is aggravated by the high number of overweight/obese women. According to Aroor *et al* (2018) obese women have significantly increased arterial stiffness as opposed to obese men.

Moreover, arterial compliance and stiffening were independently associated with diastolic dysfunction in women but not in men, signifying that greater aortic stiffness during early systole may reduce the efficacy of the vascular system in women. Pre-puberty, women have higher PP and stiffer large arteries than age-matched men. However, post-puberty, men develop stiffer large arteries whereas women have more distensible large arteries (Ahimastos *et al.* 2003). The changes that occur in both genders because of sex hormones lead to non-significant differences in large arterial stiffness in the post-pubertal stage. Therefore, studies that show a higher arterial stiffness in women are likely a reflection of the current state of health of an individual and not a depiction of early childhood differences between men and women. Consequently, the overweight/obese women are at a greater risk of CVD as opposed to men within the same weight group.

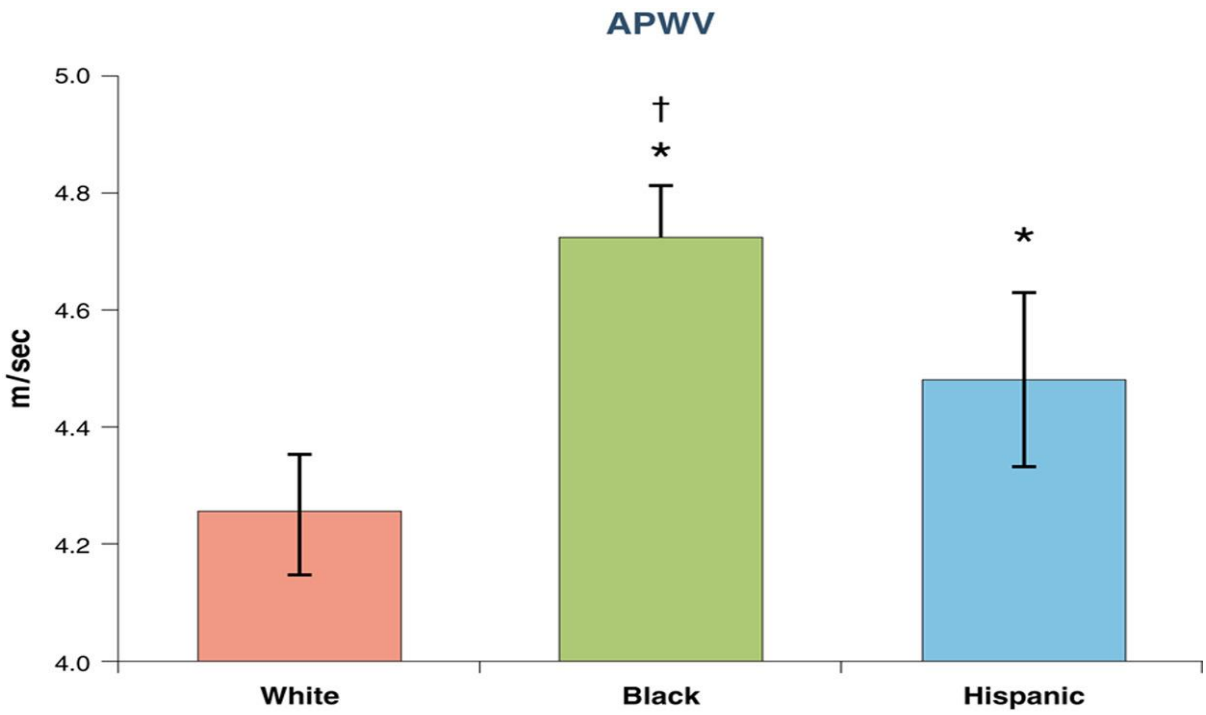


Figure 1. 2: Graph showing differences in least square mean and 95% confidence interval of Aortic Arch Pulse Wave Velocity (APWV) amongst different ethnicities. Model adjusts for age, sex, BMI, height, mean arterial BP, use of antihypertensive medication, HR, total cholesterol (TCHOL), diabetes mellitus, and cigarette smoking (Goel *et al*. 2017).

Ethnicity determines overweight/obesity-related behaviours. People from black ethnic groups are more likely to have obesogenic lifestyles than Caucasians. Furthermore, cultural dictates common in some cultures such as the view that overweight/obese women are more desirable as opposed to normal weight women aggravate the obesogenic behaviours. (Falconer *et al.* 2013). Therefore, a predisposition for arterial stiffness in the black community is aggravated by the high incidence of overweight/obesity. de Lima Santos *et al* (2011) found that the population of African ancestry had increased incidence of higher PWV as opposed to other population groups. Furthermore, they proposed the notion that expression of genes related to arterial stiffness could be the cause of the observed ethnic differences. In accordance with the finding of the above study, there is an urgent need to continually monitor as well as describe factors that contribute to arterial stiffness in people of African ancestry to reduce the disease burden of CVD in this population. A recent study by Schutte *et al* (2020) reiterated the high incidence of arterial stiffness in people of African ancestry. Ethnic disparities coupled with the adverse impact of adiposity will increase susceptibility of people of African ancestry to vascular events leading to mortality and should therefore receive early preventative strategies and treatment. In addition to vascular events, cardiac changes are also likely to occur due to overweight/obesity.

1.2.3. Association between overweight/obesity and cardiac changes

Left ventricular mass index (LVMI) is the ratio of the dimension of the weight of the left ventricle (LV). Accordingly, LVMI is a parameter utilised in echocardiography. Echocardiography is the procedure of using sound waves to produce images of the heart in order to assess the action of the heart (Libhaber *et al.* 2008; Crowley *et al.* 2011; Maunganidze *et al.* 2013). Increased LVMI is a pre-symptomatic marker of cardiac change (Seferovic *et al.* 2018).

Body mass index (BMI) as a measure of overweight/obesity is positively associated with LVMI (Rashid *et al.* 2014). Hence, it is notionally plausible to assume that despite all cofounders, an increase in BMI will result in an increase in LVMI. Left ventricular mass index (LVMI) can be used to diagnose left ventricular hypertrophy (LVH), the hallmark of cardiac remodelling characterised by the thickening and enlargement of the left ventricle, the heart's main pumping chamber. Therefore, a high LVMI is linked to LVH, which is closely coupled with adverse

cardiovascular events such as an inability of the heart to pump enough blood to the body and loss of heart function (cardiac arrest) (Mizukoshi *et al.* 2016).

There are ethnic differences between people of African ancestry and those of European ancestry in the association between LVMI and LVH. People of African ancestry have a higher prevalence of LVH than those of European ancestry (Bidulescu *et al.* 2011). Contrary to most studies, Libhaber *et al* (2008) found that arterial stiffness predicts LVMI independent of BP in people of African ancestry, particularly women. The preceding study highlights the importance of assessing factors that influence LVMI on an ethnic level. Overweight/obesity is one such factor that determines LVMI. The presence of overweight/obesity in people of African ancestry will likely have a far more potent role in increasing LVMI as opposed to other ethnic groups.

Body mass index, which is associated with LVMI, is not enough to assess adiposity. Therefore, WC is needed to enable categorisation according to general and central adiposity. This will enable better assessment of the impact of adiposity on LVMI. According to Lee *et al* (2008), WC is more efficient in determining gender-specific cardiovascular risk factors. Biological factors linked with female adiposity play a discriminatory role leading to overweight/obesity being much more associated with LVM changes in women than in men (De Simone *et al.* 2011). Findings from the Fels longitudinal study showed that age, BMI, and WC were independently associated with LVM in men and women. With general obesity having a stronger associated with LVM in women. In men, both general and abdominal obesity were linearly associated with LVM (Flegal *et al.* 2009). Their study highlighted the complexity of cardiovascular interpretations of the inter associations of body composition. Prompting the consideration of factors involved in obesity-induced LV geometry remodelling.

Abdominal obesity can be present in individuals regarded as non-obese by the criterion of BMI. Therefore, the impact of WC as an index of overweight/obesity provides a basis for the recognition of adipose-related risk of LVH. Shin *et al* (2007) showed that abdominal obesity is a risk factor of LVM increase in individuals regarded as non-obese according to BMI. These findings stress the value of WC in the assessment of cardiovascular events. Nonetheless, most studies use BMI alone as a measure of obesity and hence they fall short of determining the full extent of overweight/obesity as BMI only accounts for general obesity. The effects of adiposity are much easier to assess using both indices of overweight/obesity.

1.3 Overweight/obesity and metabolic function.

1.3.1 The relationship between lipid profiles, adiposity, and cardiovascular events.

Higher adiposity is associated with lipid abnormalities (Van Gaal *et al.* 1995; Tóth *et al.* 2012; Eslami *et al.* 2019). As shown in figure 1.3, the hallmark of overweight/obesity-induced dyslipidaemia is high serum triglycerides (TRGL) partly due to increased free fatty acid (FFA). According to figure 1.3, adipose tissue contributes toward an increase in FFA through its effect on the liver. The resultant increase in TRGL will lead to the impairment of lipolysis though the action of very low-density lipoproteins (VLDL). Lipolysis is the process by which fats are degraded in the body through the action of enzymes. The impairment of lipolysis will result in increased fat accumulation in the body (Klop *et al.* 2013).

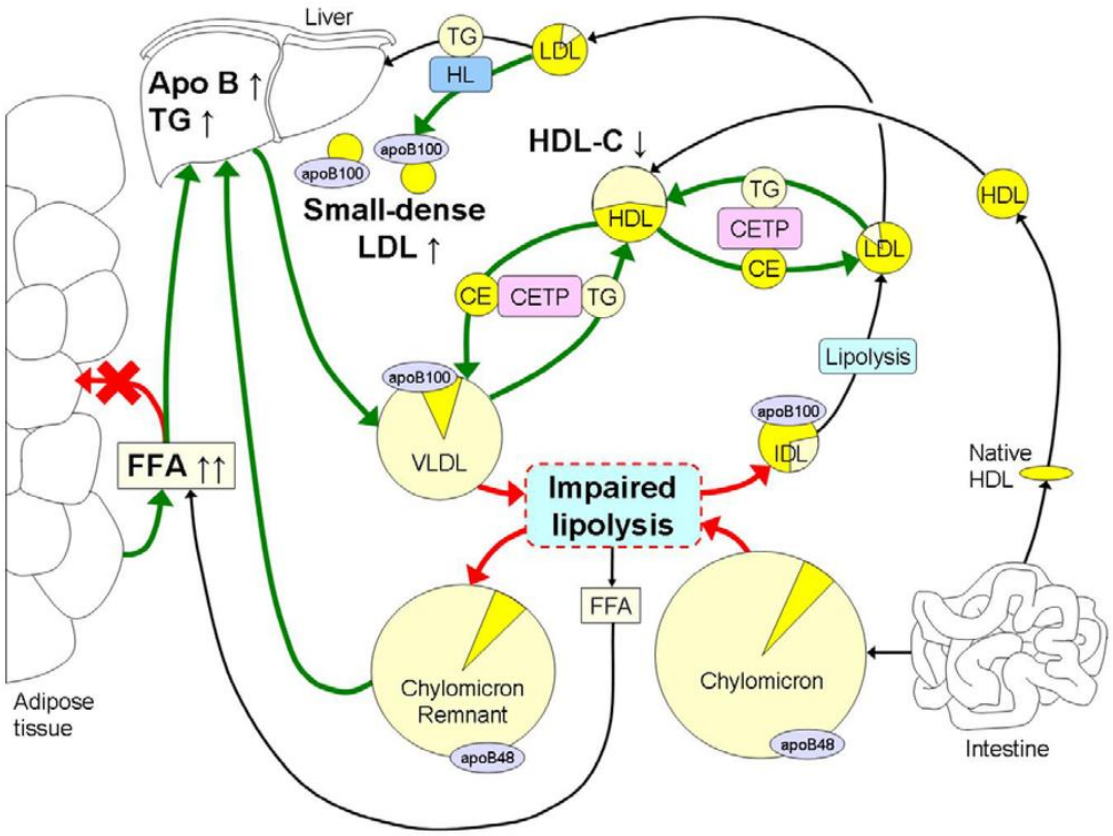


Figure 1. 3: The progression of obesity-induced dyslipidaemia (Klop *et al.* 2013). FFA, free fatty acids; TRGL, triglycerides; LDL, low density lipoproteins; HDL, high-density lipoproteins; VLDL, very low-density lipoproteins; CETP, cholesteryl ester-transfer-protein; HL; hepatic lipase; Intense yellow colour, cholesterol; light yellow colour, TRGL content; Green arrows; Obesity-induced increases in metabolic processes; Red arrows, obesity-induced reductions in the metabolic processes.

Dyslipidaemia is characterised by high serum total cholesterol (TCHOL), TRGL, LDL and low HDL (Klop *et al.* 2013; Jung and Choi, 2014; Telles *et al.* 2018). Components of circulating lipid profile may be deposited within the intima of the artery wall. Subsequently being involved in the atherogenic process (Hedayatnia *et al.* 2020). Moreover, high TCHOL is a leading risk factor for CVD such as stroke and coronary heart disease (CHD) (Ma 2004). Although lipid abnormalities lead to cardiovascular complications, it is worth noting that the disease burden will be influenced ethnicity and gender. Mathur *et al* (2011) found that people of African ancestry are more likely to be multimorbid. Therefore, lipid abnormalities are more likely to present with profound adverse effects on the cardiovascular system in this population.

1.3.2 The relationship between serum hormone levels, adiposity, and cardiovascular health.

Insulin is a peptide hormone that maintains normal blood glucose levels by enabling cellular glucose uptake and lipid metabolism (Wilcox, 2005). Overweight/obesity is associated with insulin resistance (IR) and hyperinsulinemia (Kahn and Flier, 2000; Gallagher and LeRoith 2010; Al-Ghamdi *et al.* 2018). Insulin resistance is known as the decreased ability of tissues to respond to insulin and in overweight/obese individuals IR is mitigated by excess adipose tissue which leads to the increased secretion of FFA and dysregulated secretion of adipokines. Pro-inflammatory adipokines and FFA reach metabolic tissues and modify glucose uptake as well as inflammatory responses. Moreover, FFA and their metabolites, such as ceramides and acyl-coenzyme A can weaken insulin signalling by favouring protein kinases. Overweight/obesity induced lipolysis also promotes the accumulation of macrophages in adipose tissue. Thereby contributing toward overweight/obesity-related IR (Jung and Choi, 2014).

High fat diets are linked to IR as fatty acid composition is likely a key factor in the long-term development of IR. Moreover, non-esterified fatty acids (NEFA) derived from dietary lipids may alter glucose stimulated insulin secretion (GSIS), decrease peripheral insulin sensitivity and increase hepatic glucose output (Wilcox, 2005). The inhibition of GSIS is through activation of protein kinase C and intramyocellular accumulation of diacylglycerol. Furthermore, NEFA cause hepatic IR by inhibiting insulin-mediated suppression of glycogenesis. This in turn leads to high glucose concentrations which has a deleterious effect on pancreatic islet function (Conte *et al.* 2004).

Hyperinsulinemia and IR can promote LVH via several interconnected mechanisms that involve lipotoxicity. Abnormal insulin regulation can result in an increase in hepatic angiotensin synthesis. Resulting in increased secretion of angiotensin II, a cardiomyocyte growth factor. Angiotensin II will promote fibrosis, apoptosis and myocardial hypertrophy (Brady 2016) Angiotensin II can contribute toward myocardial hypertrophy directly through the activation of angiotensin type-1, a protein-linked receptor present on cardiac myocytes that activates protein kinase C. Moreover, angiotensin II activates proto-oncogenes to stimulate hypertrophy of cardiac myocytes (Gavras and Gavras, 2002)

Hyperinsulinemia can result in over-activation of the SNS. The activation of the SNS may affect cardiac structure directly through substances with α1 adrenergic agonist activity (such as noradrenaline) that have been shown to induce myocyte hypertrophy (Kahan and Bergfeldt, 2005) or indirectly through the increase in both heart rate and cardiac contractility, resulting in increased BP levels (Shereef and Kandeel, 2019). Increased BP contributes to the left ventricle working harder to overcome the elevated afterload pressure. In HT, the heart contracts against a chronically high pressure. This can lead to the development of LVH (Berman and Bhardwaj, 2019). The relationship between BP and cardiac structure cannot be assumed to be linear in all population, hence there is a need to evaluate target organ damage in a population specific manner.

Leptin is peptide hormone that is associated with overweight/obesity and is associated with impaired vasodilation (Gonzalez *et al.* 2013) through the activation of mitogen-activated protein kinases and phosphatidylinositol-3 kinase to increase the proliferation and migration of vascular smooth muscle cells, promoting endothelial dysfunction and enhancing the effects of angiotensin II on BP via modulating the SNS and increasing FFA oxidation (Tsai *et al.* 2016). As a result of the impaired vasodilation associated with overweight/obesity-related leptin, arteries will become less compliant and stiffer and therefore arterial stiffness (as a sign of vascular damage) will occur.

The impact of insulin and leptin may be subject to ethnic variations. Although the disparities are vague in some studies, the dependence of these hormones on visceral adiposity is an important contributor. There is evidence (Hasson *et al.* 2015) to suggest that overweight/obese people of African ancestry might be at greater risk of IR as opposed people of European ancestry. Therefore, the difference in body fat and fat distribution is an important factor that contributes towards ethnic disparities in the function of leptin and insulin (Hunma *et al.* 2018).

Adipose tissue promotes the secretion of aldosterone independent of the systemic renin-angiotensin system (RAS) (Kawarazaki and Fujita, 2016). Aldosterone has been suggested as having an indirect role in promoting endothelial dysfunction. The investigators blocked aldosterone with spironolactone and reported improved endothelial function as well as increased NO bioactivity in heart failure patients. These effects were substantiated when the investigators demonstrated that aldosterone infusion induced endothelial dysfunction in hypertensive patients (Epstein, 2001).

1.4 Justification

There is a high prevalence of overweight/obesity in South Africa especially in people of African ancestry (Schutte, 2019; Otitoola *et al.* 2020) and a number of studies have shown that overweigh/obesity is associated with cardiovascular target organ damage. Therefore, it is possible that the increase in cardiovascular disease in South Africa is due to the high incidence of obesity in the African communities. Hence, current strategies that focus mainly on the control of BP in an effort to reduce the rising trend of cardiovascular diseases may not be effective. For any strategy to be effective, it must include both pharmaceutical intervention and proper assessment of adiposity. Body mass index and WC are currently the most widely used indices of adiposity, but they are mostly used independently. Therefore, their combined impact on cardiovascular organs is not well understood. To properly comprehend adipose-related cardiovascular events unique to this population may require the assessment of the combined effects of BMI and WC on cardiovascular parameters. In this study, we used BMI and WC as indices of overweight/obesity to assess the impact of adiposity on preclinical cardiovascular target organ changes.

1.5. Hypothesis

The use of both indices of obesity (BMI and WC) provides better evaluation of cardiovascular target organ damage as opposed to using only one index.

1.6. Aim of the study

The aim of this study was to determine the impact of the indices of obesity on cardiovascular target organ changes in an urban developing community of African ancestry.

1.6.1 The objectives of the present study were therefore to:

- Determine the prevalence of obesity using BMI and WC as indices of general and visceral obesity, respectively.
- Investigate if the impact of obesity on blood pressure is dependent on body fat distribution.
- Determine the relationship between the indices of obesity and plasma lipid profiles.
- Determine the impact of the indices of obesity on arterial stiffness.
- Evaluate the relationship between the indices of obesity and 24-hour urinary sodium excretion rate.
- To determine the impact of adiposity on cardiac geometry by assessing the association between left ventricular mass index and the indices of obesity.
- Assess the role of both general and visceral obesity on preclinical diastolic dysfunction.

CHAPTER 2

Methods

2.1 Study group

The study was conducted at the University of the Witwatersrand Medical School, Johannesburg, South Africa and was approved by the University of the Witwatersrand's Committee for Research in Human Participants (Medical), approval number **M190649** (Appendix 1). Five hundred and fifty-one South Africans of African ancestry were recruited in and around Johannesburg (Figure 2.1). The age of the participants was 18 years and above and there was no upper age limit.

Figure 2. 1: An example of an area (Johannesburg, Braamfontein) where some of the participants were recruited.

2.2 Clinical and demographic data

Participants were invited to the Human Nutrition Clinic where the details of the study were explained. After giving consent to participate in the study, a standardised questionnaire was administered (Appendix 4). The questionnaire was designed in such a way that participants could answer most of the questions with a simple "yes" or "no", with a few sections requiring short answers. The specific answers to date of birth, gender, previous medical history, family history of hypertension and cardiovascular events, the presence of non-communicable diseases, prior and current drug therapy, occupation, level of education, smoking status, alcohol a

caffeine consumption and exercise frequency. For women, the use of contraceptives, history of pregnancies as well as menstrual history was recorded.

2.3 Anthropometric measurements

Anthropometric assessments were measured according to the international standards for anthropometric assessments (Stewart *et al.* 2011). Weight measurements were recorded using an electronic scale (Healthometer Professional) to the nearest 0.1 kg. During all the measurements, the participants were asked to take their shoes off, and minimal clothing was worn which allowed access to areas of measurements. Participants were asked to step on the scale and stand still without supporting themselves on any object and weight was recorded when the scale had stopped fluctuating. Height was measured using a stadiometer (Seca portable stadiometer) to the nearest 0.1 cm. When the measurement was taken the head of the participant was placed in the Frankfort plane with the body standing upright and a sliding headboard was lowered to the vertex of the head. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Classification of participant as being underweight, normal, overweight, or obese was done according to table 2.1. Waist circumferences was determined using a tape measure with participants wearing minimal clothing on the abdominal region. Waist circumference was determined at the narrowest width midway between the iliac crest and the lowest rib to the nearest 0.1 cm at the end of a gentle expiration. Waist circumference cut-off values; normal WC (≤94 cm in men: ≤80 cm in women) vs increased WC (>94cm in men: >80 cm in women) (World Health Organisation (WHO), 2008).

Table 2. 1: Body mass index (BMI) indices threshold values.

BMI (kg/m^2)	Weight Classification	Relative Risk of disease
<18.5	Underweight	
18.5 – 24.9	Normal	No risk
25.0 – 29.9	Overweight	Increased risk
30.0 – 34.9	Obese (Class I)	High risk
35.0 – 39.9	Obese (Class II)	Very high risk
≥40.0	Morbidly Obese	Extremely High risk

Adapted from World Health Organization. 2000. Obesity: Preventing and managing the global epidemic.

2.4 Conventional blood pressure measurements

Brachial blood pressure (BP) was measured using an automated sphygmomanometer (Omron, Kyoto, Japan). The participants were required to rest for 5 to 10 minutes with their legs uncrossed, touching the floor and their back rested against the chair. Participants were required to rest the arm at which the BP was measured on a table that was set beside the chair at an elevation close to the heart level. Caution was taken by using a cuff suitable to the arm circumference of each participant. Five consecutive measurements were taken at one-minute intervals. The five measurements were averaged to determine the participants' systolic and diastolic BP in mm Hg and resting heart rate. Measurements at ≥140 mm Hg systolic and 90 mm Hg diastolic were defined as hypertensive states. Furthermore, participants who received anti-hypertensive treatment or had elevated BP as noted during clinical measurements were classified as hypertensives.

2.5 Twenty Four-Hour ambulatory blood pressure measurements

Twenty four-hour BP monitoring was performed using oscillometric monitors (SpaceLabs, model 90207) (Figure 2.2). The non-dominant arm was selected for BP monitoring. The size of the cuff was the same as that which was used for conventional BP measurements. The monitors were programmed to measure BP at 15-minute intervals from 06:00 to 22:00 and then 60-minute intervals from 22:00 to 06:00. Participants kept a diary card for the duration of the monitoring to note the time of going to bed in the evening and getting up in the morning to determine the awake and sleep periods of the day. Participants were also asked to document any oral intake and medication. Participants continued with normal daily activities during the monitoring. Intra-individual means of the ambulatory measurements were weighted by the time-interval between successive recordings (Bawa-Allah *et al.* 2019). Ambulatory BP data were expressed as 24-hour average systolic and diastolic BP, the percentage decrease in BP at night (mean day-mean night/mean day x 100), the difference between day and night BP and the ratio of day-to-night BP.

Figure 2. 2: Spacelabs model 90207 ambulatory BP.

2.6 Pulse wave velocity measurement

Measurements of arterial stiffness were performed as described by Shiburi *et al* (2006). Arterial stiffening was measured using a high-fidelity SPC-301 micromanometer (Millar Instrument, Inc., Houston, Texas), interfaced with a computer employing SphygmoCor software version 9.0 (AtCor Medical Pty. Ltd., West Ryde, New South Wales, Australia). The participants rested in the supine position for 15 minutes; then the carotid, femoral and brachial waveforms were recorded by applanation tonometry at an 8-s period. The pulse was calibrated by manual measurements of BP before the measurements were recorded. The aortic pulse wave was calculated using a validated generalised transfer function. Before measuring pulse wave velocity, distances from the suprasternal notch to the carotid artery (labelled as distance A), and from the suprasternal notch to the femoral artery (labelled as distance B) were measured. Thus, pulse wave velocity was calculated as the difference between distance B and A (femoral and carotid). The pulse transmit time was determined from the average of 10 consecutive beats (the mean time difference between sites A and B). The magnitude of the augmented pressure wave (AP) was determined as the difference between central systolic BP and the inflection

point at the end of the first systolic shoulder. Lastly, aortic pulse wave velocity was determined as the ratio of the distance in metres to the transit time in seconds.

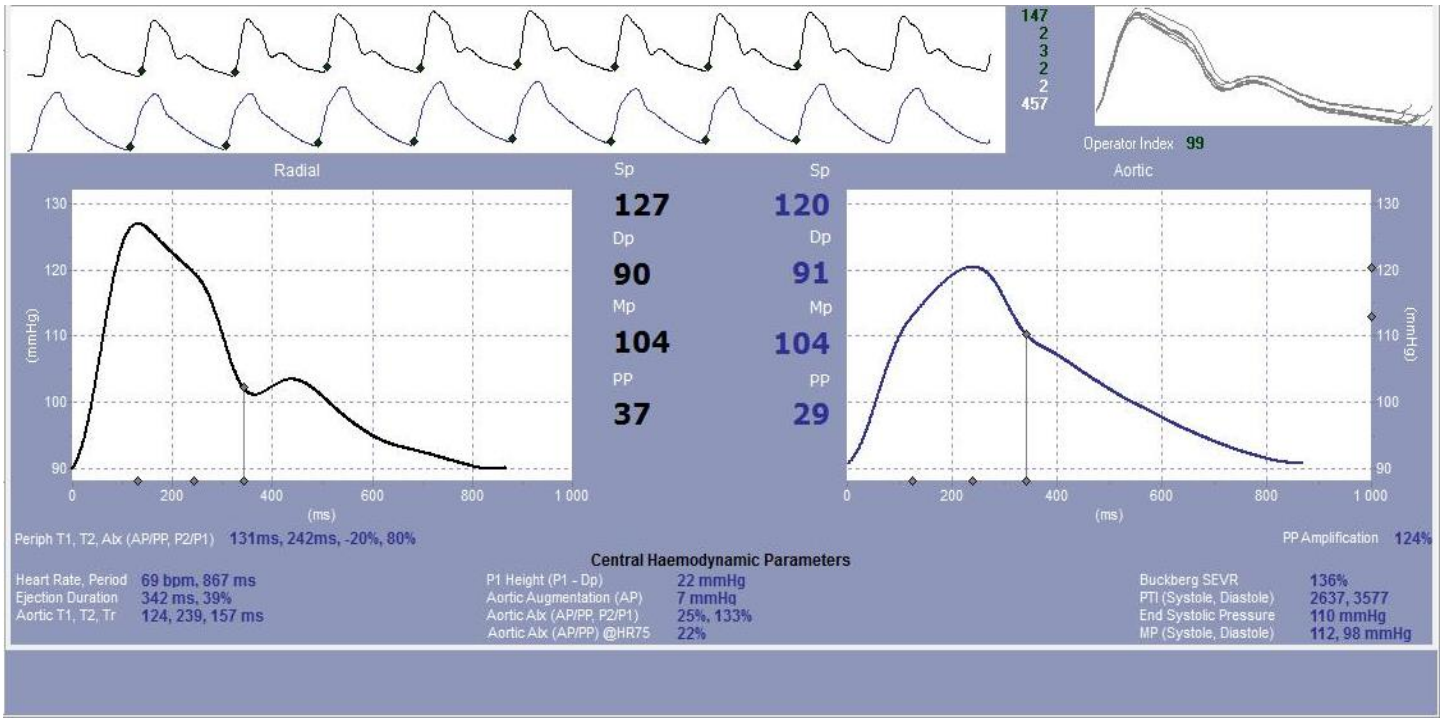


Figure 2. 3: Example of a pulse wave recording obtained to determine central haemodynamic. The figure shows central haemodynamic parameters, the radial artery pulse wave obtained from applanation tonometry, and the aortic pulse wave derived from a population-based transfer function built into the software. Sp, systolic blood pressure (BP); Dp, diastolic BP; MP, mean arterial pressure; PP, pulse pressure; HR, heart rate.

2.7 Echocardiography

Echocardiographic measurements were used to assess the size of the left ventricle to detect left ventricular hypertrophy. The measurements were performed according to the method described by Sliwa *et al* (2002), and analysed according to the American Society of Echocardiographic convention (Sahn *et al.* 1978). Participants were required to be in a supine position. A pulse colour Doppler Hewlett Packard model 5500 recorder coupled to a 2.5 MHz transducer was used to conduct a two-dimensional guided M-mode echocardiography. The transducer was placed on the chest perpendicular to the chest wall or pointed inferiorly and laterally at the end

of the long axis (Sahn *et al.* 1978). Data obtained in the short-axis view allowed for measurements of the septal wall thickness, posterior wall thickness, and the left ventricle diameter during late diastole and systole. Left ventricular mass was derived from an anatomically validated formula and indexed to height 2.7 (Devereux *et al.* 1986). Left ventricular wall thickness, left ventricular mean wall thickness, left ventricular hypertrophy and left ventricular concentricity were defined as described by Nunez *et al* (2005).

2.8 Twenty four-hour urine excretion measurements

Upon completion of measurements, participants were issued specimen bottles to collect 24-hour urine samples. For anatomical reasons, female participants were issued beakers to use and then transfer the urine into the specimen bottles. Subsequently, these specimen bottles were collected from the participants after 24- hours. Urine bottles were labelled as daytime or night-time sample to separate and differentiate between the two collected samples. This was done to allow separate determination of the electrolyte excretion rates and ratios between daytime and night-time. Participants were instructed on how to differentiate between the times for the sample collection. Based upon the 95% confidence intervals for each group, a 24-hour urine sample was considered acceptable if 24-hour urine creatinine (mmol) was >3.5 and <35 for men and >3.5 and <30 for women. Samples with urine volumes <500 ml/day were also assumed to be incomplete urine collections. These approaches are standard approaches and have been published on numerous occasions by other groups (Maseko *et al.* 2006).

2.9 Blood sampling

Participants were asked to fast overnight prior to clinical visit. Following an overnight fast, venous blood of about 18 ml was drawn from the median cubital vein of the participants' arm. Blood was centrifuged at 1500 rmp for 15 minutes. Red 4 x 9ml tubes were used for plasma and purple 4 x 9ml were used for serum. After centrifuge, we alloquatt for different tests into 8 cryo tubes. These tubes were used for different tests including lipid and hormone assessment. The 5ml tubes containing pure blood were taken to Central Laboratory Services (CLS) for analysis which included creatinine, electrolyte concentrations and serum lipid profiles. The lipid profiles included triglycerides, total cholesterol, high-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol concentrations. Blood glucose and

glycated haemoglobin were also assessed. Serum concentrations of insulin, renin, leptin, and aldosterone were taken. The cut-off values for the diagnosis of any disorders arising from the above parameters were defined. These data were used to identify medical conditions, syndromes that may affect BP.

2.10 Inclusion criteria

Participants who had all measurements taken and had completed 24-hour urine collections and the 24-hour ambulatory BP measurement were included for analysis.

2.11 Data Analysis

Database management and statistical analyses were performed using SAS software, version 9.4 (The SAS Institute Inc., Cary, North Carolina, USA). The distribution of data was tested for normality using histograms. Continuous data and characteristics of participants was expressed as means ± SD or as frequencies (%). BMI and waist circumference assessed in separate. Data was analysed according to gender to determine sex-specific effects. Potential confounders were defined as variables shown in the literature to be predictors of BP, namely: smoking status, alcohol use, diabetes, and hypertension. Pearson's correlation coefficient was used to determine the association between education status and indices of overweight/obesity; lipid profile and indices of overweight/obesity; left ventricular mass index and indices of overweight/obesity. Sodium excretion rates were assessed to determine the 24-hour sodium excretion rate. GraphPad was to represent the association between serum leptin levels and measures of overweight/obesity; pulse wave velocity and measures overweight/obesity; left ventricular mass index and measures overweight/obesity. P value < 0.05 considered significant.

CHAPTER 3

Results

Table 3.1 gives a description of the demographic, anthropometric, and general clinical characteristics of the participants in the present study categorised according to BMI. The average age of the men was 43.7±18.6 vs 44.9±17.9 for women. Women had a significantly higher BMI than men (P<0.0001). More than 70% of the women were overweight/obese while 50% of men were overweight/obese. Men regularly smoked tobacco and consumed alcohol more than women. There was a high incidence of diabetes and hypertension among overweight/ participants.

Table 3.2 lists participant's characteristics according to WC recorded to the nearest 0.1cm. A greater percentage of women (57%) had increased WC. Contrary to women, fewer men (12%) had increased WC. The average WC for men was 86.4±14.8 vs 31.1±7.6 for women. More men regularly smoked tobacco and consumed alcohol than women. In contrast, women had a higher percentage of diabetes and hypertension.

Table 3.3 shows the relationship between BMI, WC, and education status. Men had no significant correlation between BMI/WC and education status (p=0.5796 for BMI and p=0.9160 for WC). There was a significant negative correlation between BMI/WC and education status in women (p=0.0007 for BMI and p<0.0001 for WC).

Table 3. 1: General characteristics of the study population stratified according to BMI.

	Total Population				Men				Women			
	All	Normal BMI	Overweight/ Obese	P value	All	Normal BMI	Overweight/ Obese	P value	All	Normal BMI	Overweight/ Obese	P value
Number	551	188	363		204	102	102		347	86	261	
Age (years)	44.5±18.1	34.7±17.3	49.5±16.4	<0.0001*	43.7±18.6	36.3±17.5	51.1±16.8	<0.0001	44.9±17.9	32.7±16.9	48.9±16.3	<0.0001*
BMI (kg/m^2)	28.9±7.4	21.4±2.4	32.8±5.9	<0.0001*	25.3±5.4	21.1±2.3	29.5±4.1	<0.0001	31.1±7.6	21.7±2.4	34.1±5.9	<0.0001*
WC (cm)	90.1±16.2	74.5±7.9	98.4±13.0	<0.0001*	86.4±14.8	75.6±7.8	97.6±11.6	<0.0001	92.3±16.6	73.1±7.9	98.7±17.5	<0.0001*
% tobacco	14.9	27.1	8.5		34.8	38.2	31.4		9.5	13.9	8.0	
% alcohol	18.9	27.1	14.6		33.8	47.7	20.6		3.7	3.5	3.8	
% Diabetic	8.3	2.7	11.3		7.8	2.2	13.7		8.7	3.5	10.3	
%Hypertensive	29.2	12.8	37.7		20.1	12.7	27.5		34.6	12.8	41.8	

BMI, body mass index; WC, waist circumference; Normal BMI ≥ 18.5 and < 25 kg/m^2; overweight BMI ≥25 and < 30 kg/m^2; Obese BMI ≥30 kg/m^2; values expressed as a percentage or mean ±standard deviation; P value < 0.05 considered significant.

Table 3. 2: General characteristics of the study population stratified according to waist circumference.

	Men				Women			
	All	Normal WC	Increased WC	P value	All	Normal WC	Increased WC	P value
Number	204	180	24		347	149	198	
Age (years)	43.7±18.6	41.7±18.5	59.1±11.3	<0.0001*	44.9±17.9	35.5±16.9	51.9±15.1	<0.0001*
BMI (kg/m^2)	25.3±5.4	24.1±4.1	34.2±5.4	<0.0001*	31.1±7.6	25.1±5.3	35.5±5.7	<0.0001*
WC (cm)	86.4±14.8	82.9±11.4	112.4±9.5	<0.0001*	92.3±16.6	76.3±7.6	103.8±10.7	<0.0001*
%Regular tobacco	34.8	36.7	20.8		9.5	12.8	46.9	
%Regular alcohol	33.8	37.2	8.3		3.7	5.4	2.9	
%Diabetic	7.8	4.0	33.3		8.7	2.0	13.6	
%Hypertensive	20.1	17.8	37.5		34.6	18.1	46.9	

WC, waist circumference corrected for age, hypertension, diabetes, tobacco, and alcohol use; BMI, body mass index; normal WC (≤94 cm in men; ≤80 cm in women) vs increased WC (>94cm in men; >80 cm in women); values expressed as a percentage or mean ±standard deviation; p value < 0.05 considered significant.

Table 3.3: The relationship between education status and indices of overweight/obesity

		Total population			Men			Women		
		R^2	CI	P value	R^2	CI	P value	R2	CI	P value
Education status vs										
	BMI	-10	-0.16 to -0.02	0.0069*	0.03	-0.08 to 0.14	0.5796	-0.14	-0.22 to -0.10	0.0007*
	WC	-13	-0.19 to -0.06	0.0002*	-0.01	-0.12 to 0.11	0.9160	-0.19	-0.27 to -0.11	<0.0001*

BMI, body mass index; WC, waist circumference corrections were made for age, hypertension, diabetes, tobacco, and alcohol use; R^2, Coefficient of determination; CI; confidence interval; values expressed as mean ±standard deviation; P value < 0.05 considered significant.

Table 3.4 shows the relationship between BMI, WC, and lipid profiles. Men had a significant positive correlation between BMI/WC and TCHOL, LDL, TRGL and HDL ($p=0.0178$**,** $p<0.0001$, $p=0.0028$ and $p<0.0001$ respectively) of men. BMI was not significantly correlation with TCHOL ($p=0.5008$) and LDL ($p=0.5134$) in women. However, TRGL ($p=0.0175$) and HDL ($p<0.0001$) were significantly correlated with BMI. Furthermore, WC was significantly correlated with TRGL and HDL ($p=0.0009$ and $p<0.0001$ respectively).

Table 3.5 shows the lipid profiles and Sodium of the study population stratified according to BMI. The lipid profile of the total population was significantly different between normal and overweight/obese participants ($p<0.0001$). Overweight/obese women had significantly high TCHOL and TRGL ($p=0.0006$ and $p=0.0003$ respectively) as compared to normal BMI women. High density lipoprotein (HDL) was significantly high in overweight/obese men as opposed to normal BMI men ($p<0.0001$); contrary to women where LDL was significantly high ($p<0.0001$) in overweight/obese overweight/obese women as opposed to normal BMI women.

Table 3.6 show the lipid profiles and sodium concentration of the study population stratified according to WC. Men with increased WC had significantly high HDL ($p=0.0002$) compared to men with normal WC. There was no significant difference in TCHOL, TRGL, LDL and Na^+ ($p=0.3266$, $p=0.0554$, $p=0.3420$ and $p=0.2964$ respectively) between men with normal WC and men with increased WC. Women with increased WC had significantly high TCHOL ($p=0.0020$), TRGL ($p<0.0001$), HDL ($p<0.0001$), LDL ($p<0.0001$), Na^+ ($p=0.0027$) compared to women with normal WC.

Table 3. 4: The relationship between BMI, WC, and lipid profile.

		Men			Women		
		R^2	CI	P value	R2	CI	P value
BMI (kg/m^2) vs							
	TCHOL	0.12	0.02 to 0.22	0.0178*****	-0.02	-0.10 to 0.50	0.5008
	LDL	0.12	0.10 to 0.30	<0.0001*****	-0.03	-0.50 to 0.10	0.5134
	TRGL	0.15	0.40 to 0.25	0.0028*****	0.10	0.20 to 0.16	0.0175*****
	HDL	-0.34	-0.42 to -0.24	<0.0001*****	-0.22	-0.29 to -0.14	<0.0001*****
WC (cm) vs							
	TCHOL	0.13	0.03 to 0.23	0.0144*****	-0.03	-0.10 to 0.05	0.4736
	LDL	0.14	0.04 to 0.24	0.0073*****	0.04	-0.04 to 0.12	0.2922
	TRGL	0.21	0.11 to 0.31	<0.0001*****	0.13	0.05 to 0.20	0.0009*****
	HDL	-0.34	-0.43 to -0.23	<0.0001*****	-0.24	-0.31 to -0.16	<0.0001*****

BMI, body mass index; corrections were made for age, hypertension, diabetes, smoking and alcohol intake; TCHOL, total cholesterol; TRGL, triglycerides; HDL, high density lipoproteins; LDL; CI, Confidence Interval; R^2, Coefficient of determination.

Table 3. 5: Lipid profiles and urinary sodium concentration of the study population stratified according to BMI.

	Total Population				Men				Women			
	All	Normal BMI	Overweight/ Obese	P value	All	Normal BMI	Overweight/ Obese	P value	All	Normal BMI	Overweight/ Obese	P value
Number		188	363		204	102	102		347	86	261	
TCHOL (mmol/l)	4.61±1.10	4.29±0.99	4.77±1.26	<0.0001*	4.49±1.01	4.28±0.96	4.69±1.02	0.0030*	4.67±1.15	4.32±1.02	4.79±1.17	0.0006*
TRGL (mmol/l)	1.28±1.39	0.96±0.18	1.44±1.62	<0.0001*	1.52±1.85	1.11±0.84	2.38±7.25	0.0028*	1.14±1.03	0.79±0.39	1.25±1.15	0.0003*
HDL (mmol/l)	1.39±0.41	1.55±0.47	1.30±0.33	<0.0001*	1.31±0.45	1.46±0.51	1.17±0.34	<0.0001*	1.43±0.37	1.65±0.39	1.35±0.33	0.9108*
LDL (mmol/l)	2.66±0.97	2.31±0.86	2.85±0.98	<0.0001*	2.53±0.86	2.31±0.81	2.74±0.85	0.0004*	2.74±1.03	3.32±0.92	2.88±1.02	<0.0001*
Na^+ (mmol/day)	110.58±82.6	118.74±101.9	102.72±71.60	0.1753	107.36±72.65	102.46±77.82	111.99±67.60	0.4198	112.49±88.09	139.8±124.1	104.64±73.19	0.0087*

TCHOL, total cholesterol; TRGL, triglycerides; HDL, high density lipoproteins; LDL, low density lipoproteins; Na^+, 24-hour urinary sodium excretion rate; Normal BMI ≥ 18.5 and < 25 kg/m^2; overweight BMI ≥25 and < 30 kg/m^2; Obese BMI ≥30 kg/m^2; values expressed mean ±standard deviation; p value < 0.05 considered significant.

Table 3. 6: Lipid profiles and urinary sodium concentration of the study population stratified according to waist circumference.

	Men			Women		
	Normal WC	Increased WC	P value	Normal WC	Increased WC	P value
Number	180	24		149	198	
TCHOL (mmol/l)	4.47±1.02	4.66±0.99	0.3266	4.47±1.03	4.83±1.21	0.0020*
TRGL (mmol/l)	1.42±1.86	2.23±1.61	0.0554	0.84±0.41	1.36±1.27	<0.0001*
HDL (mmo/l)	1.36±0.46	0.99±0.22	0.0002*	1.57±0.40	1.32±0.29	<0.0001*
LDL (mmol/l)	2.51±0.87	2.68±0.73	0.3420	2.52±0.97	2.91±1.04	<0.0001*
Na^+ (mmol/day)	105.48±72.86	124.79±70.87	0.2964	130.59±105.78	99.53±70.44	0.0027*

TCHOL, total cholesterol; TRGL, triglycerides; HDL, high density lipoproteins; LDL, low density lipoproteins; Na^+, 24-hour urinary sodium excretion rate; WC, waist circumference corrected for age, hypertension, diabetes, tobacco, and alcohol use; normal WC (≤94 cm in men; ≤80 cm in women) vs increased WC (>94cm in men; >80 cm in women); values expressed as mean ±standard deviation; p value < 0.05 considered significant.

Table 3. 7: Haemodynamic characteristics (mm Hg) of the study population stratified according to BMI.

	Total Population				Men				Women			
	All	Normal BMI	Overweight/ Obese	P value	All	Normal BMI	Overweight/ Obese	P value	All	Normal BMI	Overweight/ Obese	P value
Number	551	188	363		204	102	102		347	86	261	
SBPC	128.4±20.9	120.6±18.0	120.6±18.0	<0.0001*	129.6±18.2	125.2±16.9	133.9±18.5	<0.0001*	127.7±22.3	115.2±17.9	131.8±22.1	<0.0001*
DBPC	83.6±11.9	80.4±10.8	80.4±10.8	<0.0001*	84.8±10.4	82.9±9.2	86.8±11.9	0.0061*	82.9±12.7	77.5±11.7	84.7±12.5	<0.0001*
SBP24	118.8±15.3	114.8±12.5	121.0±16.2	<0.0001*	120.7±12.8	118.7±11.4	122.7±13.9	0.0246*	117.8±16.5	110.1±12.2	120.4±16.9	<0.0001*
DBP24	72.9±10.6	70.1±9.0	74.3±11.0	<0.0001*	73.6±9.9	71.6±9.3	75.5±10.3	0.0024*	72.4±10.9	68.4±8.4	73.7±11.3	<0.0001*
SBPN	111.9±17.4	106.8±14.7	114.5±18.3	<0.0001*	112.9±14.9	109.9±13.7	115.8±15.5	0.0026*	111.3±18.7	103.1±13.7	114.1±19.3	<0.0001*
DBPN	65.1±15.0	61.5±10.4	66.9±12.4	<0.0001*	65.3±11.9	62.4±10.9	68.3±12.2	<0.0001*	65.0±12.1	60.6±9.7	66.5±12.5	<0.0001*
SBPD	123.0±15.0	119.7±12.7	119.7±12.7	<0.0001*	125.3±12.8	123.9±11.28	126.6±14.1	0.1600	121.7±16.0	114.7±12.5	124.1±16.4	<0.0001*
DBPD	77.9±10.8	75.7±9.6	75.7±9.6	<0.0003*	78.9±10.4	77.4±9.9	80.5±10.4	0.0421*	77.4±10.9	73.7±8.8	78.6±11.4	0.0002*

SBPC, conventional systolic pressure; DBPC, conventional diastolic blood pressure; SBP24, 24-hour systolic blood pressure; DBP24, 24-hour diastolic blood pressure; SBPN, night-time systolic blood pressure; DBPN, night-time diastolic blood pressure; SBPD, daytime systolic blood pressure; DBPD, daytime diastolic blood pressure; BMI, body mass index; Normal BMI ≥ 18.5 and < 25 kg/m^2; overweight BMI ≥25 and < 30 kg/m^2; Obese BMI ≥30 kg/m^2; values expressed as mean ±standard deviation; P value < 0.05 considered significant.

Table 3.7 gives the haemodynamic characteristics of the study participants stratified according to BMI. Overweight/obese participants had significantly high SBPC ($p<0.0001$) and DBPC ($p=0.0061$ for men and $p<0.0001$ for women) compared to normal weight participants. Moreover, the 24-hour ambulatory monitoring showed a significant difference between normal BMI vs overweight/obese in both men ($p=0.0246$) and women ($p<0.0001$). A similar trend was observed with night-time BP between normal BMI vs overweight/obese in both men ($p=0.0026$) and women ($p<0.0001$). Normal BMI vs overweight/obese was a significantly different ($p<0.0001$) in women.

Table 3.8 shows the haemodynamic characteristics of the study participants stratified according to WC. There was no significant difference between conventional BP of men with normal WC and men with increased WC. Women with increased WC had significantly high conventional BP compared to women with normal WC ($p<0.0001$). There was no significant difference between men with increased WC and those with normal WC in the 24-hour (SB24, $p=0.4495$ and DB24, $p=0.3139$), nighttime ($p=0.1825$) and daytime ($p=0.7975$) ambulatory BP. Women with increased WC had significantly high ($p< 0.0001$) 24-hour, nighttime, and daytime ambulatory monitoring values as compared to women with normal WC.

Table 3. 8: Haemodynamic characteristics (mm Hg) of the study population stratified according to waist circumference.

	Men				Women			
	All	Normal WC	Increased WC	P value	All	Normal WC	Increased WC	P value
Number	204	180	24		347	149	198	
SBPC	129.6±18.2	129.4±18.4	131.1±16.9	0.6612	127.7±22.3	119.9±19.8	133.4±22.4	<0.0001*
DBPC	84.8±10.4	84.9±10.4	84.6±9.1	0.7955	82.9±12.7	79.1±11.8	85.7±12.7	<0.0001*
SBP24	120.7±12.8	120.2±12.7	122.8±13.0	0.4495	117.8±16.5	113.1±14.6	121.3±17.0	<0.0001*
DBP24	73.6±9.9	73.4±10.3	75.6±6.9	0.3139	72.4±10.9	69.9±9.9	74.3±11.2	<0.0001*
SBPN	112.9±14.9	112.4±14.7	116.7±16.2	0.1825	111.3±18.7	105.9±16.7	115.4±19.1	<0.0001*
DBPN	65.3±11.9	64.7±12.2	70.1±8.7	0.0204*	65.0±12.1	61.9±10.9	67.4±12.5	<0.0001*
SBPD	125.3±12.8	125.1±12.9	126.4±12.6	0.7253	121.7±16.0	117.9±14.2	124.7±16.7	<0.0001*
DBPD	78.9±10.4	78.9±10.7	79.6±7.9	0.7975	77.4±10.9	75.2±10.1	79.0±11.3	0.0005*

SBPC, conventional systolic pressure; DBPC, conventional diastolic blood pressure; SBP24, 24-hour systolic blood pressure; DBP24, 24-hour diastolic blood pressure; SBPN, night-time systolic blood pressure; DBPN, night-time diastolic blood pressure; SBPD, daytime systolic blood pressure; DBPD, daytime diastolic blood pressure; Means corrected for age, hypertension, diabetes, tobacco and alcohol use; normal WC (≤94 cm in men; ≤80 cm in women) vs increased WC (>94cm in men; >80 cm in women); values expressed as mean ±standard deviation; P value < 0.05 considered significant.

Table 3.9 shows plasma hormone concentrations of the study population stratified according to BMI. In the total population, overweight/obese participants had significantly high insulin ($p=0.0066$) and leptin ($p<0.0001$) levels compared to normal BMI participants. Overweight/obese men had significantly high insulin and leptin levels ($p=0.0018$ and $p<0.0001$ respectively) compared to men with normal BMI. Overweight/obese women had significantly high leptin and ARR levels ($p<0.0001$ and $p=0.0162$ respectively) compared to women with normal BMI.

Table 3.10 shows plasma hormone concentrations of the study population stratified according to WC. There was no significant difference in renin, aldosterone and ARR concentrations ($p=0.6829$, $p=0.1504$ and $p=0.8817$ respectively) between men with increased WC and men with normal WC, however, insulin ($p<0.0001$) and leptin ($p<0.0001$) were significantly high in men with increased WC compared to men with normal WC. Leptin ($p<0.0001$) and ARR ($p=0.0113$) were significantly high in overweight/obese women compared to women with normal WC. There was an insignificant change in renin, aldosterone, and insulin ($p=0.6879$, $p=0.1332$ and $p=0.7053$, respectively) between women with normal WC and women with increased WC.

Table 3.9: Hormone levels of the study population stratified according to BMI.

	Total Population				Males				Females			
	All	Normal BMI	Overweight/ Obese	P value	All	Normal BMI	Overweight/ Obese	P value	All	Normal BMI	Overweight/ Obese	P value
Number	551	188	363		204	102	102		347	86	261	
Renin (ng/mL)	36.54±70.31	35.25±54.19	37.19±77.17	0.7020	37.48±71.76	34.5±55.6	40.35±84.70	0.6749	35.97±69.53	36.16±52.77	35.9±74.0	0.7884
Aldosterone (pg/mL)	191.84±163.35	176.49±154.21	199.56±167.45	0.1648	189.55±164.09	179.4±173.0	199.3±155.3	0.6204	193.2±163.15	172.9±128.6	199.7±172.4	0.2200
Insulin (mmol/l)	14.01±16.63	10.94±15.56	15.62±16.96	0.0066*	13.06±18.17	8.9±13.5	17.2±21.1	0.0018*	14.61±15.61	13.5±17.6	14.9±14.9	0.6532
Leptin (ng/mL)	25.14±25.43	10.99±11.84	32.08±27.38	<0.0001*	8.55±8.79	4.4±6.3	12.0±9.1	<0.0001*	35.74±26.88	18.8±12.2	41.3±28.1	<0.0001*
ARR	27.34±55.62	26.88±77.26	27.56±41.88	0.0896	28.67±73.38	35.8±99.4	22.3±39.8	0.2306	26.51±40.86	15.14±25.8	29.8±43.8	0.0162*

ARR, Aldosterone renin ratio; BMI, body mass index; Normal BMI ≥ 18.5 and < 25 kg/m^2; overweight BMI ≥25 and < 30 kg/m^2; Obese BMI ≥30 kg/m^2; values expressed as mean ±standard deviation; P value < 0.05 considered significant.

Table 3. 10: Hormone levels of the study population stratified according to waist circumference.

	Men				Women			
	All	Normal WC	Increased WC	P value	All	Normal WC	Increased WC	P value
Number	204	180	24		347	149	198	
Renin (ng/mL)	37.48±71.76	38.22±74.42	32.07±48.65	0.6829	35.97±69.56	35.39±47.64	36.39±81.86	0.6879
Aldosterone(ng/mL)	189.55±164.09	183.19±165.89	234.09±146.29	0.1504	193.21±163.15	174.91±163.79	206.30±161.85	0.1332
Insulin (mmol/l)	13.06±18.17	11.05±13.75	27.77±34.12	<0.0001*	14.61±15.61	13.70±17.09	15.26±14.48	0.7053
Leptin (ng/mL)	8.55±8.79	7.49±7.96	17.33±10.71	<0.0001*	35.74±26.88	21.05±13.04	47.52±28.90	<0.0001*
ARR	28.67±73.38	28.88±77.03	26.74±20.68	0.8817	26.51±40.86	18.75±32.69	32.14±45.18	0.0113*

ARR, Aldosterone renin ratio; WC, waist circumference corrected for age, hypertension, diabetes, tobacco, and alcohol use; normal WC (≤94 cm in men; ≤80 cm in women) vs increased WC (>94cm in men; >80 cm in women); values expressed as mean ±standard deviation; P value < 0.05 considered significant.

Figure 3.1 shows the association between pulse wave velocity and measures of obesity (BMI and WC). Participants with increased BMI had significantly high PWV ($p<0.0001$) compared to participants with normal BMI. Furthermore, participants with increased WC had significantly high PWV ($p<0.0001$) compared to participants with normal WC.

Figure 3.2 shows the association between left ventricular mass index and measures of obesity (BMI and WC). Participants with increased BMI had significantly high LVMI ($p<0.0001$) compared to participants with normal BMI. Furthermore, participants with increased WC had significantly high LVMI ($p<0.0001$) compared to participants with normal WC.

Figure 3.3 shows the association between serum leptin levels and measures of obesity (BMI and WC). Participants with increased BMI had significantly high serum leptin levels ($p<0.0001$) compared to participants with normal BMI. Furthermore, participants with increased WC had significantly high serum leptin levels ($p<0.0001$) compared to participants with normal WC.

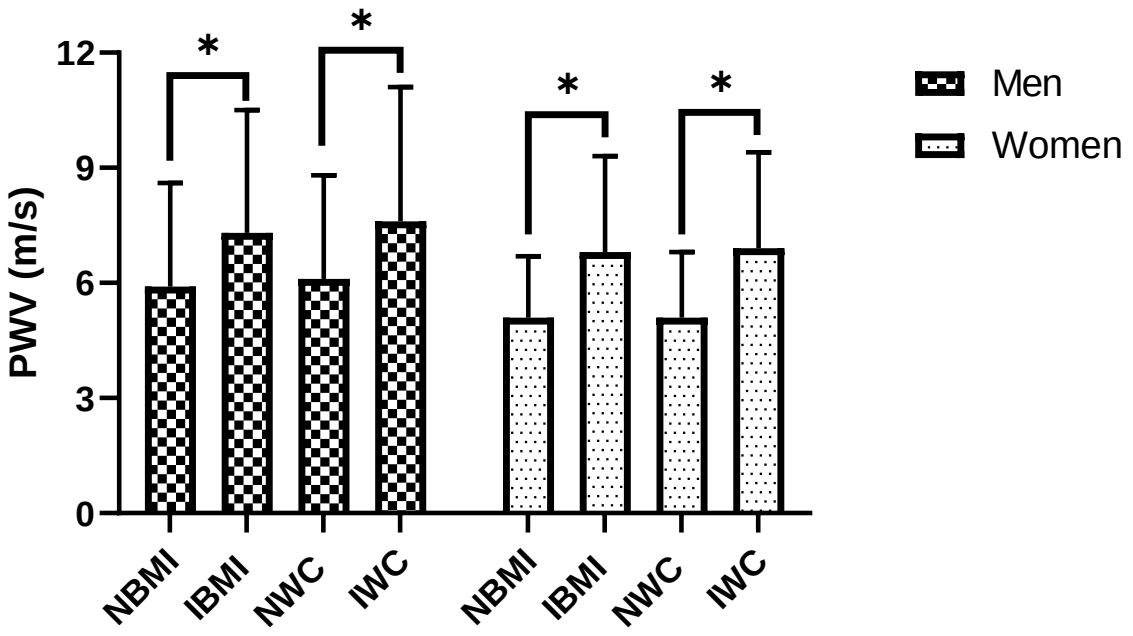


Figure 3. 1: The independent association of body mass index and waist circumference on pulse wave velocity.

NBMI, normal body mass index (18.5 – 24.9 Kg/m^2); IBMI, increased body mass index (≥25.0 Kg/m^2); NWC, normal waist circumference (≤94 cm in men; ≤80 cm in women); IWC, increased waist circumference (>94cm in men; >80 cm in women) corrected for age, hypertension, diabetes, tobacco, and alcohol use; error bars; standard deviation; *, statistically significant.

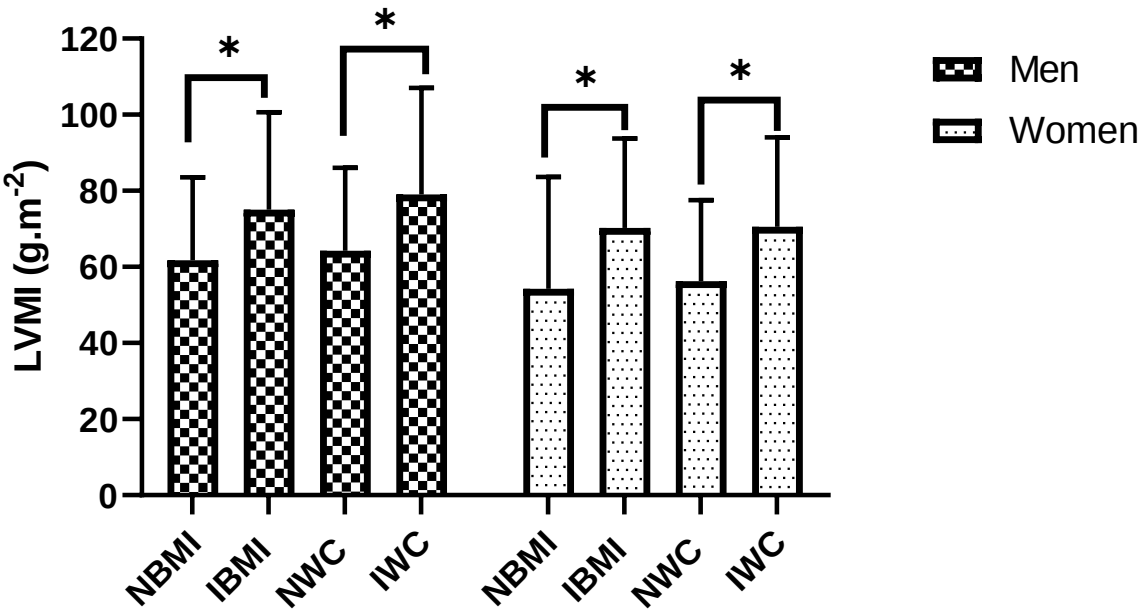


Figure 3. 2: The independent association of body mass index and waist circumference on left ventricular mass index.

LVMI, left ventricular mass index; NBMI, normal body mass index (18.5 – 24.9 Kg/m^2); IBMI, increased body mass index (≥25.0 Kg/m^2); NWC, normal waist circumference (≤94 cm in men; ≤80 cm in women); IWC, increased waist circumference (>94cm in men; >80 cm in women) corrected for age, hypertension, diabetes, tobacco, and alcohol use; error bars; standard deviation; *, statistically significant.

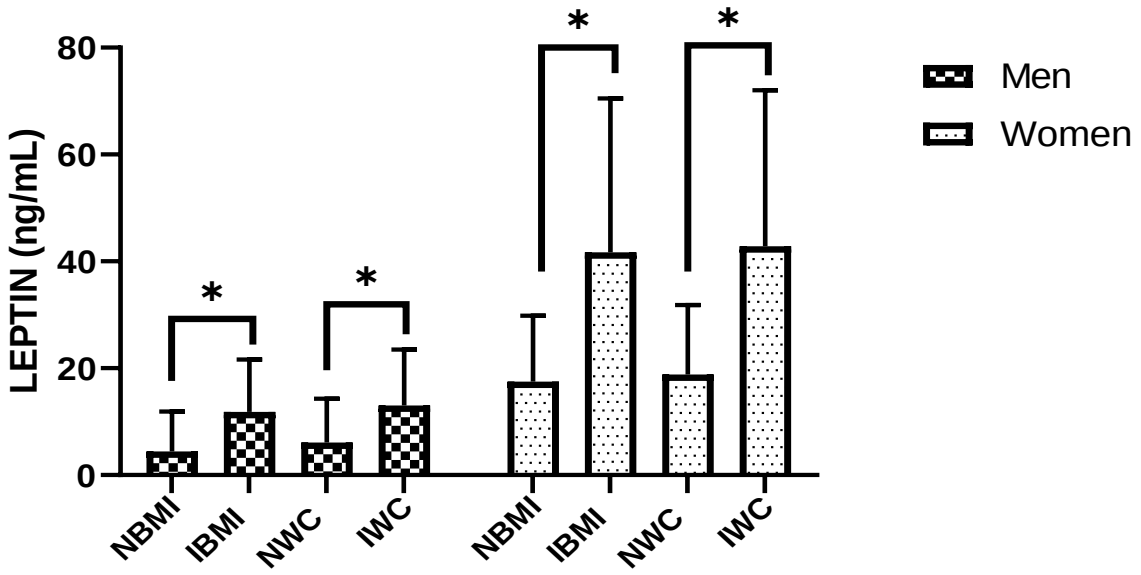


Figure 3. 3: The independent association of body mass index and waist circumference on serum leptin concentrations.

NBMI, normal body mass index (18.5 – 24.9 Kg/m^2); IBMI, increased body mass index (≥25.0 Kg/m^2); NWC, normal waist circumference (≤94 cm in men; ≤80 cm in women); IWC, increased waist circumference (>94cm in men; >80 cm in women). corrected for age, hypertension, diabetes, tobacco, and alcohol use; error bars; standard deviation; *, statistically significant.

Figure 3.4 shows the combined effects of indices of obesity (BMI and WC) on pulse wave velocity. Participants that had both increased BMI and increased IWC had significantly high PWV ($p<0.0001$) as compared to participants with increased BMI and normal WC and participants with normal BMI and normal WC. Furthermore, participants with increased BMI and normal WC had significantly high PWV ($p<0.0001$) compared to participants with normal BMI and normal WC.

Figure 3.5 shows the combined effects of indices of obesity (BMI and WC) on left ventricular mass index. Participants that were categorised as non-dippers had significantly high LVMI ($p<0.0001$) as compared to participants within the dippers category. Furthermore, Reverse dippers had significantly high LVMI ($p<0.0001$) compared to dippers and non-dippers.

Figure 3.6 shows the combined effects of indices of obesity (BMI and WC) on serum leptin levels. Participants that had both increased BMI and increased IWC had significantly high serum leptin levels ($p<0.0001$) as compared to participants with increased BMI and normal WC and participants with normal BMI and normal WC. Furthermore, participants with increased BMI and normal WC had significantly high serum leptin levels ($p<0.0001$) compared to participants with normal BMI and normal WC.

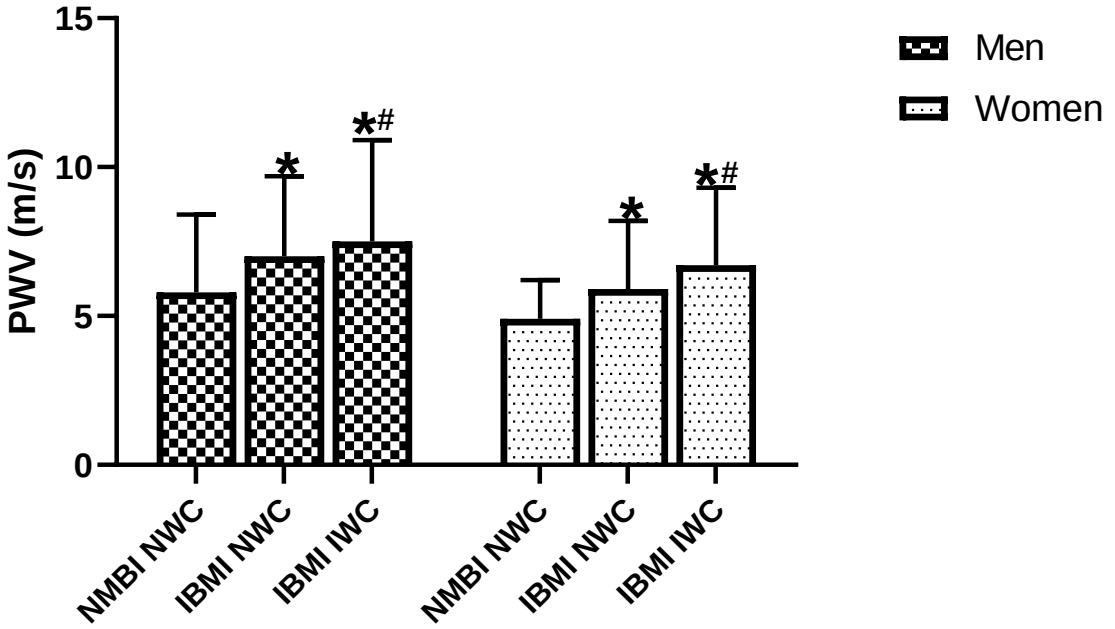


Figure 3. 4: The combined effects of body mass index and waist circumference on pulse wave velocity.

NBMI, normal body mass index (18.5 – 24.9 Kg/m^2); IBMI, increased body mass index (≥25.0 Kg/m^2); NWC, normal waist circumference (≤94 cm in men; ≤80 cm in women); IWC, increase waist circumference (>94cm in men; >80 cm in women) corrected for age, hypertension, diabetes, tobacco, and alcohol use; error bars, standard deviation; *, statistical significance to NMBI NWC; *$^{\#}$, statistical significance to NMBI NWC and IBMI NWC.

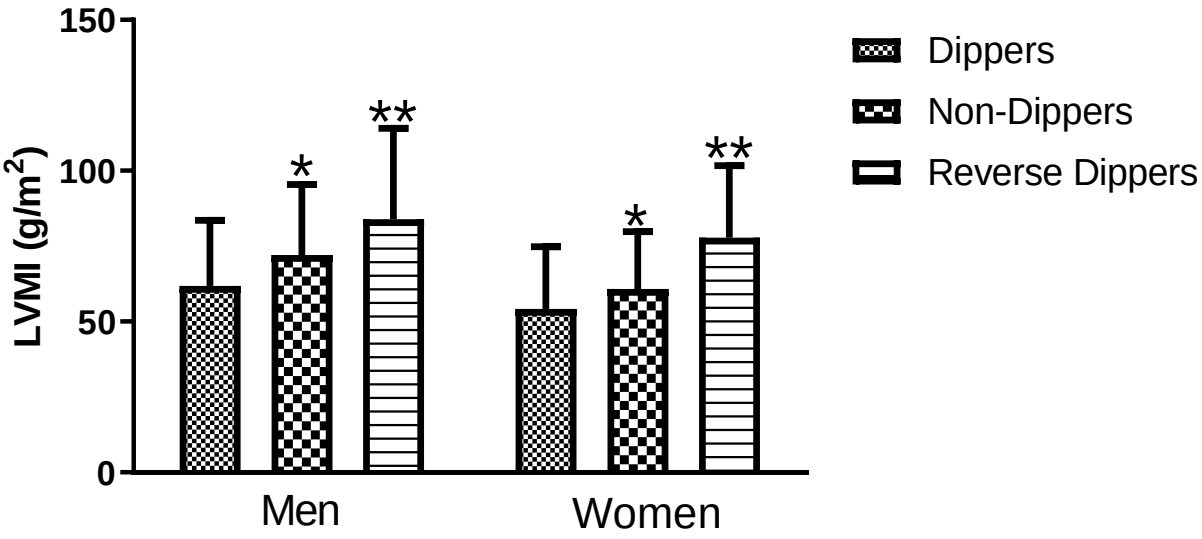


Figure 3. 5: The combined effects of body mass index and waist circumference on left ventricular mass index.

LVMI, left ventricular mass index; Waist circumference (>94cm in men; >80 cm in women) corrected for age, hypertension, diabetes, tobacco, and alcohol use; error bars, standard deviation; *, statistical significance.

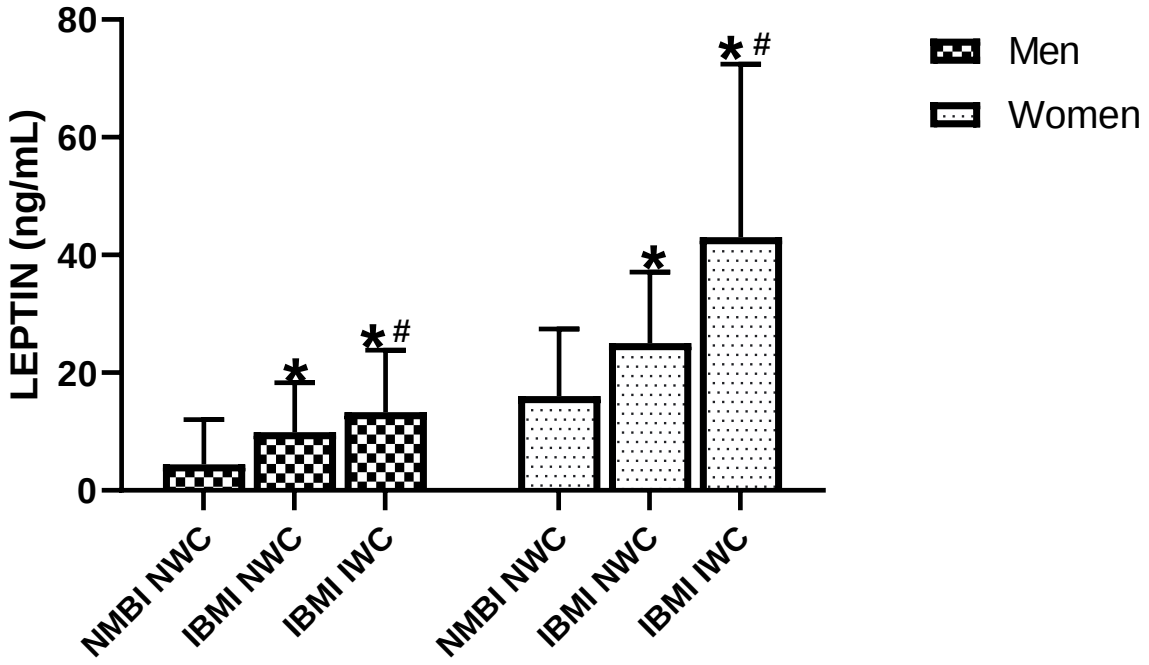


Figure 3. 6: The combined effects of body mass index and waist circumference on serum leptin concentrations.

NBMI, normal body mass index (18.5 – 24.9 Kg/m^2); IBMI, increased body mass index (≥25.0 Kg/m^2); NWC, normal waist circumference (≤94 cm in men; ≤80 cm in women); IWC, increase waist circumference (>94cm in men; >80 cm in women) corrected for age, hypertension, diabetes, tobacco, and alcohol use; error bars, standard deviation; *, statistical significance to NMBI NWC; *#, statistical significance to NMBI NWC and IBMI NWC.

Table 3.11 shows the relationship between BMI, WC, and LVMI. Men had a significant positive correlation between BMI/WC and LVMI ($p<0.0001$). Furthermore, women also had a significant positive correlation between BMI/WC and LVMI ($p=0021$).

Table 3.11: The relationship between BMI, WC and LVMI.

		Total Population			Men			Women		
		R^2	CI	P value	R^2	CI	P value	R^2	CI	P value
BMI vs										
	LVMI	0.24	0.16 to 0.31	<0.0001*	0.33	0.19 to 0.45	<0.0001*	0.21	0.10 to 0.31	<0.0001*
WC vs										
	LVMI	0.21	0.12 to 0.21	<0.0001*	0.28	0.12 to 0.41	<0.0001*	0.17	0.06 to 0.27	0.0021*

BMI, body mass index; WC, waist circumference corrections were made for age, hypertension, diabetes, tobacco, and alcohol use; LVMI, left ventricular mass index; R^2, Coefficient of determination; CI; confidence interval; values expressed as mean ±standard deviation; P value < 0.05 considered significant.

CHAPTER 4

Discussion

4.1 The prevalence of overweight/obesity in African communities.

Our results indicate that there is a high prevalence of obesity in this population, 66% of the participants were either overweight or obese; with women having a higher prevalence of overweight or obesity (75% compared to men 50%). This is consistent with previous studies conducted in this population. A study by Maseko *et al* (2018) showed that 71% of the participants were either overweight or obese, with women having a higher prevalence of obesity (75%) compared to men (47%). Since overweight/obesity is one of the leading risk factors for cardiovascular diseases (Ortega *et al*. 2016), the gender disparities in the prevalence of obesity need thorough investigation. We speculated that education status may be playing a significant role on the gender differences in the prevalence of obesity. Similar to a study by Kim *et al* (2017), our results show a negative correlation between BMI and the level of education in the total population, indicating that people with a higher level of education had a lower BMI compared to people with a lower level of education. However, in our study we did further analysis after stratifying participants according to gender and our results showed that the level of education in both genders was similar. In both groups the highest level of education was grade 12 (high school). Even though the level of education was similar between men and women, the negative correlation between BMI and education status was only in women, there was no significant association between BMI and education in men. These findings imply that education influences BMI in women but not in men. Contrary to our findings, Dursun *et al* (2018) found that education status influences BMI in both men and women however the relationship was not similar in the two gender groups. Their results show that BMI and education are negatively correlated in women while this relationship is positive in men. Their findings suggest that education prompts women to maintain a healthy BMI while it increases the inclination towards an unhealthy body weight in men. Further analysis revealed that while educated women practised healthy lifestyles, educated men tended to engage in a more sedentary lifestyle by spending more time on the internet and social media activities (Dursun *et al.* 2018). The relationship between BMI and education status was confirmed when we stratified participants according to WC. Similar to BMI, there was a negative correlation between WC and education status in women but not in men. Furthermore, this negative correlation between education and adiposity was much stronger for WC compared to BMI. The poor literacy in resource limited African communities especially in women could account for the increased high incidence of obesity in this group.

Even though BMI is a good indicator of an increase in body fat, it has serious limitations because it does not take body composition and fat distribution into account (Flegal *et al.* 2009). This means that fat and muscle will not be categorised as accordingly, leading to possible flaws in the comparison of the effects of fat distribution on cardiovascular health. For example, bodybuilders may be classified as obese because of their increased body weight. However, their increased weight is due to increased muscle mass and not body fat. To account for both general and abdominal obesity, we classified the participants according to BMI and WC, with BMI being indicative of general obesity and WC showing the presence or absence of abdominal obesity. As with the assessment of BMI, more women (57%) had an increased WC compared to men (12%). There were gender differences in the overlap between BMI and WC. There was a greater overlap between general and central obesity in women compared to men. Only 28% of the men who were overweight/obese had increased WC, while 76% of the overweight/obese women had increased WC as well. None of the men with increased WC had normal BMI while only 5% of the women with increased WC had normal BMI. This implies that even though general obesity can exist independent of central obesity, it is rare for central obesity to exist independent of general obesity. Consequently, WC may be a better index of adiposity than BMI in this population and it may explain why WC is more strongly associated with target organ damage than BMI. Research shows that WC as an index of central obesity can be utilised as an indicator of the amount of central fat. An increased WC is closely associated with increased fat build up in the abdominal region. The extent to which central obesity may present itself is dependent on gender. Numerous studies, such as that by (Smith and Essop, 2009; Mikkola *et al.* 2013) detail the gender differences that ultimately influence risk factors in both genders. Men are predisposed to abdominal fat accumulation (Nedungadi and Clegg, 2009). Contrary to our results which show that more men are predisposed to general obesity (50%) than to central obesity (12%).

4.2 The relationship between blood pressure and the indices of obesity.

Whether BMI and WC have different or similar effects on BP in this population is currently unknown. Moreover, there is no evidence on whether the coexistence of both forms of obesity on a single individual amplifies their effects on BP. To answer these questions, we stratified

the participants according to BMI and WC and calculated the mean BP of each group. The means were adjusted for age, alcohol intake, cigarette smoking, HT, and diabetes. When participants were stratified according to BMI, the 24-hour, night-time, daytime, and conventional BP values of the overweight/obese participants was significantly higher than those of normal BMI participants. These differences persisted even after the participants were separated according to gender. This is not unique to our study, numerous studies, including one by Kotsis *et al* (2005) have shown that a high BMI is associated with high BP. Comparison of the data from our study with the above mentioned study is not without its setbacks. Gender distribution and study design differ. Despite having both genders, they did not stratify according to gender like our current study. Our results further show that despite the similar BP values between the overweight/obese men and women, the BP values of the normal BMI men were significantly higher than the BP values of normal BMI women. This can be attributed to the high proportion of men with normal BMI who smoke cigarettes (38.2%) and drink alcohol (47%) compared to women (13.9%) and (3.5%) respectively. It would appear that the high prevalence of alcohol and cigarette smoking in men was met by a sharp increase in BP. Numerous studies detail the effects of alcohol and cigarette smoking on BP (Mantzoros *et al.* 1998; Bigaard *et al.* 2003; Akbartabartoori *et al*. 2005; Fagard, 2009). Alcohol promotes SNS activation as well as the discharge of sympathetic amines. The increased sympathetic outflow leads to increased heart rate, vasoconstriction as well as oxidation reactions (Husain *et al.* 2014). Furthermore, alcohol leads to impairment of the baroreceptors as well as stimulation of the renin-angiotensin-aldosterone system (RAAS) (Grogan and Kochar, 1994; O'Keefe *et al*. 2007; Husain *et al*. 2014; Zatu *et al.* 2016). Over-activation of the RAAS leads to sodium retention, increased blood volume and increased BP (Muñoz-Durango *et al.* 2016). Nicotine leads to increased heart rate, hardened arterial walls and consequently elevated BP. Smoking can also lead to atherosclerosis as it promotes the build-up of plaque (Bigaard *et al.* 2003; Baldassarre *et al.* 2009; Fagard 2009). The current study adds to the existing knowledge about the risks of alcohol consumption and cigarette smoking.

When the participants were stratified according to WC, the results were like those observed when participants were classified according to BMI. Participants with an increased WC had higher BP values than those with normal WC. However, in men this difference was not statistically significant because of the low percentage of men (12%) with an increased WC. The differences in the BP values between individuals with increased BMI and WC and those

with normal BMI and WC can be explained in the context of the differences in the plasma leptins of the two groups. Our results show that overweight/obese individuals had significantly higher leptin concentrations compared to the normal weight individuals. The elevated leptin levels can be attributed to the high amount of adipose tissue in overweight/obese individuals since leptin is primarily synthesised by adipocytes. These findings are similar to those of a study by Van Zyl *et al* (2017). They found that leptin concentrations were significantly high in obese African women as compared to those of normal weight. Having assessed only 135 African women, their study used BMI to account for obesity and they did not contrast general and central obesity. The mechanism of how leptin influences BP is well established in a number of studies (Schutte *et al.* 2005; Barba *et al.* 2003; Nishina *et al.* 2003). Leptin is a 16-KDa protein which is secreted by white adipose tissue. By acting on the sympathetic nervous system (SNS), leptin stimulates sympathetic activation, especially in the kidneys. This leads to sodium retention and systemic vasoconstriction. The long-term retention of sodium leads to an increase in BP. Vasoconstriction leads to a decrease in vessel volume and an increase in resistance. Therefore, BP will be elevated (Bełtowski, 2006; Bravo *et al*. 2006). Sympathetic Nervous System activation is a major contributor of BP elevation in overweight/obese individuals.

4.3 The association between indices of overweight/obesity and lipid profiles.

The impact of overweight/obesity on lipid metabolism are reliant on the locality of the adipose tissue (Feingold and Grunfeld, 2000). Soares *et al* (2019) found that both indices of overweight/obesity were significantly associated with adverse lipid profiles in men and women. However, associations were stronger for measures of general obesity as opposed to those of abdominal obesity. Therefore, their study supports BMI as a more dependable indicator of dyslipidaemia as opposed to WC. Several other studies have supported BMI as a better predictor of overweight/obesity-induced lipid abnormalities (Shamai *et al.* 2011; Yang *et al.* 2017; Eslami *et al*. 2019; Taliyan *et al.* 2019). Notwithstanding the supposed superiority of BMI in the assessment of lipid abnormalities, Crowther *et al* (2006) found that abdominal obesity is an important risk factor for lipid abnormalities in women of African ancestry.

Several studies have shown that increased adiposity is associated with an increase in plasma lipid profiles (Feingold and Grunfeld, 2000; Shamai *et al.* 2011; Klop *et al.* 2013). Whether the influence of BMI and WC on plasma lipid concentrations is similar or different in this

population is currently unknown. As expected, when participants were stratified according to BMI; TCHOL, TRGL and LDL were significantly higher in overweight/obese individuals compared to normal. This trend was observed even after participants were separated according to gender. Overweight men and women had higher TCHOL, TRGL and LDL compared to normal weight men and women. An abnormal amount of lipids in the blood is known as dyslipidaemia (Feingold and Grunfeld, 2000). Obesity is associated with uncontrolled fatty acid release from adipose tissue through lipolysis. The result is an increase in the delivery of fatty acids to the liver and consequently synthesis of very low-density lipoprotein (VLDL). An increase in fatty acids also results in decreased activity of lipoprotein lipase (LPL) and mRNA expression in adipose tissue (Klop *et al.* 2013). Furthermore, lipolysis of chylomicrons is inhibited due to increased VLDL in the liver. This promotes hypertriglyceridemia which triggers the exchange of TRGL for cholesterol esters (LDL and HDL). Therefore, there is a reduction in TRGL content in LDL and a decrease in HDL-cholesterol concentration. Hepatic lipase hydrolyses the TRGL content in LDL, leading to the development of dense LDL particles that put an individual at risk of developing CVD (Jung and Choi, 2014). Our results also show that there was a significant decrease in HDL in generally obese men as opposed to normal weight men. This was also true for women, but the difference was not significant. The results in our study show that general obesity is a risk factor for lipid derangement. The impact of overweight/obesity on lipid metabolism are reliant on the locality of the adipose tissue (Feingold and Grunfeld, 2000). Similar to our study, Soares *et al* (2019) found that generally obese participants had significantly higher lipid levels as opposed to normal weight participants. Their study found that the change in lipid levels with increasing BMI were mostly similar in magnitude between men and women. This was reaffirmed by our results. Although their study assessed BMI, they did not assess the relationship between WC and lipid profiles. Thereby they did not contrast general obesity to central obesity.

The uniqueness of our study is that we measured WC as well so that we could compare general and central obesity in relation to plasma lipids. When we stratified participants according to WC, gender differences were observed. There was a significant difference in plasma lipid profiles (TCHOL, TRGL and LDL) of females with an increased WC compared to those with normal WC while no statistically significant difference was observed in men. The observed lack of statistically significant difference may be due to the lower number of men in the high WC group. However, even without the statistical significance difference, a trend effect could

be observed. Men in the increased WC group had higher lipid profiles compared to the normal WC group. Therefore, an increase in plasma lipid profiles is independent of the type of adiposity. An increase in either BMI or WC is associated with an increase in plasma lipids. Contrary to TCHOL, TRGL and LDL, HDL was higher in individuals with normal WC compared to those with increased WC.

4.4 The impact of adiposity on cardiovascular target organs.

We found that both indices of overweight/obesity (BMI/WC) were significantly associated with PWV. Pulse wave velocity is a measure of arterial stiffness (Schutte *et al.* 2020). An accurate measure of PWV gives insight into the condition of the arteries and essentially highlights the presence or absence of vascular damage. Overweight/obesity is associated with excess adiposity which leads to elevated serum leptin levels. To understand the association between overweight/obesity and PWV, we evaluated the serum leptin levels of the population. In our analysis, we found that overweight/obese participants had significantly high serum leptin levels. Leptin has a direct effect on PWV through its ability to induce oxidative stress, SNS activation, release of endothelin 1 and diminish NO-bioavailability. These changes lead to peripheral resistance and vasoconstriction (Muñoz-Durango *et al.* 2016). Therefore, elevated serum leptin levels evident in this study population are likely associated with impaired vasodilation. Furthermore, Tsai *et al* (2016) showed that leptin increases proliferation and migration of vascular smooth muscle cells through its ability to stimulate phosphorylation and activate mitogen-activated protein kinases. Therefore, our data suggests that leptin may be the predominant determinant of PWV in this population, however, further research is needed to ascertain the threshold of leptin levels in relation to arterial stiffness in this population. Having shown the association between indices of adiposity and arterial stiffness, we wanted to see if the indices of adiposity have a direct effect of cardiac changes.

We also investigated the association between the indices of obesity and LVMI. Our results show that LVM was significantly increased in individuals with increased BMI and WC compared to individuals with normal BMI and normal WC. An increase in LVM is initially an adaptation to increased afterload to the left ventricle (Nagueh *et al.* 2009), however, over time myocyte slippage occurs, and the condition progresses to heart failure. These results show that overweight/obese individuals are at a high risk of developing heart failure. In a stepwise

regression analysis, correcting for covariates, we found a strong independent relationship between LVMI and both BMI and WC. This relationship remained statistically significant even after correcting for HT status. Since HT is a main contributor to heart failure, these findings indicate that in this community, even normotensive people who are overweight/obese are in danger of developing heart failure. Since the relationship between adiposity and LVM was independent of HT status, we speculated that the increased LVM in overweight/obese individuals was due to the higher TRGL in this group. These cardiac changes could be due to impairment of adipocyte-mediated storage of superfluous fuel, resulting in excess TRGL being stored in ectopic tissues such as the heart. The subsequent accumulation of lipid droplets in the cytosol mitochondria promotes organ dysfunction and consequently dilated cardiomyopathy. In addition to TGRL, we also found that serum insulin levels were significantly high in overweight/obese participants as opposed to those with normal. Overweight/obesity is also associated with hyperinsulinemia. Hyperinsulinemia is an independent cardiovascular risk factor associated with activation of the SNS which might affect LVM directly due to growth-stimulating effects. Sympathetic nervous system activation increases heart rate, this could also be playing an indirect role in LVM changes (Shereef and Kandeel, 2019). BMI. Therefore, hyperinsulinemia is a likely contributor of LVM changes in this population. As previously stated, we found that leptin levels were significantly high in participants with increased BMI/WC. Hyperleptinemia, a condition which is synonymous with overweight/obesity is associated with cardiomyocyte apoptosis, reactive oxygen species in the heart and direct inducement of cardiac hypertrophy (Brady, 2016). Hence hyperleptinemia is associated with LVM increase. Leptin also has an indirect association with LVM through its ability to affect sodium. Leptin causes sodium retention (Bravo *et al*. 2006). Increased Na^+ can directly affect LVM through its ability to sensitise the heart to hypertrophic stimulus of pressure load. In our study, we found that serum Na^+ were significantly high in overweight/obesity women. Other studies have shown that BMI is associated with LVM (Avelar *et al.* 2007; Ballo *et al.* 2007; Korre *et al.* 2016), however most of the studies were conducted on individuals from first world countries hence our study sought to further assess this relationship in a purely South African population.

Having established that the indices of obesity (BMI/WC) are both independently associated with vascular damage and cardiac changes in this population, we sought to investigate the combined effects of these indices. To investigate the combined effects, we divided our

participants into three groups based on their BMI and WC status; normal BMI (NBMI) and normal WC (NWC); increased BMI (IBMI) and normal WC (NWC); increased BMI (IBMI) and increased WC (IWC). None of the participants were in the normal BMI and increased WC category, indicating that WC does not increase independent of BMI. To the best of our knowledge, this is the first study to assess target organ damage according to these categories that show the combined impact of both indices of obesity on vascular and cardiac changes. Our results show that individuals with increased BMI and WC had a significantly higher PWV and LVMI compared to those with normal BMI and increased WC. Therefore, the use BMI and WC independently in the assessment of arterial stiffness and cardiac changes is inferior to using the two indices together. These combined effects show us the importance of both BMI and WC when assessing cardiac and vascular damage.

4.5 Gender differences in urinary sodium excretion

Our results show a reduced sodium excretion in women but not men. The higher incidence of overweight/obesity in women leads to higher leptin levels in women. The long splice variant leptin receptor present in the renal medulla suggests a functional role of leptin in renal biology (Kshatriya *et al.* 2011). Chronic elevation of leptin, as a characteristic of overweight/obesity, leads to a reduction in natriuresis through the up-regulation of Na/K-ATPase pump. These actions lead to salt retention and reduce urinary salt excretion. The results from the present study show a greater susceptibility of black overweight/obese women to hypernatremia, a condition where there is too much sodium in the blood. This could result in adverse cardiac outcomes such as elevated cardiac enzymes and LV contractile dysfunction.

4.6 Conclusion

According to our findings, more women are overweight/obese compared to men irrespective of the index of obesity used. Our results show that educated women of African ancestry are more likely to have a lower BMI that women who are not educated. However, this association does not appear in men. The present study has further demonstrated that overweight/obesity has adverse effects on cardiovascular health in people of African descent independent of their HT status. This indicates that obesity may be more detrimental to cardiovascular health in this population than previously reported. Since our results link adiposity to increased BP and increased LVM independently, strategies to reduce the rising incident of heart disease in this population should not just target BP control but should also focus on the reduction of excess adiposity. Controlling BP to target values may not protect overweight/obese individuals from developing heart disease. Furthermore, our results highlight the importance of using both BMI and WC in the assessment of the impact of adiposity on the cardiovascular system. Most studies have shown WC to be a more important index of adiposity as it is more closely associated with cardiovascular target organ damage than BMI. However, our findings indicate even in individuals with normal WC, both arterial stiffness and LVM were increased if these individuals were in the overweight/obesity BMI category. To the best of our knowledge, this is the first study to demonstrate that a normal WC does not prevent cardiovascular target organ damage if BMI is elevated. On the other hand, a normal BMI can be an indication of cardiovascular health independent of WC because in this population there are no individuals with normal BMI and increased WC. If BMI is reduced to the normal range, WC becomes normal as well. Therefore, in this population, any lifestyle intervention strategy, whether exercise or diet, should focus primarily on the reduction of BMI. Furthermore, there is a need for more educational campaigns on health consciousness for individuals to alleviate the poor literacy in resource limited African communities, particularly in women.

4.7 Possible study limitations and future perspective

The cohort of the present study was comprised of more women than men. Although random recruitment provides a better representation of the public, it is common to find that men are reluctant to participate. This could be because of the unwillingness of men to take part in such studies as with the case where fewer men regularly visit doctors as opposed to females. It is probable that the small number of men in this study could have created a gender bias. We did not measure testosterone and oestrogen levels in men and women, respectively. The association between adiposity and sex hormones is a vital part of understanding cardiac changes in both genders. Future studies should assess the association between overweight/obesity, cardiac or vascular changes and sex hormones. Furthermore, hormones such as resistin and adiponectin should also be assessed to ascertain the impact of indices of overweight/obesity on these hormones. Although our study demonstrates a positive association between indices of increased BMI/WC and cardiac/vascular damage, future studies should include underweight as a subgroup to study the effects of underweight on cardiac and vascular changes. The combined use of BMI and WC provided more predictive power as opposed to using only one index to measure obesity. Therefore, future studies should consider incorporating this assessment method to account for the presence/absence of both forms of obesity.

References

Ahimastos, A.A., Formosa, M., Dart, A.M., and Kingwell, B.A., 2003. Gender Differences in Large Artery Stiffness Pre- and Post Puberty. *The Journal of Clinical Endocrinology and Metabolism*, **88**, 5375–5380.

Akbartabartoori, M., Lean, M.E.J., and Hankey, C.R., 2005. Relationships Between Cigarette Smoking, Body Size and Body Shape. *International Journal of Obesity*, **29**, 236–243.

Al-Ghamdi, S., Shubair, M.M., Aldiab, A., Al-Zahrani, J.M., Aldossari, K.K., Househ, M., Nooruddin, S., Razzak, H.A., and El-Metwally, A., 2018. Prevalence of Overweight and Obesity Based on the Body Mass Index; A Cross-Sectional Study in Alkharj, Saudi Arabia. *Lipids in Health and Disease*, **17**, 1–8.

Aroor, A.R., Jia, G., and Sowers, J.R., 2018. Cellular Mechanisms Underlying Obesity-Induced Arterial Stiffness. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology*, **314**, 387–398

Avelar, E., Cloward, T. V., Walker, J.M., Farney, R.J., Strong, M., Pendleton, R.C., Segerson, N., Adams, T.D., Gress, R.E., Hunt, S.C., and Litwin, S.E., 2007. Left Ventricular Hypertrophy in Severe Obesity: Interactions Among Blood Pressure, Nocturnal Hypoxemia, and Body Mass. *Hypertension*, **49**, 34–39.

Baldassarre, D., Castelnuovo, S., Frigerio, B., Amato, M., Werba, J.P., De Jong, A., Ravani, A.L., Tremoli, E., and Sirtori, C.R., 2009. Effects of Timing and Extent of Smoking, Type of Cigarettes, and Concomitant Risk Factors on the Association Between Smoking and Subclinical Atherosclerosis. *Stroke*, **40**, 1991–1998.

Ballo, P., Motto, A., Mondillo, S., and Faraguti, S.A., 2007. Impact of Obesity on Left Ventricular Mass and Function in Subjects With Chronic Volume Overload. *Obesity*, **15**, 2019–2026.

Bawa-Allah, A.B., Mashao, M.M., Nyundu, T.F., Phukubje, E.M., Mlambo, B.W., Ngema, M. V., Nkosi, B.G., and Maseko, M.J., 2019. Twenty-Four Hour Ambulatory Blood Pressure Reference Values in Africans. *Blood Pressure Monitoring*, **24**, 103–109.

Bełtowski, J., 2006. Role of Leptin in Blood Pressure Regulation and Arterial Hypertension. *Journal of Hypertension*, **24**, 789–801.

Berman, M.N. and Bhardwaj, A., 2019. *Physiology, Left Ventricular Function*. StatPearls. StatPearls Publishing.

Bidulescu, A., Liu, J., Musani, S.K., Fox, E.R., Samdarshi, T.E., Sarpong, D.F., Vaccarino, V., Wilson, P.W., Arnett, D.K., Din-dzietham, R., Taylor, H.A., Gibbons, G.H., and Fail, C.H., 2011. Association of Adiponectin With Left Ventricular Mass in Blacks: The Jackson Heart Study. *American Heart Association*, **4**, 747–753.

Bigaard, J., Tjønneland, A., Thomsen, B.L., Overvad, K., Heitmann, B.L., and Sørensen, T.I.A., 2003. Waist Circumference, BMI, Smoking, and Mortality in Middle-Aged Men and Women. *Obesity Research*, **11**, 895–903.

Brady, T.M., 2016. The Role of Obesity in the Development of Left Ventricular Hypertrophy Among Children and Adolescents. *Current Hypertension Reports*. **18**, 1–7.

Bravo, P., Morse, S., Borne, D., Aguilar, E., and Reisin, E., 2006. Leptin and Hypertension in Obesity. *Vascular Health and Risk Management*, **2**, 163–169.

Chen, J.Y,, Ye, Z.X., Wang, X.F., Chang, J., Yang, M.W., Zhong, H.H., Hong, F.F., and Yang, S.L,, 2018. Nitric Oxide Bioavailability Dysfunction Involves in Atherosclerosis. *Biomedicine and Pharmacotherapy*, **97**, 423–428.

Chirinos, J.A., 2012. Arterial stiffness: Basic Concepts and Measurement Techniques. *Journal of Cardiovascular Translational Research*, **5**, 243–255.

Conte, J.K., Gmyr, V., Bouckenooghe, T., and Muharram, G., 2004. Non-Esterified Fatty Acids are Deleterious for Human Pancreatic Islet Function at Physiological Glucose Concentration. *Diabetologia*, **47**, 463–469

Crowley, D.I., Khoury, P.R., Urbina, E.M., Ippisch, H.M., and Kimball, T.R., 2011. Cardiovascular Impact of The Pediatric Obesity Epidemic: Higher Left Ventricular Mass is Related to Higher Body Mass Index. *Journal of Pediatrics*, **158**, 709-714.

Crowther, N.J., Ferris, W.F., Ojwang, P.J., and Rheeder, P., 2006. The Effect of Abdominal Obesity on Insulin Sensitivity and Serum Lipid and Cytokine Concentrations in African Women. *Clinical Endocrinology*, **64**, 535–541.

Devereux, R.B., Alonso, D.R., Lutas, E.M., Gottlieb, G.J., Campo, E., Sachs, I., and Reichek, N., 1986. Echocardiographic Assessment of Left Ventricular Hypertrophy: Comparison

to Necropsy Findings. *The American Journal of Cardiology*, **57**, 450–458.

DuPont, J.J., Kenney, R.M., Patel, A.R., and Jaffe, I.Z., 2019. Sex Differences in Mechanisms of Arterial Stiffness. *British Journal of Pharmacology*, **176**, 4208–4225.

Dursun, B., Cesur, R., and Mocan, N., 2018. The Impact of Education on Health Outcomes and Behaviors in a Middle-Income, Low-Education Country. *Economics and Human Biology*, **31**, 94–114.

Epstein, M., 2001. Aldosterone as a Determinant of Cardiovascular and Renal Dysfunction. *Journal of the Royal Society of Medicine*, **94**, 378–383.

Eslami, O., Shahraki, M., and Shahraki, T., 2019. Obesity Indices in Relation to Lipid Abnormalities Among Medical University Students in Zahedan, South-East of Iran. *International Journal of Preventive Medicine*, **10**, 1–17.

Fagard, R.H., 2009. Smoking Amplifies Cardiovascular Risk in Patients With Hypertension and Diabetes. *Diabetes Care*, **32** , 429–431.

Feingold, K.R. and Grunfeld, C., 2000. *Obesity and Dyslipidemia*. Endotext. MDText.com, Inc.

Flegal, K.M., Shepherd, J.A., Looker, A.C., Graubard, B.I., Borrud, L.G., Ogden, C.L., Harris, T.B., Everhart, J.E., and Schenker, N., 2009. Comparisons of Percentage Body Fat, Body Mass Index, Waist Circumference, and Waist-Stature Ratio in Adults. *The American Journal of Clinical Nutrition*, **89**, 500–508.

Van Gaal, L., Zhang, A. and De Leeuw, I.H., 1995. Human Obesity: From Lipid Abnormalities to Lipid Oxidation. *International Journal of Obesity Related Metabolic Disorders*, **19**, 21–26.

Gallagher, E.J. and LeRoith, D., 2010. Insulin, Insulin Resistance, Obesity, and Cancer. *Current Diabetes Reports*, **10**, 93–100.

Gavras, I. and Gavras, H., 2002. Angiotensin II as a Cardiovascular Risk. *Journal of Human Hypertension*, **16**, 2–6.

Goel, A., Maroules, C.D., Mitchell, G.F., Peshock, R., Ayers, C., McColl, R., Vongpatanasin, W., and King, K.S., 2017. Ethnic Difference in Proximal Aortic Stiffness: An Observation

From the Dallas Heart Study. *JACC: Cardiovascular Imaging*, **10**, 54–61.

Gonzalez, M., Lind, L., and Söderberg, S., 2013. Leptin and Endothelial Function in The Elderly : The Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) Study. *Atherosclerosis*, **228**, 485–490.

Gordan, R., Gwathmey, J.K., and Xie, L.-H., 2015. Autonomic and Endocrine Control of Cardiovascular Function. *World Journal of Cardiology*, **7**, 204.

Grogan, J.R. and Kochar, M.S., 1994. Alcohol and Hypertension. *Archives of Family Medicine*, **3**, 150–154.

Hall, J.E., Da Silva, A.A., Do Carmo, J.M., Dubinion, J., Hamza, S., Munusamy, S., Smith, G., and Stec, D.E., 2010. Obesity-Induced Hypertension: Role of Sympathetic Nervous System, Leptin, and Melanocortins. *Journal of Biological Chemistry*, **285**, 17271–17276.

Hasson, B.R., Apovian, C., and Istfan, N., 2015. Racial/Ethnic Differences in Insulin Resistance and Beta Cell Function: Relationship to Racial Disparities in Type 2 Diabetes Among African Americans Versus Caucasians. *Current Obesity Reports*, **4**, 241–249.

Hedayatnia, M., Asadi, Z., Zare-Feyzabadi, R., Yaghooti-Khorasani, M., Ghazizadeh, H., Ghaffarian-Zirak, R., Nosrati-Tirkani, A., Mohammadi-Bajgiran, M., Rohban, M., Sadabadi, F., Rahimi, H.R., Ghalandari, M., Ghaffari, M.S., Yousefi, A., Pouresmaeili, E., Besharatlou, M.R., Moohebati, M., Ferns, G.A., Esmaily, H., and Ghayour-Mobarhan, M., 2020. Dyslipidemia and Cardiovascular Disease Risk Among The MASHAD Study Population. *Lipids in Health and Disease*, **19**, 42.

Hermann, M., Flammer, A., and Lüscher, T.F., 2006. Nitric Oxide in Hypertension. *Journal of Clinical Hypertension*, **8**, 17–29.

Hunma, S., Ramuth, H., Miles-Chan, J.L., Schutz, Y., Montani, J.P., Joonas, N., and Dulloo, A.G., 2018. Do Gender and Ethnic Differences in Fasting Leptin in Indians and Creoles of Mauritius Persist Beyond Differences in Adiposity? *International Journal of Obesity*, **42**, 280–283.

Husain, K., Ansari, R.A., and Ferder, L., 2014. Alcohol-Induced Hypertension: Mechanism and Prevention. *World Journal of Cardiology*, **6**, 245.

Huxley, R., Mendis, S., Zheleznyakov, E., Reddy, S., and Chan, J., 2010. Body Mass Index,

Waist Circumference and Waist:Hip Ratio as Predictors of Cardiovascular Risk. A Review of The Literature. *European Journal of Clinical Nutrition*, **64**, 16–22.

Jia, G., Aroor, A.R., and Demarco, V.G., 2015. Vascular Stiffness in Insulin Resistance and Obesity. *Frontiers in Physiology*, **6**, 1–8.

Jung, U.J. and Choi, M.S., 2014. Obesity and its metabolic complications: The Role of Adipokines and The Relationship Between Obesity, Inflammation, Insulin Resistance, Dyslipidemia and Nonalcoholic Fatty Liver Disease. *International Journal of Molecular Sciences*, **15**, 6184–6223.

Kahan, T. and Bergfeldt, L., 2005. Left Ventricular Hypertrophy in Hypertension: Its Arrhythmogenic Potential. *Heart*, **91**, 250–256.

Kahn, B.B. and Flier, J.S., 2000. Obesity and Insulin Resistance. *Journal of Clinical Investigation*, **106**, 473–481.

Kannan, A., 2014. Renal Sympathetic Nervous System and The Effects of Denervation on Renal Arteries. *World Journal of Cardiology*, **6**, 814.

Kawarazaki, W. and Fujita, T., 2016. The Role of Aldosterone in Obesity-Related Hypertension. *American Journal of Hypertension*, **8**, 17–29.

Kim, T.J., Roesler, N.M., and von dem Knesebeck, O., 2017. Causation or Selection – Examining The Relation Between Education and Overweight/Obesity in Prospective Observational Studies: A Meta-Analysis. *Obesity Reviews*, **18**, 660–672.

Klop, B., Elte, J.W.F., and Cabezas, M.C., 2013. Dyslipidemia in Obesity: Mechanisms and Potential Targets. *Nutrients*, **5**, 1218–1240.

Koolhaas, C.M., Dhana, K., Schoufour, J.D., Ikram, M.A., Kavousi, M., and Franco, O.H., 2017. Impact of Physical Activity on The Association of Overweight and Obesity With Cardiovascular Disease: The Rotterdam Study. *European Journal of Preventive Cardiology*, **24**, 934–941.

Korre, M., Porto, L.G.G., Farioli, A., Yang, J., Christiani, D.C., Christophi, C.A., Lombardi, D.A., Kovacs, R.J., Mastouri, R., Abbasi, S., Steigner, M., Moffatt, S., Smith, D., and Kales, S.N., 2016. Effect of Body Mass Index on Left Ventricular Mass in Career Male Firefighters. *American Journal of Cardiology*, **118**, 1769–1773.

Kotchen, T.A., 2010. Obesity-Related Hypertension: Epidemiology, Pathophysiology, and Clinical Management. *American Journal of Hypertension*, **23**, 1170–1178.

Kotsis, V., Stabouli, S., Bouldin, M., Low, A., Toumanidis, S., and Zakopoulos, N., 2005. Impact of Obesity on 24-hour ambulatory Blood Pressure and Hypertension. *Hypertension*, **45**, 602–7.

Kotsis, V., Stabouli, S., Papakatsika, S., Rizos, Z., and Parati, G., 2010. Mechanisms of Obesity-Induced Hypertension. *Hypertension Research*, **33**, 386–393.

Kshatriya, S., Liu, K., Salah, A., Szombathy, T., Freeman, R.H., Reams, G.P., Spear, R.M., and Villarreal, D., 2011. Obesity Hypertension: The Regulatory Role of Leptin. *International Journal of Hypertension*, **2011**, 1–9.

Lean, M.E.J., Han, T.S., and Morrison, C.E., 1995. Waist Circumference as a Measure for Indicating Need for Weight Management. *British Medical Journal*, **311**, 158–161.

Lee, C.M.Y., Huxley, R.R., Wildman, R.P., and Woodward, M., 2008. Indices of abdominal Obesity are Better Discriminators of Cardiovascular Risk Factors than BMI: A Meta-Analysis. *Journal of Clinical Epidemiology*, **61**, 646–653

Libhaber, E., Woodiwiss, A.J., Libhaber, C., Maseko, M., Majane, O.H., Makaula, S., Dessein, P., Essop, M.R., Sareli, P., and Norton, G.R., 2008. Gender-Specific Brachial Artery Blood Pressure-Independent Relationship Between Pulse Wave Velocity and Left Ventricular Mass Index in a Group of African Ancestry. *Journal of Hypertension*, **26**, 1619–1628.

de Lima Santos, P.C.J., de Oliveira Alvim, R., Ferreira, N.E., de Sa Cunha, R., Krieger, J.E., Mill, J.G., and Pereira, A.C., 2011. Ethnicity and Arterial Stiffness in Brazil. *American Journal of Hypertension*, **24**, 278–284.

Ma, H., 2004. Cholesterol and Human Health. *Nature and Science*, **2**, 17–21.

Mackenzie, I.S., Wilkinson, I.B., and Cockcroft, J.R., 2002. Assessment of Arterial Stiffness in Clinical Practice. *QJM - Monthly Journal of the Association of Physicians*, **95**, 67–74.

Mantzoros, C.S., Liolios, A.D., Tritos, N.A., Kaklamani, V.G., Doulgerakis, D.E., Griveas, I., Moses, A.C., and Flier, J.S., 1998. Circulating Insulin Concentrations, Smoking, and Alcohol Intake are Important Independent Predictors of Leptin in Young Healthy Men.

Obesity Research, **6**, 179–186.

Maseko, M., Mashao, M., Bawa-Allah, A., Phukubje, E., Mlambo, B., and Nyundu, T., 2018. Obesity Masks The Relationship Between Dietary Salt Intake and Blood Pressure in People of African Ancestry: The Impact of Obesity on The Relationship Between Sodium and Blood Pressure. *Cardiovascular Journal of Africa*, **29**, 172–176.

Maseko, M.J., Majane, H.O., Milne, J., Norton, G.R., and Woodiwiss, A.J., 2006. Cardiovascular Topics Salt intake in an Urban, Developing South African Community. *Cardiovascular Journal of South Africa*, **17**, 16–18.

Mathur, R., Hull, S.A., Badrick, E., and Robson, J., 2011. Cardiovascular Multimorbidity: The Effect of Ethnicity on Prevalence and Risk Factor Management. *British Journal of General Practice*, **61**, 262–270.

Maunganidze, F., Norton, G.R., Maseko, M.J., Libhaber, C.D., Majane, O.H.I., Sareli, P., and Woodiwiss, A.J., 2013. Relationship Between Glomerular Dysfunction and Left-Ventricular Mass Independent of Haemodynamic Factors in a Community Sample. *Journal of Hypertension*, **31**, 568–575.

Mikkola, T.S., Gissler, M., Merikukka, M., Tuomikoski, P., and Ylikorkala, O., 2013. Sex Differences in Age-Related Cardiovascular Mortality. *Plos One*, **8**, 63347–63347.

Mitchell, G.F., 2014. Arterial Stiffness and Hypertension. *Hypertension*, **64**, 13–18.

Mizukoshi, K., Takeuchi, M., Nagata, Y., Addetia, K., Lang, R.M., Akashi, Y.J., and Otsuji, Y., 2016. Normal Values of Left Ventricular Mass Index Assessed by Transthoracic Three-Dimensional Echocardiography. *Journal of the American Society of Echocardiography*, **29**, 51–61.

Muniyappa, R. and Sowers, J.R., 2013. Role of insulin Resistance in Endothelial Dysfunction. *Reviews in Endocrine and Metabolic Disorders*, **14**, 5–12.

Muñoz-Durango, N., Fuentes, C.A., Castillo, A.E., González-Gómez, L.M., Vecchiola, A., Fardella, C.E., and Kalergis, A.M., 2016. Role of The Renin-Angiotensin-Aldosterone System Beyond Blood Pressure Regulation: Molecular and Cellular Mechanisms Involved in End-Organ Damage During Arterial Hypertension. *International Journal of Molecular Sciences*, **95**, 67–74.

Nagueh, S.F., Appleton, C.P., Gillebert, T.C., Marino, P.N., Oh, J.K., Smiseth, O.A., Waggoner, A.D., Flachskampf, F.A., Pellikka, P.A., and Evangelisa, A., 2009. Recommendations for The Evaluation of Left Ventricular Diastolic Function By Echocardiography. *European Journal of Echocardiography*, **10**, 165–193.

Nedungadi, T.P. and Clegg, D.J., 2009. Sexual Dimorphism in Body Fat Distribution and Risk for Cardiovascular Diseases. *Journal of Cardiovascular Translational Research*, **2**, 321–327.

Nordstrand, N., Gjevestad, E., Dinh, K.N., Hofsø, D., Røislien, J., Saltvedt, E., Os, I., and Hjelmesæth, J., 2011. The Relationship Between Various Measures of Obesity and Arterial Stiffness in Morbidly Obese Patients. *BMC Cardiovascular Disorders*, **11**, 1–8.

Nunez, E., Arnett, D.K., Benjamin, E.J., Liebson, P.R., Skelton, T.N., Taylor, H., and Andrew, M., 2005. Optimal Threshold Value for Left Ventricular Hypertrophy in Blacks: The Atherosclerosis Risk in Communities Study. *Hypertension*, **45**, 58–63.

O'Keefe, J.H., Bybee, K.A., and Lavie, C.J., 2007. Alcohol and Cardiovascular Health. The Razor-Sharp Double-Edged Sword. *Journal of the American College of Cardiology*, **50**, 1009–1014.

Ortega, F.B., Lavie, C.J., and Blair, S.N., 2016. Obesity and Cardiovascular Disease. *Circulation Research*, **118**, 1752–1770.

Otitoola, O., Oldewage-Theron, W., and Egal, A., 2020. Prevalence of Overweight and Obesity Among Selected Schoolchildren and Adolescents in Cofimvaba, South Africa. *South African Journal of Clinical Nutrition*, **0**, 1–6.

Pal, S. and Radavelli-Bagatini, S., 2013. Association of Arterial Stiffness With Obesity in Australian Women: A Pilot Study. *The Journal of Clinical Hypertension*, **15**, 118–123.

Pierce, G.L., Zhu, H., Darracott, K., Edet, I., Bhagatwala, J., Huang, Y., and Dong, Y., 2013. Arterial Stiffness and Pulse-Pressure Amplification in Overweight/Obese African-American Adolescents: Relation With Higher Systolic and Pulse Pressure. *American Journal of Hypertension*, **26**, 20–26.

Rahmouni, K., Correia, M.L.G., Haynes, W.G., and Mark, A.L., 2005. Obesity-Associated Hypertension: New Insights Into Mechanisms. *Hypertension*, **45**, 9–14.

Rashid, M.A., Qureshi, B.A., Ahmed, N., and Sherwani, M.A., 2014. Impact of Body Mass Index on Left Ventricular Mass. *Journal of Ayub Medical College, Abbottabad*, **26**, 167–169.

Rothman, K.J., 2008. BMI-related Errors in The Measurement Of Obesity. *International Journal of Obesity*, **32**, S56–S59.

Safar, M.E., Czernichow, S., and Blacher, J., 2006. Obesity, Arterial Stiffness, and Cardiovascular Risk. *Journal of the American Society of Nephrology*, **17**, 109–111.

Sahn, D.J., Allen, H.D., Anderson, R., and Goldberg, S.J., 1978. Echocardiographic Diagnosis of Atrial Septal Aneurysm in an Infant with Hypoplastic Right Heart Syndrome. *Chest*, **73**, 227–230.

Sata, Y., Head, G.A., Denton, K., May, C.N., and Schlaich, M.P., 2018. Role of The Sympathetic Nervous System And Its Modulation in Renal Hypertension. *Frontiers in Medicine*, **5**, 1–10.

Schutte, A.E., 2019. Urgency for South Africa to Prioritise Cardiovascular Disease Management. *The Lancet Global Health*, **7**, e177–e178.

Schutte, A.E., Kruger, R., Gafane-Matemane, L.F., Breet, Y., Strauss-Kruger, M., and Cruickshank, J.K., 2020. Ethnicity and Arterial Stiffness. *Arteriosclerosis, Thrombosis, and Vascular Biology*, **40**, 1044–1054.

Schutte, R., Huisman, H.W., Schutte, A.E., and Malan, N.T., 2005. Leptin is Independently Associated With Systolic Blood Pressure, Pulse Pressure and Arterial Compliance in Hypertensive African Women With Increased Adiposity: The POWIRS Study. *Journal of Human Hypertension*, **19**, 535–541.

Seferovic, J.P., Tesic, M., Seferovic, P.M., Lalic, K., Jotic, A., Biering-Sørensen, T., Giga, V., Stankovic, S., Milic, N., Lukic, L., Milicic, T., MacEsic, M., Gajovic, J.S., and Lalic, N.M., 2018. Increased Left Ventricular Mass Index is Present in Patients With Type 2 Diabetes Without Ischemic Heart Disease. *Scientific Reports*, **8**, 1–7.

Seifalian, A., Filippatos, T., Joshi, J., and Mikhailidis, D., 2010. Obesity and Arterial Compliance Alterations. *Current Vascular Pharmacology*, **8**, 155–168.

Senbanjo, I.O. and Oshikoya, K.A., 2012. Obesity and Blood Pressure levels of Adolescents in

Abeokuta, Nigeria. *Cardiovascular Journal of Africa*, **23**, 260–264.

Shamai, L., Lurix, E., Shen, M., Novaro, G.M., Szomstein, S., Rosenthal, R., Hernandez, A. V., and Asher, C.R., 2011. Association of Body Mass Index and Lipid Profiles: Evaluation of a Broad Spectrum of Body Mass Index Patients Including The Morbidly Obese. *Obesity Surgery*, **21**, 42–47.

Shereef, A. and Kandeel, N., 2019. The Relation Between Insulin Resistance and Left Ventricular Mass in Hypertensive Nondiabetic Patients. *Journal of Indian College of Cardiology*, **9**, 100–104.

Shiburi, C.P., Staessen, J.A., Maseko, M., Wojciechowska, W., Thijs, L., Van Bortel, L.M., Woodiwiss, A.J., and Norton, G.R., 2006. Reference Values for SphygmoCor Measurements in South Africans of African Ancestry. *American Journal of Hypertension*, **19**, 40–46.

Shin, J., Lee, J.U., Kim, K.S., Kim, S.G., Kim, J.H., Lim, H.K., and Lee, B.H., 2007. Influence of Abdominal Circumference on The Inappropriateness of Left Ventricular Mass and Diastolic Function in Non-Obese Patients. *Journal of Cardiology*, **49**, 323–329.

De Simone, G. De, Devereux, R.B., Chinali, M., Roman, M.J., Barac, A., Panzac, J.A., Lee, E.T., and Howard, B. V., 2011. Sex Differences in Obesity-Related Changes in Left Ventricular Morphology: The Strong Heart Study. *Journal of Hypertension*, **29**, 1431–1438.

Sliwa, K., Skudicky, D., Candy, G., Bergemann, A., Hopley, M., and Sareli, P., 2002. The Addition of Pentoxifylline to Conventional Therapy Improves Outcome in Patients With Peripartum Cardiomyopathy. *European Journal of Heart Failure*, **4**, 305–309.

Smith, C. and Essop, M.F., 2009. Gender Differences in Metabolic Risk Factor Prevalence in a South African Student Population. *Cardiovascular Journal of Africa*, **20**, 178–182.

Snijder, M.B., Stronks, K., Agyemang, C., Busschers, W.B., Peters, R.J., and Van Den Born, B.J.H., 2015. Ethnic Differences in Arterial Stiffness The Helius Study. *International Journal of Cardiology*, **191**, 28–33.

Soares, A.L.G., Banda, L., Amberbir, A., Jaffar, S., Musicha, C., Price, A., Nyirenda, M.J., Lawlor, D.A., and Crampin, A., 2019. Sex and Area Differences in The Association

Between Adiposity and Lipid Profile in Malawi. *BMJ Global Health*, **4**, 1–11.

Stewart, A., Marfell-Jones, M., and International Society for Advancement of Kinanthropometry., J.H., 2011. *International standards for anthropometric assessment*. International Society for the Advancement of Kinanthropometry.

Strazhesko, I., Tkacheva, O., Boytsov, S., Akasheva, D., Dudinskaya, E., Vygodin, V., Skvortsov, D., and Nilsson, P., 2015. Association of Insulin Resistance, Arterial Stiffness and Telomere Length in Adults Free of Cardiovascular Diseases. *Plos One*, **10**, 1–12.

Taliyan, S., Yadav, S.K., and Gupta, B.K., 2019. Correlation Of Lipid Profile & Body Mass Index (Bmi) Of Patients At A Tertiary Care Hospital: A Cross Sectional Study. *International Journal of Medical and Biomedical Studies*, **3**. 240–242.

Telles, S., Pal, S., Sharma, S.K., Singh, A., Kala, N., and Balkrishna, A., 2018. The Association Between The Lipid Profile and Fasting Blood Glucose With Weight Related Outcomes in Healthy Obese Adults. *BMC Research Notes*, **11**, 1–6.

Tóth, P.P., Potter, D., and Ming, E.E., 2012. Prevalence of lipid abnormalities in The United States: The National Health and Nutrition Examination Survey 2003-2006. *Journal of Clinical Lipidology*, **6**, 325–330.

Tsai, J.P., Wang, J.H., Chen, M.L., Yang, C.F., Chen, Y.C., and Hsu, B.G., 2016. Association of Serum Leptin Levels With Central Arterial Stiffness in Coronary Artery Disease Patients. *BMC Cardiovascular Disorders*, **16**, 1–7.

Visscher, T.L.S., Seidell, J.C., Molarius, A., van der Kuip, D., Hofman, A., and Witteman, J.C.M., 2001. A Comparison of Body Mass Index, Waist-Hip Ratio and Waist Circumference as Predictors af All-Cause Mortality Among The Elderly: The Rotterdam Study. *International Journal of Obesity*, **25**, 1730–1735.

Wilcox, G., 2005. Insulin and Insulin Resistance. *The Clinical Biochemist. Reviews*, **26**, 19–39.

Wolk, R., Shamsuzzaman, A.S.M., and Somers, V.K., 2003. Obesity, Sleep Apnea, and Hypertension. *Hypertension*, **42**, 1067–1074.

World Health Organisation (WHO), 2008. WHO | Waist Circumference and Waist–Hip Ratio. Report of a WHO Expert Consultation. Geneva, Switzerland. 8-11 December 2008.

World Health Organization., 2000. Obesity : preventing and managing the global epidemic report of a WHO consultation (No. 894). World Health Organization. Geneva, Switzerland.

Yang, Z., Ding, X., Liu, J., Duan, P., Si, L., Wan, B., and Tu, P., 2017. Associations Between Anthropometric Parameters and Lipid Profiles in Chinese Individuals With Age 40 Years and BMI <28kg/m^2. *Plos One*, **12**, 1–11.

Zatu, M.C., Van Rooyen, J.M., Kruger, A., and Schutte, A.E., 2016. Alcohol Intake, Hypertension Development and Mortality in Black South Africans. *European Journal of Preventive Cardiology*, **23**, 308–315.

Zhou, M.S., Wang, A., and Yu, H., 2014. Link Between Insulin Resistance and Hypertension: What is The Evidence From Evolutionary Biology? *Diabetology and Metabolic Syndrome*, **6**, 1–8.

van Zyl, S., van der Merwe, L.J., van Rooyen, F.C., Joubert, G., and Walsh, C.M., 2017. The Relationship Between Obesity, Leptin, Adiponectin and The Components of Metabolic Syndrome in Urban African Women, Free State, South Africa. *South African Journal of Clinical Nutrition*, **30**, 8–13.

APPENDICES

Appendix 1: Ethical clearance certificate

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R14/49 Mr KF Nkoana

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M190649

NAME: (Principal Investigator)	Mr KF Nkoana
DEPARTMENT:	School of Physiology Medical School University
PROJECT TITLE:	Left ventricular geometry and diastolic function: the role of traditional medicine
DATE CONSIDERED:	2019/06/28
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Professor M Maseko
APPROVED BY:	CB Penny Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2019/10/01

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

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the 3rd Floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to submit details to the Committee. I agree to submit a yearly progress report. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in June and will therefore reports and re-certification will be due early in the month of June each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

02/10/2019
Date

PLEASE QUOTE THE CLEARANCE CERTIFICATE NUMBER IN ALL ENQUIRIES

Appendix 2: Change of Title

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172076

Reference: Mrs Sandra Benn
E-mail: sandra.benn@wits.ac.za

06 January 2021
Person No: 2281608
TAA

Mr KF Nkoana
PO Box 2798
0700
South Africa

Dear Mr Kgothatso Nkoana

Master of Science in Medicine: Change of title of research

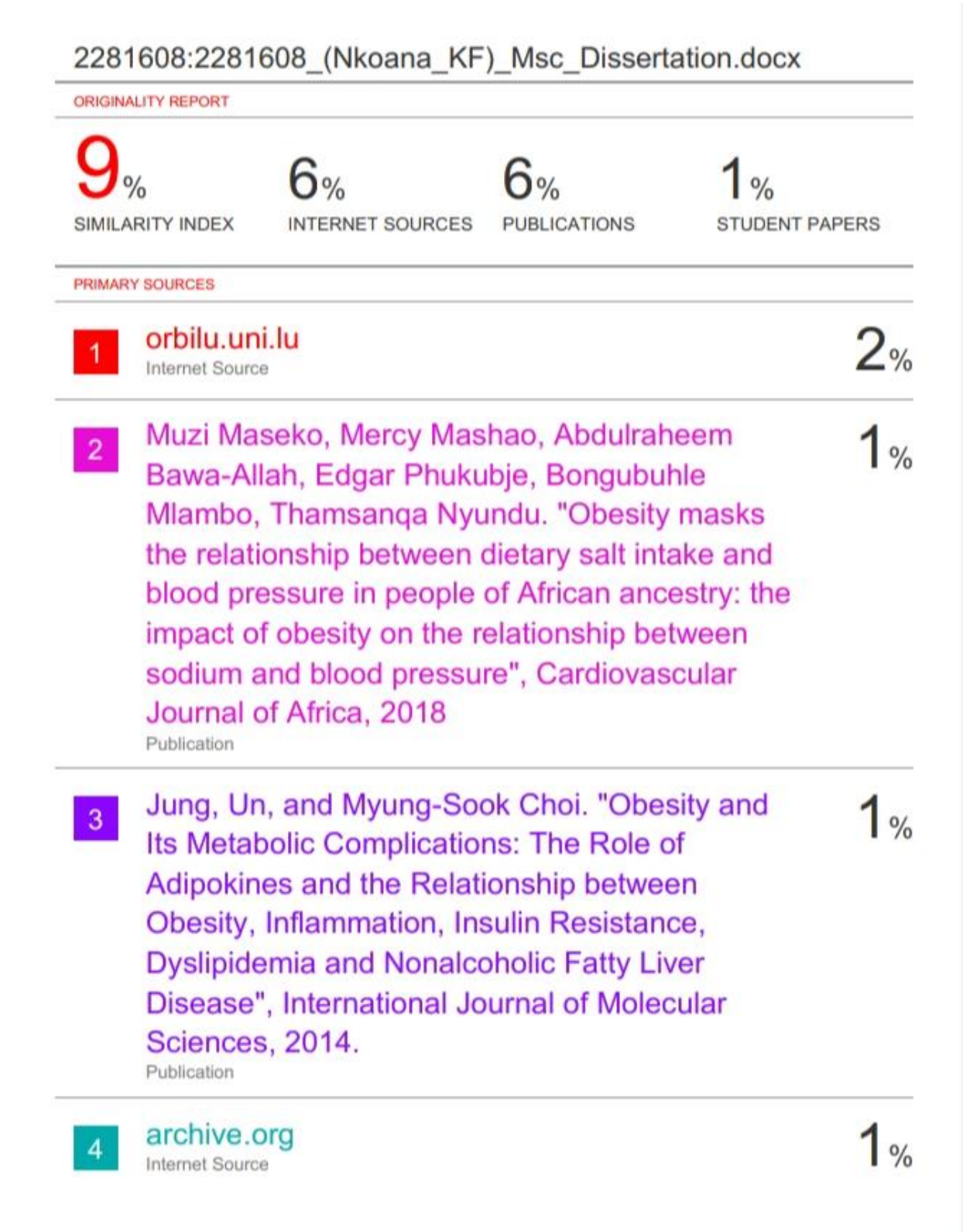
I am pleased to inform you that the following change in the title of your Dissertation for the degree of **Master of Science in Medicine** has been approved:

From:	**Left ventricular geometry and diastolic function: the potential role of garlic, ginger and prickly pear.**
To:	**The impact of the indices of adiposity on cardiovascular target organ damage in people of African ancestry**

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

Appendix 3: Plagiarism report



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	200801 Publication	
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Appendix 4: Questionnaire

Human Nutrition Research Laboratory
South African Hypertension and Diet Study (SAHDS)

D#: _____

1.	**Personal information**								
	Participant No.		Gender		Male		Date of Birth		Ethnicity
1.					Female		Age		
2.	**Medical History**								
2.1	**History of non-communicable diseases?**		YES		NO		**Examples, Hypertension, Chronic Kidney disease, Diabetes**		
	If YES, specify								
2.2	**Are you using hypertension treatment or Medicinal plants?**						YES		NO
2.2.1	**If YES, how long (in years)?**								
2.2.2	**Describe the regimen**								
2.3	**Please, specify whether some of your relatives currently suffer (or have suffered) from high blood pressure (hypertension)**								
2.3.1	**Your Father**						Yes		No
	Your grandfather (Father's side)						Yes		No
	Your grandmother (Father's side)						Yes		No
	Your mother						Yes		No

	Unknown	
	Unknown	
	Unknown	
	Unknown	

	Your grandfather (mother's side)	Yes		No		Unknown	
	Your grandmother (Mother's side)	Yes		No		Unknown	
	1 or more of your own children	Yes		No		Unknown	
	1 or more of your own grandchildren	Yes		No		Unknown	
	1 or more brothers or sisters of your father	Yes		No		Unknown	
	1 or more brothers or sisters of your mother	Yes		No		Unknown	
	1 or more of your own brothers or sisters	Yes		No		Unknown	

2.4	**Marital status**	Single		Married		Widowed	
2.5	**Are you still attending school?**	Yes		No			
2.6	**Which is the highest level of education which you successfully completed?**						
2.7	**Do you currently exert any professional or occupational activity?**	**Yes**		**No**			
	If yes: What is your present occupation? Please, provide a detailed description of your current job below.						
2.8	**If you currently do not exert any professional activity, which was the last job you had?**						
2.8.1		**Years**					

2.8.2	**Please, provide a detailed description of your activities at your previous work.**						
3.	**Please, specify whether you suffer from diseases affecting your:**						
3.1.1	**Heart**	Yes		No		Unknown	
3.1.2	**Kidneys**	Yes		No		Unknown	
4.	**Were you ever told by a doctor or health professional that you have an elevated blood pressure?**	Yes		No		Unknown	
5.	**Are you currently in good health?**	Yes		No		Unknown	
6	**Did you ever take or are you taking now drugs which eliminate salt and make you pass urine more frequently or in larger amounts? If yes, explain below**	Yes		No		Unknown	
7.	**Did you ever take pain-killers on a regular basis, for instance against headaches, tooth pain, painful periods, etc... ? If yes, explain below**			Yes		No	
8.	**Did you take medicines during the past 2 weeks? if yes, explain below**			Yes		No	
9.1	**Do you currently smoke? If yes, explain the frequency, type and amount per day**			Yes		No	

9.2	**Did you smoke in the past? If yes, explain below**				
10.1	**Do you currently consume alcoholic beverages? If yes, explain the frequency, type and amount per day below**	Yes		No	
10.2	**Did you consume alcohol beverages in the past? If yes, explain**	Yes		No	
11	**Do you drink coffee or caffeine-containing beverages (cola) on a regular base? If yes, give details below**	Yes		No	
12.	**Do you practice any sports activities on a regular basis? If yes, explain the frequency, type and intensity below**	Yes		No	
Please note that this section is for females only					
13.1	**Did you already have your periods?**	Yes		No	
13.2	**Have you ever taken "The Pill"? If yes, explain the regimen below**	Yes		No	
13.3	**Have you ever used other contraceptive methods? If Yes, explain the regimen below**	Yes		No	

14.1	**Are you pregnant at present?**	Yes		No		Unknown		
14.2	**Have you been pregnant before?**			Yes		No		
15.	**This section is for women 30 years and older**							
15.1	**Do you still have your periods? If No, explain below**			Yes		No		
15.2	**At present are your periods suppressed by taking "the pill"?**			Yes		No		
15.3	**At present are your periods suppressed by any other contraceptive method? If Yes, explain the regimen below**			Yes		No		
END								

DECLARATION

Please, provide your signature to give your approval or disapproval to use this information in our study.

Signature: _____ Date: _____