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THE IMPACT OF OBESITY ON THE RELATIONSHIP BETWEEN PULSE-WAVE VELOCITY AND 24-HOUR URINARY ELECTROLYTE EXCRETION

Brian Godfrey Nkosi

A dissertation submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in fulfilment of the requirements for the degree of

Master of Science in Medicine

Johannesburg, 2020

DECLARATION

I, Brian Godfrey Nkosi declare that this dissertation is my own unaided work, except where stated. It is being submitted for the degree of Master of Science in Medicine in the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg. The work contained in this dissertation has not been submitted for any degree or examination in this University, or any other University.

Brian Godfrey Nkosi on this …….....day of…… 2020

I certify that the studies contained in this dissertation have the approval of the Committee for Research in Human Participants of the University of the Witwatersrand, Johannesburg. The ethics approval number is M180521

Brian Godfrey Nkosi on this …….....day of…… 2020

……..	……..
Muzi J. Maseko (Supervisor)	Abdulraheem Bawa-Allah (Co-Supervisor)
Date……	Date……

DEDICATIONS

This dissertation is dedicated to my mother Deliwe Lotty Nkosi, without whom this would not be possible.

&

In loving memory of my father

Sipho Reka Nkosi

1954 – 2007

Thank you for encouraging me to go after my dreams. You're dearly missed.

ABSTRACT

An upsurge in overweight or obesity in South Africa is largely implicated as a contributing factor in the rise of cardiovascular diseases. Hypertension and arterial stiffness are largely promoted by dietary habits including high salt and low potassium consumption. This is especially of greater concern in a salt-sensitive population with a high incidence of obesity such as this. Since the high incidence of obesity in this population and previous reports of obesity masking the relationship between urinary sodium excretion and blood pressure, the role of obesity in modifying the relationship between urinary electrolytes and pulse wave velocity was investigated. One-hundred-and-fifty South African individuals of African ancestry were randomly recruited in and around Johannesburg. The participants were divided into two groups according to BMI, namely normal weight (BMI<25 but > than 18) and overweight/ obese (BMI≥25) individuals. Blood pressure was measured using 24-hour ambulatory BP monitoring, while electrolyte excretion was assessed by the collection of 24-hour urine samples. Arterial stiffness was indexed by use of carotid-femoral pulse wave velocity (PWV) measurement. Urinary daytime K^+ excretion was directly associated with 24-hour systolic BP (P=0.019) and daytime systolic BP (P=0.024). Night-time Na^+:K^+ ratio was directly associated with 24-hour systolic BP in the overweight/ obese group (P= 0.034). Night-time Na^+:K^+ ratio was directly associated with systolic (P= 0.006) and diastolic BP (P= 0.040) in the overweight/ obese group. Twenty-four-hour Na^+:K^+ ratio was significantly associated with night-time systolic BP (P= 0.021). Pulse wave velocity was directly associated with BMI (P<0.001), and WC (P<0.001). No relationship was observed between PWV and 24-hour urinary electrolytes. Overweight/ obesity diminishes arterial compliance and reduces arterial compliance thus leading to increases in BP. However, obesity does not influence the relationship between urinary electrolyte excretion and PWV.

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LIST OF ABBREVIATIONS

ABPM	Ambulatory blood pressure monitoring
BMI	Body mass index
BP	Blood pressure
CHD	Coronary heart disease
CRS	Cardiorenal metabolic syndrome
CVD	Cardiovascular disease
CKD	Chronic kidney disease
DASH	Dietary Approaches to Stop Hypertension
ECM	Extracellular matrix
eNOS	endothelial nitric oxide synthase
HAART	Highly active antiretroviral therapy
IL-6	Interleukin-6
INTERSALT	International Cooperative study on Salt

MMP	matrix metalloproteases
Na^+:K^+	Sodium-to-potassium ratio
NDoH	National Department of Health
NHANES	National Health and Nutrition Examination Survey
NIDS	National Income Dynamics Study
NIH	National Institutes of Health
NO	Nitric oxide
PP	Pulse pressure
PWV	Pulse wave velocity
RAAS	Renin-angiotensin-aldosterone system
TGF-β1	Transforming growth factor beta 1
TNF	Tumour necrosis factor
VSMC	Vascular smooth muscle cells
WCE	White coat effect

WCH	White coat hypertension
WHR	Waist-to-hip ratio

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CHAPTER 1: INTRODUCTION

1.1 Introduction

The prevalence of excess weight and obesity continues to rise globally, in both developing and developed countries (Huxley *et al.*, 2010; NCD Risk Factor Collaboration (NCD-RisC), 2016; Negash *et al.*, 2017). The past few decades have seen the rate of obesity triple in developing countries, as the wave of urbanisation approaches its peak. The World Health Organisation (WHO) defines overweight and obesity as excessive, or atypical, build-up of fat that poses a significant risk to general health. Body mass index (BMI), is a raw measure of overweight or obesity, it is quantified by the individuals weight divided by the square of their height in meters. A BMI that is greater or equal to 25, but less than 30 kg/m^2, is indicative of overweight, while obesity is determined by a BMI greater or equal to 30 kg/m^2.

Obesity is currently considered one of the major health problems threatening the global population, others include malnutrition, underweight and infectious diseases (Haidar and Cosman, 2011). Urbanisation, among other factors, is implicated in the recent rise of obesity prevalence. It is accompanied by the adoption of the Western lifestyle, characterised by increased caloric intake, and coupled with a highly sedentary lifestyle.

The WHO and the International Obesity Task Force have reported that over 1.1 billion adults worldwide are overweight, while 312 million of adults worldwide are obese (Hossain *et al.*, 2007). Additionally, more than 155 million children worldwide are overweight or obese, with approximately 42 million of these children being under 5 years of age. However, for the purposes of this review focus will be placed on the prevalence of overweight/ obesity in adults or individuals aged 18 and older.

The paradoxical co-existence of undernutrition and obesity in developing countries is more common than expected (Kimani-Murage, 2013; Frongillo and Bernal, 2014). In low income countries, the lower-class population is likely underweight and malnourished. In contrast, in middle income countries, lower-class individuals have a high risk of obesity (Dinsa *et al.*, 2012). Unexpectedly, in middle income countries, numerous poor families have malnourished children born from obese parents. Studies have elucidated this phenomenon using the “thrifty gene” hypothesis.

The "thrifty gene" hypothesis states that low birth weight increases the chances of obesity later in life (O'Dea, 1995). The epigenetic changes that occur *in utero*, as a result of specific nutrient deficiency are the basis for foetal programming for a nutrient poor postnatal environment (Venniyoor, 2020). It is proposed that the primary thrifty gene is identified as PTEN (Venniyoor, 2020). The current epidemic involving metabolic disease, obesity and obesity related cancers develop when the PTEN deficient individual that has been programmed for a nutrient-poor environment with limited metabolic capacity is born into a nutrient-rich environment (Venniyoor, 2020). There have been extensive debates on the validity of this hypothesis (Baig *et al.*, 2011), however, an alternative explanation for the existence of such a paradox could be the increased availability of calorie dense foods in developing countries, that are far more accessible than healthier food options. Overweight/ obesity is highly prevalent in middle income countries in Asia, Latin America, Europe and some countries in Africa.

1.2 Obesity in South Africa

In concert with numerous developing countries across the world, some countries in Africa have also reported rapidly rising rates of obesity in children and adults despite the paradoxical presence of malnutrition and underweight as previously detailed (Kimani-Murage, 2013; Modjadji and Madiba, 2019). The Southern Africa region is especially affected by the rising trend in BMI. South Africa, a middle-income country, paints a notably worrying picture. In 2008, male members of the population presented with an average BMI of 26.9 kg/m^2 compared to the world average of 23.8 kg/m^2 (Finucane *et al.*, 2011). Females presented with an average of 29.5 kg/m^2 compared to the world average of 24.1 kg/m^2, at the time (Finucane *et al.*, 2011).

Between 2000 and 2008, the average rate of growth was reported as 2.9 kg/m^2 per decade and 1.6 kg/m^2 for males and females respectively. Interestingly, between 1980 and 2000 the rate of growth was approximately 0.7 kg/m^2 and 0.6 kg/m^2 per decade for males and females respectively (Finucane *et al.*, 2011). These values, both BMI and the increasing growth rate, evidence the rapid increase in the distribution of overweight or obese people. During the decade between 1998 and 2008, the estimated percentage of overweight or obese adult South Africans

increased from 29.1 to 31.1% in males and 56.2 to 59.5% in females (Ardington and Case, 2009).

In recent findings from the National Department of Health (NDoH) 2016, the percentage of overweight/ obese males seems to have remained at 31%, whereas in females it was reported at 68% (NDoH *et al.*, 2016). It is evident that females are more vulnerable to obesity, as indicated by the high risk to excess weight gain. However, it is worth considering that the consistency of the male prevalence is mostly due to an uneven sample size in the National Income Dynamics Study (NIDS) from which the prevalence of overweight or obesity was recorded between 1998 to 2008 (Leibbrandt *et al.*, 2009).

1.3 Reasons for the Obesity epidemic in South Africa

1.3.1 Urbanisation

Several reports on the obesity epidemic in South Africa list globalisation as a crucial driving mechanism toward nutritional transition (Manning *et al.*, 1974; Kruger *et al.*, 2005; Turok, 2012; Micklesfield *et al.*, 2013). The African population in South Africa has had more freedom of movement and increased exposure to the global market economy. This has led to a shift away from traditional foods rich in fibre and low in fat, toward highly refined food, dairy and meat products rich in saturated fats (Bourne *et al.*, 2002a; MacIntyre *et al.*, 2002). Consequently, globalisation augments the risk of obesity in the urbanised groups by fostering an environment that is optimal for high consumption of fat and sugar rich food (Pang and Guindon, 2004; Goryakin *et al.*, 2015).

Unplanned and accelerated urbanisation augments the changes in physical activity and traditional diets, increasing access to high fat foods and tobacco products all of which are risk factors for non-communicable diseases (Vorster *et al.*, 2000). Individuals who migrate from rural villages to seek better life in the city often inhabit informal settlements, commonly located in the periphery of cities. Therefore, these conditions have significant ramifications for accessibility to healthy

food as they likely lead to a stronger inclination toward more affordable fat and sugar-rich food in urban Africans (Vorster *et al.*, 2000; Bourne *et al.*, 2002a).

1.3.2 Dietary habits

According to some studies, there is a weak relationship between fat intake, dietary energy and the BMI of average South Africans (Bourne *et al.*, 1994; Kruger *et al.*, 2002). However, the dietary habits of urban individuals seems to indicate otherwise, pointing to the likelihood that urbanisation may have a distinct influence on dietary habits (Bourne *et al.*, 1994; Kruger *et al.*, 2002; MacIntyre *et al.*, 2002). Several studies implicate high fat intake in the rising obesity trends in South Africa (Vorster *et al.*, 2000; MacIntyre *et al.*, 2002; Kruger *et al.*, 2005). One study reported increases in fat consumption across five different levels of urbanisation (MacIntyre *et al.*, 2002). More than 30% of the energy consumed by urban subjects originated from fat, while among rural subjects, fat contributed to 22.9% of the energy consumed. Furthermore, they detailed that on average daily fat consumption among urban South Africans was 23 g more than that of rural subjects. In rural and township areas, markets and street vendors carry high fat dairy products, inexpensive processed meats, fried fat cakes ("vetkoeks") and a limited supply of fruit and vegetables (Bourne *et al.*, 1994; Cress-Williams, 2001; Chopra and Puoane, 2003; Faber and Kruger, 2005). What then remains in the urban South African, is a diet that significantly consists of fat rich foods and minimal weight control, which ultimately favours excess weight gain. This is further aggravated by the cultural perceptions that barely encourage weight control, and healthy diet.

1.3.3 Body weight perception and cultural factors

In African countries, culture greatly influences eating habits (Mokhtar *et al.*, 2001; Case and Menendez, 2009; Adom *et al.*, 2017). This is evidenced by the encouragement of overeating at social gatherings, where there is an overabundance of food. In some countries in Africa, select foods are associated with social status (Renzaho, 2004). These foods have become more

accessible to urban South Africa and are commonly high in energy and fat. They include animal fats, meat, chocolates, soft drinks and fried foods (Renzaho, 2004). According to a previous study on developed countries, when white women were compared to non-westernised and some westernised black women, they found that the latter individuals had adopted a bigger ideal body size leading to greater acceptance of being overweight (Kumanyika, 1993). In addition, they were shown to experience less pressure from men to be thin, making them less likely to desire thinness.

Interestingly, the African population holds an entirely different perception of body size. National surveys and regional studies seem to indicate that few overweight or obese women view themselves as being overweight or obese (Mvo *et al.*, 1999; Senekal *et al.*, 2001; Puoane *et al.*, 2002, 2005; Faber and Kruger, 2005). Furthermore, the communities of African ancestry generally perceive moderately overweight women as attractive, and this is associated with affluence, dignity and respect. In some cases, thinness or normal weight is associated with illnesses like tuberculosis and HIV/AIDS (Chopra and Puoane, 2003; Puoane *et al.*, 2005). Unfortunately, countless overweight and obese South Africans choose not to lose weight even with the awareness of the health consequences of their being overweight (Faber and Kruger, 2005; Puoane *et al.*, 2005). This acceptance and normalisation of overweight or obesity impedes the efficacy of weight-control programmes in these communities (Faber and Kruger, 2005). Nevertheless, recent findings on black female students indicate that the Western cultural norms pertaining eating habits, body perception, weight management and physical activity are also being assimilated (Steyn *et al.*, 2000; Senekal *et al.*, 2001).

1.3.4 HIV/AIDS and highly active antiretroviral therapy

South Africa currently faces a variety of devastating epidemics, namely non-communicable diseases, obesity and HIV/AIDS (Mayosi *et al.*, 2009; Vorster, 2010; Wyk *et al.*, 2013). HIV/AIDS stands as a leading cause of mortality in South Africa, in the face of having HIV-related deaths almost halved from 1997 to 2012 (Wyk *et al.*, 2013). The rise in non-communicable diseases has been largely associated with the obesity epidemic (Devanathan *et al.*,

2013; Averett *et al.*, 2014). In the past, HIV/AIDS was characterised as the 'wasting' disease, largely due to weight loss being marked as a universal prognostic marker of disease progression of HIV (Koethe and Heimburger, 2010). As previously described, this perception strongly shaped cultural beliefs among black South Africans. Interestingly, weight loss and wasting as a result of HIV infection, has been questioned in developing countries (Puoane *et al.*, 2005; Hurley *et al.*, 2011; Matoti-Mvalo and Puoane, 2011).

The rising prevalence of overweight and obesity are high amongst HIV-infected individuals on treatment. The rate of overweight and obesity seem to mimic those of the general population (Crum-Cianflone *et al.*, 2010; Tate *et al.*, 2012; Lakey *et al.*, 2013; Hernandez *et al.*, 2017). Some preliminary studies indicate these high rates of overweight and obesity, in countries like Nigeria (Anyabolu, 2016). Other studies further illustrate this rising rate amongst treated black South African females where the prevalence of overweight ranged from 28% to 32% and obesity from 20% to 37% (Hurley *et al.*, 2011; Malaza *et al.*, 2012; Wrottesley *et al.*, 2014). Studies have proven that the initiation of highly active antiretroviral therapy (HAART) results in weight gain and an increased prevalence of hypertension and metabolic syndrome (Sani *et al.*, 2013).

Interestingly, South Africa presents with a high prevalence of both overweight and obesity, through statistics obtained from various HIV clinics (Hernandez *et al.*, 2017; Huis in 't Veld *et al.*, 2018). A substantial proportion of those starting HAART, become overweight/ obese within a year (Hurley *et al.*, 2011). Since obesity leads to the incidence of non-communicable disease, and considering that those on HAART are more vulnerable to various non-communicable diseases, the synergistic effect is likely devastating, because both overweight and obesity are involved in increased multimorbidity in individuals receiving HAART (James *et al.*, 2001; Bradshaw *et al.*, 2003; Hall *et al.*, 2011; Kim *et al.*, 2012).

1.3.5 Pharmaceutical iatrogenesis

In addition to HAART, quite a few commonly used medications such as antidiabetics, antihypertensives, antihistamines, contraceptives, protease inhibitors, psychotropic medications and steroid hormones , have been previously associated with increased weight gain (McAllister *et*

al., 2009). The adverse effects of weight gain as result of using such medications is the increased risk of developing hypertension, type II diabetes and ultimately poor compliance to medication in general (McAllister *et al.*, 2009). Challenging as it may be to estimate the full impact of drug-induced weight gain, the mere identification that most commonly prescribed drugs may induce significant weight gain, supports the assumption that drug-induced weight gain contributes to the prevalence of obesity (McAllister *et al.*, 2009). For this review, in the context of South Africa, antihypertensives, antidiabetics, and contraceptives will be briefly discussed.

In South Africa, the rising prevalence of hypertension is a strong indicator of likely high use of antihypertensive therapy (Seedat, 2000; Bourne *et al.*, 2002b). Some studies have reported increases in the use of antihypertensive therapy, between 2008 and 2015, Cois and Ehrlich found that the estimated proportion of treated hypertensive subjects increased by 34.3% in women and 54.7% in men (Cois and Ehrlich, 2018). Some reports mention β-adrenergic blockers as key culprits in antihypertensive induced weight gain, however this is not a consistent finding (Kumpusalo and Takala, 2001). In a separate study patients on metoprolol tartrate were compare to those on carvedilol, for hypertension, they found an average weight gain of 1.19 kg which suggests that weight gain was not due to a class effect (Messerli *et al.*, 2007).

A similar increasing trend is reported with diabetics, as the prevalence of the disease is at a rise in the country, especially among the elderly. Bertram and colleagues reported that between 2000 and 2008, the prevalence of diabetes rose from 5.5% to 9% (Bertram *et al.*, 2013). Antidiabetic medications such as insulin, thiazolidine, and sulfonylureas have been shown to cause significant weight gain, however this is said to be combatable through adherence to diet and exercise or combination therapy with metformin (Ness-Abramof and Apovian, 2005; McAllister *et al.*, 2009). It is worth considering that the effects of these medications on weight gain may be heightened if individuals are on both antihypertensives and antidiabetics, in light of the causative relationship between these diseases, this is something that is worthy of further investigation.

For women, the use of contraceptive pills has also been shown to lead to increased weight gain, while findings are conflicting, this is largely due to the inability to distinguish weight changes due to contraceptive use from weight changes as a result of dietary and physical activity changes (McAllister *et al.*, 2009). Some studies show that contraceptives lead to water retention, while

others suggest that the weight gain is due to the use of progestins such as depot medroxyprogesterone (Carpenter and Neinstein, 1986; Mangan *et al.*, 2002; McAllister *et al.*, 2009). In South Africa the contraceptive prevalence rate was reported at 64.6%, most of these being through the use of oral contraceptives (Harries *et al.*, 2019). This places women at higher vulnerability toward excess weight over and above those previously mentioned.

1.3.6 Gut microbiome

The human digestive tract is home to a large number of microorganisms such as archaea, bacteria, fungi, protozoa, and viruses, cooperatively known as gut microbiota (Balzola *et al.*, 2010). They serve a variety of functions that include: the production of additional energy that would not be accessible to the host by breaking down soluble fibre, producing vitamins like biotin, folate and vitamin K, safeguarding colonization by pathogens and aiding the development of a mature immune system (Davis, 2016). Recent evidence indicates that the intestinal microbiome is inherently associated with overall health including overweight/ obesity risk (Davis, 2016; Aoun *et al.*, 2020).

Obesity and some metabolic disorders related to obesity, have been characterised by explicit alterations in the function and composition of the human gut microbiome (Davis, 2016). A study exploring the mechanisms behind this showed that intestinal gut microbiota can influence the energy balance equation on both sides (Bäckhed *et al.*, 2007). They do this by influencing the utilization of energy from the diet and by influencing host genes that regulate storage and expenditure (Bäckhed *et al.*, 2007). Additionally, the composition of the gut microbiome is not fixed, and can be influenced by several dietary components, specifically the consumption of the high fat/high sugar “Western” diet (Turnbaugh *et al.*, 2008). This diet has been shown to increase the abundance of *Firmicutes* at the expense of *Bacteroidetes* in animal models, a ratio that is commonly found in obese humans (Duncan *et al.*, 2008; Turnbaugh *et al.*, 2008; Zhang *et al.*, 2009). Moreover, antibiotic use has also been shown to alter the composition of the gut microbiome, their use has also been linked to the development of obesity resulting in a similar disruption to the ratio between *Firmicutes* and *Bacteroidetes* (Cox and Blaser, 2015).

1.3.7 Physical activity levels

Regional studies on the South African population paint a compelling picture on physical activity (Levitt *et al.*, 1993, 1999; Kruger *et al.*, 2002). Elderly individuals and young women who did not finish school, reported with low physical activity levels. Studies conducted in the Western Cape found that 30-40% of the subjects reported with low physical activity levels during their periods of work and leisure (Levitt *et al.*, 1993, 1999). In the Northern Province less than a third of the study sample, including rural and urban individuals, could be characterised as moderately active. Subjects who were residents on farms presented with the highest level of activity, due to daily walking, hard physical labour and some sporting activity (Kruger *et al.*, 2003).

There are several environmental factors that circumvent the engagement of ideal physical activity by South Africans (Levitt *et al.*, 1999; Bourne *et al.*, 2002a; Kruger *et al.*, 2003). For instance, the absence of education on physical activity in most South African school, especially those localised in township or rural areas, and the excessive viewing of television that encourages sedentary life, all contribute to the rising prevalence of obesity in school children (Kruger *et al.*, 2005). Seemingly, urbanisation in South Africa contributed to the decline in traditional game play, which in these communities, proved to be a functional mode of engaging in basic physical activity (Bourne *et al.*, 2002b). Yet, it is in the most inactive subjects where the highest serum cholesterol, mean systolic blood pressure, and low-density lipoprotein cholesterol levels are found (Kruger *et al.*, 2003). In the peri-urban regions of the Western Cape, the lack of physical activity has been identified as a significant risk factor for type 2 diabetes mellitus (Levitt *et al.*, 1993).

1.4 Sex differences of obesity prevalence

Across the world, men and women are vulnerable to varied risks of obesity. Evidence from the WHO details that in most countries, obesity is of higher prevalence in women than men (World Health Organisation, 2018). Presently, it is not apparent as to whether sex or gender differences, or both, contribute to the obesity pandemic (Kruger *et al.*, 2012). To comprehend the sex or gender differences, adequate elucidation of these terms is desirable. “Sex” differences have been

used recently in literature to refer to variables that are entirely biological (Kruger *et al.*, 2012), while "gender" differences denote socially defined variances between men and women . Furthermore, by definition, "gender" differences involve variables associated with possible interactions between biological and environmental factors (Regitz-Zagrosek, 2012). Thus, gender will be used to refer to the roles of behavioural and psycho-sociodemographic variables.

Results from a recent study on African teenagers indicated that girls were predominantly more susceptible to overweight/ obesity compared to boys, like African adults (Jinabhai *et al.*, 2007). Some studies in Brazil showed similar risks of overweight/ obesity among men and women (Doak *et al.*, 2000). Interestingly, studies in China and Malaysia reported a higher prevalence in men rather than women (Ismail *et al.*, 1995; Ge *et al.*, 1996). However, global studies still echo a clear trend with women presenting with a higher prevalence of overweight/ obesity than men (Garawi *et al.*, 2014; Morales‐Luna, 2019). Furthermore, in most developing countries overweight in females now surpasses underweight (Mendez *et al.*, 2005).

Recent findings suggest that several risk factors are responsible for the rising prevalence in obesity (Duncan *et al.*, 2011; Hruby and Hu, 2015; Thibault *et al.*, 2016). These factors are those primarily acting on shifting the calorie intake and expenditure balance, such as increased urbanisation, which encourages a reduction in physical activity (Kruger *et al.*, 2005; Turok, 2012). This is explained by the abundant availability and affordability of calorie dense foods, consequently leading to increased consumption of calories and an increasingly Westernised diet (Aroor *et al.*, 2018a). Numerous studies point to the transition away from traditional food and the importation of high-fat foods into low- and middle-income countries as a key role player in the upsurge of obesity cases in South Africa (Bourne *et al.*, 1994; MacIntyre *et al.*, 2002; Duncan *et al.*, 2011). While all these factors contribute to the obesity pandemic in the developing world, in isolation, they cannot explain the higher obesity rates in women as compared to men.

1.4.1 Sex differences in adiposity

The patterns of fat storage, mobilisation, consumption as a metabolic fuel, and the consequence of inadequate or excessive fat store, are varied in men and women (Power and Schulkin, 2008; Zore *et al.,* 2018). The observed variances may express developed adaptive differences that are derived from the differences in reproductive costs between males and females (Power and Schulkin, 2008). Nutritionally, reproduction is more metabolically demanding for women than it is for men. Male reproductive effort is significantly overshadowed by the cost of gestation and lactation. Therefore, the asymmetry in the cost of reproduction is mirrored in the asymmetry of fat utilisation as fuel and storage. Thus, in the current section of the review, the differences in fat metabolism and storage, between men and women, will be discussed.

The differences in body fat proportion and fat distribution between males and females begin early in life with further enhancement during puberty (Power and Schulkin, 2008). Metabolic and hormonal variances between sexes are considered key role players in the variances observed. These differences may further contribute to the differences in health risks attributable to obesity. Nielson *et al,* reported that women have larger adipose store than men across all races, this finding was consistent even after they corrected for BMI (Nielsen *et al.,* 2004). Their findings indicated that the mean body fat percentage for normal weight women, with a BMI between 18 and 25 kg/m^2, was similar to that of obese men (BMI > 30 kg/m^2).

Interestingly, body fat percentage sex differences in adiposity are present at birth. Female infants are reported to have greater subcutaneous fat than male infants for all gestational ages (Rodríguez *et al.,* 2005). Furthermore, prepubertal females are said to have significantly more fat in their pelvis and legs than prepubertal males (He *et al.,* 2004). The distribution of body fat is varied between men and women. Women store more adipose tissue in their femoral and gluteal region, while men are more likely to have greater stores of abdominal fat with greater vulnerability to abdominal adiposity (Nielsen *et al.,* 2004). In addition, women accumulate more subcutaneous depots, while men typically have greater amounts of visceral adipose tissue (Lemieux *et al.,* 1993).

The sex-specific differences in fat distribution are influenced by numerous factors, such as hormonal status and diet. An example of a contributor to the sex bias in adipose tissue distribution, could be the rate of direct fatty acid uptake by tissues, in the process that takes place independent of lipoprotein lipase activity (Zore *et al.*, 2018). Lipoprotein lipase is an enzyme that is responsible for the breakdown of triglycerides into free fatty acids. In women the direct uptake of free fatty acid is higher in the gluteal and femoral depot (Karastergiou *et al.*, 2012; Karpe and Pinnick, 2015). In men the direct uptake is in the abdominal depot (Mundi *et al.*, 2014).

Critical findings made from studies conducted in the 1980's, evidence that the heritability of overall adiposity and subcutaneous fat mass is approximately 30% (Bouchard *et al.*, 1988). A study conducted in 1990 further corroborated their results with findings from Caucasian male twins that presented with 31% heritability of waist-to-hip ratio (Selby *et al.*, 1990). However, a recent population study from 2013 estimated the heritability of the same trait at 39% (van Dongen *et al.*, 2013). Some estimates of fat distribution heritability indicate a higher percentage in women than men. Interestingly the heritability and fat distribution vary across ethnic groups. For African women, the impact of childhood circumstance has been linked to the rising prevalence in obesity (Case and Menendez, 2009).

The conditions of early life might have enduring epigenetic, sex-specific effects on eating behaviours, regulation of appetite, and body weight patterns these may lead to developmental programming of health and disease. A range of experimental animal studies have reported discrepancies on the impacts of early life nutritional deprivation on male and females. The physiological mechanisms behind these differences are not fully understood (Lingas and Matthews, 2001; Cupples, 2005; Mcmillen and Robinson, 2005; Knight *et al.*, 2007). In some cases male and female rats have been demonstrated to have varied responses to the exposure of early postnatal hypothalamic neuropeptides known to modulate the appetite regulation system (Varma *et al.*, 2003; Wagner and Scholz, 2003).

Animal studies, on early gestational undernutrition, reported that malnutrition during the first 2 weeks of gestation was linked to lower than normal fat accumulation and weight gain in male rats (Anguita *et al.*, 1993). However, in female rats they observed greater than normal fat

accumulation and weight gain. Thus, these authors hypothesized that this difference could be due to the differences in the activity of the hypothalamus between males and females.

In humans, research conducted on the influence of early life nutritional deprivation was conducted largely on individuals who survived famine (Ravelli *et al.*, 1999). Their findings showed that women who were residents of provinces that were severely affected by famine, had a significantly higher risk of obesity compared to other women. Interestingly, the risk of obesity in men seemed to have no relationship with the incidence of famine (Luo *et al.*, 2010). Generally, these findings on early life nutritional undernutrition show that deprivation may have differential, sex-related, effects on the regulatory mechanisms for energy intake and expenditure.

As previously detailed, studies on the African population confirm that overweight or obese Africans are not immune to the chronic health risks associated with obesity (Case and Menendez, 2009; Scott *et al.*, 2012). Included in these chronic health risks, amongst others, is hypertension, stroke, coronary heart disease (CHD), and diabetes. Evidence obtained from South Africa reveals that overweight or obese women are at a higher risk of developing hypertension, with congestive heart failure and stroke as the two most prominent killers among individuals aged 50 and above (Kahn *et al.*, 1999). Therefore, the role of obesity in the engenderment of cardiovascular diseases (CVD) is worth deliberating.

1.5 Obesity and Cardiovascular Disease

The rising prevalence of cardiovascular disease (CVD), is quickly becoming a leading cause of morbidity and mortality throughout the world. External forces govern the development of CVDs, such as individual, environmental, political, technological, and socioeconomic conditions; similar to overweight or obesity (Keates *et al.*, 2017). In developing countries, such conditions are the main drivers in the increasing prevalence of CVD, as they influence the life course of the risk of CVD (Keates *et al.*, 2017). Developing countries are thus likely vulnerable to progressive urbanisation, which has been linked to the current rise in CVD (Sliwa *et al.*, 2016). Urbanisation coincides with the widespread adaptation of unhealthy lifestyles facilitated by urban life, such as, alcohol abuse, low levels of physical activity, tobacco use, and unhealthy diets (Manning *et al.*,

1974; Burkitt, 1982; Segal and Walker, 1986; Rossouw, 1990; Bourne *et al.*, 2002a; Keates *et al.*, 2017).

Evidence shows that the adoption of urban lifestyles, in the context of Africa, may have replaced the cardioprotective properties of the rural lifestyle that is indigenous to the population (Manning *et al.*, 1974; Poulter *et al.*, 1984; Bourne *et al.*, 2002a; Keates *et al.*, 2017). Thus, it is important to consider that urbanisation, and therefore the adaptation of the urban diet to the African population, engenders the consumption of unhealthy foods, particularly processed foods, which then encourage the development of cardiovascular complications and overweight or obesity (Manning *et al.*, 1974; Bourne *et al.*, 2002a). Thus, it is possible that the rise in cardiovascular problems in this population occurs as a result of the high salt, carbohydrate, and fat content of the urban diet, coupled with the depressed levels of activity (Seedat, 2000; Steyn K *et al.*, 2008; Tibazarwa and Damasceno, 2014). Additionally, stressors associated with the adaptation to urbanisation, socioeconomic status, epigenetics, and other factors, further compound on the dietary effects creating conditions that favour the rapid development of CVD (Steyn K *et al.*, 2008; Keates *et al.*, 2017).

Africa is considered a primary contributor to the global burden of CVD, with 38% of all deaths due to non-communicable disease linked to CVD (Keates *et al.*, 2017). In 2013, sub-Saharan Africa alone reported with a projected 1 million deaths, which were as a result of CVD (Mensah *et al.*, 2015). These fatalities contributed to approximately 5.5% of the global CVD-related deaths, and approximately 11.3% of the global CVD-related deaths occurred in Africa alone (Mensah *et al.*, 2015).

Numerous developing countries in Africa are in a phase of epidemiological transition, where there is a notable rise in both communicable and non-communicable diseases (Mayosi *et al.*, 2009). Countries such as South Africa not only face an extensive threat of communicable and non-communicable diseases, but there are additional threats such as those related to injury and perinatal and maternal disorders. Cardiovascular disease, however, remains a prominent non-communicable disease. The notable rise in non-communicable diseases, in South Africa, is driven largely by the increase in related risk factors in rural and urban areas – more so in the face of an ageing population, and significantly reduced mortality as a result of HIV/AIDS.

It is apparent that the factors contributing to the upsurge in overweight or obesity in South Africa largely overlap with those fostering the rise in CVD. Urbanisation and socioeconomic factors seem to drive the facilitation of epidemiological transition, where there is a notable rise in both communicable and non-communicable diseases in numerous developing countries in Africa (Mayosi *et al.*, 2009). This not only stresses the need for management of these disease, but further emphasises the need for their prevention.

The consequences of obesity on the cardiovascular system extend beyond an abnormal metabolic profile, an assortment of changes or adaptations in the function and cardiac structure ensue as adipose tissue collects in excess amounts, even without comorbidities. Thus, obesity may influence cardiac function through its impact on risk factors such as hypertension, dyslipidaemia, inflammatory markers, glucose intolerance, prothrombic state, obstructive sleep apnoea and mechanisms that are yet to be elucidated (Poirier *et al.*, 2006). Overall, the state of being overweight or obese is associated with an assortment of cardiac complications such as heart failure, CHD, and sudden death, as a result of the sever impact of overweight or obesity on the cardiovascular system.

1.5.1 Haemodynamic Consequences of Obesity

In previous studies, obesity is repeatedly shown to result in the increase of total blood volume, and ultimately cardiac output, as a result of increased metabolic demand due to excess body weight (Kasper *et al.*, 1992; Alpert, 2001). Hence, with any assumed level of activity, cardiac workload for obese subjects is significantly higher (Mattsson *et al.*, 1997; Poirier and Després, 2001). When compared to lean individuals, studies show that obese individuals generally present with higher cardiac output accompanied by reduced peripheral resistance. The surge in cardiac output in the obese is largely owed to the increase in stroke volume, as the heart rate has been shown to increase little if at all.

Additionally, the Frank-Starling curve in obesity is shifted to the left, due to cumulative increases in volume and left ventricular filling pressure. Over time these changes may lead to ventricular chamber dilation, which may then lead to increases in wall stress. These conditions favour

increases in myocardial mass, and may eventually lead to left ventricular hypertrophy, usually the eccentric form (Messerli, 1986; Ku *et al.*, 1994). In normotensive obese individuals, left atrial enlargement may occur, characteristically in the setting of increased left ventricular mass. However, left atrial enlargement may not only be present with left ventricular diastolic dysfunction, but as a physical manifestation of the physiological adaption to increased blood volume (Sasson *et al.*, 1996). Consequently, left atrial dilation may facilitate the additional risk of atrial fibrillation linked to obesity (Wang *et al.*, 2004).

Stamler and colleagues, conducted a hypertension screening on Americans, where they found that most patients with high blood pressure were overweight (Stamler *et al.*, 1978). The incidence of hypertension, in this study, was shown to be 6 times more frequent in obese individuals than in lean men and women. In addition to the high frequency of hypertension in the obese, weight gain has also been shown to be a potent risk factor for the subsequent development of hypertension in young subjects. According to reports from the National Institutes of Health (NIH) body weight increases of 10 kg higher, were associated with 3 mm Hg higher systolic and 2.3 mm Hg higher diastolic pressure from baseline measures (Dyer and Elliott, 1989). Consequently, the increase in blood pressure translated into a projected 24% increased risk for stroke and 12% increased risk for CHD.

Yet, findings from the National Health and Nutrition Examination Survey (NHANES) III detail more precise estimations for the incidence of high blood pressure for each age group and BMI status (Brown *et al.*, 2000). The prevalence of high blood pressure for men, aged 20 years and older, progressively increased form 15% at a BMI less than 25 kg/m^2 to 42% at a BMI of 30 kg/m^2 and greater. This trend was similar in women, of the same age range, the prevalence of hypertension was also reported at 15% for BMI less than 25 kg/m^2 to 38% with a BMI of 30 kg/m^2 and above.

The tendency of hypertension to rise with increasing BMI, was comparable among black, white and Mexican Americans (Brown *et al.*, 2000). However, the age adjusted estimates were higher amid blacks at all BMI categories. Previous studies have well recognised the technical difficulties of indirect blood pressure measurement in obese patients, that may produce overestimated imprecise measures of blood pressure (King, 1967; Kirkendall *et al.*, 1980; Nielsen and Janniche,

2009). However, a previous study exploring the efficacy and predictive value of ambulatory blood pressure monitoring, compared to that of office BP, in obese vs non-obese participants proved the that the method was as useful in overweight or obese patients (Palatini *et al.*, 2016).

1.5.2 Ambulatory Blood Pressure Monitoring

Ambulatory blood pressure monitoring (ABPM) has been repeatedly recommended as the reference standard for the diagnosis of hypertension and CVD risk (Hermida *et al.*, 2015). The time course evaluation of blood pressure over a 24-hour period can only be realised with the use of ABPM. Various studies that have investigated the impact of ABPM, found that it can predict morbidity and mortality in a way that surpasses clinical measurements (Redon et al., 1998; Ben-Dov et al., 2007; Hermida et al., 2015; Etyang et al., 2016). Ambulatory blood pressure monitoring can provide basic estimates of true blood pressure variations (Pickering *et al.*, 2007).

Plausibly, ABPM reveals physiological states that are not captured by resting office measurements (Pickering *et al.*, 2007). Blood pressure follows a distinct circadian pattern, associated with lower levels during the onset of sleep and high levels during wake periods (Giles, 2006). Interestingly, there is a marked upsurge during the morning hours, concurring with the transition from sleep to wakefulness. The normal variation between sleeping and waking systolic and diastolic blood pressure is characterized by a 10 - 20% decline in blood pressure (Ohkubo *et al.*, 1997). For normotensive subjects, the diurnal rhythm of blood pressure is more pronounced (Narkiewicz *et al.*, 2002). However, a similar observation is made in primary hypertensive individuals, but the diurnal rhythm is set at a higher level.

Nevertheless, in some subjects, whether normotensive or hypertensive, a phenomenon exists where the nocturnal blood pressure fall is diminished (<10%). A pattern of this nature is termed a non-dipping pattern, in contrast to the normal dipping pattern. In some cases, the blood pressure may rise during the night, in what is called a reverse-dipping pattern, common in chronic kidney disease (CKD) patients. Non-dipping is common in overweight/ obese individuals, with other causes such as daytime hyperactivity, renal disease, poor sleep quality, and an overactive

sympathetic nervous system. It is postulated that individuals who exhibit the non-dipping characteristics are at higher risk of extracardiac and cardiac morbidity.

Individuals with higher levels of BMI are reported to have a high incidence of isolated office, or white coat, hypertension. One study reported the prevalence of white coat hypertension at 12.5% for underweight patients, 22% for normal weight patients, 31.7% for overweight patients and 35.3% for obese patients. The high incidence of isolated office hypertension in the obese highlights the importance of 24-hour ambulatory blood pressure monitoring in these individuals. In addition, it is established that obesity is related to obstructive sleep apnoea, a common respiratory disorder defined by recurrent cessation of nocturnal breathing caused by upper airway collapse.

As a result of excess weight and increased metabolic demand, obese individuals have a higher breathing workload and ventilatory demand, respiratory muscle incompetence, reduced expiratory reserve volume and functional reserve capacity and the closure of peripheral lung units. Therefore, often there is a ventilation-perfusion mismatch which commonly presents in supine position. A study investigating the role of obesity-related obstructive sleep apnoea on blood pressure reported higher systolic and diastolic 24-hour blood pressure in asymptomatic subjects (Correa *et al.*, 2017). Their findings further emphasised the worth of ABPM in the screening of asymptomatic obstructive sleep apnoea in obese patients, this was again confirmed in another study using a validated scoring system model where ABPM variables proved useful in identifying the risk of obstructive sleep apnoea (Torres *et al.*, 2015). They found that the best model included mean daytime BP, mean nocturnal heart rate and minimal diastolic nighttime BP. The collection of the previously identified CVD risks, such as hypertension, dyslipidaemia, inflammatory markers, glucose intolerance, prothrombic state and obstructive sleep apnoea are contributors in the development of arterial stiffness. Therefore, the development and impact of obesity on arterial compliance will be reviewed.

1.6 Arterial compliance

The cardiovascular system encompasses a divaricating system of conduits that function to transport blood from the heart to the systemic capillaries (Carroll, 2007). The exchange of nutrients and waste products takes place between blood and tissue cells. Large arteries perform the function of an elastic reservoir, storing a portion of energy of cardiac contraction that serves to maintain pressure and flow during diastolic phases (Wagenseil and Mecham, 2009).

The smallest arteries and arterioles, locations with the greatest hemodynamic resistance combined with precapillary sphincters, create variable resistance that governs the rate of blood flow to the tissues (McVeigh and Yoon, 2000). The arterial system, comprised of high resistance terminals and elastic conduits, forms a hydraulic filter that modifies the output of the heart into steady capillary flow. Unfortunately, in the development of arterial stiffness, the elasticity of the conduit is lost (Avolio, 2013). Prevailing diseases, such as diabetes mellitus, hypertension and mere aging, augment changes in vasculature that lead to arterial stiffening (Lyle and Raaz, 2017). These diseases can act on vasculature differently and synergistically, accelerating the progression of arterial stiffness (Lyle and Raaz, 2017). The resultant outcome is the loss of steady capillary flow that imposes devastating damage to endothelial cells (Lyle and Raaz, 2017).

The stiffening of arteries increases systolic BP, left ventricular workload and hypertrophy; this is due to diminished arterial elasticity and distensibility (Gavish and Izzo, 2016). In addition, diastolic blood pressure decreases, and the result is reduced coronary blood flow (Ohtsuka *et al.*, 1994). The measures of arterial stiffness, such as pulse-wave velocity (PWV), have proven to be significant predictors of cardiovascular events in kidney disease and hypertension (Townsend, 2015). In normotensive individuals PWV has been shown to be an independent predictor of stroke and heart disease (Quinn *et al.*, 2012). Investigators utilize a variety of approaches to measure arterial stiffness, such as non-invasive ultrasound, magnetic resonance imaging, oscillometry, and tonometry and invasive methods such as pressure catheter measurements (Townsend, 2016). Currently, the gold standard used for assessing arterial stiffness is PWV, which involves the use of high-fidelity applanation tonometry. The use of applanation tonometry, for measuring PWV, has been shown to be accurate, simple, and reproducible. Therefore, PWV is easily applicable for the estimation of CV risk.

1.6.1 Measurement of Arterial Stiffness

During systole, when the left ventricle contracts, the ejection of blood into the ascending aorta sharply dilates the aortic wall (De Heer *et al.*, 2011; Hoit, 2014). When the aortic wall dilates, a pulse wave is generated and propagates along the arterial tree at a limited speed (Safar *et al.*, 2002). Pulse wave velocity is quantified based on the evaluation of central artery haemodynamics. The velocity at which this wave propagates forms an index of arterial stiffness and distensibility (Graham *et al.*, 2008). A high velocity confers higher inflexibility of the vascular wall and low distensibility.

Ventricular ejection generates pulse pressure that is spread through the arterial tree at a speed that is controlled by geometric and elastic traits of the arterial wall, as well as the density of the conducted blood (Safar and Lévy, 2007; Vennin *et al.*, 2017). Considering that blood is an incompressible fluid that is contained in elastic arteries the propagation of energy occurs mainly along the arterial walls (Secomb, 2016). Therefore, the major factors that contribute to the PWV are the properties of the arterial wall, its thickness and the arterial lumen diameter (Avolio, 2013). Pulse wave velocity can be measured at various sections of the arterial tree between two pulse-wave palpable regions (McDonald, 1968; Townsend *et al.*, 2015; Vlachopoulos *et al.*, 2015; Tomiyama *et al.*, 2016). Since the aorta is the largest component of elasticity, carotid femoral PWV provides the simplest, reproducible and non-invasive evaluation of local stiffness (Frimodt-Møller *et al.*, 2008; Segers *et al.*, 2020).

The carotid-femoral measurement favours the recording of pulse pressure at two distinct points of the aorta, at the carotid and the femoral artery, as well as the distance between the two pressure waves recorded at each site (Millasseau *et al.*, 2005). Usually the measurement is initiated at the site of the common carotid and then the femoral artery, using tonometry or standard blood pressure transducers (Millasseau *et al.*, 2005). This method allows for adequate measurement of the foot of the wave and calculating the time delay between the carotid and femoral waves. Among the pathogenic consequences of an inelastic aorta is an overstated blood pressure response during daily activities, this induces an increased cardiac and vascular workload

(Brunner *et al.*, 2015). General and central adiposity are common consequences of the obesity epidemic (Selvaraj *et al.*, 2016). Both general and central adiposity have been related to increased CVD risk and aortic stiffness (Brunner *et al.*, 2015). Hence, understanding the mechanisms of arterial stiffness in the context of obesity is of clinical importance.

1.6.2 Structural Changes in Arterial Stiffness

The endothelium serves as a monolayer of cells with a little tensile strength that can alter the mechanical behaviour of arterial vessels (DeMarco *et al.*, 2014). Haemodynamic forces and extrinsic factors determine the changes that occur in vasculature. Examples of such extrinsic factors are glucose regulation, salt and hormones or vasoactive substances (Galley and Webster, 2004). The production and release of vasoactive substances that affect structure and vascular tone, aid in altering the mechanical behaviour of arterial vessels. The arterial media sustains most of the tensile strain. The constituencies of the media – smooth muscle, elastin, and collagen – vary considerably between blood vessels in relation to their site, physiological function, and form (Galley and Webster, 2004). Thus, arterial stiffness is not evenly distributed in the vascular tree, but is often uneven, commonly occurring in conduit and central vessels and absent in peripheral arteries.

Elastin, collagen, proteoglycans and glycoproteins, make up the extracellular matrix (ECM) of the vessel wall (Yue, 2014). Elastin and collagen maintain the elasticity and structural integrity of the ECM ergo the vessel wall. The balance between these molecules is kept in a steady but dynamic state by the regulation of potent catabolic matrix metalloproteases (MMPs) (Liu *et al.*, 2015). They act through their elastinolytic and collagenolytic capacity, leading to ECM degradation by creating broken and frayed elastin molecules and uncoiling collagen, respectively. The inflammatory mediators, such as polymorphonuclear neutrophils, macrophages, as well as the vascular cells, primarily produce elastases and collagenases.

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1.6.3 Obesity-Related Arterial Stiffness

Increasing evidence has demonstrated that arterial stiffness in obesity is a strong and independent predictor of chronic kidney disease (CKD), CVD and cognitive functional decline. Vascular stiffness is an antecedent of atherosclerosis, cardiac diastolic function, systolic hypertension and blunted cerebral and coronary flow (Aroor *et al.*, 2018b). Furthermore, the cardioprotective properties afforded to women, in the setting of obesity, are lost during the perimenopausal phase (Aroor *et al.*, 2013; Manrique *et al.*, 2016).

The loss of CVD protection in women, during this perimenopausal phase, explains their increased susceptibility to arterial stiffness. Similar to previous discussions on the causes of obesity-associated CVD, findings maintain that the combination of Westernised dietary habits and sedentary lifestyle is the harbinger of obesity-related arterial stiffness (Aroor *et al.*, 2013; DeMarco *et al.*, 2014; Cote *et al.*, 2015; Weberrub *et al.*, 2016). Interestingly, the obesity-related progression of vascular stiffness is highly prevalent in women than men.

According to recent findings, arterial stiffness is reported to be related to the mechanisms of cardiorenal metabolic syndrome (CRS), a collection of collaborative cardiac and metabolic risk factors, such as overweight or obesity, insulin resistance, metabolic dyslipidaemia, impaired renal function and hypertension (Pojoga *et al.*, 2013; Aroor *et al.*, 2017). While arterial stiffness is known to increase with advancing cardiovascular age, obesity, diabetes and insulin resistance significantly accelerate this process (Jia *et al.*, 2014; Liao and Farmer, 2014). The progression of arterial stiffness is complex, ushered by the interaction between various intravascular immune cells, vascular cellular components, the extracellular matrix (ECM), and perivascular adipose tissue (PVAT) (Aroor *et al.*, 2013; Jia *et al.*, 2015; Candela *et al.*, 2017).

Among the various mechanisms that govern the development of arterial stiffness is: (1) the function of endothelial irregularities in the advancement of diminished endothelial nitric oxide synthase (eNOS), activation and the related increases in vascular stiffness (Aroor *et al.*, 2018a); (2), the contributions of vasoactive factors in encouraging arterial stiffness; (3), the recently recognised role of cell-specific mineralocorticoid receptor (MR) activation in promoting stiffening of the endothelial cell cortex through Na^+ channel (ENaC) activation and the influence

of blunted NO bioavailability; (4), the concept that decreases in NO bioavailability prompt transglutaminase 2 (TG2) activation, an enzyme that facilitates collagen cross-linking thus leading to vascular fibrosis; (5)lastly, the contributions of oxidative stress and maladaptive immune inflammatory responses in the engenderment of arterial stiffening and endothelial dysfunction. These mechanisms will be discussed as follows.

Arterial stiffness in the context of obesity is linked to structural and functional aberrations in the intimal, medial and adventitial structures of vasculature (Shirwany and Zou, 2010). The endothelium, a constituent of the arterial intima, is separated from the media by the internal elastic lamina. The media is a layer that, in larger vessels, comprises of concentrically arranged layers of elastic lamina that are interspersed with collagen and smooth muscle cells (Luft, 2012; Stenmark *et al.*, 2013).

On the other hand, the adventitial layer is rich with adipose tissue, collagen, fibroblasts and immune cells, while arterial stiffness is mediated by plasma-derived factors, in addition to factors derived from various layers of the vascular wall. Furthermore, complex cell-cell communication between the different layers of the vascular wall modulate structure and function of the non-cellular and cellular components (Zieman *et al.*, 2005; Sazonova *et al.*, 2011; Jia *et al.*, 2015; Liu *et al.*, 2015). The incidence of intimal thickness is an intricate process that involves the development of fibrotic remodelling and endothelial dysfunction.

While the remodelling of the ECM that is owed to the qualitative and quantitative aberrations in collagen and elastin is broadly studied, recent studies have identified MMPs as the key regulators of the ECM (Liu *et al.*, 2015). Nevertheless, insulin resistant and prediabetic states, characterised by increased arterial stiffness, are linked to the thickening of the vascular wall. This implies that the mechanisms associated with vascular cells are critical determinants of vascular stiffness. In addition to the role of endothelial cells and vascular smooth muscle cells (VSMC) , obesity-associated arterial stiffness is also advanced by immune and vascular adipose cell dysfunction (Fleenor *et al.*, 2014; Du *et al.*, 2015; Villacorta and Chang, 2015; Candela *et al.*, 2017). Thus, the significance of ECM and cellular interaction is emphasised in obesity-related arterial stiffness (Jia *et al.*, 2015; Manrique *et al.*, 2016).

1.6.3.1 Hyperinsulinemia and increased Renin-Angiotensin-Aldosterone System activation

The advancement of CKD and CVD with obesity and CRS is antecedent to insulin resistance linked to hyperinsulinemia (Seifalian *et al.*, 2010; Bender *et al.*, 2013; Muniyappa and Sowers, 2013). Previous studies support this perspective through the demonstration of reduced vasorelaxation responses to insulin, and not acetylcholine, prior to the onset of hypertension in aged rats and in rats developing spontaneous hypertension (Li *et al.*, 2010; Schiffrin, 2014). The development of systemic and cardiovascular insulin resistance in the setting of obesity, is largely due to the interplay between diet and the activation of tissue and systemic renin-angiotensin-aldosterone system (RAAS) (Kumar *et al.*, 2012; Muniyappa and Yavuz, 2013).

A high fructose diet has been shown to lead to increased vascular production of angiotensin II and uric acid. This then highlights the significance of tissue RAAS activation and hyperuricaemia in the upregulation of cardiovascular remodelling and stiffness (Aroor *et al.*, 2013). Bearing in mind that in the state of obesity and insulin resistance RAAS activity is upregulated, findings show that angiotensin II and aldosterone act synergistically to promote cardiovascular remodelling and stiffness (Rautureau *et al.*, 2011; Bender *et al.*, 2013). Recent studies highlight the role of cell-specific vascular MR activation, in vascular remodelling and stiffening, in the setting of diet-induced obesity (Pojoga *et al.*, 2013; Jia *et al.*, 2015, 2016).

In normotensive subjects, elevations in plasma aldosterone are associated with insulin resistance and obesity, and patients with hyperaldosteronism have insulin resistance (Whaley-Connell *et al.*, 2010; Bender *et al.*, 2013; Jia *et al.*, 2016). Numerous studies on humans and animal models of obesity, report the improvement of cardiovascular function through treatment with MR antagonists (Kithas and Supiano, 2010; Baldo *et al.*, 2011; Aroor *et al.*, 2013; De Marco *et al.*, 2015). The expression of Endothelin-1, a vasoactive peptide released by endothelial cells, is upregulated by RAAS activation. It is also considered a vital initiator of increased vascular stiffness and remodelling (Muniyappa and Yavuz, 2013; Nar *et al.*, 2013).

1.6.3.2 Sympathetic Nervous System Activation

Several studies report a recurrent relationship between overweight/ obesity and increased sympathetic nervous system (SNS) activity an important contributor to arterial stiffness and hypertension (Sowers, 2013; DeMarco *et al.*, 2014). A combination of factors common in obesity, namely obstructive sleep apnoea, hyperleptinemia, hyperinsulinemia, untimely activation of tissue and systemic RAAS, and baroreflex dysfunction are associated with disproportionate activation of the SNS (Aroor *et al.*, 2013; DeMarco *et al.*, 2014). The exact mechanisms that govern the contributions of increased SNS to arterial stiffness are yet to be elucidated.

1.6.3.3 Adipocyte Derivatives

Metabolic perturbations in adipose tissue as a result of obesity, alter the secretion of bioactive hormones and molecules, such as angiotensin, aldosterone stimulating factors, aldosterone, leptin, resistin, adiponectin, interleukin (IL)-6, tumour necrosis factor- α (TNF- α), and monocyte chemoattractant protein-1 (Gollasch, 2012; Ray *et al.*, 2014; Nosalski and Guzik, 2017). Vascular sensitivity to insulin may be impaired by increased circulation of adipocyte-derived cytokines. This increased circulatory concentration of adipocyte-derived inflammatory cytokines can increase the mobilisation and activation of vascular pro-inflammatory cells, known to supplement the development of arterial stiffness. Also, increased lypolytic activity in visceral adipose tissue, in the context of insulin resistance, prompts the increase in free fatty acids. Free fatty acids are known to hinder insulin-induced reuptake of glucose and the adipose, vascular and tissue metabolic signalling of insulin (DeMarco *et al.*, 2014; Jia *et al.*, 2015). Diminished metabolic signalling of insulin in endothelial cells incites reduced NO production, thus promoting endothelial cell stiffness and eventually vascular stiffening.

1.6.3.4 Endothelial dysfunction

Endothelial cell signalling further plays a significant role in arterial stiffening, as well as VSMC tone (Kohn *et al.*, 2015; Harvey *et al.*, 2016). Haemodynamics or mechanical stimulation affect VSMC tone by altering calcium signalling through cell stretch (Sanders, 2009; DeMarco *et al.*, 2014). Furthermore, paracrine mediators have a similar effect, namely NO, reactive oxygen species (ROS), endothelin, and angiotensin II (Sanders, 2009). Nitric oxide is a substance recurrently produced by endothelial cells from L-arginine by eNOS (Förstermann and Sessa, 2012). Among its numerous functions NO acts as a modulator of vascular tone, promoting vasodilation, NO also offers protection to blood vessels against platelet and cellular induced vascular damage that could lead to endothelial dysfunction (Michel and Vanhoutte, 2010; Zhao *et al.*, 2015).

Endothelial dysfunction is clinically indicated by a faulty vasodilatory response to acetylcholine, partly due to an imbalance between NO and vasoconstrictor substances, oxygenases and endothelial-derived hyperpolarizing factor (Shirwany and Zou, 2010). In some instances, NO itself is reduced, due to limited expression and overriding eNOS inhibitor expression (Michel and Vanhoutte, 2010; Förstermann and Sessa, 2012). Stress hormones and AGEs are also known to reduce NO bioavailability due to the activation of ROS (Sena *et al.*, 2008; Boudina, 2013). Furthermore, dietary salt is shown to enhance arterial stiffness with increasing age (AlGhatrif *et al.*, 2017). This is confirmed by the observed improvement of arterial compliance in older adults consuming a low-sodium diet (Gates *et al.*, 2004; Jablonski *et al.*, 2009, 2013).

1.6.4 Arterial Stiffness and Salt Consumption

Animal studies investigating hypertension have shown that elevated dietary salt can promote arterial stiffness independently of BP (Safar *et al.*, 2000). While the reduction of sodium has been demonstrated to ameliorate the stiffening of arteries in hypertensive humans (Gates *et al.*, 2004; Todd *et al.*, 2010). Human studies provided evidence of an independent effect of salt on arterial stiffness (Avolio *et al.*, 1985, 1986). A study investigating a Chinese population, two groups were studied, a rural population that consumed low salt, and an urban population that consumed

higher levels of salt (Avolio *et al.*, 1985). In the rural group, the PWV was lower when the groups were compared at similar BPs. Likewise, in a group that consumed a low salt diet, the arterial stiffness was lower when the group was compared to an age and BP matched group with normal salt consumption (Avolio *et al.*, 1986).

In another study, PWV was measured in normotensive participants who voluntarily consumed a low-salt diet (Dickinson *et al.*, 2014). The participants were compared with age and BP matched participants who were on a normal sodium diet. In the low-salt group, participants aged 20 to 66 years, presented with considerably low PWVs, measured in the legs, arms and aorta as compared to the control group. They concluded that subjects on a low-salt diet have reduced arterial stiffness independent of BP.

The mechanisms that govern increases in arterial stiffness, due to increased salt consumption, appear to be driven by the profibrotic effects of transforming growth factor beta 1 (TGF-β1) (Ying *et al.*, 2008). In an animal study, when rats were fed a high salt diet for 7-day the endothelial production of TGF-β1 increased despite an increase in BP. High salt is known to increase basal levels of NO production, by way of TGF-β1 signalling. The mechanisms of TGF-β1 signalling assists in reducing the ill effects of TGF-β1 initially, however, as described above endothelial function and NO synthesis are reduced by high salt intake.

In human studies, through the monitoring of 24-hour urinary sodium excretion, South African individuals were found to have high levels of Na^+ excretion which is believed to be a result of high salt intake (Maseko *et al.*, 2006). Studies have further shown that excess salt consumption, accompanied by salt sensitivity, not only results in BP elevations, but also presents with several deleterious effects.

In vitro studies showed that increased salt intake promotes shear stress within the vascular walls, this then promotes the production of transforming growth factor beta 1 (TGF-β1) and NO (Sanders, 2009). These elements become critical contributors of the outcome, as NO serves as a vasodilator and an inhibitor of endothelial TGF-β1. During high salt intake NO serves not only as a vasodilator but to mitigate the production of TGF-β1. However, due to factors such as vascular aging, NO production decreases and TGF-β1 production remains unregulated (Sanders, 2009).

The consumption of high levels of salt is known to increase tonicity of the blood resulting in increased aldosterone release which overtime results in endothelial dysfunction (Sanders, 2009). NO is largely produced by endothelial cells and their dysfunction would then decrease NO bioavailability (Sanders, 2009). The outcome would then be elevated levels of TGF-β1, decreased arterial compliance and peripheral vasoconstriction all synergistically resulting in end-organ damage (Sanders, 2009). Interestingly, the action of TGF-β1 may be further augmented in clinical populations that have already reduced endothelial function. Additionally, oxidative stress brought about by the peripheral vasoconstriction and the damage of endothelial cells, would further result in the production of ROS that would lead to additional damage to organs and surrounding vasculature (Sanders, 2009). These vascular changes are observed in salt sensitive hypertensives.

1.7 Dietary Electrolytes

In the body there are detailed physiological systems that regulate the level of electrolytes (Mishra *et al.*, 2018). The regulation of sodium and potassium concentration, among other electrolytes, is vital for the optimum efficiency of countless physiological purposes. For instance, sodium chloride (NaCl) or dietary salt, is essential for the maintenance of serum osmolarity and extracellular fluid volume (Franco and Oparil, 2006). While potassium also assists in the regulation of fluid balance, muscular contractions, and neurological signalling (Zacchia *et al.*, 2016).

Slight variations in the plasma concentration of sodium and potassium may have direct adverse effects on the electrical activity of cells, plasma volume, acid-base balance, interstitial fluid volumes, plasma osmotic pressure, and cardiovascular systems response to circulating endogenous pressor mediators (Grollman, 1961). In normal individuals, the ill effects of extreme declines in sodium, through urinary excretion or sweat, are sustained. Alternatively, in the event of acute or chronic changes in salt consumption, the body is capable of rapidly expelling excess salt loads without any significant changes in blood pressure or volume homeostasis (Franco and Oparil, 2006).

It is commonly believed that excess dietary salt consumption results in an increase in BP. However, contrary to this notion, not all individuals with excess dietary salt consumption will develop hypertension. There is inter-individual variability when it comes to effects of dietary sodium on BP. The variability occurs as a result of variances in the sensitivity to salt. Hence, individuals who are salt-sensitive are more likely to develop hypertension at an accelerated rate than those who are not (Angeloni, 2016).

In recent years, salt has been intensely studied, especially regarding its contribution to hypertension and cardiovascular mortality. The relationship between dietary salt and hypertension has been the subject of persisting debate for many decades. In a world-wide epidemiological study of a large cohort (n=10079), known as the International Cooperative study on Salt (INTERSALT) study (Rose *et al.*, 1988). It was reported that there was no significant relationship between 24-hour sodium excretion and blood pressure . While, 8 years later, when the INTERSALT data was extrapolated, the data indicated that reducing salt consumption, by one third of the current mean level, would lower BP by approximately 4 mm Hg systolic and 2.5 mm Hg diastolic in hypertensive patients, and by 2 mm Hg systolic and 1 mm Hg diastolic in normotensive individuals (Elliott *et al.*, 1996).

Albeit, the extrapolation of the data being a re-analysis bears its own limitations, thus it is pertinent to note that different individuals are variably vulnerable to the BP-elevating effects of sodium (Luft and Weinberger, 1997). On a population basis, BP is reasonably affected by the changes in sodium intake. For some individuals the response to acute or chronic salt reduction or increase exhibits large BP changes. Individuals, whose blood pressure responds dramatically to changes in salt consumption, are known as “salt-sensitive” (Franco and Oparil, 2006). It was shown by Weinberger et al, that salt sensitive subjects had a notably higher increase in systolic and diastolic pressure over time, compared to salt-resistant subjects (Weinberger and Fineberg, 1991).

1.7.1 Salt sensitivity

The sensitivity of BP to salt, commonly known as salt sensitivity, is defined as a physiological change in BP, in office, of 5 – 10% or at least 5mmHg following changes in salt intake (Sullivan, 1991). An alternative definition of salt sensitivity is an increase in mean arterial blood pressure, measured by ABPM, of at least 4mmHg following an increase in salt intake (De La Sierra *et al.*, 2002). In these cases, the BP of these individuals responds directly to changes in sodium intake (Elijovich *et al.*, 2016). Commonly, in some individuals, when salt consumption is increased, the excess salt is excreted through the kidneys or by perspiration. However, regulatory mechanism may be impaired in some individuals resulting in excess salt retention which is demonstrated by elevated BP.

Generally, salt sensitivity presents itself as a major public health concern. The estimated occurrence of salt-sensitivity is 51% in hypertensive patients, and 26% in normotensive individuals (Weinberger *et al.*, 1986). Increased salt loading, together with higher salt-sensitivity, remains one of the main risk factors for the susceptibility to essential hypertension. Nevertheless, changes in BP as a result of changes in salt intake are not consistent.

There are a variety of factors that separate a salt-sensitive and salt resistant population, these may be demographic, physiological, environmental and genetics characteristics (Weinberger, 1996). Furthermore, salt sensitivity is likely driven by age, gender, genetic factors, race, BMI and diet. Lastly, there are comorbidities associated with salt-sensitivity, for example; diabetes, hypertension, metabolic syndrome and chronic kidney disease (Franco and Oparil, 2006; Elijovich *et al.*, 2016). Salt-sensitivity is commonly observed in individuals of African descent, older adults, and in individuals with other comorbidities or in pre-hypertensives or hypertensives (Weinberger, 1996).

Populations of African descent, display an augmented BP response to variations in salt intake than Caucasians, independent of baseline BP (Weinberger *et al.*, 1982). Findings further indicate that beyond ethnicity, obese individuals and females are independently vulnerable to salt sensitivity, however, the evidence for such associations bears insufficient statistical power (Weinberger and Fineberg, 1991; J. He *et al.*, 2009). Research shows that obesity increases

sympathetic activity and salt sensitivity (Esler *et al.*, 2006; Kotsis *et al.*, 2010; Ando, 2014). While dietary behaviour has been implicated as a key contributor of salt sensitivity.

Blood pressure was found to respond significantly in conditions of low-potassium intake and in conditions of poor-quality diet when compared to the Dietary Approaches to Stop Hypertension (DASH) diet (Weinberger *et al.*, 1982; Morris *et al.*, 1999; Sacks *et al.*, 2001). Developing countries in Africa have been shown to have one of the highest levels of salt consumption that measure far beyond the recommended allowance (Maseko *et al.*, 2006). What is of concern, in this case, is the high salt consumption that is met by salt sensitivity which is known to result in elevated BP worse-so in the context of obesity.

1.7.2 Renal Consequences of obesity

The composition of the overweight/ obese diet is largely constituted of energy-dense foods, but also sodium rich foods without an adequate intake of potassium (Ebrahimi *et al.*, 2018). A previous study has reported on the existent relationship between sodium, potassium, phosphate calcium and iron with blood pressure as well as other cardiovascular events and diseases (Cai *et al.*, 2016; Elfassy *et al.*, 2018). Therefore, the concentration of such electrolytes is commonly indicative of a patient's nutritional status and dietary intake.

Due to the rise of energy rich diets across the world, and the high salt consumption observed in South Africa, a dysregulation in sodium and potassium and other electrolyte concentrations is observed (Reisin, 1990; Ndanuko *et al.*, 2017). Considering the role of sodium and potassium in the physiological regulation of body composition, the occurrence of electrolyte dysregulation promotes the risk of hypertension and vascular disease.

Furthermore, the altered activity of the renal system may result in impaired or altered renal excretion of electrolytes like sodium and potassium, possibly resulting in their build-up in the body (Oyadomari and Mori, 2004). Studies have proposed that the increases in electrolyte concentration in overweight/ obese individuals is solely due to the consumption of calorie dense diet (Ebrahimi *et al.*, 2018). However, other findings seem to indicate that electrolyte

dysregulation is associated with obesity independent of the dietary content (Nam *et al.*, 2017). Still, findings from previous studies maintain that reduced potassium, an electrolyte linked positively to dietary healthfulness, and an elevated ratio of sodium to potassium are associated with obesity and consequential hypertension (Cai *et al.*, 2016).

1.7.3 Salt intake and Obesity

Previous studies have extensively explored the possible relationship between sodium consumption and obesity. Earlier studies recount a likely association between sodium intake and obesity that shows that higher consumption of sodium is linked to an increased incidence of obesity (Grimes *et al.*, 2013a). The conclusion drawn from these findings is likely due to the increased consumption of high-energy foods as a result of consuming sodium. High consumption of salt is known to prompt thirst and increased appetite. Consequently, it seems to encourage the consumption of high sugar carbonated drinks with a substantial caloric content (He *et al.*, 2008; Grimes *et al.*, 2013b).

However, thus far, few studies seem to report a persistent link between sodium intake, as measured by 24-hour urinary sodium excretion, and obesity independent of caloric intake in adults. For instance, a longitudinal study on the Danish adult population reported that sodium intake, determined by 24-hour urinary excretion of sodium, had no significant relationship with changes is body weight and waist circumference. However, sodium intake seemed to be significantly related with body fat gain and loss in fat-free mass (Larsen *et al.*, 2013).

Additionally, a cross-sectional study conducted on young Japanese women noted a positive relationship between sodium intake, also measured form 24-hour urinary excretion of sodium, and both general and abdominal obesity (Murakami, 2015). Furthermore, another cross-sectional study on the United Kingdom population demonstrated that sodium intake, measured by 24-hours urinary excretion of sodium, was related to an increased risk of higher body fat mass and obesity (Ma *et al.*, 2015).

The positive relationships reported between sodium intake on obesity are further confirmed in animal models and in human studies. An animal study using rat models revealed that chronic sodium overload augmented the development of obesity. They further demonstrated that high sodium loading enhances the incorporation of glucose into lipids and increases the lipogenic capacity of white adipose tissue. This in turn increases plasma leptin production, encourages the hypertrophy of adipocytes and eventually leading to excess fat build-up (Fonseca-Alaniz *et al.*, 2007).

In addition, a study conducted on rabbits showed that salt loading modifies the influence of leptin on the SNS and the cardiovascular system (Mohammad *et al.*, 2010). Correspondingly, a cross-sectional investigation on healthy adolescents in the Unites States described a positive association between high sodium consumption and adiposity and plasma leptin concentration (Zhu *et al.*, 2014). Though this study used dietary recall as a measure of salt intake. Still, these findings seem to suggest that chronic sodium intake increases the production and resistance of leptin. The mechanism behind this development are likely through energy homeostasis dysregulation thus contributing to the engenderment of obesity (Nam *et al.*, 2017).

Among other dysregulations, shown to arise as a result of salt loading in favour of the development of obesity, are metabolic disorders such as insulin resistance and type 2 diabetes (Vedovato *et al.*, 2004). Based on 24-hour urinary sodium excretion, as a measure of sodium intake, high sodium intake is reported as a risk factor of metabolic syndrome (Ge *et al.*, 2015). In addition, studies on mice reported that high sodium intake encourages tissue inflammation (Kleinewietfeld *et al.*, 2013). While results from these studies are somewhat inconsistent, there have been similar findings made from numerous human studies.

Reports of sodium loading resulting in increased inflammatory response, related to target organ damage, have been made on patients with a history of hypertension and myocardial infarction (Costa *et al.*, 2012; Yilmaz *et al.*, 2012). In the previously mentioned study on adolescents from the United States, a positive association was determined between sodium intake and increase production of TNF- α, a key role player in autoimmune disorders and chronic inflammation (Zhu *et al.*, 2014). An interesting perspective to be discussed involves the changes of sodium handling

in the presence of obesity and obesity's contribution to the engenderment of CVD as a result of altered sodium handling.

1.7.4 Sodium handling in Obesity

According to the principle of renal-body fluid feedback that governs arterial pressure control, through the mechanisms of natriuresis and diuresis, higher blood pressure values are favoured in the instance of obesity (Guyton, 1990). This would lead to the development of aberrations in the mechanisms that would normally raise blood pressure, with the aim of increasing sodium and water excretion by way of natriuresis and diuresis. Considering that fluid excretion surpasses intake, the extracellular fluid volume would decrease, thus reducing venous return and consequently reducing cardiac output for blood pressure to return to normal. On the contrary, when blood pressure declines, the kidney will retain water to re-establish normal arterial pressure. Therefore, pressure natriuresis normally functions as a key contributor towards the stabilisation of body fluids and blood pressure (Kotsis *et al.*, 2010).

While during the initial phases of obesity, prior to significant depletion in nephrotic function due to glomerular injury, sodium retention occurs as a result of increased renal tubular reabsorption. Compensatory mechanisms may be initiated for instance, increasing renal vasodilation, increased glomerular filtration rate and increasing the amount of filtered water and electrolytes. Consequently, incomplete compensation may lead to extracellular-fluid expansion, which results in a hypertensive adjustment of pressure natriuresis (Hall *et al.*, 2000). In the resetting of the renal-fluid apparatus to a hypertensive level, hypertension is mirrored as a result of volume overload. An additional cause of pressure natriuresis shift, toward elevated blood pressure in obesity, is the probability of changes in intrarenal forces. The changes in intrarenal forces are commonly a result of histological modifications in the renal medulla that might compress the loops of Henle and the vasa recta (Hall, 1997).

As previously discussed, numerous studies have demonstrated frequently high levels of plasma RAAS component levels in relation to obesity (Massiéra *et al.*, 2001; Ruano *et al.*, 2005; Kidambi *et al.*, 2007). An earlier study reported an approximate twofold increase in plasma renin

activity following 5-weeks of a high fat diet in dogs (Hall *et al.,* 1993). Furthermore, the restriction of fat successfully lowered RAAS components, showing that the level of adiposity had significant influence on the regulation of the RAAS system. Normally, the RAAS functions as a blood pressure regulatory system that primarily thwarts extreme variations in arterial pressure due to sodium intake.

If the production of angiotensin II is stopped, in an individual on a high-salt diet, a decreased rate of blood pressure elevation is observed. This is marked by leftward shift in the renal function curve toward the initial blood pressure reading. Regardless of the marked sodium retention and consequential volume expansion that is observed in obesity, numerous mechanisms are accountable for the increased activation of the RAAS. Renal secretion of renin appears to be triggered by changes in the intrarenal physical forces, that are caused by fat accumulation in and around the renal medulla (Hall, 1997).

As a result of the present histological changes that cause the compression of the renal medulla, the filtrate flow rate is reduced at the loop of Henle which leads to protracted time of sodium reabsorption (Rocchini, 2002). By the time the filtrate reaches the distal tubular calls, decreased levels of sodium are detected by the macula densa, which leads to a spike in renin secretion via tubuloglomerular feedback.

Recently, findings have expounded upon the physiological mechanisms behind adipose tissue induced blood pressure elevation. They have established that adipose tissue-derived angiotensin can infiltrate vascular circulation. Adipose cells are considered repositories of all RAAS components. This is confirmed by the plethora of renin, angiotensin II angiotensinogen and angiotensin II receptors identified within adipose masses. The abundance of such molecules and receptors suggests a local tissue angiotensin system is established at the adipocyte level (Campbell, 1987). The derivatives of tissue RAAS and circulatory RAAS are constantly interacting with each other. The local production and cellular uptake of angiotensin I and II, by cells expressing angiotensin II receptors, is almost instant (Re, 1989).

The production of angiotensinogen acts as both the cause and effect of adipocyte hypertrophy, leading to blood pressure elevation through angiotensin II activity. This induces direct water and

sodium retention, vasoconstriction, and elevated production of aldosterone. Therefore, angiotensin II imposes salt-sensitive high blood pressure in obesity, due to its high production rates that are not suppressed by volume expansion (Hall *et al.*, 2019).

Previous studies on the black population of South African have determined the commonly underlying incidence of salt-sensitivity (Barlow *et al.*, 1982; Rayner *et al.*, 2001; Jones and Rayner, 2020). Seeing that obesity further engenders this state emphasises the importance of studies on electrolyte excretion, and blood pressure in obese individuals of this population. Studies have repeatedly demonstrated the hypotensive effect of potassium supplementation, whose intake is scarcely observed in overweight/ obese individuals (Elfassy *et al.*, 2018). Aside from its hypotensive effects, the consideration bears great significance due to the interplay of sodium with potassium in physiological regulation (Udensi and Tchounwou, 2017).

1.7.5 Hypotensive effect of Potassium

Previous studies have repeatedly reported on potassium's blood pressure lowering effect, with some detailing the sensitivity of African individuals towards potassium's hypotensive effect (Krishna, 1990). The mechanisms behind potassium's observed hypotensive effect are varied, and some are yet to be further elucidated. The probable mechanisms behind the antihypertensive effect of potassium are through the action of (1) natriuresis/diuresis, (2) altered response to vasoactive hormones, (3) increases in vasodilator hormones, (4) direct vascular effect and (5) increased baroreceptor sensitivity (Treasure and Ploth, 1983; Krishna, 1990; Linas, 1991).

The alterations in potassium intake yield prominent changes in sodium balance (Keith and Binger, 1935; Krishna *et al.*, 1987) . Sodium retention is a consistent characteristic of potassium depletion, that leads to an increase in blood pressure, by leading to an increase in the intracellular concentration of sodium, increase in extracellular fluid volume, shifting the pressure-natriuresis relationship and stimulating the production of circulating Na^+-K^+-ATPase inhibitor (Yamori *et al.*, 1981).

A study on the influence of potassium on blood pressure measured urinary sodium and potassium excretion rates in subjects on low and normal potassium diets (Krishna *et al.*, 1989). Subjects on a low potassium diet excreted significantly less sodium compared to those on a normal potassium diet. Interestingly, the supplementation of potassium had a hypotensive effect. Evidently, this relationship is largely reliant on the amount of sodium ingested. In individuals on a high potassium and low sodium diet, the hypotensive effect may not be as pronounced, due to the blood pressure lowering effects of sodium restriction. Potassium has also been shown to act as a diuretic and natriuretic, promoting increased urine and urinary sodium excretion respectively (Suzuki *et al.*, 1981; Treasure and Ploth, 1983). Thus, leading to the lowering of blood pressure.

Direct infusion of potassium into the renal artery, in rats and dogs, has resulted in rapid diuresis and natriuresis (Vander, 1970). The effect of potassium as a diuretic and natriuretic is thought to be mediated by the inhibition of proximal tubule reabsorption of sodium (Wright *et al.*, 1971). In chronic studies involving rats, the inclusion of potassium in the diet resulted in sustained diuresis and natriuresis (Suzuki *et al.*, 1981). Further evidence in humans, both hypertensive and normotensive, report a similar effect of potassium (Brunner *et al.*, 1970). It is possible that this mechanism is one by which blood pressure could be altered, especially in salt-dependant forms of hypertension.

Potassium has been also shown to have varied effects on the renin-angiotensin system. Acute or chronic administration of potassium can suppress the secretion rates of renin (Vander, 1970). Considering that potassium exhibits a natriuretic effect, the direct suppression of renin activity by a high potassium diet could be superseded by a negative sodium or water balance. Therefore, in some settings, a paradoxical increase in renin following high potassium intake may be observed. This has been demonstrated in human studies that plasma renin activity increases as potassium intake was increased (Fujita *et al.*, 1984; Tabuchi *et al.*, 1985).

A human study was conducted to investigate the interaction between potassium and renin in adrenalectomized patients on fixed gluco- and mineralocorticoid replacement therapy (Miller *et al.*, 1975). Subjects were studied under balanced conditions of fixed sodium intake, 100 to 150 mEq/day. When potassium intake was increased, sodium excretion and plasma renin activity markedly increased from 1.2 to 12.5 ng/ml/hr. These findings demonstrated that the increase in

plasma renin activity, observed with potassium intake, was as a result of potassium-induced natriuresis, as opposed to the direct effect of potassium.

Along the RAAS system, potassium intake has been shown to increase aldosterone production from the adrenal glomerulosa (Linas, 1991). Potassium acts by stimulating a crucial enzyme in the aldosterone pathway by upregulating the angiotensin II-induced production of aldosterone. Clinical studies have observed an increase in plasma or urinary aldosterone after supplementation with potassium, however, this observation is not uniform (Iimura *et al.*, 1981; Fujita and Ando, 1984; Fujita *et al.*, 1984; Krishna *et al.*, 1989). The influence of potassium supplementation on the metabolism of catecholamines has been inconsistent.

Potassium supplementation has not been carefully evaluated when it comes to its effect on vasodilatory hormones. One study reported increased plasma prostaglandin E_2 concentration after supplementation with potassium (Tabuchi *et al.*, 1985). The administration of potassium has produced variable effects on norepinephrine and angiotensin II pressor sensitivity, and the influence on baroreceptor sensitivity is small and erratic. Therefore, it is plausible to consider that the mechanism behind the modest decrease in blood pressure following potassium administration is facilitated by potassium induced natriuresis, diuresis and decreases in volume.

The high salt intake that is observed in individuals from developing countries within Sub-Saharan Africa is mainly due to the adoption of the western diet, which is known to be high in salt as compared to traditional African diets (Odermatt, 2011). In the state of overweight/ obesity the effects of such a diet, accompanied by the underlying prevalence of salt-sensitivity in this population, are enhanced. The long-term high consumption of salt, through certain diets, further exacerbates the effects of salt sensitivity and has been shown to be associated with the development of obesity, insulin resistance and metabolic syndrome via unknown mechanisms (Allison, 2018). The state of overweight/ obese then amplifies salt-sensitivity, creating perfect conditions for the elevation of blood pressure. In this vicious cycle high salt intake or salt-sensitivity likely poses extensive damage to vasculature thus diminishing arterial compliance and distensibility.

In view of these findings, and the high probability of the development of hypertension in this group, there is a shortage of research exploring the role of obesity in electrolyte handling that has significant effects on BP. Furthermore, there is a significant shortage in studies investigating the contributions of obesity on arterial distensibility while monitoring the excretion of electrolytes in the African population. Though, some studies have investigated African-Americans, they cannot be used as a sole sample of the African population (Hall *et al.*, 2012). The external forces vary significantly between these groups; such as, environmental, political, socioeconomic, technological and sociocultural conditions (Barros and Offenbacher, 2009). These factors are highlighted innumerably in literature as role players in the development of overweight/ obesity and CVD. Thus, it is imperative to perform more investigations on the African population, where urbanisation is at its rise and socio-economic statuses are problematic. The purpose of the present study is to explore the effects of overweight/ obesity on the excretion of urinary electrolytes in the African population, and whether these effects, if any, contribute to arterial distensibility and if the changes in arterial distensibility are translated in ambulatory BP measurements. It is suspected that due to the population's aversion to salt-sensitivity, overweight/ obesity will enhance this, and lead to increased arterial stiffness through the increase of salt-consumption, likely as a result of the overweight/ obese diet, and eventually lead to salt-retention. Therefore, we may observe an increase in BP as a result of the possible increase in arterial stiffness. The objectives of the study can therefore be summarised as follows:

1.8 Objectives

The objectives of the present study were:

1. To investigate the effect of being overweight/ obese on office and ambulatory blood pressure.
2. To determine the effect of the overweight/ obese state on urinary electrolyte excretion rate
3. To investigate the effects of overweight/ obesity on the relationship between the urinary electrolyte excretion rate and ambulatory BP, as changes in PWV can manifest in BP readings.
4. To determine the effects of the overweight/ obese state on pulse wave velocity.
5. To determine the effects of overweight/ obesity on the relationship between pulse wave velocity and ambulatory BP, since BP is influenced by arterial compliance
6. To determine the effect of overweight/ obesity on the relationship between pulse wave velocity and urinary electrolyte excretion rate

CHAPTER 2: METHODS AND MATERIALS

2.1 Participants

One hundred and fifty South African individuals of black African ancestry with a minimum age of 18 years, and no upper age limit, were randomly recruited in and around Johannesburg. The participants commonly belonged to the predominant ethnic groups (tribes), namely; Nguni, Venda, Tsonga and Sotho. This study was cross-sectional, with no controls, and no pharmacological, dietary or lifestyle interventions. The sample size was determined by inference from a previous study of a similar design (Elliott, 1991). All study protocols were approved by the Human Research Ethics Committee (HREC) – Medical, of the University of the Witwatersrand (clearance certificate no: M180521). The data collection for this study was conducted in the Human Nutrition Research Laboratory (HNRL) at the University of Witwatersrand, School of Physiology, forming part of the ongoing South African Hypertension and Diet Study (SAHDS).

2.1.1 Inclusion criteria

Participants were to meet the following criteria for study enrolment:

1. Capable of comprehending and willing to provide valid informed consent prior to any protocol procedures being performed
2. Male or female participants 18 years of age or above at time of consent
3. Be of African descent

2.1.2 Exclusion criteria

Participants were excluded if any of the following conditions were met:

1. Suffer from cardiovascular, pulmonary or renal problems, chronic physical or psychological disorders, diabetes or any recurring sicknesses.
2. Be on antihypertensive or blood pressure raising medication, diuretics or any stimulants.

Of the 150 participants recruited, only 119 participants had complete ambulatory blood pressure and pulse wave velocity. However, only 89 participants presented with complete urine collection.

2.2 Measurements and procedures

2.2.1 Demographic data and anthropometric measurements

The study procedures and aims were thoroughly explained, and participants were asked to give consent for their participation in the study. A standardised questionnaire was used to collect demographic data, medical history, and the use of any blood pressure altering medication (APPENDIX B). The contents of the study, and questionnaire, were thoroughly explained to the participants in the language of their understanding. Research assistants who are fluent in the respective languages were available to assist in clarifying details of the questionnaire, and to help participants in answering questions where language was a barrier. However, most of the subjects were sufficiently proficient in English. The questionnaire further gauged the participants level of education, prior or current occupation, prior or current lifestyle habits (smoking, alcohol and caffeine consumption), and the level of physical activity, through a series of "Yes" or "No" questions and 0-10 rating scores. For females, the use of contraceptives, menstrual cycle phase, and history of pregnancy was also assessed.

2.2.2 Body weight, height and waist-to-hip ratio

All anthropometric measurements were made while the participants were standing erect with their feet together and back straight. The height and weight of the participants was measured to the nearest 0.1 m and 0.1 kg respectively. Body Mass Index (BMI) was later calculated using the standard formula $[BMI = weight\ (kg)/height\ (m)^2]$to obtain units of kg/m^2. To obtain the waist-to-hip ratio, a known measure of obesity, waist and hip circumferences were measured. Waist circumference was measured at the waistline after participants had removed clothing. The iliac crest was palpated, along with the last palpable rib, and the measuring tape was wrapped all the way around the waist, above the level of the iliac crest in line with the navel, while ensuring that the tape measure was parallel to the ground and not coiled. The participants were asked to take two normal breaths. Upon exhaling on the second breath, the tape measure was tightened so it fit comfortably around the waist, without depressing the skin, then the reading was noted (Donato, 1998). For hip circumference, the widest part of the participant's buttocks was

determined, and the tape measure was wrapped all the way around this location and thus hip circumference was measured.

2.3 Conventional BP

Standard blood pressure measurements were taken using an automated OMRON HBP-1300 Professional Blood Pressure Monitor (OMRON Corp., Shiokoji Horikawa, Kyoto Japan). The OMRON Blood Pressure Monitor is calibrated to provide accurate readings like those obtained from traditional mercury sphygmomanometer. Study investigators were trained to measure blood pressure accurately using the OMRON, during the pilot phase of the study. During this training, to ensure accuracy, a qualified nurse was present to ensure accurate cuff placement and participant posture. The participants remained in an upright seated position for 10 minutes prior to the measurement being taken. The blood pressure cuff was placed on the non-dominant arm of the participant. Blood pressure measurements were repeated 5 times at 1-minute intervals to allow participants to rest in between. The 5 measurements were averaged to obtain a mean systolic and diastolic reading as well as the mean arterial pressure and heart rate.

2.3.1 Ambulatory Blood Pressure

Ambulatory blood pressure measurements were obtained using the SpaceLabs Medical 90217 Ambulatory Blood Pressure monitors (OSI Systems Inc., Hawthorne, California, USA). At the end of each clinic visit, the cuff was fitted on the participants' non-dominant arm, the way conventional blood pressure readings are taken (Figure 2.1). The monitors were programmed to measure daytime blood pressure (06:00 to 22:00) at 15-minute intervals and night-time blood pressure (22:00-06:00) at 60-minute intervals to limit sleep interruption. For calibration monitors were attached to a mercury sphygmomanometer, through a Y-connector to ensure measurements agreed with those from standard mercury sphygmomanometer. The cuff size was determined by the measured arm circumference, performed by wrapping the measuring tape around the circumference of the left arm at the mid-point of the tip of the shoulder and the tip of the elbow.

A paediatric cuff was given to participants with arm circumference ≤24-cm, a standard adult cuff for 24- to 32-cm, and a large adult cuff for >32-cm.

Normal blood pressure values for the clinical readings were set at <130 mm Hg systolic (but not <90mm Hg) and <80 mm Hg diastolic (but not <60). Normal values for ambulatory blood pressure were set, in accordance with recommendations from the American Heart Association Council on High Blood Pressure Research, at 130/80 mm Hg for 24-hour ambulatory BP (Pickering *et al.*, 2005). Concomitantly, normal daytime and night-time BP were defined <135/85 mm Hg and <120/70 mm Hg, respectively. A diary card was given to participants for the duration of the blood pressure monitoring, to denote 'asleep' and 'awake' time. All noted diary sleep and wake times were used to average sleep and wake BP readings. Data from participants who enrolled in the study and did not meet the quality control criteria for inclusion, minimum number of readings (5-10 reading during both intervals) and overall measurement duration (>20 hours), were excluded from analysis.

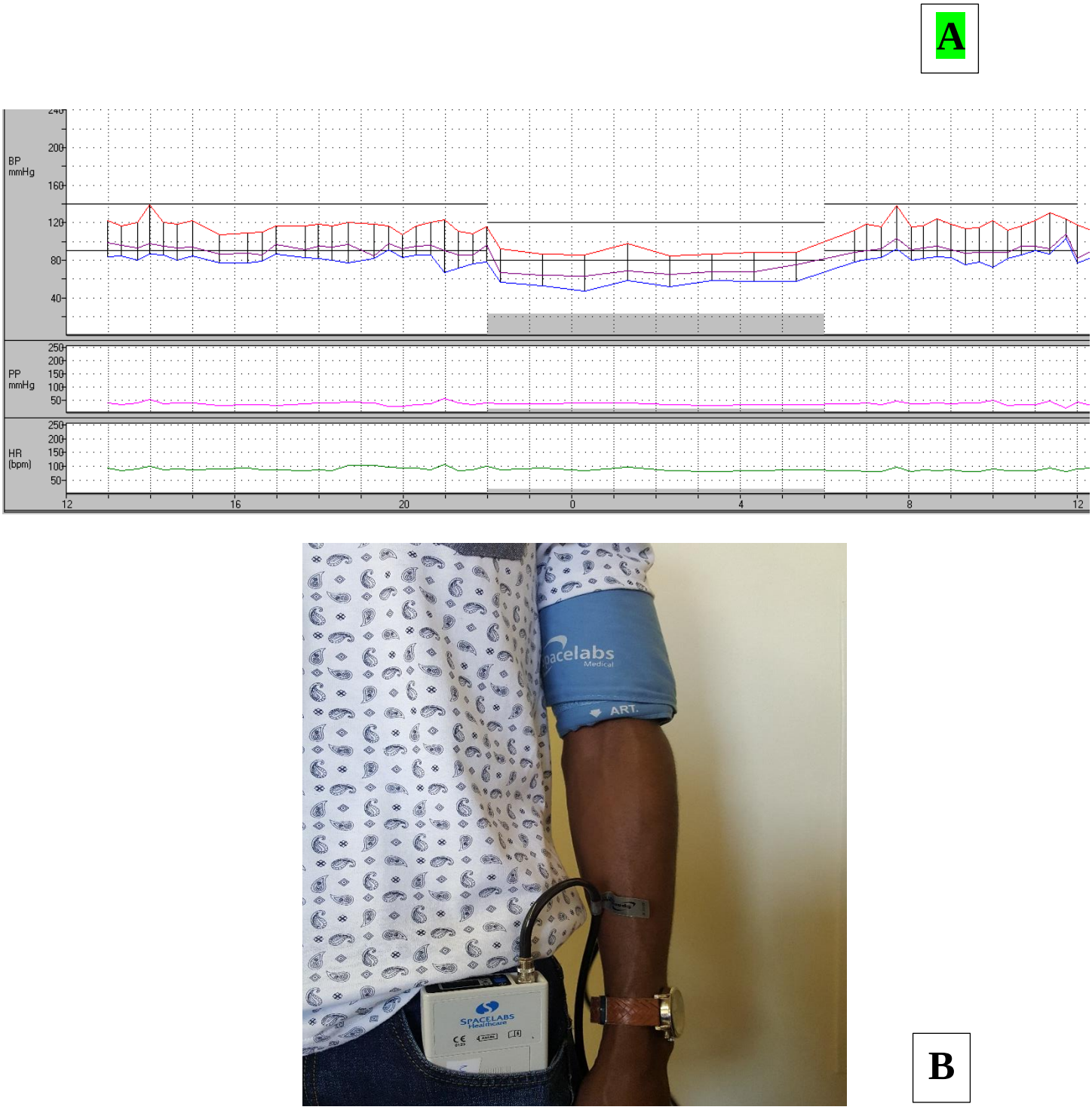


Figure 2.1 (A) An illustration showing a normal 24-hour ambulatory blood pressure recording. (B) A demonstration of how the ambulatory blood pressure cuff and monitor were fitted on the participants.

2.4 Urinary electrolyte excretion

To accompany the ambulatory blood pressure monitor, participants were given two urine bottles to collect their urine. One bottle was used for the collection of a daytime urine sample, and the other for the collection of a night-time urine sample. The urine samples were retrieved from the participants 24-hours after the clinical visit simultaneously with the ambulatory BP monitor. Samples were thereafter stored at -80°C for bulk analysis by the Clinical Laboratory Services (CLS) in Braamfontein, Johannesburg. Sodium and potassium concentrations were measured, and daytime and night-time excretion rates were calculated from the product of urine volume and electrolyte concentration. A 24-hour urine volume of ≥500 ml/day was considered an acceptable volume for analysis, as determined by studies (Maseko *et al.*, 2006, 2018), and the accepted creatinine (mmol) concentration was within between 3.5 and 35 for males and 3.5 and 30 for females.

2.5 Pulse wave assessment

Pulse wave velocity (PWV) for each participant was measured using applanation tonometry (Figure 2.2). The pulse wave procedure was conducted to measure arterial compliance or elasticity. Applanation tonometry records arterial pressure waveforms that are used to calculate Augmentation Indices (AIx) and PWV. The analysis was interfaced with SphygmoCor software (AtCor Medical Pty. Ltd., West Ryde, New South Wales, Australia); version 9.0 ran by a computer operating on Windows 7. Aortic PWV was computed by sequential recordings of the arterial pressure waveforms, at the carotid and femoral arteries. The distance between sampling sites and the suprasternal notch was measured. Distance A was named after the distance between the carotid to the suprasternal notch, and distance B was from the suprasternal notch to the femoral artery. Thus, pulse wave velocity was calculated as the difference between distance B and A. The pulse transmit time was determined from the average of 10 consecutive beats (the mean time difference between sites A and B). Aortic pulse wave velocity was determined as the ratio of the distance in metres to the transit time in seconds.

Pulse wave velocity measurements were taken after the participants had rested for 15 minutes in supine position. The carotid, femoral and radial pulses were palpated and marked for the placement of the probe. A high-fidelity SPC-301 micromanometer-tipped probe (Millar Instrument, Inc., Houston, Texas), the size of a pen was used to measure central pressures. The micromanometer-tipped probe was placed at the marked site where the carotid, femoral and pulses were palpated. Thereafter, arterial waveforms were captured on the software which subsequently calculated the average PWV. The pulse wave velocity was measure between the carotid and femoral arteries providing a carotid-femoral PWV reading. I also measured the PWV between the carotid and radial arteries to obtain the carotid-radial PWV. However, only the carotid-femoral PWV readings were used as they are considered the standard measure of arterial stiffness compared to carotid-radial measures.

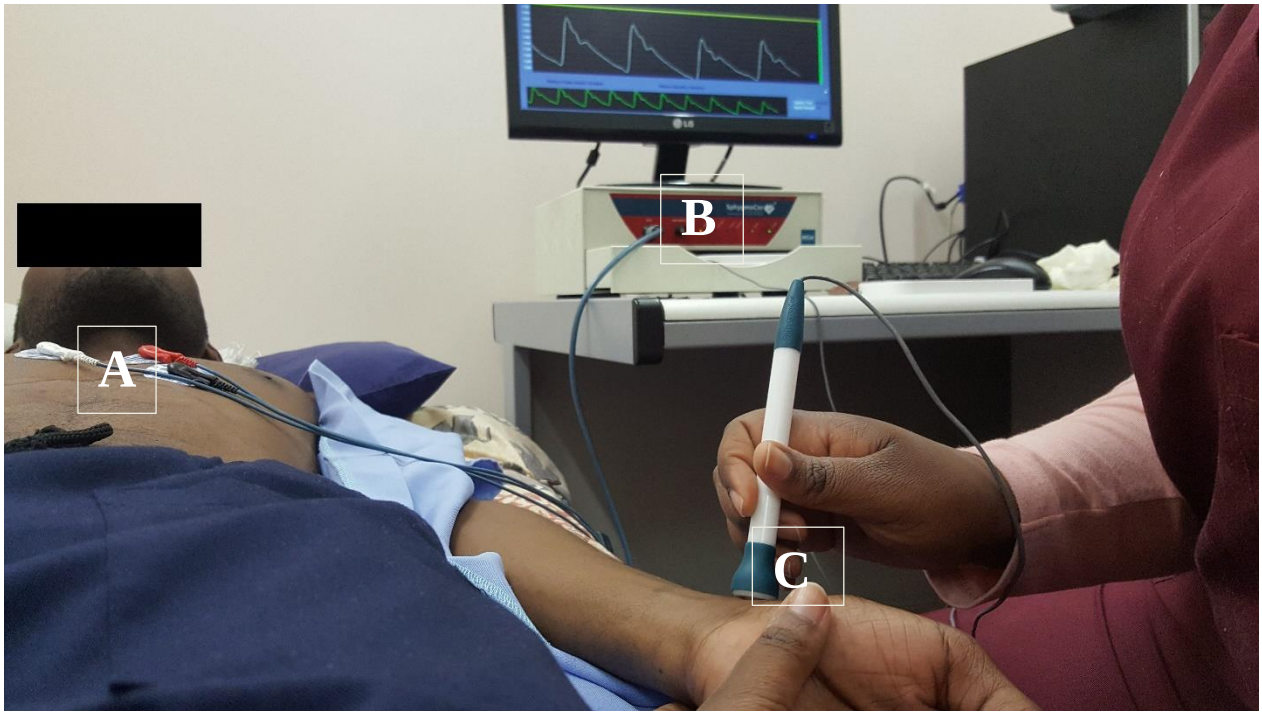


Figure 2.2 An illustration of the assessment of pulse wave velocity. (A) electrocardiograph electrodes, (B) SphygmoCor device with interface, (C) applanation tonometer.

2.6 Statistical analysis

All statistical analyses were performed using the standard STATA software package version 15.1 (StataCorp LLC). Data and descriptive statistics were expressed as mean ± SD, and $P < 0.05$ was considered statistically significant. The central limit theorem was applied, as random sampling was performed thus normal distribution was approximated. An unpaired t-test was used to determine the differences between normal weight and overweight/ obese participants. To determine an independent relationship between 24-hour urinary electrolytes excretion and 24-hour BP a multivariate regression analysis was conducted. Multivariate regression analysis was also performed to investigate independent relationships between PWV and 24-hour urinary electrolytes excretion, also when investigating the relationship between PWV and 24-hour BP. The confounding variables that were included were age, sex, and BMI as continuous variable. Categorical confounders included alcohol consumption and smoking status.

CHAPTER 3: RESULTS

3.1 Clinical and demographic characteristics

Table 3.1 depicts the general clinical and demographic information of the study participants. The overweight and obese groups were grouped together as there was no significant difference when the groups were compared to each other. However, when the groups were combined the effects of increasing BMI were apparent. An unpaired t-test was used to compare means. The overweight/ obese group accounted for 51.26% of the recruited participants and presented with a mean BMI of 31.56±5.11kg/m^2. Participants in the overweight/ obese group presented with higher body weight (81.63±13.99 vs 59.74±8.31 kg, P<0.0001), and waist circumference (92.02±13.17 vs 71.42±6.11 cm, P<0.0001). However, the WHR between the groups were similar (0.83±0.13vs 0.79±0.15, P=0.1276).

In the total population, most of the participants were female (59.70%), as well as in both normal weight (53.45%) and overweight/ obese groups (65.57%). Overweight/ obese participants were significantly older than their normal weight counterparts (36.38±16.94 vs 22.62±6.05 years, P<0.0001). Participants characterised as normal weight presented with a higher percentage of individuals who consumed alcohol regularly (32.76%), and smokers (18.97%).

Table 3.1 General characteristics of participants stratified according to body mass index

	Total sample	Normal weight[a]	Overweight[b]/ Obese[c]	P-Value
No. of participants	119	58	61	
Age (y)	29.67±14.53	22.62±6.05	36.38±16.94	<0.0001***
Males (%)	40.34	46.55	34.43	
Females (%)	59.66	53.45	65.57	
Height (cm)	162.79±8.90	164.76±8.60	160.92±8.85	0.0180*
Weight (kg)	70.87±15.91	59.74±8.31	81.63±13.99	<0.0001***
Waist circumference (cm)	81.63±14.53	71.42±6.11	92.02±13.17	<0.0001***
WHR	0.81±0.14	0.79±0.15	0.83±0.13	0.1276
BMI (kg/m^2)	26.84±6.21	21.96±2.08	31.56±5.11	<0.0001***
Alcohol consumption (%)	22.70	32.76	13.11	
Smokers (%)	14.29	18.97	9.84	
Hypertensive (%)	9.24	10.34	8.20	
Diabetics (%)	5.04	3.44	6.56	

Data presented as mean ± SD. Abbreviations: WHR, waist-to-hip ratio; BMI, body mass index. Significance level p<0.05; * Depicts statistically significant relationship. *P<0.05; ** P<0.01; ***P<0.0001.

[a] Normal weight was defined as BMI < 25 kg/m^2, [b]Overweight was defined as BMI ≥ 25 < 30 kg/m^2, obese was defined as BMI ≥ 30 kg/m^2

3.2 Hemodynamic characteristics

Conventional BP and ambulatory BP are shown in Table 3.2. The heart rate, when compared between the normal weight and overweight/ obese participants was not different (64.93±11.70 vs. 63.95±11.03 bpm, *P* =0.6395). However, overweight/ obese participants had a significantly higher office systolic BP reading (122.66±17.27 mm Hg) compared to (115.19±10.65 mm Hg, *P*<0.001) the normal weight group. Yet, office diastolic BP showed no dissimilarity between the normal weight (74.89±9.10 mm Hg) and the overweight/ obese groups (78.54±13.45 mm Hg).

Overweight/ obese participants presented with a higher pulse pressure (44.12±11.51 mm Hg vs. 40.29±8.14 mm Hg, *P* =0.0397). However, the daytime BP readings for overweight/ obese participants did not differ significantly from the normal weight individuals (systolic: 117.69±11.78 vs. 114.42±10.22 mm Hg *P* =0.1092; diastolic: 76.20±9.82 vs. 73.91±7.61 mm Hg, *P* =0.1592, overweight/ obese and normal weight respectively).

There was no difference in night-time BP between normal weight and overweight/ obese participants, (systolic: 104.59±10.27 vs. 108.09±14.43 mm Hg *P* =0.1318; diastolic: 63.71±7.71 vs 65.31±9.98 mm Hg, *P* =0.3315, respectively). Similarly, 24-hour BP indices were also not different between normal weight and overweight/ obese participants, (systolic: 111.04±9.94 vs. 114.80±11.79 mm Hg *P* =0.0631; diastolic: 70.53±7.31 vs. 72.69±9.71 mm Hg, *P* =0.1747, respectively).

Table 3.2 Hemodynamic parameters of study participants stratified by body mass index

Variables	Total sample	Normal weight[a]	Overweight[b]/ Obese[c]	P-Value
Clinic Heart rate (bpm)	64.44±11.34	63.95±11.03	64.93±11.70	0.6395
Clinic SBP (mm Hg)	118.99± 14.82	115.19±10.65	122.66±17.27	0.0056**
Clinic DBP (mm Hg)	76.98±11.91	74.89±9.10	78.54±13.45	0.0888
Clinic Pulse Pressure (mm Hg)	42.24± 10.14	40.29±8.14	44.12±11.51	0.0397*
24-h SBP (mm Hg)	112.95±11.38	111.04±9.94	114.80±11.79	0.0631
24-h DBP (mm Hg)	71.63±8.65	70.53±7.31	72.69±9.71	0.1747
Daytime SBP (mm Hg)	116.09±11.12	114.42±10.22	117.69±11.78	0.1092
Daytime DBP (mm Hg)	75.08±8.84	73.91±7.61	76.20±9.82	0.1592
Night-time SBP (mm Hg)	106.32±12.57	104.59±10.27	108.09±14.43	0.1318
Night-time DBP (mm Hg)	64.50±8.90	63.71±7.71	65.31±9.98	0.3315

Data presented as mean±SD. Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; bpm, beats per minute. Significance level P <0.05. * Depicts statistically significant relationship. *P<0.05; ** P<0.01; ***P<0.0001

[a] Normal weight was defined as BMI < 25 kg/m^2, [b]Overweight was defined as BMI ≥ 25 < 30 kg/m^2, obese was defined as BMI ≥ 30 kg/m^2

3.3 Urinary electrolyte excretion, in overweight/ obese and normal weight participants

The results obtained from urinary electrolyte excretion are shown in Table 3.3. Due to the requirement of 24-hour urine volume ≥500 ml/day not being met, only 89 samples were included for statistical analysis. There were no differences observed in any of the electrolytes measured between overweight/ obese and normal weight participants. Sodium, potassium and creatinine excretion rates were not statistically different between both groups during daytime, night-time or the overall 24-hour period. Additionally, sodium: potassium (Na^+: K^+) ratios between both groups, overweight/ obese and normal weight, were also not significantly different during all periods of measurement.

Table 3.3 Daytime, Night-time and 24-hour electrolyte excretion rates and relative Night-time: Daytime ratios divided by body mass index status

Variables	Total sample (n=89)	Normal weight[a] (n=43)	Overweight[b]/ Obese[c] (n=46)	P-Value
24-hour				
Na^+ (mmol/day)	96.45±52.50	97.56±52.50	93.78±53.39	0.7373
K^+ (mmol/day)	30.66±19.34	31.95±20.82	27.53±15.08	0.2523
Na^+: K^+	3.67±1.94	3.67±1.95	3.66±1.96	0.9808
Creatinine (mmol/day)	9.13±10.90	9.96±14.40	8.39±6.43	0.5037
Daytime				
Na^+ (mmol/day)	107.22±58.08	108.32±58.17	104.48±58.98	0.7581
K^+ (mmol/day)	37.45±23.29	39.05±24.93	33.64±18.69	0.2479
Na^+: K^+	3.45±2.01	3.36±1.78	3.66±2.51	0.5198
Creatinine (mmol/day)	9.75±7.81	9.75±7.81	7.66±4.60	0.1247
Night-time				
Na^+ (mmol/day)	96.78±55.07	97.66±57.03	94.52±50.76	0.7842
K^+(mmol/day)	29.12±19.73	30.32±20.92	26.07±16.26	0.2858
Na^+: K^+	4.05±2.39	3.98±2.26	4.21±2.73	0.6673
Creatinine (mmol/day)	9.87±7.40	9.87±7.40	7.69±5.09	0.1071

Data presented as mean±SD. Abbreviations: Na^+, sodium; K^+, potassium; Na^+: K^+, sodium potassium ratio. Significance level $P<0.05$. *Depicts statistically significant relationship. *$P<0.05$; ** $P<0.01$; ***$P<0.0001$

[a] Normal weight was defined as BMI < 25 kg/m^2, [b]Overweight was defined as BMI ≥ 25 < 30 kg/m^2, obese was defined as BMI ≥ 30 kg/m^2

3.4 Relationship between 24-hour BP and daytime potassium

Ambulatory blood pressure measurements were used to investigate if electrolyte excretion contributed to BP. All associations tested between BP indices and urinary electrolytes were adjusted for by including age, gender, smoking status, and alcohol intake to the multiple linear regression analysis. No relationship was observed between 24-hour BP (systolic and diastolic) and 24-hour sodium, potassium and sodium-to-potassium ratio in both normal weight and overweight/ obese participants (Table 3.4). However, 24-hour systolic BP was directly associated with daytime potassium excretion in the normal weight group (R^2= 0.239, P= 0.019). While no association was observed between 24-hour systolic BP and daytime potassium excretion in the overweight/ obese group (R^2= 0.158, P= 0.124).

3.5 Relationship between 24-hour BP and the night-time sodium-to-potassium ratio

The sodium-to-potassium ratio was not associated with 24-hour BP in both the normal weight and overweight/ obese groups during daytime (Table 3.4). Night-time sodium and potassium excretion were not independently associated with 24-hour BP in both normal weight and overweight/ obese participants. Yet, the night-time sodium-to-potassium ratio was directly associated with 24-hour systolic BP in the overweight/ obese group (R^2= 0.202, P= 0.034). This was not the case with the normal weight group as no association was observed between 24-hour systolic BP and the sodium-to-potassium ratio (R^2= 0.145, P= 0.403).

Table 3.4 Relationships between Urinary electrolyte excretion and 24-hour blood pressure in Normal weight and Overweight/ Obese participants

	Normal weight[a]				Overweight[b]/ Obese[c]			
	Systolic		Diastolic		Systolic		Diastolic	
	β (95%CI)	P	β (95%CI)	P	β (95%CI)	P	β (95%CI)	P
24-hour								
Na^+	0.02 (-0.04 to 0.09)	0.420	0.003 (-0.04 to 0.04)	0.874	-0.02 (-0.09 to 0.06)	0.644	0.007 (-0.05 to 0.07)	0.814
K^+	0.10 (-0.09 to 0.30)	0.288	0.02 (-0.11 to 0.15)	0.765	-0.06 (-0.24 to 0.12)	0.507	-0.06 (-0.20 to 0.08)	0.405
Na^+:K^+	-0.83 (-2.32 to 0.66)	0.265	-0.63 (-1.69 to 0.43)	0.238	1.30 (-0.65 to 3.25)	0.187	-0.61 (-1.60 to 0.37)	0.219
Daytime								
Na^+	0.03 (-0.02 to 0.07)	0.304	-0.02 (-0.05 to 0.01)	0.308	-0.04 (-0.10 to 0.03)	0.252	-0.02 (-0.07 to 0.03)	0.461
K^+	0.16 (0.03 to 0.29)	0.019*	0.05 (-0.05 to 0.14)	0.308	-0.13 (-0.29 to 0.04)	0.124	-0.09 (-0.22 to 0.04)	0.177
Na^+:K^+	-1.30 (-3.08 to 0.46)	0.142	-0.98 (-2.08 to 0.13)	0.082	0.63 (-1.08 to 2.33)	0.461	0.28 (-1.05 to 1.61)	0.674
Night-time								
Na^+	0.04 (-0.02 to 0.09)	0.196	0.02 (-0.01 to 0.05)	0.237	-0.004 (-0.08 to 0.07)	0.912	0.01 (-0.05 to 0.07)	0.785
K^+	0.04 (-0.12 to 0.20)	0.619	0.003 (-0.10 to 0.10)	0.956	-0.11 (-0.30 to 0.08)	0.263	-0.04 (-0.20 to 0.11)	0.580
Na^+:K^+	0.53 (-0.74 to 1.81)	0.403	0.38 (-0.39 to 1.15)	0.325	1.70 (0.13 to 3.26)	0.034*	0.63 (-0.66 to 1.93)	0.329

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; Na^+, sodium; K^+, potassium; Na^+:K^+, sodium-to-potassium ratio; 95%CI, 95% confidence intervals, Age, gender, smoking status, and alcohol intake were adjusted for in the multiple linear regression analysis. Significance level p<0.05.*Depicts statistically significant relationship. *P<0.05; ** P<0.01; ***P<0.0001. [a] Normal weight was defined as BMI < 25 kg/m^2, [b]Overweight was defined as BMI ≥ 25 < 30 kg/m^2, obese was defined as BMI ≥ 30 kg/m^2

3.6 Relationship between daytime systolic BP and the daytime potassium in normal weight participants

Multiple regression analysis showed no relationship between sodium, potassium, sodium-to-potassium ratio and daytime systolic or diastolic BP in the overweight/ obese group during daytime, night-time and 24-hour period. Although, in the normal weight group daytime systolic BP was directly associated with the daytime potassium excretion (R^2= 0.217, P= 0.024) (Table 3.5). However, there was no relationship between both systolic BP and diastolic BP and sodium or the sodium-to-potassium ratio during daytime in the normal weight group. Furthermore, night-time electrolyte excretion or across the complete 24-hours were not associated with either systolic or diastolic daytime BP.

Table 3.5 Relationships between Urinary electrolyte excretion and Daytime blood pressure in Normal weight and Overweight/ Obese participant

	Normal weight[a]				Overweight[b]/ Obese[c]			
	SBP		DBP		SBP		DBP	
	β (95%CI)	P	β (95%CI)	P	β (95%CI)	P	β (95%CI)	P
24-hour								
Na^+	0.03 (-0.04 to 0.09)	0.411	0.002 (-0.04 to 0.05)	0.943	-0.01 (-0.08 to 0.07)	0.881	0.007 (-0.05 to 0.07)	0.815
K^+	0.11 (-0.09 to 0.31)	0.264	0.03 (-0.11 to 0.17)	0.630	-0.03 (-0.20 to 0.14)	0.747	-0.05 (-0.20 to 0.10)	0.477
Na^+:K^+	-0.84 (-2.39 to 0.71)	0.279	-0.63 (-1.69 to 0.43)	0.238	1.00 (-0.89 to 2.89)	0.292	0.05 (-1.61 to 1.71)	0.953
Daytime								
Na^+	0.03 (-0.03 to 0.08)	0.328	-0.01 (-0.05 to 0.02)	0.395	-0.02 (-0.09 to 0.04)	0.461	-0.02 (-0.07 to 0.03)	0.456
K^+	0.17 (0.02 to 0.31)	0.024*****	0.05 (-0.05 to 0.16)	0.314	-0.11 (-0.27 to 0.05)	0.180	-0.09 (-0.23 to 0.04)	0.160
Na^+:K^+	-1.21 (-3.12 to 0.69)	0.205	-1.01 (-2.28 to 0.26)	0.116	0.66 (-0.97 to 2.29)	0.418	0.27 (-1.11 to 1.65)	0.693
Night-time								
Na^+	0.05 (-0.01 to 0.10)	0.104	0.03 (-0.004 to 0.07)	0.082	0.006 (-0.07 to 0.08)	0.871	-0.01 (-0.06 to 0.07)	0.863
K^+	0.07 (-0.10 to 0.24)	0.416	0.03 (-0.08 to 0.14)	0.552	-0.07 (-0.26 to 0.12)	0.443	-0.04 (-0.20 to 0.12)	0.603
Na^+:K^+	0.48 (-0.87 to 1.82)	0.477	0.35 (-0.50 to 1.23)	0.400	1.51 (-0.01 to 3.03)	0.052	0.40 (-0.95 to 1.76)	0.551

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; Na^+, sodium; K^+, potassium; Na^+:K^+, sodium-to-potassium ratio; 95%CI, 95% confidence intervals, Age, gender, smoking status, and alcohol intake were adjusted for in the multiple linear regression analysis. Significance level $P<0.05$. *Depicts statistically significant relationship. *$P<0.05$; **$P<0.01$; ***$P<0.0001$. [a] Normal weight was defined as BMI < 25 kg/m^2, [b]Overweight was defined as BMI ≥ 25 < 30 kg/m^2, obese was defined as BMI ≥ 30 kg/m^2

3.7 Relationship between night-time BP and the 24-hour sodium-to-potassium ratio

The 24-hour urine concentration of sodium, potassium and the sodium-to-potassium ratio in the normal weight group had no relationship with night-time BP (Table 3.6). Similarly, in the overweight/ obese group, 24-hour urinary concentration of sodium and potassium had no independent relationship with night-time BP. However, the 24-hour sodium-to-potassium ratio was directly associated with night-time systolic BP (R^2= 0.246, P= 0.021). Night-time diastolic blood pressure was not associated with the 24-hour sodium-to-potassium ratio in the overweight/ obese group R^2= 0.232, P= 0.073).

3.8 Relationship between night-time BP and the night-time sodium-to-potassium ratio

Daytime urinary electrolyte excretion showed no relationship with night-time systolic or diastolic BP in both normal weight and overweight/ obese groups (Table 3.6). However, the night-time sodium-to-potassium ratio was directly associated with systolic (R^2= 0.284, P= 0.006) and diastolic BP (R^2= 0.253, P= 0.040) in the overweight/ obese group. The individual electrolytes, namely sodium and potassium presented with no association with night-time BP in both groups, during daytime, night-time and the overall 24-hour period.

Table 3.6 Relationships between Urinary electrolyte excretion and Night-time blood pressure in Normal weight and Overweight/ Obese participants

	Normal weight[a]				Overweight[b]/ Obese[c]			
	Systolic		Diastolic		Systolic		Diastolic	
	β (95%CI)	P	β (95%CI)	P	β (95%CI)	P	β (95%CI)	P
24-hour								
Na^+	0.02 (-0.04 to 0.09)	0.491	-0.003 (-0.05 to 0.04)	0.899	-0.03 (-0.12 to 0.06)	0.557	0.003 (-0.06 to 0.06)	0.926
K^+	0.07 (-0.14 to 0.29)	0.493	0.009 (-0.13 to 0.15)	0.902	-0.14 (-0.35 to 0.07)	0.176	-0.10 (-0.23 to 0.04)	0.163
Na^+:K^+	-0.73 (-2.37 to 0.91)	0.375	-0.50 (-1.59 to 0.57)	0.347	2.75 (0.44 to 5.06)	0.021*****	1.42 (-0.14 to 2.99)	0.073
Daytime								
Na^+	0.03 (-0.02 to 0.09)	0.206	-0.01 (-0.05 to 0.02)	0.517	-0.05 (-0.13 to 0.03)	0.233	-0.02 (-0.07 to 0.03)	0.426
K^+	0.14 (-0.014 to 0.30)	0.073	0.03 (-0.08 to 0.13)	0.620	-0.14 (-0.34 to 0.06)	0.152	-0.09 (-0.23 to 0.04)	0.270
Na^+:K^+	-1.50 (-3.53 to 0.52)	0.140	-0.97 (-2.26 to 0.32)	0.137	0.86 (-1.21 to 2.93)	0.404	0.22 (-1.10 to 1.53)	0.737
Night-time								
Na^+	0.015 (-0.05 to 0.08)	0.638	0.008 (-0.03 to 0.05)	0.698	-0.02 (-0.11 to 0.07)	0.664	-0.003 (-0.06 to 0.06)	0.930
K^+	0.004 (-0.18 to 0.19)	0.964	-0.01 (-0.12 to 0.11)	0.874	-0.07 (-0.42 to 0.03)	0.086	-0.09 (-0.24 to 0.06)	0.229
Na^+:K^+	0.48 (-1.21 to 1.66)	0.748	0.14 (-0.77 to 1.04)	0.762	2.56 (0.78 to 4.34)	0.006******	1.29 (0.06 to 2.51)	0.040*

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; Na^+, sodium; K^+, potassium; Na^+:K^+, sodium-to-potassium ratio; 95%CI, 95% confidence intervals, Age, gender, smoking status, and alcohol intake were adjusted for in the multiple linear regression analysis. Significance level $P<0.05$. *Depicts statistically significant relationship. *$P<0.05$; **$P<0.01$; ***$P<0.0001$. [a] Normal weight was defined as BMI < 25 kg/m^2, [b]Overweight was defined as BMI ≥ 25 < 30 kg/m^2, obese was defined as BMI ≥ 30 kg/m^2

3.9 Relationship between carotid-femoral pulse-wave velocity and BMI

A linear regression analysis was conducted to determine the relationship between carotid-femoral pulse-wave velocity (cfPWV) and BMI. The results indicated a direct relationship between cfPWV and BMI, $P<0.0001$ (Figure 3.3A). Waist circumference, a common measure of abdominal obesity, had direct linear relationship with cfPWV, when a linear regression analysis was conducted, $P<0.0001$ (Figure 3.3B).

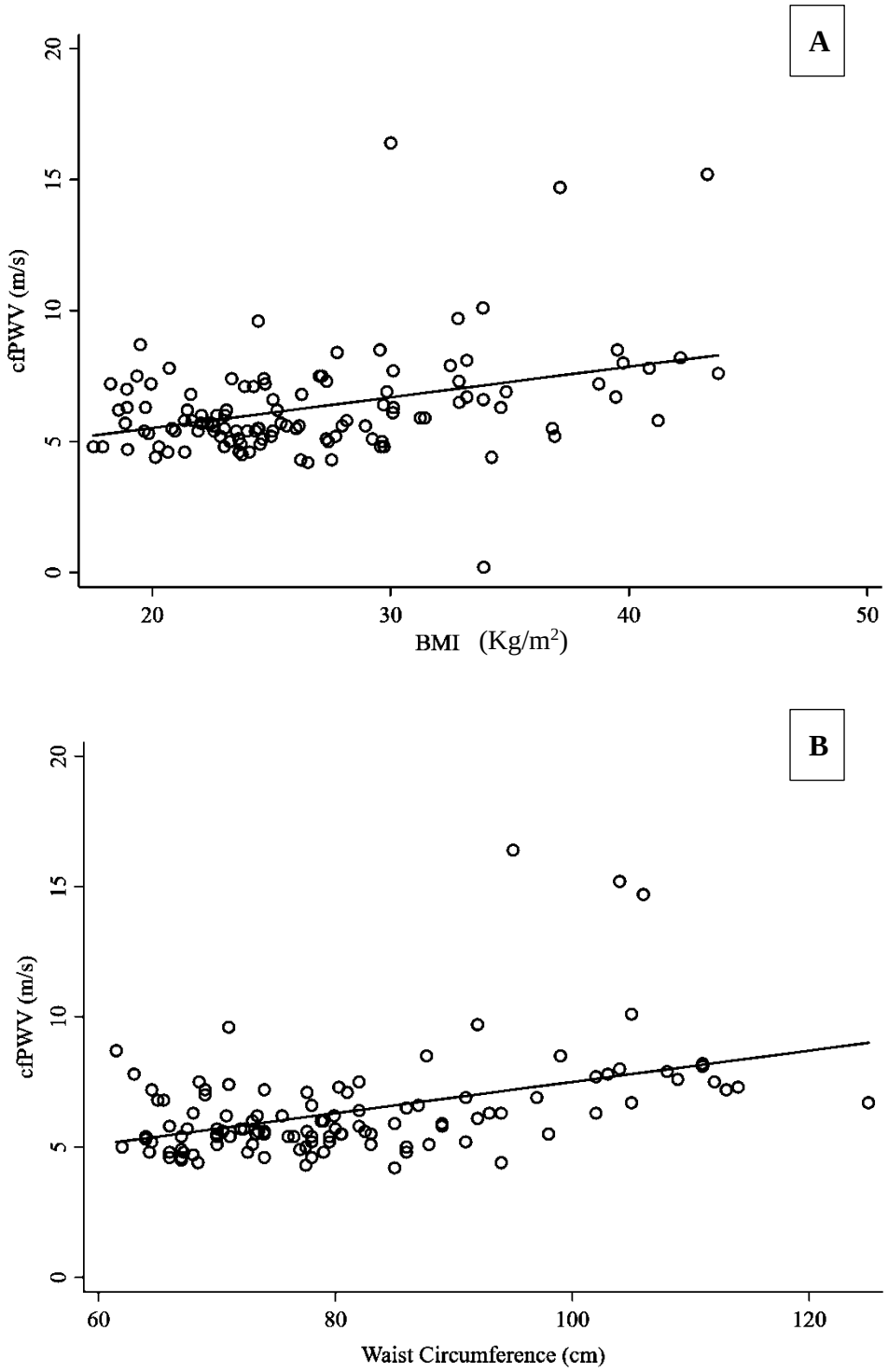


Figure 3.3 (A) Relation between carotid-femoral PWV and BMI (r = 0.130, *P*<0.0001). (**B)** Relation between carotid-femoral PWV and waist circumference (r = 0.193, *P*<0.0001)

3.10 Relationship between ambulatory blood pressure parameters and pulse-wave velocity in overweight/ obese and normal weight subjects

Multiple linear regression analysis was conducted to determine independent relationships between ambulatory blood pressure parameters and cfPWV (Table 3.7). In all the analyses conducted, age, sex, BMI, smoking status and alcohol consumption were adjusted for.

Daytime systolic (β=0.04, P=0.013) and diastolic (β=0.09, P<0.0001), night-time diastolic (β=0.06, P=0.012), 24-hour systolic (β=0.03, P=0.028) and diastolic (β=0.09, P<0.0001) BP were significantly correlated to cfPWV in normal weight subjects except night-time systolic BP (β=0.02, P=0.301). However, in overweight/ obese subjects all indices of BP were significantly correlated with cfPWV. Daytime, Night-time and 24-hour systolic BP were strongly correlated with cfPWV (β=0.11, P<0.0001; β=0.07. P=<0.0001, and β=0.08. P=<0.0001 respectively).

Table 3.7 Relationships between blood pressure indices and PWV in Normal weight and Overweight/ Obese participants

	Normal weight[a]			Overweight[b]/ Obese[c]		
	β	**95% CI**	**P**	**β**	**95% CI**	**P**
24-h SBP (mm Hg)	0.03	0.004 to 0.6	0.028*	0.08	0.04 to 0.12	<0.0001***
24-h DBP (mm Hg)	0.09	0.04 to 0.13	<0.0001***	0.09	0.03 to 0.14	0.003**
Daytime SBP (mm Hg)	0.04	0.01 to 0.07	0.013*	0.11	0.04 to 0.17	<0.0001***
Daytime DBP (mm Hg)	0.09	0.05 to 0.13	<0.0001**	0.08	0.02 to 0.13	0.006*
Night-time SBP (mm Hg)	0.02	-0.02 to 0.05	0.301	0.07	0.03 to 0.11	<0.0001***
Night-time DBP (mm Hg)	0.06	0.01 to 0.10	0.012*	0.09	0.03 to 0.14	0.002**

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; 95% CI, 95% confidence interval. Age, gender, BMI and smoking status were adjusted for in the multiple linear regression analysis. Significance level P <0.05. *Depicts statistically significant relationship. *P<0.05; ** P<0.01; ***P<0.0001. [a] Normal weight was defined as BMI < 25 kg/m^2, [b]Overweight was defined as BMI ≥ 25 < 30 kg/m^2, obese was defined as BMI ≥ 30 kg/m^2

3.11 Pulse-Wave Velocity and urinary electrolyte excretion

The relationship between urinary electrolyte excretion and cfPWV was assessed (Table 3.8). Multiple regression analysis was conducted to explore possible independent relationships between pulse-wave velocity and each of urinary electrolytes excreted during daytime, night-time and across the 24-hours. In each analyses age, sex, BMI, smoking status and alcohol consumption were adjusted for. None of the electrolytes measured, namely Na^+, K^+ and the Na^+:K^+ ratio was independently related to cfPWV in both the normal weight and overweight/ obese groups.

Table 3.8 Relationships between Urinary electrolyte concentrations and PWV in Normal weight and Overweight/ Obese participants

	Normal weight[a]			Overweight[b]/ Obese[c]		
	β	**95% CI**	**P**	**β**	**95% CI**	**P**
24-h Na^+ (mmol/L)	-0.002	-0.01 to 0.01	0.595	-0.01	-0.02 to 0.01	0.466
24-h K^+ (mmol/L)	0.01	-0.02 to 0.03	0.561	-0.004	-0.04 to 0.03	0.802
24-h Na^+:K^+	-0.11	-0.279 to 0.05	0.168	-0.07	-0.44 to 0.30	0.695
Daytime Na^+ (mmol/L)	-0.01	-0.01 to 0.0003	0.065	-0.004	-0.02 to 0.01	0.399
Daytime K^+ (mmol/L)	-0.01	-0.02 to 0.01	0.388	-0.01	-0.04 to 0.02	0.367
Daytime Na^+:K^+	-0.08	-0.28 to 0.11	0.384	0.08	-0.23 to 0.38	0.620
Night-time Na^+ (mmol/L)	0.004	-0.001 to 0.01	0.182	0.34	-0.02 to 0.01	0.342
Night-time K^+ (mmol/L)	0.01	-0.01 to 0.02	0.286	-0.01	-0.04 to 0.02	0.544
Night-time Na^+:K^+	0.02	-0.10 to 0.15	0.720	0.06	-0.22 to 0.35	0.652

Abbreviations: Na^+, sodium; K^+, potassium; Na^+:K^+, sodium potassium ratio; 95% CI, 95% confidence interval. Age, gender, BMI, smoking status and alcohol consumption were adjusted for in the multiple regression analysis. Significance level P <0.05. [a] Normal weight was defined as BMI < 25 kg/m^2, [b]Overweight was defined as BMI ≥ 25 < 30 kg/m^2, obese was defined as BMI ≥ 30 kg/m^2

CHAPTER 4: DISCUSSION

4. Discussion

4.1 Prevalence of obesity

The findings of the present study indicate that there is a high prevalence of overweight/ obesity in this population (51.3%). This finding highlights the increasing burden of overweight and obesity in South Africa, while mirroring the worldwide trend. The present study strongly agrees with the high prevalence of overweight/ obesity reported in this population by previous studies, where the prevalence was reported at 45.1% (Puoane *et al.*, 2002) and in some cases 56.2% (Case and Menendez, 2009). Furthermore, the results of a study that was conducted by our lab on individuals from the same population, also demonstrated the rising prevalence in overweight and obesity, with 71% of the participants being overweight/ obese, however these individuals were older in age. (Maseko *et al.*, 2018). The high prevalence in the aforementioned study, demonstrates where the current population could be projected over the years, if not higher. The findings from the current study, compared to the previous, suggest that the prevalence of overweight/ obesity in this population starts rising much earlier in age, since our population was younger than the previous study.

The rising prevalence in overweight/ obesity, in this population, could be explained by the socioeconomic transition and urbanisation faced by developing countries, such as South Africa (Sartorius *et al.*, 2015). Socioeconomic factors and urbanisation have led to the adaptation of lifestyles that favour decreased physical activity and increased consumption of calorie dense foods. This is evidenced by the increased rate of obesity across all economic levels and age groups. Presently, there is an increasing rate of urbanisation in the black population in South Africa that may well impact on the progression of obesity and its CVD sequalae. The effects of urbanisation and the socioeconomic transition impact the population of black South Africans more than other races, especially due to nutritional patterns over the years. This explains the reports that suggest an increased likelihood of being overweight/ obese, if one is South African of African ancestry and more-so if they reside in urban areas. (Negash *et al.*, 2017).

In 1940 it was reported that the black population of South Africa consumed a traditional diet with fat intake constituting 16% of total calories (Fox and Janisch, 1940). By 1990, in urban black populations, fat intake increased to 26% of all calories consumed (Mollentze *et al.*,

1993). This is likely due to increased availability and low cost of unhealthy food, coupled by the use of labour-saving mechanical means of transportation. Therefore, the number of calories ingested has increased while energy expenditure decreased. Evidently so, the impact of high overweight/ obesity in the black South African population requires further investigation, as women in this population are even more susceptible to the risk of obesity than males.

4.2 Gender disparities of obesity

In the present study, females constituted a higher percentage of overweight/ obese (65.57%) participants while males only constituted 34.43% of the total sample (Table 3.1). The sex differences in obesity indicate an underlying relationship between being overweight/ obese and being female. Similar studies on this population show that being female further increases the risk of overweight/ obesity (Negash *et al.*, 2017). In 2016 the National Department of Health (NDoH) reported that based on BMI, 31% of South African men and 68% women were overweight or obese in this population (NDoH *et al.*, 2016). This closely agrees with our participants, and with results from other low- and middle-income countries (NCD Risk Factor Collaboration (NCD-RisC), 2016).

Current discussions on the global gender disparities of obesity suggest that countless sociocultural dynamics across the world aggravate gender disparities in excess weight gain (Kanter and Caballero, 2012). Cultural assimilation through complex sociocultural pathways, contributes largely to weight gain in both men and women (Micklesfield *et al.*, 2013). For instance, the nutritional transition within developing countries, such as South Africa, has had a greater impact on the levels of physical activity specifically in women. The perception of obesity among black South African women is influenced by traditional and cultural beliefs that view obesity as a suggestion of wealth, beauty and good health, worsening the incidence of obesity in the females of this population (Dandala *et al.*, 2018).

In addition, in the black South African population, overweight/ obesity is considered a reflection of the husband's ability to nurture his wife and family (Puoane *et al.*, 2002). Some findings go as far as indicating that in the rural black communities there is no word for obesity (Dandala *et al.*, 2018). Thus, the normalisation of excess weight gain leaves the development of obesity unregulated from early ages and exacerbated by the cultural perception of thinness as an indicator of disease and conditions like HIV/AIDS (Clark *et al.*, 1999; Dandala *et al.*, 2018). In addition to gender, age has also been considered as a contributing factor to overweight/ obesity.

4.3 Age disparities in obesity

The population in the present study was relatively young, with an average age of 29.67±14.53 years. The close association between overweight/ obesity with age, is reported often in similar populations (Darebo *et al.*, 2019). In the previous study conducted by our lab, the average age of the population was 45.3±18.5 years (Maseko *et al.*, 2018). In the present study, individuals who were classified as overweight/ obese were 36.38±16.94 years old, while in the previous study the average age for the overweight/ obese group was 50.4±18.3 years old. In the same breath it should be noted that sample bias, with regard to age, may have contributed to the findings made on our population. This is mostly due to the fact that the normal weight and overweight/ obese participants were not matched by age. Thus, the observed differences should be considered in this light, since age is considered a crucial contributing factor.

The present results indicate that the rise in the overweight/ obesity prevalence begins earlier on and not only later in age, as suggested by previous reports. The increasing prevalence in overweight/ obesity in young adults confirms this. As demonstrated by our study and others, the prevalence of obesity starts rising earlier on in life. For instance, in the Western Cape, school learners between 7 to 18 years of age, reported with 22.9% prevalence in overweight/ obesity, with most of the overweight/ obese learners being black female individuals. (Negash *et al.*, 2017).

It is worth considering that with increasing age the likelihood of being overweight/ obese may increase significantly. The determinant of excess body weight gain is rooted in the relationship between energy intake and expenditure. Considering the probable decline in the physical activity of older individuals, it is likely that energy intake far surpasses expenditure (Jura and Kozak, 2016). Aging is also associated with various changes in individual physiology leading to increases in adiposity, fat deposition in skeletal muscle and slowed metabolic rates (Slawik and Vidal-Puig, 2006).

There is limited data on the impact of early onset overweight or obesity on blood pressure and other haemodynamic parameters. Hence, in this study we investigate the haemodynamic differences between the normal weight and overweight/ obese individuals. Our results show that there is no significant difference in 24-hour, night-time and daytime BP between the two groups. However, the clinic BP was significantly higher in the overweight/ obese compared to the normal weight group.

4.4 Relationship between overweight/ obesity and BP

In the present study, participants classified as overweight/ obese presented with clinical systolic BP of 122.66±17.27 mm Hg, compared to 115.19±10.65 mm Hg in normal weight individuals (Table 3.2). Interestingly, there was no statistically significant difference in ambulatory BP between overweight/ obese and normal weight individuals during daytime, night-time and across the 24hour period. Previous studies, detail the effects of overweight/ obesity on BP (Kotsis *et al.*, 2005; Jing *et al.*, 2017). One study reported elevated clinical systolic BP in the overweight/ obese group compared to the healthy group (Jing *et al.*, 2017). In this case the term clinical BP is in reference to measures of BP taken in a clinical setting or in office. However, they found consistently elevated daytime, night-time and 24-hour systolic BP and elevated night-time diastolic BP in the overweight/ obese group. Another study made a similar observation, showing increased systolic and diastolic BP in the overweight and obese during the day, night and across the 24-hour period (Kotsis *et al.*, 2005).

Interestingly, previous studies have shown that clinic/ office BP more closely relates with BMI, findings that agree with the findings of the present study (Garrison *et al.*, 1987; Jones *et al.*, 1994; Cigolini *et al.*, 1995). Several factors have been investigated regarding the cardiovascular risks associated with obesity, including the manifestations of obesity that involve diabetes, hyperinsulinemia, hyperlipidaemia, and hypertension (da Silva *et al.*, 2009). These conditions commonly present together and are often referred to as metabolic syndrome, while they are mostly triggered by excess weight gain (Han and Lean, 2016). Excess weight has been shown to impose increased metabolic demand on the body, this leads to increased total blood volume and cardiac output (Kasper *et al.*, 1992; Alpert, 2001). The increase in cardiac output in the overweight/ obese is largely owed to the increase in stroke volume.

The observed increase in office BP and not ambulatory BP in the overweight/ obese group points to an underlying mechanism, in addition to increases in total blood volume. Firstly, age should be considered as a contribution factor in the observed differences in BP, because the overweight/ obese group was older than the normal weight group. It is valuable to consider that the observed difference in office BP was partly due to age. However, other mechanisms could have contributed together with age to result in the observed difference, since the

increased BP was observed only in office and not ambulatory BP. The occurrence of regionalized sympathetic nervous system (SNS) activation in obesity, has been proven, this is likely a consequence of metabolic syndrome, yet the mechanisms behind it remain elusive (Haynes *et al.*, 1998). Grassi et al, provided evidence that overweight or obese participants present with high skeletal muscle sympathetic nerve activity compared to the normal weight participants (Grassi *et al.*, 1995). This finding was made using a direct measure of SNS activity, known as the microneurography. In addition, the SNS plays a pivotal role in short-term regulation of vascular tone, including the upregulation of renal tubular sodium reabsorption, myocardial excitability and vascular smooth muscle growth (Haynes *et al.*, 1998).

It has been proposed that hyperleptinemia mediates an increase in SNS activity in obesity. This is seen in metabolic syndrome, which is a cluster of conditions associated with high levels of leptin. Leptin is released by adipocytes in proportion to the amount of adipose tissue and mass (da Silva *et al.*, 2009). Despite the evidence showing that obesity is linked to reduced sensitivity to the anorexic effects of leptin (Kalil and Haynes, 2012), leptins ability to increase sympathetic activity seems to remain intact. The increase in clinic systolic BP may have been due to the increase sensitivity of the SNS coupled with the increase in total blood volume. The anxiety associated with having blood pressure taken in clinical setting, met by possible SNS sensitivity and increase in total blood volume due to obesity, could be responsible for the observed increase in office systolic BP (Kotsis *et al.*, 2005). The absence of a heart rate increase can be explained by a previous study showing that arterial pressure and heart rate were not affected by hyperleptinemia in obesity.

4.5 Impact of overweight/ obesity on pulse pressure

Our results indicate that the overweight / obese participants had a significantly higher pulse-pressure (PP), compared to the normal weight participants. The PP in the present study was above the normal reference value of 40 mm Hg. Similarly, a study on African American adults demonstrated a direct and persistent relationship between PP and BMI (Kwagyan *et al.*, 2005). They also reported that BMI emerged as an independent predictor of raised PP. Furthermore, in their study, PP had a strong correlation with systolic BP but not diastolic pressure. This observation is consistent with the findings of the present study

A well reported mechanism behind the high PP observed in overweight/ obese participants, involves the changes presented by overweight/ obesity on arterial compliance (Kotsis *et al.*, 2005; Kwagyan *et al.*, 2005). The inverse relationship between PP and arterial compliance has been previously described (Burton, 1965; Ferguson and Randall, 1986). In addition, obesity has been previously associated with decreases in arterial compliance (Ferguson and Randall, 1986; Balkestein *et al.*, 1999). Body weight may influence arterial compliance, and consequently PP, through various mechanisms.

For instance, in obese individuals, the increase in the autonomic systems adrenergic activity may lead to a decline in arterial distensibility and compliance (Ferrannini, 1992). While the heart rate was not significantly increased in the overweight/ obese participants, in the present study, it is possible that stroke volume was increased to raise cardiac output in order to accommodate the increased metabolic demand of excess body mass as previously described. Various studies have reported higher resting cardiac output and stroke volume in overweight/ obese individuals, with normal or slightly elevated heart rate (Alexander, 1993; Collis *et al.*, 2001; Garrett, K. Lauer, K. Christopher, 2004). This observation has been shown to be dependent on the severity of obesity, with morbidly obese individuals presenting with significantly higher resting cardiac output and stroke volume (Poirier *et al.*, 2006; Ashraf and Baweja, 2013). Eventually cardiac size and morphology is augmented, and myocardial function is diminished.

According to Young-Laplace's equation (T=PR), the increase in stroke volume would lead to raised peak systolic arterial pressure (P), larger ascending aortic systolic radius (R) and tension (T) consequential of the non-linear relation between pressure and the aortic radius therefore leading to reduced arterial compliance (Bighamian and Hahn, 2014; Klabunde, 2017). Moreover, in some cases the amount of excess adipose tissue observed in obesity, may hinder the expansion of vessels and create conditions where the intra-arterial force required to prevent vascular collapse and facilitate blood delivery to tissue is augmented (Britton and Fox, 2011; Nosalski and Guzik, 2017). However, in the present study there was no relationship between pulse pressure and pulse wave velocity.

4.6 Overweight/ obesity and urinary electrolyte excretion

The findings from the present study showed no difference in sodium excretion between the normal weight and overweight/ obese group during the 24-hour period, daytime and night-time (Table 3.3). Considering the lack of studies looking at 24-hour urinary excretion separated into periods of excretion namely daytime, night-time and the overall 24-hour period and how the excretion is affected by obesity, previous studies of similar design report conflicting findings. One study found that 24-hour sodium excretion was significantly higher in the overweight/ obese compared to normal weight participants, indicating increased sodium intake (Powell *et al.*, 2000). Another study showed similar findings reporting a higher 24-hour sodium excretion in the overweight/ obese group compared to the normal weight group (Oh *et al.*, 2015). Investigators associated this relationship with sodium's direct relationship with BMI. However, a study on a similar population showed reduced 24-hour sodium excretion in overweight/ obese women compared to normal weight women (Maseko *et al.*, 2018). In this case the salt-retention was assumed to be due to excess weight-induced increases in plasma leptin concentration, which have been shown to hinder sodium excretion through reducing the potency of pressure natriuresis by triggering NO secretion.

Similarly, there was no statistically significant difference in potassium excretion between the overweight/ obese and normal weight participants (Table 3.3). Previous studies have reported predominantly high concentrations of plasma renin activity, plasma angiotensinogen, Ang II and aldosterone concentrations, that have been associated with human obesity and excess weight (Massiéra *et al.*, 2001; Ruano *et al.*, 2005; Kidambi *et al.*, 2007). One would assume that this would lead to excessive potassium loss as aldosterone aims to retain sodium in the overweight/ obese group. Since this was not the case in the results of the present study, for both sodium and potassium, it is possible that urine samples were insufficient, in light of the high interindividual variation in electrolyte excretion, to show differences in sodium excretion between the normal weight and the overweight/ obese group.

4.7 Relationship between potassium excretion values and BP

The relationship between urinary electrolyte excretion and ambulatory BP was investigated. Neither 24-hour, daytime and night-time Na^+ nor the Na^+:K^+ ratio were associated with 24-hour BP in the normal weight group. Interestingly, only daytime urinary K^+ had a direct

association with 24-hour systolic BP in normal weight individuals, even after correcting for covariates (Table 3.4). Daytime K^+ excretion had a similar direct relationship with daytime systolic BP in the normal weight group (Table 3.5). While, no significant association was observed between 24-hour, daytime and night-time BP and potassium across all periods of measurement in the overweight/obese group. These findings contradict previous findings on blood pressure and urinary potassium excretion (Rose *et al.*, 1988; Liu *et al.*, 2000; Hedayati *et al.*, 2012; Mente *et al.*, 2014a).

A recent study similarly assessed the association between blood pressure and the urinary electrolyte excretion of potassium in normal weight adults from the United States (Jackson *et al.*, 2018). Potassium excretion was inversely associated with systolic BP contrary to what was found in the present study. Furthermore, a study on black Nigerian, Jamaican and United States individuals consistently showed an inverse relationship between both systolic and diastolic BP and urinary potassium excretion (Tayo *et al.*, 2012).

The findings of the present study are an unexpected outcome; however, earlier studies do show that the haemodynamic effects of potassium are not always consistently demonstrated in normotensive adults like the current population (Wilson *et al.*, 1999). This finding may tell of a unique relationship between potassium and blood pressure in our population. However, due to the paucity of studies investigation urinary electrolytes and their contribution to BP on the black South African population, and the current evidence that contradicts the present study's findings, the need for further research on this relationship on our population is emphasized. A previous study reported that potassium's hypotensive effect depends largely on sodium intake, thus it is likely that the observed relationship between BP and potassium was affected by amount of sodium consumed and excreted (Sharma *et al.*, 2014). Thus, investigating the relationship between urinary sodium-to-potassium ratio and BP may paint a clearer picture.

4.8 Blood pressure and sodium-to-potassium excretion

Twenty-four-hour systolic BP was directly associated with the night-time sodium-to-potassium ratio in the overweight/ obese group (Table 3.4). Interestingly, night-time blood pressure was associated with the sodium-to-potassium ratio during night-time and the 24-hour period in the overweight/ obese group (Table 3.6). There were no associations observed between the sodium-to-potassium ratio and blood pressure in the normal weight group. One

study investigating the association between 24-hour urinary electrolyte excretion and 24-hour blood pressure, reported an age related, dose-response of 24-hour urinary sodium and the sodium-to-potassium ratio with night-time blood pressure. These findings are in concert with the findings from our overweight/ obese individuals.

A review on the relationship between the sodium-to-potassium ratio and blood pressure identified 8 out of 22 countries and multiple countries from the Prospective Urban Rural Epidemiology (PURE) study, as crucial demonstrators of the relationship between the sodium-to-potassium ratio and blood pressure (Mente *et al.*, 2014b). They reported a strong association between the sodium-to-potassium ratio with systolic and diastolic blood pressure outcomes far better than sodium or potassium alone. Our results showed a similar finding, as both systolic and diastolic night-time blood pressure were associated with the night-time sodium to potassium ratio. Night-time systolic blood pressure presented was strongly associated with the night-time sodium to potassium ratio.

The similar findings observed in other studies involve individuals who were either hypertensive or of advanced age (Schröder *et al.*, 2002; Huggins *et al.*, 2011; Kyung Kim *et al.*, 2019). However, studies investigating the influence of electrolyte intake and excretion on blood pressure, in overweight and obese participants, also detail a similar relationship (Chuang *et al.*, 2017; Ndanuko *et al.*, 2017). Although, these studies do not include normotensive individuals as a control, one study conducted on overweight/ obese children found that the urinary sodium-to-potassium ratio was positively associated with systolic blood pressure in overweight children but not in normal weight children (Chuang *et al.*, 2017). They concluded that the state of overweight or obesity enhances the relationship between sodium-to-potassium ratio and blood pressure.

The mechanism behind the pronounced relationship between night-time blood pressure and the night-time sodium-to-potassium ratio could be owed to impaired sodium excretion during the day, that is being compensated for at night. Hyperinsulinemia and elevated levels of leptin, typical in cases of overweight/ obesity, have been implicated in increasing nocturnal natriuresis which would elucidate the observed relationship in our study (Fujii *et al.*, 1999). In addition, as previously stated the combination of salt sensitivity, reported in this population, and the contributions of overweight/ obesity toward salt sensitivity and salt retention it is possible that these conditions would lead to an effect on blood pressure as observed.

Sodium alone presented with no statistically significant association with blood pressure in this population. The RAAS activity (a system that affects both sodium and potassium) is upregulated in overweight/ obesity and plays a significant role to the circadian patterns of blood pressure (Karas *et al.*, 2005). Furthermore, in the development of hypertension, excess consumption of salt and insufficient intake of potassium have been shown to contribute to blood pressure by causing vascular smooth muscle cell contraction that may lead to increased peripheral vascular resistance, thus increasing blood pressure (Adrogué and Madias, 2007). This imbalance in sodium and potassium intake is evidenced in overweight/ obese individuals, our findings suggest that an adjustment in sodium and potassium intake is warranted. The night-time sodium-to-potassium ratio was also associated with 24-hour blood pressure. This common association of the night-time sodium-to-potassium with 24-hour and night-time blood pressure shows the power of the night-time sodium-to-potassium ratio in predicting blood pressure. This is evidenced by the likelihood that the night-time sodium-to-potassium ratio contributed to the 24-hour sodium-to-potassium ratio's association with night-time systolic blood pressure.

To our knowledge this study is the first of its kind to show a linear relationship between the sodium-to-potassium ratio and systolic and diastolic night-time blood pressure in overweight/ obese normotensive African individuals. This warrants the further study of the contributions of the sodium-to-potassium ratio in controlling BP in this population, in light of its propensity toward salt sensitivity. Vascular distensibility is reported to be vulnerable to the effects of electrolyte intake, and consequently changes in blood pressure. Thus, in the following section the relationship between electrolyte excretion and arterial stiffness in the context of overweight/ obesity will be discussed.

4.9 Increased carotid-femoral pulse wave velocity in overweight/ obese participants

The findings of the present study indicate a strong linear relationship between BMI and cfPWV (Figure 3.3A). Carotid-femoral PWV was linearly associated with waist circumference (Figure 3.3B). This suggests that increases in BMI lead to an increase in arterial stiffness, as indexed by cfPWV in the present study. Several previous studies agree with our results on the contributions of overweight/ obesity toward increased PWV. A study on middle-aged adults found that abdominal obesity and visceral fat were associated with

large artery stiffness, similar to the present study (Strasser *et al.*, 2015). Furthermore, some studies have gone as far as indicating that overweight/ obesity exerts its effect on PWV as early as 20 years of age in individuals of African ancestry (Wildman *et al.*, 2003).

Our findings suggest that excess body weight presents with both short- and long-term effects on the vascular system as previously described (Wildman *et al.*, 2003). Fat deposition in the trunk has been found to be adversely related with PWV (Safar *et al.*, 2006; Strasser *et al.*, 2015). The pathophysiological mechanisms linking body fat with arterial stiffness are not yet fully elucidated. Plausible explanations include elevated lipolytic activity in visceral adipocytes, which result in increased circulatory free fatty acids (FFA) in the portal vein (Safar *et al.*, 2006). The accumulation of FFA contributes to insulin resistance. An additional mechanism, is through the increase of circulating proinflammatory cytokines and leptin, released by adipose tissue in obesity (Makki *et al.*, 2013).

High levels of leptin have been documented in overweight/ obese individuals and linked to reductions in arterial distensibility (Singhal *et al.*, 2002). Vascular endothelium and smooth muscle cells have been shown to have leptin receptors expressed, in addition to those found in the hypothalamus (Sierra-Honigmann *et al.*, 1998; Oda *et al.*, 2001). Therefore, leptin can initiate receptor -mediated changes in vascular tone and growth. In cultures, leptin has also been shown to stimulate vascular smooth muscle propagation and migration (Schäfer *et al.*, 2004). Furthermore, leptin triggers oxidative stress in endothelial cells, this prompts the transcription of oxidant-sensitive genes that contribute to atherogenesis. Moreover, experimental models and some human studies have shown that leptin increases sympathetic nervous activity, with chronic administrations of leptin leading to an increase BP (Visser *et al.*, 1999; Yasmin *et al.*, 2004). It is likely that it is through these mechanisms that overweight/ obesity is linked to CVD, especially considering the possible high levels of leptin observed in obesity.

4.10 Pulse wave velocity and 24-hour ambulatory blood pressure

When the relationship between PWV and 24-hour blood pressure was assessed we found a positive relationship between all 24-hour blood pressure indices except night-time systolic blood pressure in normal weight participants independent of age, gender, BMI and smoking status (Table 3.7). When closely observing daytime and 24-hour diastolic blood pressure, it is

apparent that they had a stronger association with PWV. However, in the overweight/ obese participants, all the 24-hour blood pressure indices were strongly correlated with PWV. Conversely, in the overweight/ obese group the daytime, night-time, and 24-hour systolic blood pressure indices had a stronger correlation with PWV.

A previous study on blood pressure and PWV on young healthy males reported a similar observation with diastolic blood pressure and PWV even after multiple regression analysis (Nürnberger *et al.*, 2003). They proposed that this observed relationship was owed to the characteristics of aortic pressure amplification in young subjects. In older individuals reflected pulse waves return to the aorta during systole, thus raising systolic blood pressure and pulse pressure. While in younger individuals the reflected pulse wave returns during diastole, thus raising diastolic BP, similar to the current population. Although our study includes both male and female participants, our normal weight participants were of younger age. It is possible that the inclusion of both genders may be responsible for the relationships observed with PWV and systolic blood pressure. Interestingly, in the overweight/ obese group systolic blood pressure had a stronger relationship with PWV.

To elucidate the findings behind the augmentation of the relationship between PWV and systolic BP in the overweight/ obese, factors that contribute to increases in peripheral vascular resistance associated with BP increases were explored. Hyperinsulinemia observed in overweight/ obesity, and increases in BP have been linked to the SNS (Landsberg *et al.*, 1991). In addition to this is are the previously detailed contributions of increased circulatory leptin in triggering SNS hyperactivity. The documented relationship between obesity, fasting insulin, hyperleptinemia and BP is likely explicated by amount of abdominal fat, assessed by waist circumference.

The suggestion that likens obesity with a “systemic inflammatory state” may also offer additional reasoning for the improved relationship between PWV and BP observed in this group (Mahmud and Feely, 2005). Obesity has been shown to have a strong correlation with IL (interleukin)-6 and C-Reactive Protein (CRP) levels (Bastard *et al.*, 1999). Interleukin-6 is a proinflammatory cytokine with numerous actions, one of which involving the stimulation of CRP production from the liver. This makes obesity fairly similar to low-grade systemic inflammation (Poirier *et al.*, 2006). Arterial stiffness has been previously associated with low-grade systemic inflammatory states, that play a significant role in affecting systolic and diastolic BP (Mahmud and Feely, 2005). High leptin levels discussed previously have been

shown to augment arterial stiffness by triggering smooth muscle growth and oxidative stress (Schäfer *et al.*, 2004). Changes in shear stress and stretch on the vascular wall trigger endothelium-dependant vasodilation, to maintain favourable magnitudes of blood pressure and low to modest shear on endothelium wall (Nichols *et al.*, 2011).

In overweight/ obesity the balance between vasodilator and vasoconstrictor activity is disturbed, due to the reduction of NO bioavailability while mitogen-activated protein-kinase pathway mediating endothelin-1 production remains unchanged. In addition, PWV in overweight/ obese individuals increases not only as a result of aortic stiffening, but the possible remodelling of small and medium sized arteries. Consequently, the sum of reflected waves arrives back at the central arteries earlier, thus augmenting systolic BP (Kotsis *et al.*, 2010).

4.11 Urinary electrolyte excretion and pulse wave velocity

Our results showed no relationship between electrolyte excretion and PWV in both the normal weight and overweight/ obese participants in a multivariate analysis after adjusting for age, gender, smoking status and alcohol intake (Table 3.8). There is a paucity of studies investigating the relationship between urinary electrolyte excretion and PWV. The numerous studies investigating such a relationship are done on hypertensive and diabetic patients, where evidence shows a direct relationship between sodium excretion, a measure of salt intake, and PWV. A few studies on normotensive, healthy participants also reveal a similar a relationship.

A study on a population sampled from a similar area as the present study, showed no significant association between the urinary sodium-to-potassium ratio and aortic PWV in a normotensive healthy population (Redelinghuys *et al.*, 2010). Another study on individuals of African ancestry showed a decrease in BP in response to salt intake reduction (He *et al.*, 2009). However, in that study the reduction in salt intake was followed by a decrease in diastolic BP, which may have contributed to the decline in PWV (He *et al.*, 2009). There was no relationship between PWV and sodium excretion in the present study. In addition, we found no association between potassium excretion and PWV, which also agrees with a few studies on healthy humans (Redelinghuys *et al.*, 2010; Wang *et al.*, 2015) and in normotensive overweight/ obese adults (Dickinson *et al.*, 2014).

CHAPTER 5: CONCLUSIONS

5.1 Conclusion

In conclusion, the present study has demonstrated that overweight/ obesity has significant implications for general and cardiovascular health in individuals of African descent. Office blood pressure measurements revealed increased pulse pressure in individuals characterised as overweight/ obese compared to their normal weight counterparts. This finding was indicative of the prevailing effects of obesity on arterial compliance. Interestingly, office blood pressure revealed increased systolic BP in the overweight/ obese group without a significant increase in the ambulatory readings when compared to the normal weight group. This finding seemed to indicate the presence of SNS sensitivity or activation, indicated by a spike in office BP, likely due to the anxiety caused by having BP measurements taken. This may have taken place as participants anticipated a bad outcome from the BP measure, this normal response may have been amplified by the proven SNS sensitivity observed in overweight/ obesity. By definition, this would imply that the white coat effect (WCE) is at play, however, this cannot be assumed without repeated daily measures of BP in and out of office. The collection of 24-hour urine samples, provided little evidence on the effects of salt and potassium excretion on the development of obesity in this population. The findings of the present study showed no evidence of the previously suggested cardioprotective properties of potassium in this population sample, which would encourage the need for increases in potassium intake as reported in previous investigations. However, relative excretion of sodium seemed to increase BP as shown by the sodium-to-potassium ratio which is considered a stronger contributor toward BP than sodium and potassium alone. Overweight/ obesity has shown deleterious effects on vascular elasticity, with individuals in this group showing decreases in arterial compliance that were strongly associated with BP in overweight or obese individuals. Although there was no relationship observed between urinary electrolyte excretion and PWV, the findings from this study indicate that overweight/ obesity has substantial effects on arterial distensibility. It is likely that overtime the augmented relationship between BP and PWV, due to overweight/ obesity, may give rise to vascular damage and ultimately essential hypertension.

5.2 Limitations and future perspective

It is important that our findings be interpreted within the context of their limitations, of which may have had bearings on the outcome of our results. Firstly, while 24-hour urinary excretion is considered the gold standard for the estimation of sodium consumption, flawed urine collection may over- or underestimate concentration and volume. For instance, if urine collection surpasses 24-hours, it may result in overestimation, otherwise if voids are missed underestimation may occur. Thus, in the present study volumes below 500 ml/day, for each daytime and night-time sample, were not included in analysis. However, there was no possible way to ensure voids were not missed. Obtaining adequate samples for urine analysis presented a challenge, due to the restrictive nature of collecting urine that hinders mobility, as participants had to travel with their samples on the day of collection. Therefore, only 89 samples underwent urinalysis. Sample size was an overall limitation on the study findings, as a significantly larger sample size, ideally above 200 would have provided a clearer outcome even if urine samples were slightly lower as in the present case. In addition to this, a larger sample size would have allowed us to separate the overweight and obese group in analysis so the varied or progressive effects of excess weight gain could be explored.

Secondly, due to the unavailability of blood samples, we were not able to assess the lipid and hormonal profile of the participants to solidly corroborate our findings. In this case, obtaining lipid profiles, and pro-inflammatory markers like IL-6 and TNF-α, would shed light on the effects of obesity on vasculature. Obtaining the plasma concentrations of leptin, glucose, and insulin would have further clarified our findings beyond educated assumptions. Furthermore, plasma concentration of potassium and sodium would have helped substantiate our findings based on excretion and further unravelling possible retention due to overweight/ obesity. Plasma electrolytes may have also explained the observed association between PWV and BP.

Thirdly, while a wide range of covariates was included in the regression models, confounding variables that included additional factors, such as plasma glucose concentration, were possibly not measured. Considering the limitations of the present study, the findings still stand in concert with evidence obtained from literature regarding the actions of overweight/ obesity on the cardiovascular system.

5.3 Possible clinical implications and recommendations

The findings in the present study show the importance of ABPM in the diagnosis of hypertension for individuals that are overweight/ obese. This is considering the reported cases of the what may possibly be the WCE in this study, and white coat hypertension in other studies on these individuals. This current study not only echoes the importance of out-of-office blood pressure monitoring, but also adds to the growing evidence pertaining the use of ambulatory blood pressure monitoring.

It has also been reported that the development of hypertension in overweight/ obese individuals is mediated by different mechanisms. Considering this, the adoption of healthier lifestyles in overweight/ obese patients is beneficial. In relation to the findings from this study and others like it, increasing potassium intake in the form of fruits and vegetables and reducing salt intake may yield promising outcomes. This however should be done in consult with physicians and dieticians in consideration of any pre-existing diseases that may be worsened by such dietary changes.

Adequate intake of potassium is important in the cardiovascular health especially for the African population that is considered salt sensitive, with salt-dependant forms of hypertension. In addition, as previous studies show that the rural diet of African individuals, prior to socioeconomic transition, had cardioprotective properties. Not only did the dietary lifestyle of rural Africans help mitigate cardiovascular disease, the lack of technological advancements that have made traveling simpler had a significant impact on physical activity levels.

Future studies should investigate the contributions of the rural diet or a potassium rich and low sodium diet accompanied by increased physical activity on blood pressure, pulse wave velocity and electrolyte excretion in the African population. Intervention studies on this population, including these lifestyle changes, would help in improving clinical recommendations, especially through investigating the types of exercise and diet recommendation. Future studies should also include repeated collection of urine samples to improve accuracy of electrolyte concentrations, to minimize collection errors, interindividual and day-to-day variations in concentration. Lastly, ambulatory PWV, as measured across 24-hours, should be investigated to determine the effects of obesity on vasculature during the night through the SNS as suggested by literature.

APPENDIX A

R14/49 Messrs B Nkosi and A Bawa-Alla

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M180521

NAME: (Principal Investigator)	Messrs B Nkosi and A Bawa-Alla
DEPARTMENT:	School of Physiology Medical School University
PROJECT TITLE:	The impact of physical activity on nocturnal blood pressure and large artery pathology, in a salt-sensitive African population
DATE CONSIDERED:	25/05/2018
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr M Maseko
APPROVED BY:	Professor CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	22/08/2018

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 3rd floor, Phillip V Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/We fully understand the conditions under which I am/we are authorised 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 resubmit to the Committee. **I agree to submit a yearly progress report.** The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **May** and will therefore be due in the month of **May** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX B

SOUTH AFRICAN HYPERTENSION AND DIET STUDY

STANDARD QUESTIONNAIRE

PARTICIPANT IDENTIFICATION

Surname:													
Name(s):													
Identification number:													
Sex:													
Date of Birth:	D	D	M	M	M	Y	Y						
House number:													
Apartment number or postal box number:													
Street:													
Town:													
Postal code (zip code):													
Telephone number:													

HOW TO COMPLETE THE QUESTIONNAIRE

(Please read this section before completing the questionnaire)

The participants may complete the questionnaire themselves. However, they may also request the help of the team of fieldworkers. After completion, the questionnaire should be inserted in the envelope which should then be closed and sealed. All information provided will be treated confidentially and will be used anonymously in the statistical analysis. For further information or help, please do not hesitate to contact the team of fieldworkers.

[T*his section will be stored separate from the remainder of questionnaire.]*

1. Marital status

Marriage status	Married	Divorced	Widowed	Single
Living with a partner	YES		NO	

2. Are you still attending school?

YES ☐ NO ☐

If no, please proceed to question 3.

If yes: please, provide the name of the institution of school?

_____

Are your studies a primary or secondary activity for you? For instance, are combining education with occupational or professional work?

YES ☐ NO ☐

3. Are you employed?

YES ☐ NO ☐

If no, please proceed to question 4.

If yes, please, provide a detailed description of your current occupation?

Duration of employment:

Since	Y	Y	Y	Y

If you had to assess your work intensity, which one of the following best describes your work intensity?

Spend most of the time sitting	YES	NO
Driving a motor vehicle	YES	NO
Pushing a wheelbarrow	YES	NO
Lifting heavy load (e.g. loading a large lorry without	YES	NO

mechanical assistance)		

4. If you are unemployed, please specify the reason

Have you been previously employed?	YES	NO
Do you have any long-lasting health problems?	YES	NO
Are you permanently incapacitated?	YES	NO
Are you retired?	YES	NO

5. If you currently unemployed, what was the last job you had and the duration of work?

_____

6. Do you practice your current occupation, or did you practice your last job as an independent self-supporting worker or professional?

YES ☐ NO ☐

If you do work as an independent self-supporting worker or professional, how many persons are working (or were working) in your company? ☐

Please specify the business sector you are/ were in

Trade	YES	NO
Industry	YES	NO
Services	YES	NO
Handicraft	YES	NO
Agriculture	YES	NO

7. Did you receive a salary for your current or former job?

YES ☐ NO ☐

Do you work now (or worked before)

- For a private person or company?	YES	NO
- For a municipal, provincial, public, or interurban service?	YES	NO

Do you work now (or worked before)

- As a full-time employee?	YES	NO
- As a part-time employee?	YES	NO

Did you have (or had before)

- a blue collar job?	YES	NO
- a white collar job?	YES	NO

8. What is the highest level of education that you successfully completed?

_____

9. **Please, specify whether some of your relatives currently suffer (or have suffered) from high blood pressure (hypertension).**

   Please tick one box for each relative.

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

10. Did you ever, or do you now suffer from a disease affecting your heart or blood vessels?

YES ☐ NO ☐

If yes, please, specify the diseases affecting your heart or blood vessels. Please, provide for each disease the date (month/year) on which the first symptoms occurred, if applicable, the date (month/year) on which you were successfully treated and the name of the doctor who cared for you.

Disease	starting date (month/year)	date of cure (month/year)	treating physician name(s) + address(es) + telephone number(s)

11. Did you ever, or do you now suffer from a disease affecting your kidneys or urinary tract?

YES ☐ NO ☐

If yes, please, specify the diseases affecting your kidney or urinary tract. Please, provide for each disease the date (month/year) on which the first symptoms occurred, if applicable, the date (month/year) on which you were successfully treated and the name of the doctor who cared for you.

Disease	starting date (month/year)	date of cure (month/year)	treating physician name(s) + address(es) + telephone number(s)

12. Have you ever or are you currently suffering from kidney stones?

YES ☐ NO ☐

Any repeated pain attacks?

YES	NO

Have you ever passed a stone in urine?	YES	NO
Have you ever undergone surgical treatment or were stones extracted endoscopically, or were stones shattered by ultrasound techniques?	YES	NO
Do you still have stones of the kidney urinary tract?	YES	NO

13. Do you have diabetes?

YES ☐ NO ☐

If yes:

Do you follow a diet and avoid eating sweet foodstuffs?	YES	NO
Are you taking pills, which lower blood sugar?	YES	NO
Are you being treated with insulin injections?	YES	NO

14. Were you ever told by a doctor or health professional that you have an elevated blood pressure?

YES ☐ NO ☐

If yes:

When was the diagnosis of high blood pressure established for the first time? (month/years) _____

Did you ever receive a treatment for an elevated blood pressure (hypertension)? YES | NO

15.

Are you currently in good health?

YES ☐ NO ☐

If no, please specify the diseases you currently have or previously had.

Please, do not repeat the diseases you already mentioned in reply to questions 10 Please, also specify the date (month/year) on which the first symptoms occurred, if applicable the date (month/year) on which you were cured and the name of the physician who cared for you.

disease	starting date (month/year)	date of cure (month/year)	treating physician (name(s) + address(es) + telephone number(s)

16. Did you ever take or are you taking now drugs to lower your blood pressure?

YES ☐ NO ☐

If yes:

Do you <u>now</u> take blood pressure lowering drug? YES ☐ NO ☐

Please, specify the name of the drug(s) and the number of tablets that you are taking per day.

name of drug	tablets/day

17. Did you ever take or are you taking diuretics/drugs which eliminate salt and make you pass urine more frequently or in larger amounts?

YES ☐ NO ☐

If yes:

Are you currently these drugs? YES ☐ NO ☐

Please, specify the name of the drug(s) and the number of tablets that you are taking each day.

name of drug	tablets/day

18. Did you ever take painkillers on a regular basis, for instance against headaches, tooth pain, painful periods, etc?

YES ☐ NO ☐

If yes

Please, specify the name of the and the number of tablets or powders per week.\

name of painkiller	amount/week

How long did you take this medication? ..... months

19. Were you on any medication in the past 2 weeks?

YES ☐ NO ☐

If yes: please, specify the drugs that you have been taken as well as the daily dose of each medicine.

name of medicine	amount/day

20. Are you an active smoker?

YES ☐ NO ☐

If yes:

How much do you smoke?

Cigarettes with filter per day _____

Cigarettes without filter per day _____

Grams of tobacco per day for hand-rolled cigarettes _____

Grams of tobacco per week for pipe _____

Small cigars per week _____

Cigars per week _____

At what age did you start smoking regularly? _____

Do you inhale the smoke?

YES	NO

21. Did you smoke in the past?

YES ☐ NO ☐

If yes

Did you smoke at least one cigarette per day in a year?

YES	NO

At what age did you smoke for the first time? _____

How much did you smoke in the past? _____

Cigarettes with filter per day _____

_____

Cigarettes without filter per day

_____

Grams of tobacco per day for hand-rolled cigarettes

_____

Grams of tobacco per week for pipe

_____

Small cigars per week

_____

Please, specify the reason(s) why you stopped smoking.

_____

_____

21. Do you consume alcoholic beverages?

YES ☐ NO ☐

If yes

How much alcohol do you currently consume?

_____

Number of glasses of beer per day

_____

Number of bottles of wine per week

_____

Number of bottles of aperitives or fortified wine per week

_____

Number of bottles of liquor per week

_____

At what age did you start drinking alcohol regularly?

_____

22. Did you regularly consume alcohol in the past?

YES ☐ NO ☐

If yes

At what age did you stop consuming alcohol regularly?

_____

Number of glasses of beer per day

_____

Number of bottles of wine per week

_____

Number of bottles of aperitives or fortified wine per week

_____

Number of bottles of liquor per week

_____

Please, specify the reason(s) why you stopped consuming alcoholic beverages on a regular basis.

_____

_____

23. Do you drink coffee or caffeine-containing beverages (cola) on a regular base?

YES ☐ NO ☐

If yes

Specify the number of cups of coffee and the number of glasses of cola you consume on average per day.

Cups of coffee _____

Glasses of cola _____

Other

Do you drink decaffeinated coffee? | YES | NO |

If yes, specify number of cups of decaffeinated coffee you drink on average per day: _____

_____

24. Please, grade on a scale from 1 to 10 the physical efforts in your daily life, including your job, sports, and activities at leisure time.

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

A few examples:

- *A civil servant who is doing only sitting work, but who walks to his workplace and in his leisure time engages in gardening could rate his physical efforts at 4-5 points.*
- *An older person who spends the whole day resting in his chair, could rate his physical effort at 1 point.*
- *A manual worker who each day has to load a truck with sand, just using a spade, cycles 20 km to and from his work place and in his leisure time has an additional job as a construction worker, could rate his physical efforts at 9-10 points.*

_____

25. Do you practice any sports activities on a regular basis?

YES ☐ NO ☐

If yes

Which sport(s) do you practice on a regular basis?
.....

At what age did you start practicing sports regularly?

_____

At present, how many hours per week do you spend practicing sport?

_____

26. Do you walk regularly?

YES ☐ NO ☐

If yes

How many hours do you walk on average per day?

_____

How many kilometres do you walk per day?

_____

27. Please, grade on a scale from 1 to 10 the psychological tensions and stress that you are currently facing in your daily life.

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

<u>A few examples</u>:

- *A student who is well taking care off by his parents, maintains friendly relations with his fellow students and does not have to fear exams, because he is very bright, might rate his stress level at 1-2 points.*
- *A housewife who has to care for many children, who hardly gets her work done and who in addition has marital problems with her husband, could rate her stress level at 9-10 points.*

- *An employee with a quiet job, without problems in his family, but who is not completely sure that he will keep his job, and therefore feels unsecure, could rate his stress level at 5-6 points.*

28. Do you agree that the results of the present examinations are sent to yourself and/or your family doctor?

If agreeable, please tick one or both boxes.

YOURSELF ☐ YOUR FAMILY DOCTOR ☐

29. For the correct interpretation of some results, it may be necessary that our team contacts your family doctor or treating physician(s). Of course, all data will be treated confidentially by the doctors responsible for this project. Do you agree that we would contact your physician(s)?

Please, tick the correct answer.

YES ☐ NO ☐

Please, provide the name, address and telephone number of your family doctor and/or treating physician(s).

.....

.....

.....

.....

THIS SECTION IS FOR WOMEN ONLY

1. Did you already have your period?	YES	NO
2. Did you ever take "the pill"?	YES	NO

Please, note that "the pill" can be prescribed, not only for birth control, but also against irregular or abundant periods and/or after natural or surgically induced menopause.

- Do you take "the pill" now?	YES	NO
- Please, specify the name of "the pill" you are taking now	YES	NO
- Overall, how long did you take "the pill"?		
3. Are you pregnant at present?	YES	NO
4. Have you been pregnant before?	YES	NO
If yes		
- How many times have you been pregnant?		
- How many miscarriages did you have?		

- How many children were born alive?	
- How many children were stillborn?	

THIS SECTION IS FOR WOMEN OLDER THAN 30 YEARS

1. Do you still have your period?	YES	NO
2. If no: Please, specify since when (month/year) your periods become irregular		
3. Please, specify since when (month/year) your periods completely disappeared.		
4. At present are your periods suppressed by taking "the pill"?	YES	NO
If yes Please, specify the name of "the pill" and the number of months that you are taking "this pill".		
- Name of "the pill":		
- Number of months:		

Did your periods disappear spontaneously? (if your periods disappeared spontaneously and if only later you underwent surgery involving your genital organs, please, reply "yes" to this question)

YES ☐ NO ☐

Please, specify the operations that you have undergone and also provide the date of surgery (month/year) and the reason for the surgical intervention.

Removal of	**date (month/year)**	**reason**	**treating physician(s) (name(s) + address(es) + telephone number(s)**
only womb			
only right ovary			
only left ovary			
both ovaries			
right ovary together with womb			
left overy together with womb			
both ovaries and womb			

- END -

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