Masked hypertension and left ventricular structure and function in young black and white adults: The African-PREDICT study

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Alone this journey seemed impossible, but with the love, support and encouragement of the following people, it was made possible.

Preface

This dissertation (Masked hypertension and left ventricular structure and function in young black and white adults: The African-PREDICT study) fulfills the requirements for the degree *Master of Health Sciences in Cardiovascular Physiology* at the Potchefstroom Campus of the North-West University. The article format for the dissertation was chosen and consists of 5 chapters as advised and approved by the North-West University.

The chapter outlay of this dissertation is as follows:

Chapter 1: Introduction and Motivation

Chapter 2: Literature Background, Aim, Objectives and Hypotheses.

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Chapter 5: Concluding Remarks and Future Recommendations

The manuscript is prepared for submission to a peer-reviewed journal, namely the *Journal of Hypertension.* The referencing style provided at the end of each chapter of the dissertation, is prepared according to the author instructions of the journal.

* To improve legibility for examination purposes I deviated from the author instructions of the *Journal of Hypertension* regarding the insertion of tables and figures in between the text of the results section in the manuscript and the page numbering style used.

Contributions of authors

Ms. NP Sekoba

Responsible for conducting the literature search, compiling the research proposal, completing the ethics application, performing all statistical analyses and writing the complete dissertation, including the manuscript for publication. The candidate was also responsible for the collection of data within the larger African-PREDICT study, such as the Sphygmocor data to assess large artery stiffness.

Prof. AE Schutte

Prof. Schutte supervised and provided intellectual input in compiling the proposal, ethics application, manuscript and interpretation of results. She gave guidance and input in the analyses of data. As the principal investigator of the African-PREDICT study, she designed the study, contributed to collection of data, gave overall professional input as well as overseeing everything.

Prof. R Kruger

Prof. Kruger co-supervised and provided expertise in the writing of the proposal, ethics application, manuscript and interpretation of results. He also gave input in the statistical analyses of data and provided guidance and expert knowledge regarding the interpretation of echocardiographic data.

Mr. P Labuschagne

Responsible for performing echocardiography measures, analysing the echocardiography data and gave intellectual input in interpreting the echocardiographic data in the manuscript.

Below is a statement from the co-authors confirming their individual contribution to the study and their permission that the manuscript may form part of this dissertation.

Hereby, I declare that I approved the aforementioned manuscript and that my role in this study as stated above is representative of my actual contribution.

Prof. AE Schutte   **Prof. R Kruger**   **Mr. P Labuschagne**

Summary

Motivation

Masked hypertension, a condition coined by Thomas Pickering, reflects a normal office and elevated out-of-office 24-h ambulatory blood pressure in untreated individuals. There are currently conflicting findings on the prevalence of masked hypertension between black and white ethnicities, and also between men and women. Most studies on masked hypertension have reported on elderly populations from Europe or the United States, or populations already diagnosed with cardiovascular disease. It is therefore imperative to seek better understanding of the frequency of masked hypertension in healthy young populations, but more importantly, to establish the possible effects of masked hypertension on subclinical organ damage. Although masked hypertension has been associated with left ventricular hypertrophy in the elderly, it is unknown if cardiac alterations are already present in young adults with masked hypertension. Masked hypertension might induce diastolic dysfunction, as shown in an elderly population. In addition, studies associating systolic dysfunction with masked hypertension are limited.

Aim

The aim of this study was to determine whether masked hypertension in young adults associates with left ventricular structure and function in black and white participants of the African-PREDICT study.

Methods

This study is affiliated with the larger African-PREDICT study (African Prospective study on Early Detection and Identification of Cardiovascular disease and hyperTension) conducted in and around the Potchefstroom area of the North West Province of South Africa. This cross-sectional study included 774 black and white men and women (aged 20-30 years) who had an office blood pressure <140/90 mmHg and no known cardiovascular disease, not taking any blood pressure

medication, no chronic disease, human immunodeficiency virus uninfected and not pregnant or breastfeeding.

Data with regards to age, sex and ethnicity was collected using a demographic and lifestyle questionnaire. Anthropometric measurements which included height, weight and waist circumference was obtained, we then calculated for body mass index (kg/m^2) and body surface area. Cardiovascular measurements included office brachial blood pressure, 24-h ambulatory blood pressure and transthoracic echocardiography. Fasted venous blood samples were collected and basic serum analyses included creatinine, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, total cholesterol, triglycerides, glucose, y-glutamyl transferase and cotinine. The Chronic Kidney Disease Epidemiology Collaboration equation was used to estimate glomerular filtrate rate from serum creatinine.

After no interaction was found for ethnicity and sex on the association between measures of left ventricular structure and function and masked hypertension, participants were stratified according to their masked hypertension status. T-tests and Chi-square tests were used to compare means and proportions between groups, respectively. Multivariable-adjusted logistic regression and multivariable-adjusted linear regression were used to investigate the relationship between left ventricular structure and function and masked hypertension. A p-value ≤0.05 was considered statistically significant.

Results

When taking into account that we excluded participants with sustained and white-coat hypertension, overall, 16.4% of the young participants had MHT. The frequency of MHT was higher among young men (27.1%) than women and higher in whites (20.3%) than blacks.

Higher left ventricular mass index was depicted in the masked hypertension group, both before (72.1 vs 80.9 g/m^2, p<0.001) and after adjusting for age, sex and ethnicity (74.4 vs 78.6 g/m^2, p=0.006).

Masked hypertensives had a 1.67 [1.05–2.71 95% CI] times higher odds of having increased left ventricular mass index than normotensives, after adjustment for age, sex, ethnicity, socio-economic status, waist circumference, estimated glomerular filtrate rate, y-glutamyl transferase and cotinine. There were no significant odds of left ventricular dysfunction nor relative wall thickness found in these masked hypertensives. We further performed multivariable-adjusted linear regression analyses, and confirmed an independent positive association between left ventricular mass index and masked hypertension (adj. R^2=0.193, β=0.08 [0.002; 0.16]; p=0.046).

Conclusion

Elevated left ventricular mass index is eminent in young masked hypertensives and poses increased risk for future left ventricular hypertrophy and cardiovascular disease in these individuals. Therefore, a false negative diagnosis of hypertension based on only clinic blood pressure, not only underestimates the true prevalence of hypertension, but also increases the risk of cardiovascular morbidity and mortality in these under-diagnosed, untreated and unaware individuals, as they already present with early onset target organ damage.

Keywords: ambulatory blood pressure monitoring, black, cardiovascular disease, ethnicity, left ventricular function, left ventricular mass index, masked hypertension, sex, young.

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List of Abbreviations

ABP	Ambulatory blood pressure
ABPM	Ambulatory blood pressure monitoring
AEE	Activity energy expenditure
BP	Blood pressure
BSA	Body surface area
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
cm	Centimetre
CVD	Cardiovascular disease
E/A	Ratio of mitral peak velocity of early and late diastolic filling
E/é	Ratio of mitral peak velocity of early filling to early diastolic mitral annular velocity
ECG	Electrocardiogram
EF	Ejection fraction
eGFR	Estimated glomerular filtrate rate
g/m^2	Grams per metre square
GGT	y-glutamyl transferase
HDL-c	High-density lipoprotein cholesterol
HIV	Human Immunodeficiency Virus
HREC	Health Research Ethics Committee

kCal/kg	Kilocalorie per kilogram
Kg	Kilogram
Kg/m^2	Kilogram per metre square
LA/Ao	Left atrial to aortic root ratio
LDL-c	Low-density lipoprotein cholesterol
LV	Left ventricular
LVH	Left ventricular hypertrophy
LVM	Left ventricular mass
LVMI	Left ventricular mass index
m	Metre
mg/dL	Milligram per decilitre
MHT	Masked hypertension
mmHg	Millimetre Mercury
mmol/L	Millimoles per litre
ms	Metre second
ng/ml	Nanogram per millilitre
OR	Odds ratio
RWT	Relative wall thickness
U/L	Units per litre
vs	Versus

WHT   White-coat hypertension

Chapter 1

Introduction & Motivation

1. Introduction

Hypertension is the leading cause of cardiovascular related morbidity and mortality [1, 2], with approximately 9.4 million deaths each year, worldwide [3]. Among the published data the prevalence of hypertension is higher in black when compared to white populations [4, 5]. The prevalence of hypertension is also highest in the African region at 46% of adults aged 25 and above [6]. Despite the highest reported rates of hypertension, the true burden of hypertension might be unknown.

Since the 19th century the importance of measuring arterial pressure for diagnosis and treatment was recognised using a mercury sphygmomanometer [7]. At that time, hypertension was reported to be the strongest predictor of future stroke and cardiovascular disease (CVD) especially heart failure and left ventricular hypertrophy (LVH). To date, diagnosis, management and treatment of hypertension are based on conventional blood pressure measurements (measurements at a clinic, also known as office blood pressure) at three separate occasions [8-11]. Noteworthy, most reports on the prevalence of hypertension are based on office blood pressure measurements. However, office blood pressure measurements are associated with a number of limitations.

In contrast to office blood pressure, the 24-h ambulatory blood pressure measurement reflects blood pressure patterns out-of-office, allowing the detection of white-coat hypertension, sustained hypertension, nighttime dipping of blood pressure, sustained normotension and masked hypertension (MHT) [12]. White-coat hypertension and MHT are respectively defined as either having only an elevated office blood pressure or elevated out-of-office blood pressure as shown in **Figure 1**. True prognostic information on hypertension is therefore more reliably provided by ambulatory blood pressure measurements, as office blood pressure measurement either overestimates or underestimates the diagnosis of hypertension [13]. Moreover office blood pressures are inferior predictors of long term CVD as compared to out-of-office blood pressures [13, 14].

With sustained normotension and sustained hypertension, the two methods (office and ambulatory measurements) are concordant. When the methods are discordant, white-coat hypertension and MHT are apparent **(Figure 1)** [15]. Mounting evidence indicate that MHT has a more detrimental effect on target organs such as the vasculature, the kidney and the heart in comparison to white-coat hypertension [15, 16], as white-coat hypertension is associated with less target organ damage or established CVD [17, 18], although both conditions are not benign. Due to the African-PREDICT study inclusion criteria, individuals with white-coat hypertension were excluded, and hence the focus of this study will be on MHT.

Sustained normotensives by both methods (True normotensives)	Sustained hypertensives by both methods (True hypertensives)
Hypertensive by office blood pressure method and normotensive by out-of-office (WCH)	Normotensive by office blood pressure method and hypertensive by out-of-office (MHT)
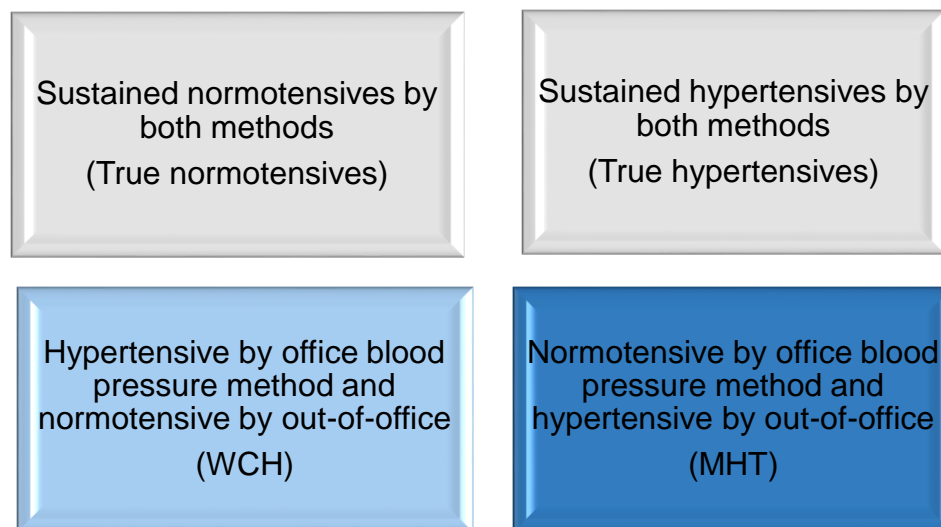
Figure 1. Office blood pressure vs out-of-office blood pressure measurement adapted from Rizonni [19]. Abbreviation: WCH, white-coat hypertension; MHT, masked hypertension.

MHT, a precursor of sustained hypertension, was first introduced several years ago [20, 21]. Studies have indicated that MHT shows the same adverse effect as sustained hypertension, with attention given to target organ damage in the kidneys, vasculature and heart [22-24]. In addition, a longitudinal study conducted in Sweden was the first study to indicate that masked hypertensives are at a greater risk of CVD than normotensives [25]. In this cohort of 578 untreated 70 year old men, 72 cardiovascular morbid events occurred over 8.4 years of follow-up, with MHT

being an independent predictor of cardiovascular morbidity. To date, studies have confirmed that masked hypertensives carry higher cardiovascular risk as compared to sustained normotensive but approaching the risk associated with sustained hypertensives [7, 26-28]. Overall, this implies that individuals that are diagnosed as normotensives in the clinical setting might be hypertensive and already be subjected to target organ damage. A delay in diagnoses of MHT not only increases the prevalence of hypertension but also increases the chances of target organ damage such as LVH and left ventricular dysfunction [29, 30].

In a population-based study of CVD among African Americans, MHT was found to associate with left ventricular structural changes, primarily LVH in an elderly population with a mean age of 60 years [23]. This finding was confirmed in the elderly [31] and clinic normotensive children [20]. Diastolic dysfunction was reported to be prevalent in the elderly population with MHT independent of LVH [30]. Masked hypertensives were found to present with similar ejection fraction, a parameter of systolic function, as normotensives [12]. These findings are further summarised in **Figure 2**. It is, however, not clear if these findings can be generalised to young adults.
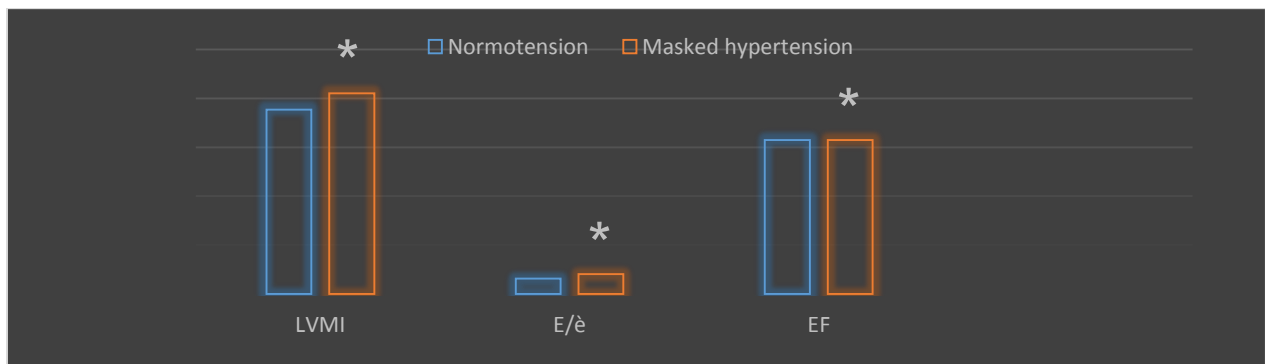
Figure 2. Left ventricular structure and function of masked hypertensives vs normotensives in an elderly population [12, 23]. Abbreviations: LVMI, left ventricular mass index; E/é ratio, ratio of mitral peak velocity of early filling to early diastolic mitral annular velocity (é); EF, ejection fraction. *: denotes $p<0.05$

Despite the negative cardiovascular effects related to MHT, the predictors of MHT including sex [24] and ethnicity [32] are poorly understood – particularly within South Africa. Although it is well

known that hypertension is predominant in blacks as compared to whites, [32] these findings do not include MHT, particularly in young adults.

2. Motivation

It has been well established that MHT is not an innocuous clinical state. Studies have associated MHT with increased target organ damage such as LVH and left ventricular dysfunction either in elderly people, clinic normotensive children or diseased populations (CVD or clinic hypertensives) [20, 23]. However, the relationship of left ventricular structure and function with MHT is not well established in healthy young black and white adults. These young adults consist of a population that is unaware of their out-of-office blood pressure profile.

Since it has been projected that hypertension will increase by 89% in sub-Saharan Africa compared with a rate of 24% in developed countries [2], it is imperative to establish the prevalence of MHT in young black and white adults as the projected prevalence might be under-estimating the expected CVD burden in sub-Saharan Africa.

To our knowledge this is the first study in the sub-Saharan African region to investigate the association of left ventricular structure and function with MHT in young black and white adults.

Key points

1. Out-of-office BP is superior to clinic BP and is a stronger predictor of CVD than clinic BP [13, 14].

2. MHT is not a benign condition and it associates with target organ damage, primarily left ventricular structural changes and left ventricular dysfunction in the elderly [12, 23, 30].

3. Most studies on MHT and its effect on target organ damage are based on the elderly, children and diseased populations [20, 31].

4. Little is known about MHT and its effect on target organ damage in young black and white adults.

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Chapter 2

Literature Background

Aim, Objectives & Hypotheses

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1. Masked hypertension

1.1. Definition

Masked hypertension (MHT) also known as "reverse white-coat", "white-coat normotensive" and/or "isolated ambulatory hypertension" [1, 2], was first described by Thomas Pickering *et al.* in 2002 [2]. MHT refers to a condition with normal clinic blood pressure (Blood pressure (BP)<140/90 mmHg) and elevated 24-h ambulatory BP≥130/80 mmHg (awake ambulatory BP≥135/85, sleep ambulatory BP≥120/70 mmHg) in untreated individuals [3]. In cases of normal office and normal out-of-office daytime blood pressure, but elevated nighttime blood pressure, the condition is termed isolated nocturnal (masked) hypertension [3, 4]. When MHT occurs in treated individuals the term masked uncontrolled hypertension is used. The European Society of Hypertension position paper suggests that MHT (untreated individuals) and masked uncontrolled hypertension (treated individuals) be used as separate entities [5]. For the purpose of this review I will focus on MHT.

1.2. Prevalence

In large prospective cohort studies the estimated prevalence of MHT in the general elderly (40-70 years) population ranges from 8.5 to 16.6% [6]. Furthermore, the prevalence of MHT ranges from 15-30% in elderly with normotensive clinic blood pressure levels [6]. Moreover, in a meta-analysis a mean prevalence of 16.8% was reported, and the differences in the prevalence of MHT between the adults (19%) and children (7%) were also noted [7]. Matsuoka and Awazu were the first to report on the prevalence (11%) of children aged ≤ 15 years [8]. Another study from Lurbe *et al.* [9] reported the prevalence of MHT in 592 youth (aged 6-18 years) to be 7.6%. Recently, Lurbe *et al.* in a follow-up study consisting of 272 youth found the prevalence to be 14.3% [10]. The Coronary Artery Risk Development in Young Adults (CARDIA) study, a prospective cohort study, reported the prevalence of MHT in young adults (18-30 years) to be 6.5% [11]. Noteworthy, there are very limited studies that reported on the prevalence of MHT in young adults, particularly in the sub-Saharan African region.

Not only does the prevalence of MHT vary because of different study populations, but also due to different definitions of MHT used in different studies [1, 12]. The 15-30% reported prevalence as mentioned above is only based on daytime and 24-h ambulatory blood pressure monitoring (ABPM). According to the European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension, the prevalence of MHT is 10-17% based on daytime ABPM only [13]. However in the Jackson Heart study – a population-based prospective cohort, when using daytime, nighttime and 24h-ambulatory measurements the prevalence is as high as 52% [14] **(Figure 1)**.
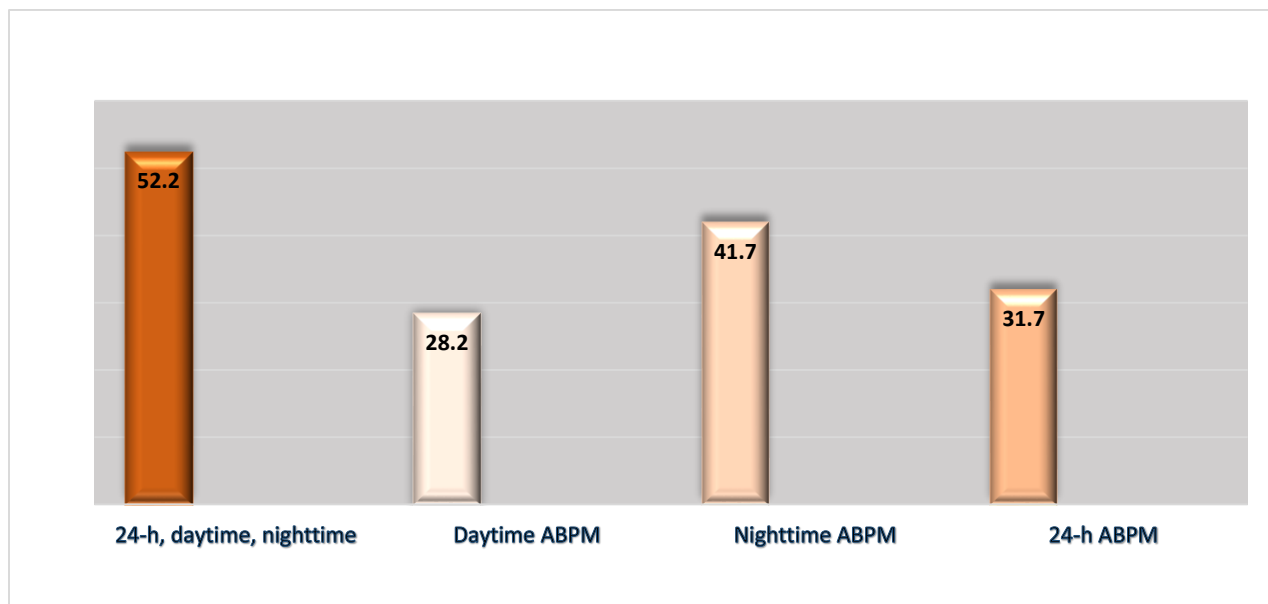
Figure 1. Prevalence of masked hypertension based on 24-h, daytime, nighttime and combined ambulatory measures reported by Booth *et al.* [14]. Abbreviation: ABPM, ambulatory blood pressure monitoring.

2. Assessment of masked hypertension

ABPM and home blood pressure monitoring have been recommended by national and international guidelines in the management of hypertension. However, ABPM is considered the golden standard method in evaluating true blood pressure patterns [15-18].

2.1. Ambulatory blood pressure monitoring

The evaluation of out-of-office blood pressures is not a recent practice but tracks back over 80 years [19], with Ayman and Goldshine in the 1940s recognising a difference between the blood pressure levels taken at the clinic setting and home setting [20]. It was only in the 1960s where a non-invasive device was brought to existence [21]. With the aid of the non-invasive device, Perloff *et al.* [22], 43 years after the publication of Ayman and Goldshine, established that ambulatory blood pressure measurements are superior to clinic blood pressure measurements [19].

Today, 24-h ABPM is known to provide automated blood pressure measurements in regular intervals over a 24-h period, comprising a complete cycle of wakefulness and sleep [18, 23]. In addition, ABPM is a better predictor of cardiovascular morbidity and mortality than clinic blood pressure. It can diagnose both white-coat hypertension and MHT [23-25]. ABPM can also detect circadian variations such as non-dipping, reverse dipping, and augmented morning surge; which are independently associated with increased risk of cardiovascular events [25-28].

Regardless of these advantages, it is well known that it is impractical to screen the entire population for MHT. It was demonstrated that such an approach would require 118.6 million adults in the United States to undergo out-of-office blood pressure measurements [29]. Another challenge besides high costs, is the limited reproducibility of ABPM [30]. It was reported that the short term (<1 month) reproducibility of MHT was moderate (68%) but long term reproducibility was poor (38%) with a shift towards sustained hypertension [31]. Lurbe *et al.* [9] after a follow-up of 45 masked hypertensive youth, found 53% to have regressed to the normotensive state, 9% progressed to sustained hypertension and 38% individuals persisted with MHT - translating to approximately 1 out of 3. Moreover, some patients are unable to wear the ABPM for the full 24-h period due to sleep disruption. To add on, a question remains, who should be screened for MHT?

2.2. Strategies on diagnosing masked hypertension

Studies suggests that clinic blood pressures be used as a guideline to screen individuals, referring to individuals with pre-hypertension who should then be considered for ambulatory measurements [32-35]. Using this approach, it was postulated that approximately 59.3 million United State adults would need to undergo ABPM although it is not cost-effective [29]. However, no study has been conducted on whether screening for MHT in clinic normotensives would be cost-effective [6]. It has been argued that since the prevalence of MHT is low in clinic normotensives as compared to clinic pre-hypertensives, it might be futile to have them as first priority [6, 34]. Therefore, another approach would be to screen individuals that already present several risk factors associated with MHT such as male gender, obesity and smoking [6, 36].

3. Predictors of masked hypertension

Several factors such as age, obesity, male gender, smoking and physical activity have been suggested to be associated with MHT [17, 37-39]. The underlying mechanism of these risk factors and their relation to MHT is not well understood. **Table 1** lists the factors that are associated with MHT, and are discussed below.

3.1. Ethnicity

The Jackson Heart Study found a higher prevalence of MHT in African Americans as compared to other international population-based studies of different ethnic groups [40]. In contrast with the above findings, Odili *et al.* [41] found similar prevalence of MHT among black Nigerians, when compared to Japanese and white people from a reference population enrolled in an international database. Supporting the findings of Odili *et al.*, early findings by Thompson *et al.* from n=352 participants of the African Prospective study on the Early Detection and Identification of hyperTension and Cardiovascular Disease (African-PREDICT; a bi-ethnic cross-sectional study), also found no evidence of ethnic difference between young South African blacks and whites in the prevalence of MHT [42].

Table 1. Factors associating with a high risk of masked hypertension [17, 37-39]

Ethnicity
Male gender
Age
Smoking
Alcohol consumption
Excess physical activity
Pre-hypertension clinic status
Obesity
Diabetes
Working or living in a stressful environment
Chronic kidney disease
Obstructive sleep apnea and non-dipping

The CARDIA Study reported similar findings as Odili *et al*. and Thompson *et al*. However, they noted that the prevalence of nocturnal hypertension, a subtype of MHT, was higher in blacks as compared to whites [11]. Kent *et al.* [43], demonstrated in a population that included HIV infected individuals, also that blacks had higher prevalence of nighttime MHT and were most likely to be non-dippers as compared to whites. However, Kent and colleagues reported no difference in the prevalence of daytime hypertension between blacks and whites.

3.2. Gender and age

Previous studies have reported MHT predominantly in men [4, 41, 44]. In a study involving 6 to 18 year old youths reported that boys (9.8 ± 1.8 years) with MHT were more likely to develop sustained hypertension as compared to masked hypertensive girls (9.3 ± 2.3 years) [10]. A study of 694 Chinese consisting of 317 men (50 ± 15.5 years) and 377 women (47.2 ± 14.4 years) also found that women were less likely than men to have MHT [45]. Similarly in an Italian study of 1,488 patients the risk of MHT was higher in men than in women [46].

Male sex is not the only risk factor contributing to MHT, but also age. The current state of knowledge indicates that advanced age relates to decreased baroreceptor sensitivity and increased blood pressure variability, resulting in an increased prevalence of MHT [4, 47]. Although this may be true, Gorostidi *et al.* [17] reported MHT to be more frequently observed in younger individuals. Moreover Pickering *et al*. [37] also suggested that MHT occurs more frequently in young people, postulating that this could be due to anxiety, as young people compared to the elderly might be calm in clinic setting and therefore masking their hypertension state.

White-coat effect, defined as the difference between clinic blood pressure and daytime blood pressure, is negative in masked hypertensives and normotensives but positive in sustained hypertensives and white-coat hypertensives [37]. Therefore, negative white-coat effect is associated with low levels of anxiety as compared to positive white-coat effect. Furthermore, in a general population, the rise of nighttime and daytime blood pressure were associated with increasing age, although clinical blood pressure level showed a steeper rise than daytime ABPM in elderly individuals as compared to the young, shown in **Figure 2** [18]. This is further supported by another study, which reported that ambulatory blood pressure rises less with increasing age as compared to clinic blood pressure [48].

In addition, age and gender do not change in office and out-of-office, implying that there are other factors such as lifestyle habits associated with MHT.
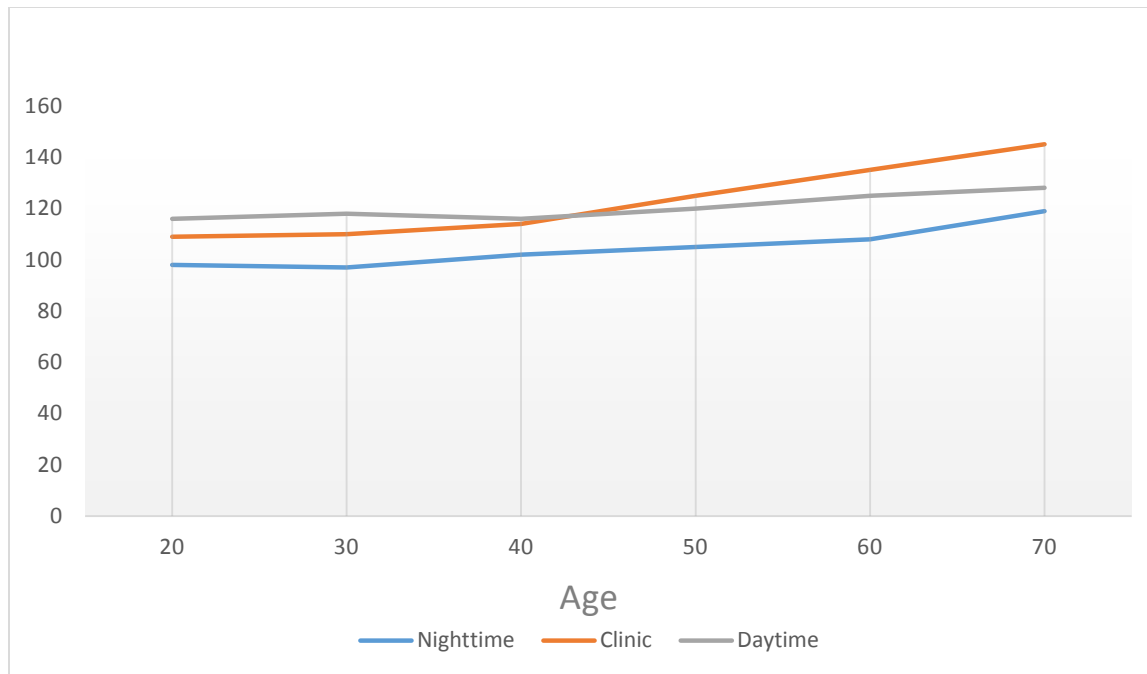
Figure 2. Clinic, daytime and nighttime blood pressure levels associated with increasing age adapted from Pickering *et al.* [18].

3.3. Health behaviours

3.3.1. Smoking

Nicotine in cigarette smoking can acutely raise blood pressure [49]. Hence, in a cross-sectional study smokers were found to have abnormal ambulatory blood pressure levels [50]. Again, Ungar *et al.* [46] reported the risk of MHT to be higher in current smokers. However, in another study it was suggested that attention should not only be given to smoking patients but to also focus on passive smokers [51], as non-smoking women in a general population exposed to passive smoking was reported to present with higher out-of-office blood pressure levels as compared to those that are not exposed to passive smoking [52].

3.3.2. Alcohol

High alcohol consumption has been associated with MHT [53]. In a Japanese study of 3,400 patients, not only excess alcohol consumption (OR: 1.38; 95% CI: 1.09–1.75) but also regular alcohol intake (OR: 1.37; 95% CI: 1.09–1.72) was associated with MHT [54]. Ishikawa *et al.* [55]

also demonstrated that patients who self-reported having at least one alcoholic drink every day had a 76% increased odds ratio for morning MHT as compared with those that do not drink alcohol every day. This could be explained by a decrease in blood pressure levels (within 4 hours) soon after alcohol intake and an increase approximately 10 hours later. Therefore excess alcohol intake causes an increase in morning surge, as shown in **Figure 3** [51, 53].

Masked morning hypertension	• Heavy drinking • Excess physical activity • Sleep apnea • Obesity/metabolic syndrome
Masked daytime hypertension	• Job strain • Smoking • Excess physical activity
Masked nighttime hypertension	• Job strain • Obstructive sleep apnea • Chronic kidney disease • Diabetes
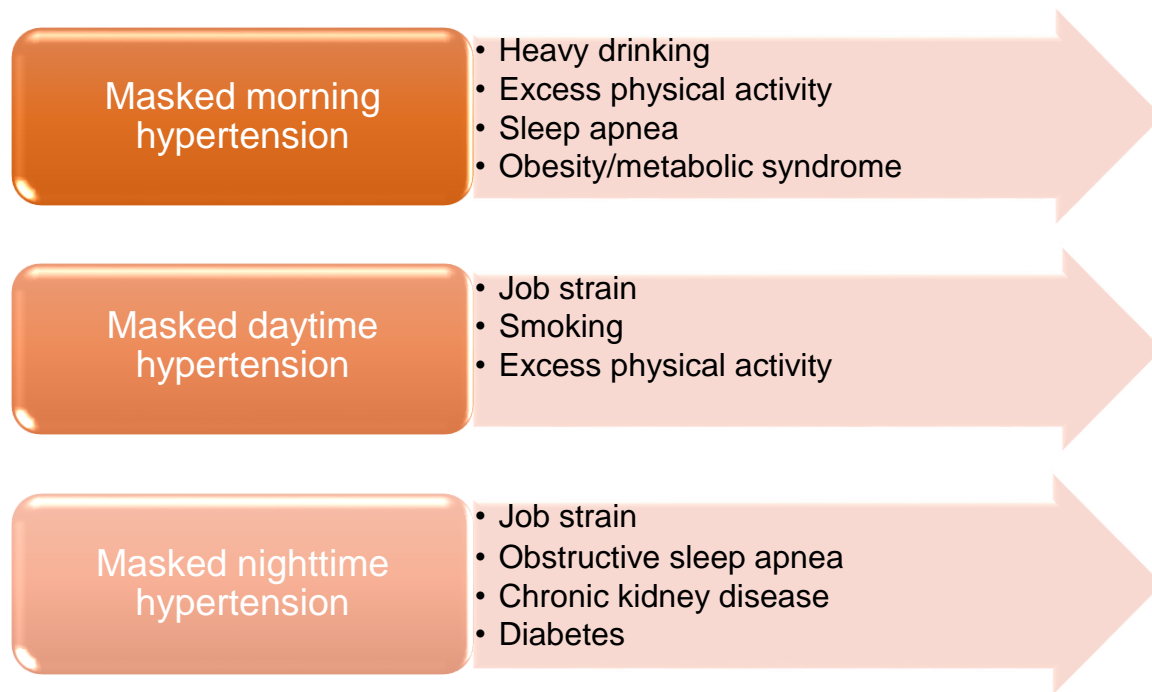
Figure 3. A summary of the risk factors of masked hypertension stratified according to masked hypertension sub-types adapted from Yano & Bakris [51].

3.3.3. Physical activity

One of the advantages of 24-h ABPM is that it can reflect blood pressure levels throughout the day when the patient is active. Therefore Leary *et al*. [56] monitored 24-h ambulatory blood pressure and activity in 431 patients. They found ambulatory blood pressures to strongly correlate to the levels of physical activity and the subjects who were more physically active tended to have higher daytime blood pressure. Furthermore, Sharman *et al.* [57] evaluated the prevalence of MHT in 72 untreated participants with a hypertensive response to exercise (defined as clinic

BP<140/90 mmHg and exercise systolic BP≥210 mmHg in men or BP≥190 mmHg in women, or diastolic BP≥105 mmHg). Sharman and colleagues found MHT to be prevalent in 58% of participants and was associated with increased left ventricular mass index (LVMI) compared to clinic normotensives without a hypertensive response to exercise.

3.3.4. Metabolic syndrome

Sedentary lifestyle and obesity are prominent in masked hypertensives. Kenny *et al.* [39] reported 17.1% prevalence of MHT in overweight and obese individuals. In the same study, it was demonstrated that individuals with MHT were not only obese, but also had 61% likelihood to have metabolic syndrome as compared to normotensives.

According to the harmonized definition from the International Diabetes Federation; the National Heart, Lung, and Blood Institute; the American Heart Association; the World Heart Federation; the International Atherosclerosis Society; and the International Association for the Study of Obesity, metabolic syndrome is defined as follows [58]:

- SBP of 130-139 mmHg or DBP of 85-89 mmHg

- Abdominal obesity defined as waist circumference ≥88 cm (women) and ≥102 (men)

- Impaired glucose (≥100 mg/dL) or diabetes

- Low high-density lipoprotein cholesterol (HDL-c): <50 mg/dL among women and <40 mg/dL among men

- High triglycerides (≥150 mg/dL)

Colantonio *et al.* [32] also found a higher prevalence of MHT in individuals with metabolic syndrome as compared to those without metabolic syndrome. However, in this study Colantonio and colleagues noted that only clinic blood pressure as compared to other components (impaired glucose, low HDL-c, high triglycerides and abdominal obesity) of the metabolic syndrome contributes to the association between metabolic syndrome and MHT. In contrast, the Finn-Home

study [59] and the Ohasama study [60] reported that waist circumference is higher among adults with MHT as compared to sustained normotensives. Moreover, other studies also found an association between high levels of glucose and triglycerides with MHT [33, 61].

Besides these unhealthy behavioural factors there also other predictors of MHT.

3.4. Mental stress

Mental stress at home or at work may result in normal clinic blood pressure levels and elevated ambulatory blood pressures due to stressful circumstances. In a study involving 2369 white-collar workers, demonstrated workers exposed to effort-reward imbalance had 53% higher odds of MHT [63]. Effort-reward imbalance is defined as an inadequate reciprocity between efforts spent at work and reward received in exchange such as salary, social esteem and career opportunities. Therefore increased demands of work, nightshifts and overtime with little remuneration can result in work stress and the likelihood of MHT [51, 63]. Again, unhealthy behaviours such as excess alcohol consumption and smoking play a role in MHT induced by stress [64].

3.5. Obstructive sleep apnea and non-dipping

Shortened sleep, observed often in adolescents, and obstructive sleep apnea are associated with MHT, particularly nocturnal hypertension [65, 66]. Drager *et al.* [67] noted that obstructive sleep apnea also associates with daytime ambulatory blood pressures, thereby indicating that obstructive sleep apnea might also affect ambulatory blood pressure beyond sleep period [68]. In a study including 130 (111 men, age=48 ± 1 years and body mass index=27.6 ± 0.4 kg/m^2) newly diagnosed obstructive sleep apnea syndrome patients, free of recognized cardiovascular disease, reported 39 (30.0%) presenting with MHT [69].

Moreover, individuals whose nocturnal blood pressure declines <10% of their mean daytime blood pressure are classified as non-dippers [70]. Non-dipping - a predictor of cardiovascular morbidity and mortality, associate with target organ damage including left ventricular hypertrophy (LVH) [71].

Of note, in patients with diabetes with autonomic dysfunction and renal dysfunction, blood pressure persistently increases mainly at night [51, 68].

3.6. Chronic kidney disease

Chronic kidney disease (CKD) is predominantly associated with non-dipping blood pressure than awake blood pressure [51, 72]. In a study including 5693 patients from a Spanish ABPM Registry with CKD stages 1-5, 7.0% had MHT [73]. In a Chronic Renal Insufficient study, patients identified by reduced glomerular filtration rate, had a prevalence of MHT as high as 28%, primarily nocturnal hypertension [74]. Moreover, in children with CKD, LVH was four times more frequent in the presence of MHT as compared to those with normal ABPM [75]. Therefore it is suggested that CKD patients that have normal office blood pressure but show adverse target organ damage such as cardiac hypertrophy, should be evaluated using ABPM [6, 51].

3.7. Diabetes

MHT is common in patients with diabetes, particularly showing increased nighttime blood pressure levels, as mentioned above [70, 76, 77]. In a study by Franklin *et al.* [76] that examined 7826 subjects from the IDACO database not taking antihypertensive medication, it was found that the prevalence of MHT was 29.3% in the clinic normotensives with diabetes and 18.8% in individuals without diabetes. In addition, MHT in diabetic patients have been associated with target organ damage such as arterial stiffness and LVH [78, 79].

4. Masked hypertension and left ventricular structure and function

It is well established that MHT associates with cardiac alterations such as increased left ventricular mass (LVM) and diastolic and systolic dysfunction in the elderly, hypertensive/ diseased population and clinic normotensive children (excluding left ventricular dysfunction) but it is unknown for young adults [80-82]. Below I will further discuss the relationship of MHT and left ventricular structure and function.

4.1. Left ventricular structure and masked hypertension

4.1.1. Background of left ventricular structure

The first definitions of left ventricular structure remodeling were developed by Linzbach, 50 years ago, today still known as concentric remodeling, eccentric hypertrophy and concentric hypertrophy depicted in **Figure 4** [83, 84]. Concentric hypertrophy and eccentric hypertrophy are caused by an increase in pressure overload and volume overload, respectively. Both Linzbach [83] and Grant *et al.* [85] based their definitions on 2 factors: 1) the presence or absence of LVH; and 2) the presence or absence of left ventricular chamber enlargement. Of interest, neither Linzbach nor Grant *et al.* defined a specific range of normal for relative wall thickness (RWT). Currently, according to the European Association of Cardiovascular Imaging and the American Society of Echocardiography, normal RWT is defined as the ratio twice the posterior wall thickness and the left ventricular diastolic diameter with values ranging from 0.32 to 0.42 [84]. When incorporating RWT cut-off values with left ventricular dilatation and LVM to classify LVH, new concepts surfaces, such as physiologic hypertrophy **(see Figure 5)**, which I will discuss in detail in the next section.
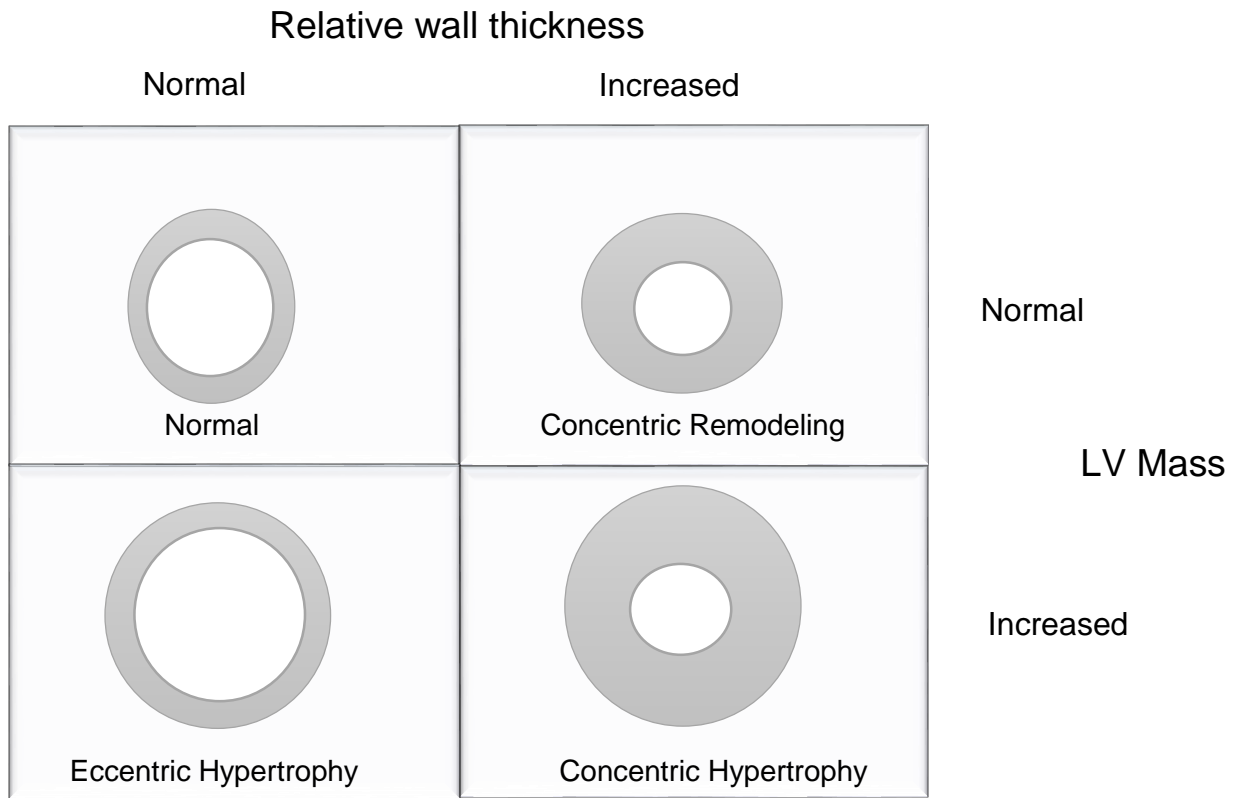
Figure 4. Four patterns of left ventricular geometry: normal LV geometry (normal LVM and lower value of RWT), eccentric LV hypertrophy (increased LVM and lower value of RWT), concentric LV hypertrophy (increased LVM and RWT) and concentric LV remodeling (normal LVM and increased RWT adapted from Drazner [86]. Abbreviation: LV, left ventricular; LVM, left ventricular mass; RWT, relative wall thickness.

End diastolic volume **LVM** **RWT** **Classification**

Left ventricular dilatation

- No
  - No
    - RWT 0.32 - 0.42 → Normal
    - RWT > 0.42 → Concentric remodeling
  - LVH → RWT > 0.42 → Concentric hypertrophy
- Yes
  - LVH
    - RWT > 0.42 → Mixed hypertrophy
    - RWT 0.32-0.42 → Physiologic hypertrophy
    - RWT < 0.32 → Eccentric hypertrophy
  - No → RWT < 0.32 → Eccentric remodeling
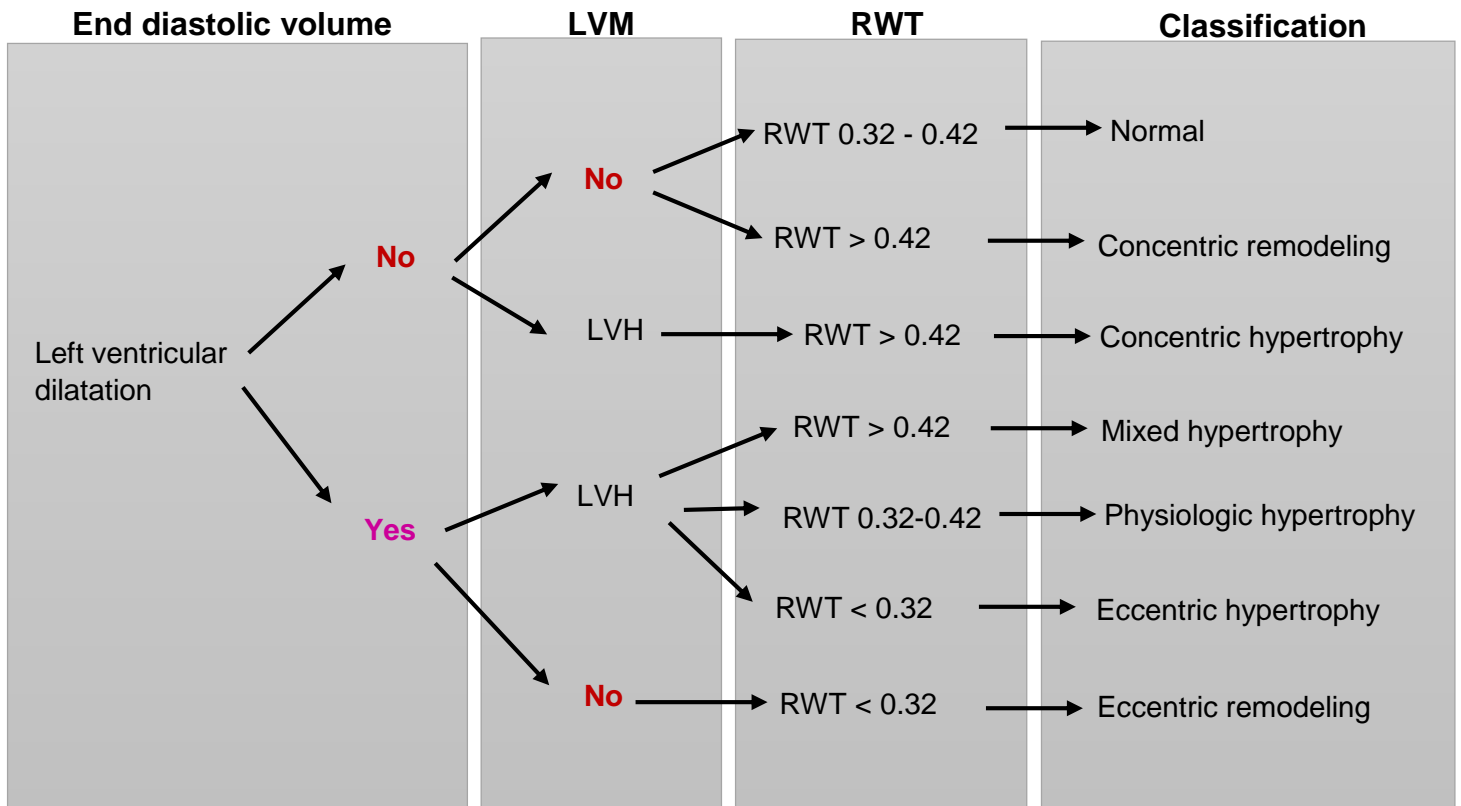
Figure 5. Patterns of left ventricular remodeling based on left ventricular dilation, left ventricular mass and relative wall thickness adapted from Gaasch & Zile [84]. Abbreviation: LVH, left ventricular hypertrophy; RWT, relative wall thickness.

4.1.2. Left ventricular hypertrophy

LVH is defined as an increase in myocardial muscle mass primarily due to enlargement or proliferation of the cardiomyocytes [87, 88]. The increase in mass plays the most important role in the adaptive response to myocardial load caused by an increase in pressure overload or volume overload, to normalise wall stress [87, 89, 90].

The increase in mass is a result of a stimulation of an intricate web of intracellular signaling cascades that activate gene expression and promote protein synthesis and stability, with consequent increases in protein content, in the number of force-generating units (sarcomeres) and in the size of individual cardiomyocytes [87].

The increase in the size of cardiomyocytes is not the only pathophysiologic change that occurs in the left ventricle, but also alterations in the extracellular matrix are observed **(Figure 6)** in the hypertrophied ventricle [91]. In this hypertrophied ventricle, fibrosis develops in the extracellular matrix, this is caused by proliferation of fibroblasts and increased accumulation of collagen type I and III, which impair contractility. These structural changes in the myocardial tissue composition contribute to left ventricular stiffness, which ultimately leads to diastolic and systolic left ventricular dysfunction [87, 92].
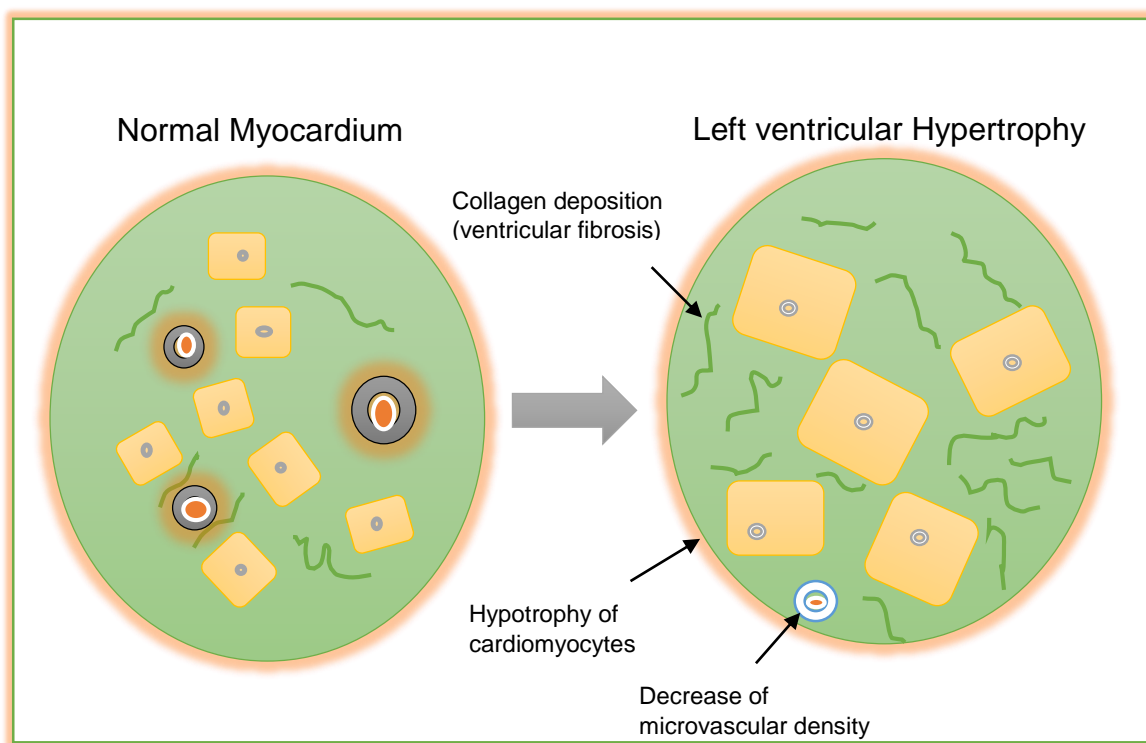
Figure 6. Extracellular changes within the hypertrophied left ventricle adapted from Angeli & Ambrosia [81].

The development of LVH is not only influenced by an increase in pressure overload (MHT) or volume overload (valvular disease). Many other factors are associated with an increase in LVM which include among others age, race, sex, obesity and physical activity [93-96]. Therefore, left ventricular structure remodeling could either be pathological or physiological.

4.1.3. Physiologic and pathologic adaptation

LVM has an indirect relationship with age while RWT increases with age. Therefore an age-related concentric remodeling with systolic and diastolic dysfunction exist [94]. The LVM is also influenced by body size; with men, obese individuals and athletes having a higher LVM as compared to women, lean individuals and non-athletes, respectively [95-97]. Hence, LVM should be corrected for height (LVM/height$^{2, 7}$, g/m$^{2, 7}$) [98]. However, the effect of obesity on LVM is still preserved. Therefore, indexing LVM for body surface area (BSA) effectively corrects not only for height, but also obesity related LVH (LVM/BSA, g/m^2) [94, 98]. On the other hand, Foster *et al.* [99] reported indexation for BSA or height to underestimate or overestimate LVM, respectively. Foster and colleagues proposed lean body mass as the ideal scaling variable for normalisation. Although lean body mass can be measured by dual-energy X-ray absorptiometry, it is clinically difficult to ascertain. Therefore LVM/height^{2,7} and LVM/BSA remain the most used indexation in research and by clinicians.

To further explain the physiologic adaption of LVH, I will mainly focus on exercise.

Exercise is characterised by myocardial adaptations sufficient to meet increased demands while maintaining normal function [88]. Isometric/strength training (anaerobic exercise) increases afterload, thereby stimulating concentric hypertrophy, while long-term endurance (aerobic) exercise increases venous return and blood volume, and hence preload, therefore stimulating eccentric LVH [88, 97, 100]. Although both physiologic adaptation and pathologic adaptation result in a form of hypertrophy, the two differ greatly, see **Table 2**. Pathologic LVH is distinguished from physiologic LVH, when the myocardial adaptations are unable to satisfy the increased demands or when they are only able to meet the increased demands at the expense of normal function [87, 88].

Figure 7 mainly demonstrates the pathologic adaptation imposed by MHT, in which it results in concentric hypertrophy. Despite this compensatory effect, LVH is associated with preclinical

cardiovascular abnormalities such as myocardial infarction and increased incidence of cardiovascular events [97, 98].

Overall physiologic adaptation may result in structural changes but the left ventricular function remains normal, while pathologic adaptation causes structural and functional changes that could lead to mortality.

Table 2. Summary of the characteristic differences between pathologic and physiologic left ventricular hypertrophy [88].

	Pathologic LVH		Physiologic LVH	
	Concentric	Eccentric	Concentric	Eccentric
Stimulator	Increased pressure (afterload)	Increased volume (preload)	Increased pressure (afterload)	Increased volume (preload)
Etiology of Stimulus	Masked hypertension	Valvular disease	Strength training	Long term endurance exercise
Ventricle morphology	Parallel addition of new myofibrils (wall thickening) and increased fibrosis	Series addition of sarcomeres (wall dilation and thinning)	Parallel addition of new myofibrils (wall thickening) with increased capillary density	Series addition of new sarcomeres (chamber volume enlargement)
Ventricular mechanics	Diastolic dysfunction with stiffness and decreased contractility	Decreased contractility often associated with side-to-side slippage of myocytes	Normal or enhanced contractility and myocardial efficiency	Normal or enhanced contractility and myocardial efficiency
Ventricular function	Abnormal	Abnormal	Normal	Normal or supranormal
Potential to regress	No	No	Yes	Yes

Figure 7. Schematic representation of hypertrophic remodeling due to increased afterload resulting in concentric remodeling adapted from Müller & Dhalla [101].
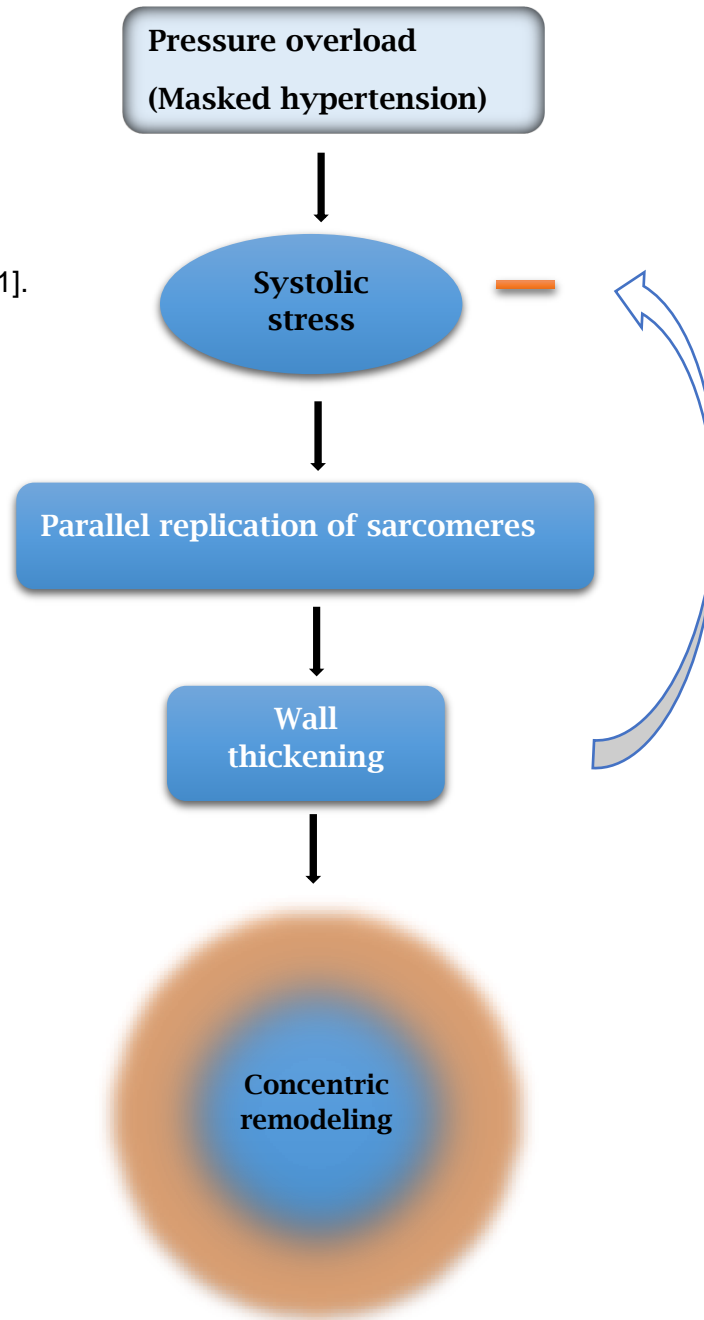
4.1.4. Masked hypertension and left ventricular structure

MHT was reported to be associated with left ventricular structural changes, primarily LVH in people older than 44 years [40, 44, 102]. In a cross-sectional study including 169 patients, masked hypertensives were found to have a higher LVMI as compared to normotensives [82]. Similarly in a meta-analysis involving 12 studies, the prevalence of LVH was reported to be higher in masked hypertensives than normotensives [44]. According to another study involving the investigation of cardiac remodeling and MHT, it was found that not only does MHT lead to LVH, but also lowering of diastolic function [103].

4.2. Left ventricular diastolic function and masked hypertension

Diastolic dysfunction is detected using the diastolic function parameters such as left atrial to aortic root ratio (LA/Ao), peak velocities of both early (E) and atrial (A) diastolic filling (E/A ratio), mitral valve deceleration time and the golden standard parameter of mitral valve competence, the E/e' ratio.

There are factors that influence these diastolic parameters, such as age. For example, E/A ratio increases with age while deceleration time decreases [104]. Heart rate, cardiac output, left atrial function, left ventricular end-systolic or end-diastolic volumes, and left ventricular elastic recoil are among other factors that influences mitral inflow [104, 105].

4.2.1. Pathophysiology of masked hypertension and diastolic dysfunction

Relaxation is the process by which, after the completion of ejection, myocardial fiber restores its length, which is between the minimal end-systolic length and the maximal end-diastolic stretch [92, 106]. That is restoration of the forces of elastic components of the heart, compressed during systole. Therefore, left ventricular diastolic dysfunction is due to impaired left ventricular relaxation which is a result of increased left ventricular chamber stiffness, resulting in increased filling pressures [107]. Masked hypertensives subjected to LVH, present with myocardial stiffness which results in diastolic dysfunction.

In addition, left ventricular diastolic dysfunction can occur in the absence of LVH [108]. Oe *et al.* [109] reported impaired diastolic function as a subclinical indicator of MHT before the development of left ventricular structural changes. This can be detected as grade I diastolic dysfunction, stiffness occurring due to ageing [92, 94].

4.2.2. Findings on masked hypertension and diastolic function

The Masked Hypertension Study, including 790 elderly participants with a mean age of 46 years old, found no difference in E/A ratio and deceleration time of masked hypertensives as compared to normotensives when age, sex, ethnicity and body mass index were adjusted for [109]. However E/e' ratio, the golden standard parameter recommended by American Society of Echocardiography, was found to be altered in masked hypertensives. Tadic *et al.* [82], not only reported increased E/e' ratio in masked hypertensives but also found E/A ratio to decrease as compared to normotensives.

4.3. Left ventricular systolic function and masked hypertension

In untreated hypertension, not only does the state of diastolic dysfunction deteriorate, but systolic dysfunction becomes prominent [94]. Systolic function is monitored through endocardial fractional shortening and left ventricular ejection fraction.

4.3.1. Findings on masked hypertension and systolic function

Left ventricular ejection fraction was reported to be normal and similar between normotensive, sustained and masked hypertensive elderly individuals [82, 103, 110]. To add on, in an ongoing, worksite-based study of the prevalence, predictors and prognosis of MHT, not only ejection fraction but also fractional shortening of masked hypertensives (mean age of 48 years old) were similar to normotensives (mean age of 45 years old) [109]. Nonetheless, little is known about the association between systolic dysfunction and MHT, particularly in young adults.

5. Integration of findings linking masked hypertension to cardiac alterations

```
                    Masked hypertension
                            │
                            ▼
                    Pressure overload
                    ╱               ╲
                   ╱                 ╲
                  ▼                   ▼
   Elderly, clinic normotensive    Young clinic
   children and diseased           normotensive adults
   population (CVD and clinic
   hypertensives) [9, 80-82]
           │                          │
           ▼                          ▼
   Left ventricular hypertrophy      ?
   [44, 103]
           │                          │
           ▼                          ▼
   Left ventricular dysfunction      ?
   [109]
            ╲                        ╱
             ╲                      ╱
              ▼                    ▼
         Susceptible to cardiovascular
         morbidity and mortality
         (myocardial infarction and stroke)
         [96, 97]
```
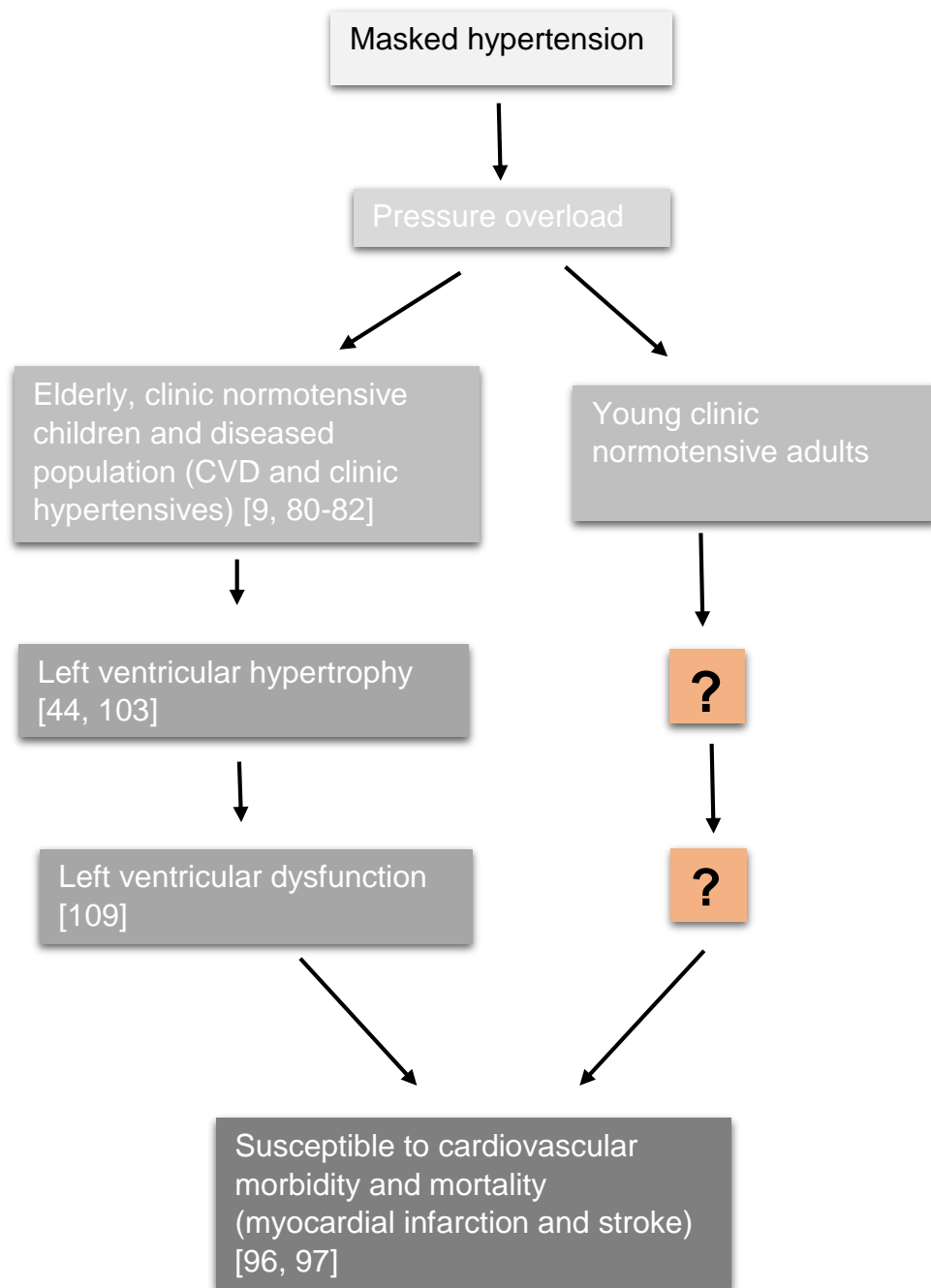
5.1. What is known?

❖ MHT is diagnosed based on daytime, nighttime and 24-h ABPM [14].

❖ The prevalence of MHT varies greatly among studies based on the different study populations used and the different definitions used to define MHT [1, 12].

❖ Despite the disadvantages of ABPM, it is of clinical importance as it can detect white-coat hypertension, MHT, morning surge, non-dipping and reverse dipping, which are associated with risk of cardiovascular disease [23-25].

❖ Individuals that should be screened for MHT are those that have a high risk cardiovascular profile [6, 36].

❖ Ethnicity, age, male gender and unhealthy behaviours increase the likelihood of MHT [17, 40, 41]. Moreover individuals with sleep apnea, diabetes and CKD are susceptible to MHT [67, 70, 73].

❖ Increased pressure due to MHT results in increased LVM and RWT as a compensatory mechanism. Therefore MHT results in target organ damage (LVH) [80-82].

❖ Left ventricular diastolic dysfunction can be a result of LVH due to MHT or it can also precede LVH in masked hypertensives [108, 109].

❖ In patients with MHT, left ventricular systolic dysfunction develops over time [94].

5.2. What is unknown?

o There is currently conflicting findings for differences in the prevalence of MHT between black and white populations [40, 42]. Therefore the prevalence of MHT in young adults from different ethnic groups is not well established.

o Controversy circles around the predominance of MHT between the elderly and young adults [4, 17].

- Although MHT has been associated with impaired left ventricular structure and function in the elderly [80-82], it is unknown if cardiac alterations are already present in young otherwise healthy adults with MHT.

6. Aim, objectives and hypotheses

The aim of this study is to determine whether masked hypertension in young adults associates with left ventricular structure and function in black and white participants of the African-PREDICT study.

Interactions for sex and ethnicity for the above mentioned relationships were determined.

The following objectives were formulated:

- To compare the frequency of masked hypertension in young black and white men and women.

- To determine whether left ventricular mass and relative wall thickness relate to masked hypertension.

- To determine whether markers of diastolic (LA/Ao ratio, E/A ratio, deceleration time and E/e' ratio) and systolic (fractional shortening and ejection fraction) function relate to masked hypertension.

The following hypotheses were formulated:

- No ethnic differences will exist regarding the frequency of masked hypertension, but a higher frequency is expected amongst men.

- Left ventricular mass and relative wall thickness will associate positively with masked hypertension.

- Adverse associations of systolic and diastolic function will exist with masked hypertension.

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Chapter 3

Study Design & Methodology

1. Study design

The African-PREDICT study (African Prospective study on Early Detection and Identification of Cardiovascular disease and hyperTension) is designed to investigate the early pathophysiology accompanying cardiovascular disease (CVD) development and to identify novel early markers or predictors by recruiting and tracking young apparently healthy black and white adults, aged 20-30 years over a period of 10-20 years. This on-going longitudinal study is conducted in and around the Potchefstroom area of the North West Province of South Africa. The on-going longitudinal design of the study allows performance of detailed baseline and continual follow-up measurements of cardiovascular and biochemical markers.

The African-PREDICT study was approved by the Health Research Ethics Committee (HREC) of the North-West University (NWU-00001-12-A1). In addition, all procedures adhere to the Declaration of Helsinki.

The current cross-sectional study, made use of existing baseline data from the first 774 participants of the African-PREDICT study population. It should be noted that no additional measurements or procedures were performed for this study. Ethical considerations, protocol procedures and precautions of this study correspond to the larger African-PREDICT study. Therefore, research from this study falls within the scope of the African-PREDICT study and no re-consent was needed, as all measurements were described in detail within the original informed consent signed by all participants. Moreover, this cross-sectional study was approved by the HREC of the North-West University (NWU-00070-17-A1) (Appendix B).

The following two tables indicate the inclusion and exclusion criteria of the study.

Table 1. Eligibility criteria and concurrent justification for inclusion in the African-PREDICT study

Inclusion Criteria	Justification
Apparently healthy with an office BP<140/90 mmHg	Apparently healthy individuals will allow the monitoring of early phases of cardiovascular disease development
Age of 20-30 years	In order to evaluate the early phases of cardiovascular impairment, young adults are included, as they are generally considered to be at the peak of health and at a stage prior to cardiovascular deterioration
Self-reported black and white ethnicity	Research has shown that black populations generally have higher blood pressure than other populations. Black participants were compared with white participants as per the aims of the study
Evenly distributed males and females (self-reported)	Inclusion enables evaluation of sex differences

Table 2. Exclusion criteria and concurrent justification in the African-PREDICT study

Exclusion criteria	Justification
Non-permanent residents of Potchefstroom or surrounding areas or not intending to return regularly to this area	The study is a longitudinal study, therefore researchers make sure that participants could be followed over the required time period
Chronic medication intake (self-reported), diagnosed Type 1 or 2 Diabetes Mellitus, elevated glucose >5.6 mmol/L and confirmed glycated haemoglobin (HbA1c) ≥6.5%, Microalbuminuria >30 mg/ml in spot morning urine or proteinuria, HIV infected, recent surgery or trauma (within the past three months), previous history of stroke, angina pectoris or myocardial infarction	Individuals with self-reported diseases (or using chronic medication for such diseases) or risk factors that may influence cardiovascular health, were excluded
Self-reported pregnancy and lactating females	Due to the known influences of hormones on cardiovascular health, pregnant and lactating women were excluded

1.1. Organisational procedures

The African-PREDICT study consists of two phases including the initial screening phase, for inclusion into the study, as well as the advanced measurement stage as shown in **Figure 1** and further explained in details below.
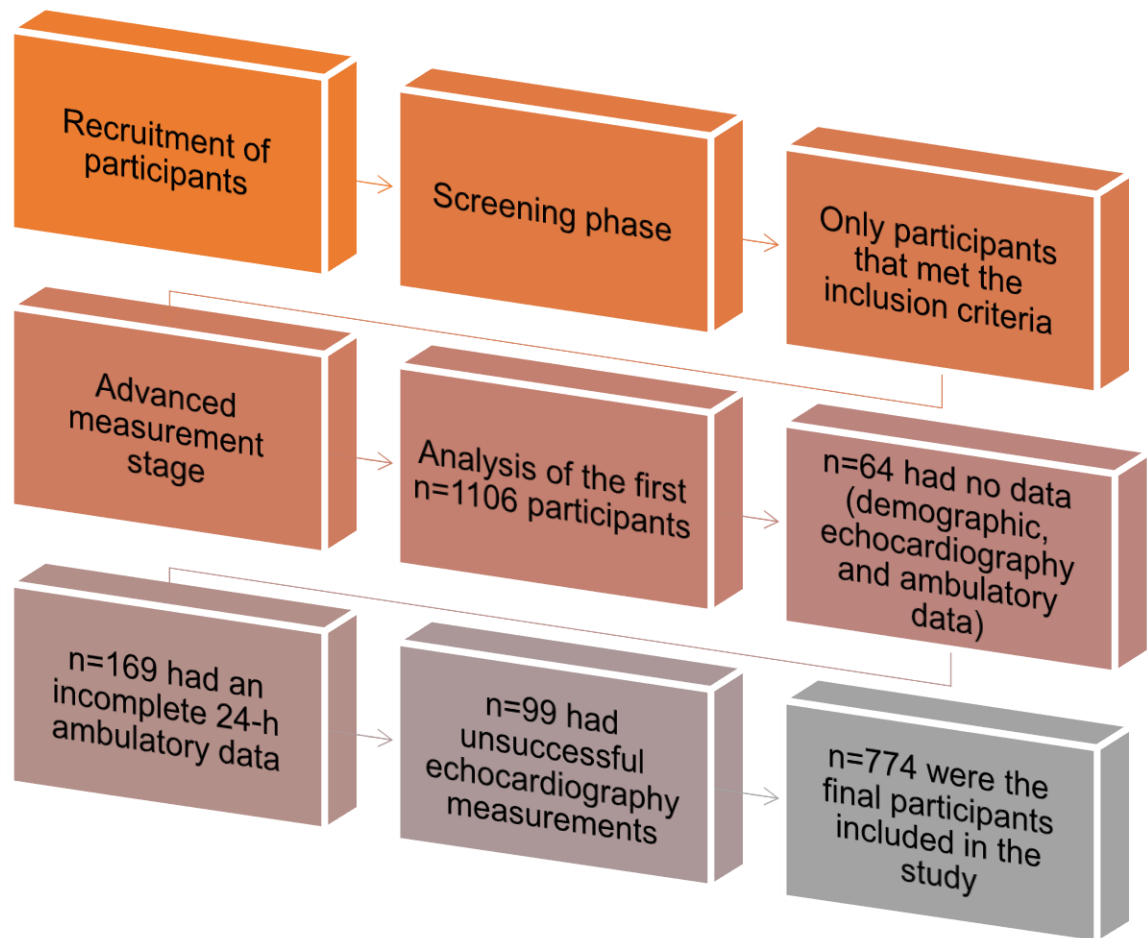
Figure 1. An outline of the study

Recruitment of the African-PREDICT study participants is done on a continual basis and began in 2012. During the recruiting process, participants were given information about the study and given time to consider. Recruited participants were required to undergo the screening process for the eligibility to participate in the study, at the Hypertension Research and Training Clinic on the Potchefstroom Campus. Upon arrival of the participants in the morning (0800), introduction to the

study team was done. All screening and advanced measurement information were explained again and given to participants and participation was voluntarily. Participants were encouraged to ask questions and gave written informed consent before measurements commenced. The study team explained that the participant could withdraw at any time without penalty. Measurements were performed by trained research staff and postgraduate students in private rooms to protect the privacy of the participants. Since individuals were asked to fast from 2200 the previous evening prior to early morning measurements, a light meal was offered after measurements.

The screening procedures included a general health and demographic questionnaire, basic testing of office blood pressure, rapid testing for blood glucose and lipids, dipstick spot urine sample test, body composition and Human Immunodeficiency Virus (HIV) testing.

2. Research measurements

2.1. Questionnaire data

In order to ascertain information of the participants' age, sex, ethnicity, socio-economic status and self-reported smoking and alcohol consumption (the risk factors of masked hypertension) [1, 2], trained research staff conducted interviews by making use of a well-structured demographic and health questionnaire.

2.2. Anthropometric and physical activity measurements

A trained researcher performed anthropometric measurements and connected physical activity monitors in a private, temperature-controlled room. These anthropometric measures such as body mass index, waist circumference and physical activity are risk factors of masked hypertension and hence, they were evaluated in this study [3, 4].

All anthropometric measurements complied with the International Standards for Anthropometric Assessment [5], and included height (m) (SECA Stadiometer, SECA), weight (kg) (SECA Electronic Scales, SECA, Birmingham, UK) and waist circumference (cm) (Lufkin Steel Anthropometric Tape), which was measured in triplicate using a non-flexible tape measure

(Holtain, Crymch, UK). Then body mass index (BMI) (weight (kg) / height (m^2)) was calculated. Body surface area was calculated using the Mosteller equation [6].

To assess physical activity, a non-invasive combined heart rate and accelerometer device, the ActiHeart (CamNtech Ltd., Cambridge, UK), was chest-worn by each participant for a maximum of 7 consecutive days. The device was designed to calculate the activity energy expenditure (AEE), corrected for weight, thereby deriving an estimated index of physical activity in kCal/kg/day.

2.3. Cardiovascular measurements

2.3.1. Clinic blood pressure

Office brachial blood pressure measurements were taken twice on each arm. This was done as Hypertension Guidelines recommend that blood pressure be measured in both arms at first visit [7]. Measures were taken with the participant seated and in a rested state, using the Dinamap® Procare blood pressure monitor (GE Medical Systems, Milwaukee, USA). It was important for the participant to be correctly seated and rested, as talking, crossing legs and unsupported back and arm during blood pressure measurement could raise the blood pressure. There was a 5 minute rest period between each measurement, and an appropriate sized blood pressure cuff was used, as an undersized cuff increases errors in measurement [8].

2.3.2. Ambulatory blood pressure monitoring

The 24-h ABPM was performed using CardioXplore devices (CardioXplore, MediTech, Budapest, Hungary), programmed to take recordings every 30 minutes during the day (0600 to 2200 hours) and hourly at night (2200 and 0600 hours). Only participants with >70% of valid BP measurements, >20 day measurements and >7 night measurements were included in the final analysis. The electrocardiogram (ECG) recordings were used to identify and exclude individuals with left and right bundle branch blocks, as bundle branch blocks are associated with increased risk of hypertension [9].

Table 3. Cut-off points of untreated masked hypertension using office and the 24-h ambulatory blood measurements according to the criteria of the European Society of Hypertension [10].

Office Blood pressure	Ambulatory blood pressure (ABP)
BP<140/90 mmHg	24h ABP≥130/80 mmHg Awake ABP≥135/85 mmHg Sleep ABP≥120/70 mmHg

*Nocturnal (masked) hypertension cut off points: office BP<140/90 mmHg, 24h ABP<130/80 mmHg, awake ABP<135/85 mmHg; sleep ABP≥ 120/70 mmHg

2.3.3. Echocardiography

To evaluate the parameters of left ventricular geometry and left ventricular function, echocardiography was used, as it is a sensitive and reliable tool compared to other techniques previously used [11].

A standard transthoracic echocardiogram was performed for each participant [12]. Echocardiography data was analysed using the EchoPAC software (GE, version 10.8.1) to determine measures of left ventricular structure and function. Each participant was scanned in a partial left decubitus position with the head of the examining table modestly elevated. Left ventricular dimensions were measured according to the recommendations of the American Society of Echocardiography, by one specialist clinical technologist [12, 13].

The relative wall thickness (RWT) was defined as the ratio of twice the posterior wall thickness and the left ventricular diastole diameter. Left ventricular mass was calculated by the corrected

Devereux formula and was normalised for body surface area, hence left ventricular mass index (LVMI) [14].

To assess left ventricular filling, a pulse wave Doppler was performed in the apical 4-chamber view. A 1-3 mm sample volume was placed between the tips of the mitral valve leaflets with parallel alignment to inflow. Parameters of left ventricular diastolic function included peak velocities of early (E) and late (A) diastolic filling (E/A ratio) and the mitral valve deceleration time. Tissue Doppler Imaging was additionally performed to calculate the velocity of the myocardial tissue movement (e' and a') in relation to the blood flow through the mitral valve on both lateral and anterior planes. Normal filling pressures (<8 mmHg) are separated from elevated filling pressures (>12 mmHg) by means of the ratio between transmitral Doppler early filling velocity to tissue Doppler early diastolic mitral annular velocity (E/é ratio). Left atrium diameter and aortic root diameter were obtained to determine LA/Ao ratio.

Global left ventricular systolic function was derived from linear measurements obtained from 2D images. Using Teichholz's formula, left ventricular end-diastolic was calculated. Endocardial fractional shortening was determined using standard methods. Furthermore, left ventricular ejection fraction was calculated from using left ventricular end-diastolic volume and end-systolic volume estimates.

2.4. Blood sampling and biochemical analysis

Participants were required to fast from 2200 the evening prior to the day of the study. Blood samples were taken with a sterile winged infusion set and syringes from the ante brachial vein. All samples were immediately taken to the onsite laboratory and aliquoted into cryovials for storage in biofreezers at −80 °C until analysis.

Basic serum analyses included creatinine, low-density lipoprotein-cholesterol (LDL-c), high-density lipoprotein-cholesterol (HDL-c), total cholesterol, triglycerides, glucose, and γ-glutamyl

transferase (GGT) using the Cobas Integra® 400 plus (Roche, Basel, Switzerland). Serum cotinine was determined with chemiluminescence method on the Immulite (Siemens, Erlangen, Germany). The CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation was used to estimate glomerular filtrate rate (eGFR) from serum creatinine [15].

The above mentioned biochemical markers are risk factors of masked hypertension [1, 16], hence they were included in the analysis of the study. In addition of self-reported smoking and alcohol information, serum cotinine and GGT respectively, were included in the study as they are objective tests of tobacco use and alcohol intake. GGT is also a known measure of non-alcoholic fatty liver disease, and is therefore not always specific to alcohol intake.

2.5. Data-handling

Data was captured and entered into a password protected database which is stored online and offline. Questionnaires were stored in a locked storage room in the Hypertension Clinic. Only the project leader, data management team and Head of the Hypertension Clinic had access to the documents.

With this existing data analyses, the data manager provided access to me, however, the data remained coded for anonymity and participant names were never disclosed to me.

2.6. Contributions of the student to the African-PREDICT study

Ms NP Sekoba aided in the collection of the African-PREDICT data by collecting data on arterial stiffness, using the Sphygmocor XCEL device. This was done while I was working in the Hypertension Clinic, where I interacted with participants, and performed the pulse wave analysis and pulse wave velocity measures. I was also responsible for entry of data into the African-PREDICT database. With reference to the present study, I cleaned and performed all statistical analyses of data used in this sub-study.

2.7. Statistical analysis

Statistical analyses were performed using Statistica version 13 (Dell software, Texas, USA) and SPSS version 24 (IBM, Armonk, NY, USA).

Data distributions were checked for normality using the Kolmogorov-Smirnov test, and logarithmically transformed if skewed. Normally distributed variables were reported as mean and standard deviation, and logarithmically transformed variables were presented by the geometric mean and 5th and 95th percentiles.

Using multiple regression analyses, the interactions of ethnicity and sex were tested for the relationships between markers of left ventricular structure and function (LVMI, RWT, E/A ratio, E/é ratio, mitral valve deceleration time, LA/Ao ratio, fractional shortening and ejection fraction) and masked hypertension.

Frequency tables and the Chi-square test were used to establish and compare the prevalence of masked hypertension. The Chi-square test was also used to compare categorical variables, and independent T-tests to compare continuous variables between black and white participants, and those with normotension and masked hypertension.

Unadjusted and adjusted odds ratios were performed using the 75th percentile of echocardiographic variables. The clinic cut-off values for the left ventricular structure and function variables were not used since the study sample represented a young, healthy population.

Multivariable-adjusted linear regression was performed to determine whether markers of left ventricular structure and function as dependent variables (LVMI, RWT, E/A ratio, E/é ratio, mitral valve deceleration time, LA/Ao ratio, fractional shortening and ejection fraction) are related to masked hypertension, as main independent variable.

We performed bivariate correlations of the dependent variables and MHT status with a range of potential confounders, to determine which variables to include in our final regression models.

Variables that were considered for inclusion included: age, sex, ethnicity, socio-economic status, waist circumference, AEE, HDL-c/triglycerides, LDL-c, glucose, GGT, cotinine, eGFR and heart rate. Of note cotinine, glucose and HDL-c/triglycerides were initially excluded.

2.8. Power analysis

Power analysis was performed using the G* Power 3 statistical analysis program [17]. We firstly computed the required effect size by sensitivity F-tests detected at an alpha level of 0.05, total sample size of masked hypertensives (n=127), and the number of predictors (11) in multiple regression analysis. An effect size of 0.215 was calculated and used in a compromise analysis to detect the implied alpha and power. Our power analysis indicated an alpha error probability of 0.0501 and power at 94.99%. Our study included 774 participants in total, with 647 in the normotensive group and 127 in the masked hypertension group. Our sample sizes were therefore sufficient to test our hypothesis.

Table 4. Power analysis report

F tests - Linear multiple regression: Fixed model, R² deviation from zero
Analysis: Compromise: Compute implied α & power
Input: Effect size f² =   0.215
β/α ratio   =   1
Total sample size   =   127
Number of predictors =   11
Output: Noncentrality parameter λ   =   27.3050000
Critical F   =   1.8719385
Numerator df =   11
Denominator df   =   115
α err prob   =   0.0501320
β err prob   =   0.0501320
Power (1-β err prob)   =   0.9498680

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Chapter 4

Manuscript for Publication

Left ventricular mass independently associates with masked hypertension in young healthy adults: The African-PREDICT study

Running title: Masked hypertension and organ damage

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Abstract

Objective: Masked hypertension is reportedly common in young adults. However, it is unknown if these masked hypertensives already present with organ damage. We determined whether a relationship exists between left ventricular structure and function and masked hypertension in young healthy adults.

Methods: In this cross-sectional study, we included 774 black and white men and women (aged 20-30 years) who had successful ambulatory blood pressure monitoring readings (>70% valid readings) and valid echocardiography done.

Results: When taking into account that we excluded participants with sustained and white-coat hypertension, overall, 16.4% of the young participants had MHT (60.6% whites; 67.7% men). When performing multivariable-adjusted logistic regression, we found masked hypertensives to have higher odds to present with increased left ventricular mass index (OR=1.67; p=0.031) compared to normotensives. In multivariable-adjusted linear regression analyses, left ventricular mass index positively and independently associated with masked hypertension (adj. R^2=0.193; β=0.08 [0.01; 0.16]; p=0.046). However, we found no independent link between echocardiographic measures of left ventricular function and masked hypertension.

Conclusion: This study highlights the importance of the early detection of masked hypertension as young apparently healthy adults already show an increased left ventricular mass index, thereby indicating increased risk for future cardiovascular disease.

Keywords: ambulatory blood pressure monitoring, black, ethnicity, left ventricular function, left ventricular mass index, masked hypertension, sex, young

Introduction

Approximately 1 out of 7 individuals with normal clinic blood pressure (BP) have masked hypertension (MHT) [1]. Masked hypertensives are at greater risk of encountering cardiovascular events as compared to white-coat hypertensives, but have a similar risk as sustained hypertensives [1-6].

Several risk factors such as age, sex, obesity, smoking, alcohol, hormonal contraceptive use and physical activity have been found to raise the risk of MHT [7-9]. Moreover, similar to sustained hypertension, masked hypertensives are at increased risk of target organ damage such as increased left ventricular mass and left ventricular dysfunction [2, 10-13]. To date, most studies have reported on elderly and diseased masked hypertensives with target organ damage [11, 14].

Despite the negative cardiovascular effects related to MHT, the relationship of MHT with left ventricular structure and function in young adults is not well known. It is imperative to establish this as seemingly healthy young adults with (undetected) MHT might be subjected to the development of early target organ damage. If MHT is already associated with increased left ventricular mass or impaired function in otherwise healthy young adults, it would highlight the importance of early detection and treatment in this population.

We therefore determined whether MHT in young adults associates with left ventricular structure and function in black and white participants of the African-PREDICT study (African Prospective study on the Early Detection and Identification of Cardiovascular disease and hyperTension).

Methods

Study population

This study forms part of the African-PREDICT study, designed to investigate the early pathophysiology accompanying cardiovascular disease (CVD) development and to identify novel early markers or predictors by following young, apparently healthy adults over time. Inclusion criteria were apparently healthy black and white men and women aged 20 to 30 years with office BP <140/90 mmHg and no known CVD, not taking any BP medication, no chronic disease, Human Immunodeficiency Virus (HIV) uninfected and not pregnant or breastfeeding.

In this cross-sectional sub-study we included n=774 participants with successful ambulatory blood pressure monitoring (ABPM) (>70% valid readings) and valid echocardiography measurements, and categorised them as normotensive or masked hypertensive. Normotensive status was based on clinic BP<140/90 mmHg and normal ABPM (24-h readings <130/80 mmHg, daytime readings <135/85 mmHg and nighttime readings <120/70mmHg). MHT status was classified as participants having normal clinic BP<140/90 mmHg, but an elevated ABPM (24-h readings ≥130/80 mmHg and/or daytime readings ≥135/85 mmHg and/or nighttime readings ≥120/70 mmHg) [15].

The study adhered to the guidelines set forth by the Declaration of Helsinki and was approved by the Health Research Ethics Committee of the North-West University (NWU-00070-17-A1). All participants provided written informed consent.

Data collection

Questionnaire data

Data with regards to age, sex and ethnicity were collected using a demographic and lifestyle questionnaire. The questionnaire also included information on socio-economic status, self-reported smoking and alcohol consumption.

Anthropometric and physical activity measurements

All anthropometric measurements complied with the International Standards for Anthropometric Assessment [16], and included height (m) (SECA Stadiometer, SECA), weight (kg) (SECA Electronic Scales, SECA, Birmingham, UK) and waist circumference (cm) (Lufkin Steel Anthropometric Tape), which was measured in triplicate using a non-flexible tape measure (Holtain, Crymch, UK). Then body mass index (BMI) (weight (kg) / height (m^2)) was calculated. Body surface area was calculated using the Mosteller equation [17].

To assess physical activity, a non-invasive combined heart rate and accelerometer device, the ActiHeart (CamNtech Ltd., Cambridge, UK), was chest-worn by each participant for a maximum of 7 consecutive days. The device was designed to calculate the activity energy expenditure (AEE), corrected for weight, thereby deriving an estimated index of physical activity in kCal/kg/day.

Clinic blood pressure

Office brachial BP measurements were taken twice on each arm, while the participant was seated and in a rested state, using the Dinamap® Procare BP monitor (GE Medical Systems, Milwaukee, USA). There was a 5 minute rest period between each measurement, and an appropriate sized BP cuff was used.

Ambulatory blood pressure monitoring

The 24-h ABPM were performed using CardioXplore devices (CardioXplore, MediTech, Budapest, Hungary), programmed to take recordings every 30 minutes during the day (0600 to 2200 hours) and hourly at night (2200 and 0600 hours). Only participants with >70% of valid BP measurements, >20 day measurements and >7 night measurements were included in the final analysis.

Echocardiography

A standard transthoracic echocardiogram was performed for each participant [18]. Echocardiography data was analysed using the EchoPAC software (GE, version 10.8.1) to determine measures of left ventricular structure and function. Each participant was scanned in a partial left decubitus position with the head of the examining table modestly elevated. Left ventricular dimensions were measured according to the recommendations of the American Society of Echocardiography, by one specialist clinical technologist [18, 19]. The relative wall thickness (RWT) was defined as the ratio of twice the posterior wall thickness and the left ventricular diastole diameter. Left ventricular mass was calculated by the corrected Devereux formula and was normalised for body surface area, hence left ventricular mass index (LVMI) [20]. To assess left ventricular filling, a pulse wave Doppler was performed in the apical 4-chamber view. A 1-3 mm sample volume was placed between the tips of the mitral valve leaflets with parallel alignment to inflow. Parameters of left ventricular diastolic function included peak velocities of early (E) and late (A) diastolic filling (E/A ratio) and the mitral valve deceleration time. Tissue Doppler Imaging was additionally performed to calculate the velocity of the myocardial tissue movement (e' and a') in relation to the blood flow through the mitral valve on both lateral and anterior planes. The ratio between transmitral Doppler early filling velocity to tissue Doppler early diastolic mitral annular velocity (E/é ratio) was also determined. Left atrium diameter and aortic root diameter were obtained to determine LA/Ao ratio. Global left ventricular systolic function was derived from linear measurements obtained from 2D images. Using Teichholz's formula, left ventricular end-diastolic was calculated. Endocardial fractional shortening was determined using standard methods. Furthermore, left ventricular ejection fraction was calculated from using left ventricular end-diastolic volume and end-systolic volume estimates.

Blood sampling and biochemical analysis

Participants were required to fast from 2200 the evening prior to the day of the study. Blood samples were taken with a sterile winged infusion set and syringes from the ante brachial vein. All samples were immediately taken to the onsite laboratory and aliquoted into cryovials for storage in biofreezers at −80 °C until analysis.

Basic serum analyses included creatinine, low-density lipoprotein-cholesterol (LDL-c), high-density lipoprotein-cholesterol (HDL-c), total cholesterol, triglycerides, glucose, and y-glutamyl transferase (GGT) using the Cobas Integra® 400 plus (Roche, Basel, Switzerland). Serum cotinine was determined with chemiluminescence method on the Immulite (Siemens, Erlangen, Germany). The CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation was used to estimate glomerular filtrate rate (eGFR) from serum creatinine [21].

Statistical analysis

Statistical analyses were performed using Statistica version 13 (Dell software, Texas, USA) and SPSS version 24 (IBM, Armonk, NY, USA). Normality was tested using the Kolmogorov-Smirnov test and visual inspection of histograms and scatter plots. Normally distributed data were expressed as the arithmetic mean and standard deviation. Skewed data were log transformed and presented by the geometric mean with 5th and 95th percentiles. We tested for the interaction of sex and ethnicity on the association between measures of left ventricular structure and function and MHT. Comparisons between two groups were assessed with independent T-tests for continuous variables and the Chi-square test for categorical variables. Multivariable logistic regression analyses were conducted and adjusted odds ratios displayed in forest plots (adjusted for age, sex, ethnicity, socio-economic status, waist circumference (except LVMI), eGFR, GGT, cotinine, heart rate for only mitral valve deceleration time and E/A ratio). As the study sample represents a young, healthy population, clinic cut-off values for echocardiography were not used

for odds ratio analyses, but the 75th percentile was used. Multivariable linear regression analysis was used to determine the association between echocardiographic parameters and MHT while adjusting for age, sex, ethnicity, waist circumference (except LVMI), socio-economic status, HDL-c/triglycerides, AEE, eGFR, GGT, cotinine, glucose and heart rate for only mitral valve deceleration time and E/A ratio. A p-value <0.05 was considered statistically significant.

Results

Table 1 shows the criteria used to classify participants as MHT. Among the study population, 127 (16.4%) participants had MHT, of whom 54 (42.5 %) were based on ambulatory nighttime readings only, and 34 (26.8 %) had MHT according to 24-h, daytime and nighttime ambulatory readings. We found no significant interactions of sex or ethnicity for the associations between left ventricular structure and function and MHT (supplementary Table S1).

Table 1. Classification of masked hypertensive participants (n=127) according to 24-h ambulatory blood pressure

	Masked hypertensive n (%)
24-h ABPM only	0 (0)
Day ABPM only	12 (9.45)
Night ABPM only	54 (42.5)
24-h and day ABPM only	15 (11.8)
24-h and night ABPM only	12 (9.45)
Day and night ABPM only	0 (0)
24-h, day and night ABPM	34 (26.8)

Abbreviations: ABPM, ambulatory blood pressure monitoring.

In Table 2 we also compared the office blood pressure classifications of normotensive and MHT participants. We found that 71.1% normotensive participants had optimal blood pressure (<120/80 mmHg), compared to only 37.0% in masked hypertensives. This translates to 63.0% of MHT participants having blood pressures exceeding 120/80 mmHg (compared to 28.9% in normotensives).

Table 2. Comparison of office blood pressure classifications of normotensive and masked hypertensive participants

Office blood pressure classification	Normotensive (n=647)	Masked hypertensive (N=127)	p value
Optimal (SBP<120 and DBP<80 mmHg) n (%)	460 (71.1)	47 (37.0)	<0.001
Normal (SBP 120-129 and/or DBP 80-89) n (%)	124 (19.2)	45 (35.4)	<0.001
High normal (SBP 130-139 and/or DBP 85-89) n (%)	48 (7.42)	28 (22.1)	<0.001
Grade I hypertension (SBP 140-159 and/or 90-99) n (%)*	15 (2.32)	7 (5.51)	0.048

*A minority of participants presented with office blood pressures in the Grade 1 Hypertension range despite having blood pressures <140/90 mmHg during screening procedures on a previous day.

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure. Data presented as number of participants and percentages.

Table 3 demonstrates the baseline characteristics of the participants categorised by MHT status. Overall, the frequency of MHT was higher among men (21.7%) than women and higher in whites

(20.3%) than blacks (for comparison by sex and ethnicity see supplementary Table S2). Masked hypertensives had higher clinic and ambulatory systolic and diastolic BP levels (all p<0.001). However, there was no difference in heart rate between the two groups. Moreover, 66.1% of masked hypertensives were non-dippers. Regarding the biochemical markers, HDL-c (1.19 vs 1.35 mmol/L) and eGFR (108 vs 112 ml/min/1.73m^2) were lower, and triglycerides (1.06 vs 0.80 mmol/L) and glucose (4.90 vs 4.59 mmol/L) higher in masked hypertensive group (all P<0.05). GGT was also elevated in MHT, while AEE was lower in MHT. There was no difference in cotinine levels, night-shift and self-reported smoking, alcohol and contraceptive use.

Table 3. Characteristics of participants stratified by masked hypertension status

	Normotensive (n=647)	Masked hypertensive (n=127)	p value
Age (years)	24.9 ± 3.10	24.9 ± 3.00	0.87
Men n (%)	231 (35.7)	86 (67.7)	<0.001
Black n (%)	344 (53.2)	50 (39.4)	0.004
Socioeconomic status			0.17
Low n (%)	251 (38.8)	42 (33.1)	
Middle n (%)	168 (26.0)	29 (22.8)	
High n (%)	228 (35.2)	56 (44.1)	
Anthropometric measures			
Weight (kg)	67.2 [48.4; 96.7]	82.3 [55.8; 124.0]	<0.001
Height (cm)	167 ± 9.09	173 ± 9.49	<0.001
Body mass index (kg/m^2)	24.2 [17.8; 34.4]	27.7 [20.1; 40.4]	<0.001
Waist circumference (cm)	77.4 [63.2; 100]	88.1 [67.2; 118]	<0.001
Systolic blood pressure (mmHg)			
Clinic	114 ± 12.0	124 ± 10.1	<0.001

24-h	114 ± 7.94	128 ± 6.79	<0.001
Daytime	119 ± 8.56	132 ± 8.49	<0.001
Nighttime	105 ± 8.44	122 ± 8.32	<0.001
Diastolic blood pressure (mmHg)			
Clinic	77.9 ± 8.65	82.0 ± 7.63	<0.001
24-h	67.9 ± 5.34	73.8 ± 5.56	<0.001
Daytime	72.8 ± 5.97	77.5 ± 6.91	<0.001
Nighttime	58.6 ± 5.79	66.4 ± 7.78	<0.001
Heart rate (beats/min)			
Clinic	66.2 ± 11.1	64.7 ± 10.7	0.16
24-h	75.1 ± 10.4	75.0 ± 11.6	0.92
Daytime	79.6 ± 10.9	78.7 ± 12.4	0.45
Nighttime	66.7 ± 11.1	67.8 ± 12.4	0.31
Non-dipping n (%)	237 (36.6)	84 (66.1)	<0.001
Left ventricular structure and function			
Left ventricular mass index (g/m^2)	72.1 ± 16.2	80.9 ± 18.7	<0.001
Relative wall thickness (cm)	0.36 ± 0.07	0.38 ± 0.08	0.027
E/A ratio	2.10 [1.43; 3.26]	2.04 [1.40; 3.08]	0.25
E/é ratio	6.45 ± 1.21	6.42 ± 1.24	0.78
Mitral valve deceleration time (ms)	231 ± 49.0	224 ± 47.5	0.13
LA/Ao ratio	1.11 ± 0.15	1.11 ± 0.14	0.99
Fractional shortening (%)	37.3 ± 4.99	36.1 ± 4.59	0.009
Ejection fraction (%)	66.9 ± 6.32	65.3 ± 6.04	0.008
Biochemical markers			
Total cholesterol (mmol/L)	4.11 [2.82; 6.04]	4.35 [2.89; 6.24]	0.014

HDL-cholesterol (mmol/L)	1.35 ± 0.38	1.19 ± 0.38	<0.001
LDL-cholesterol (mml/L)	2.59 [1.49; 4.32]	2.79 [1.38; 4.73]	0.032
Triglycerides (mmol/L)	0.80 [0.40; 1.92]	1.06 [0.50; 2.85]	<0.001
Glucose (mmol/L)	4.59 ± 0.83	4.90 ± 0.83	<0.001
eGFR (ml/min/1.73m^2)	112 ± 16.5	108 ± 16.9	0.017
Lifestyle factors			
AEE (kCal/kg/day)[a]	6.09 ± 2.97	5.37 ± 2.79	0.026
y-glutamyl transferase (U/L)	20.6 [8.80; 54.0]	25.8 [10.1; 89.7]	<0.001
Self-reported alcohol use n (%)	366 (57.1)	83 (65.4)	0.084
Cotinine (ng/ml)	3.63 [1.00; 329]	3.85 [1.00; 309]	0.79
Former and current smoking n (%)	224 (34.6)	45 (35.4)	0.86
Night shift n (%)	47 (10.3)	9 (10.1)	0.95
Contraceptive pill n (%)	98 (24.0)	15 (35.7)	0.094
Contraceptive injection n (%)	68 (16.6)	6 (14.3)	0.71

Abbreviations: E/A ratio, ratio of mitral peak velocity of early (E) and late (A) diastolic filling; E/é ratio, ratio of mitral peak velocity of early filling (E) to early diastolic mitral annular velocity (é); LA/Ao, left atrial to aortic ratio; HDL, high-density lipoprotein; LDL, low-lipid lipoprotein; eGFR, estimated glomerular filtrate rate; AEE, activity energy expenditure.

Data presented as mean ± standard deviation or geometric mean [5th and 95th percentile intervals] for logarithmically transformed variables, or number of participants and percentages.

[a]n = 594

After adjusting for age, sex and ethnicity, higher LVMI (78.6 vs 74.4 g/m^2, p=0.006) was confirmed in the MHT group (Table 4). After additional adjustment for waist circumference, we found no differences in RWT, E/A ratio, E/è ratio, LA/Ao ratio, fractional shortening, ejection fraction and mitral valve deceleration time between the groups.

Table 4. Comparison of normotensive and masked hypertension groups following adjustment for age, sex, ethnicity and waist circumference

	Normotensive (n=647)	Masked hypertensive (n=127)	p value
Systolic blood pressure (mmHg)			
Clinic	120 ± 12.2	124 ± 11.2	<0.001
24-h	116 ± 6.99	126 ± 6.43	<0.001
Daytime	121 ± 7.83	130 ± 7.20	<0.001
Nighttime	107 ± 8.24	119 ± 7.57	<0.001
Diastolic blood pressure (mmHg)			
Clinic	78.9 ± 8.91	81.0 ± 8.20	0.012
24-h	68.5 ± 5.70	73.2 ± 5.25	<0.001
Daytime	73.5 ± 6.52	76.7 ± 5.99	<0.001
Nighttime	58.9 ± 6.68	66.1 ± 6.14	<0.001
Heart rate (beats/min)			
Clinic	65.5 ± 11.1	65.4 ± 10.2	0.95
24-h	74.2 ± 10.2	75.9 ± 9.34	0.067
Daytime	78.6 ± 11.1	79.7 ± 10.2	0.33
Nighttime	65.9 ± 10.7	68.7 ± 9.88	0.006
Left ventricular structure and function			
Left ventricular mass index (g/m^2)[a]	74.4 ± 16	78.6 ± 15.4	0.006
Relative wall thickness (cm)	0.37 ± 0.08	0.37 ± 0.07	0.27
E/A ratio	2.06 [2.02; 2.10]	2.09 [2; 2.18]	0.58
E/é ratio	6.44 ± 1.30	6.43 ± 1.19	0.98
Mitral valve deceleration time (ms)	230 ± 54.1	224 ± 49.8	0.24

LA/Ao ratio	1.11 ± 0.16	1.11 ± 0.15	0.87
Fractional shortening (%)	36.9 ± 5.40	36.4 ± 4.97	0.29
Ejection fraction (%)	66.4 ± 6.84	65.9 ± 6.29	0.40

Abbreviations: E/A ratio, ratio of mitral peak velocity of early (E) and late (A) diastolic filling; E/é ratio, ratio of mitral peak velocity of early filling (E) to early diastolic mitral annular velocity (é); LA/Ao, left atrial to aortic ratio.

Data presented as mean ± standard deviation or geometric mean [5th to 95th percentile intervals] for logarithmically transformed variables.

[a]Adjusted only for sex, age and ethnicity

Figure 1 displays the results of multivariable-adjusted logistic regression analyses. We found that, when compared to the normotensive group, participants with MHT had a 1.67 [1.05-2.71 95% CI] times higher odds of having increased LVMI after full adjustment. For none of the other measures of cardiac structure or function we found a significant odds ratio.
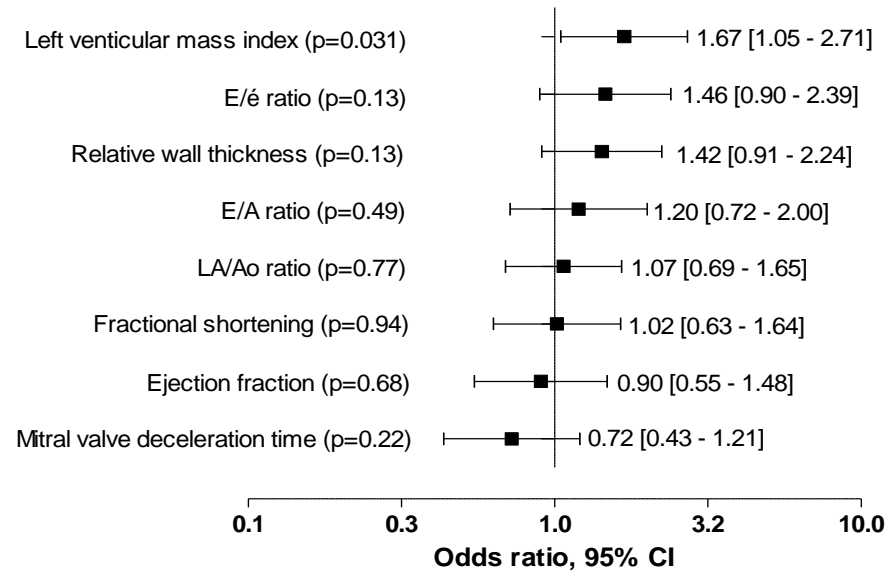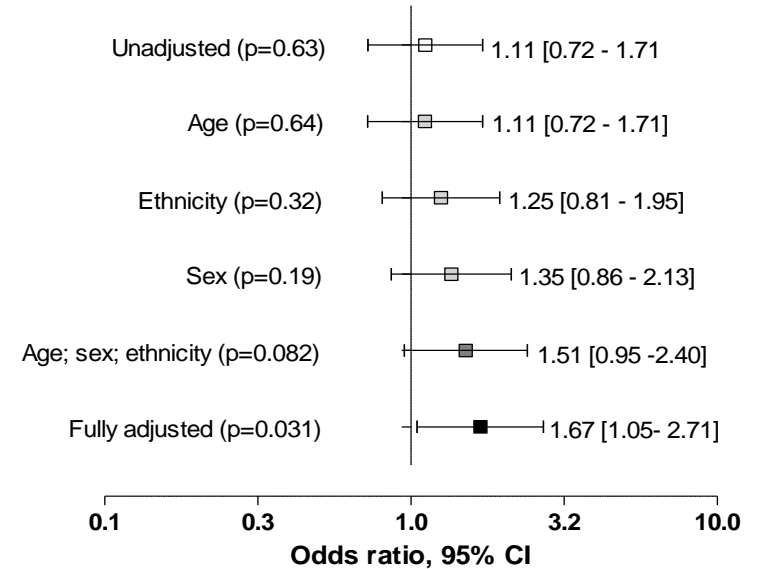
Figure 1. (A) Adjusted odds ratios with measures of echocardiography as dependent variables, adjusted for age; sex; ethnicity; socio-economic status; waist circumference (except LVMI); estimated glomerular filtrate rate; y-glutamyl transferase; cotinine. Mitral valve deceleration time and E/A ratio additionally adjusted for heart rate; (B) Unadjusted and adjusted odds ratios for left ventricular mass index

Table 5 presents multivariable-adjusted linear regression analysis with measures of left ventricular structure and function as dependent variables. We confirmed an independent positive association between LVMI and MHT in Model 1 (adj. R^2=0.194, β=0.09 [0.02; 0.16]; p=0.009), but no similar association with measures of left ventricular function and RWT. When we added glucose, HDL-c/triglycerides ratio and AEE as additional covariates to Model 2, the p-value increased and the positive association between LVMI and MHT remained (adj. R^2=0.193, β=0.08 [0.002; 0.16]; p=0.046). We further performed sensitivity analyses to determine whether adding systolic blood pressure into the model would affect the independent relationship between MHT status and LVMi. Upon including SBP, the association was lost (adj. R^2=0.205, β=0.05 [-0.03; 0.13]; p=0.25) whereas the association between SBP and MHT was significant (adj. R^2=0.152, β=0.18 [0.09; 0.28]; p<0.001).

Table 5. Multiple regression analysis with measures of left ventricular structure and function as dependent variables, and masked hypertension as independent variable

Model 1	Adjusted R^2	β [95% CI]	p value
Left ventricular mass index (g/m²)[a]	0.194	0.09 [0.0229; 0.1572]	**0.009**
Relative wall thickness (cm)	0.058	0.04 [-0.0345; 0.1155]	0.29
E/A ratio[b]	0.171	0.03 [-0.0428; 0.098]	0.44
E/é ratio	0.072	0.003 [-0.0713; 0.0776]	0.93
Mitral valve deceleration time (ms)[b]	0.020	-0.05 [-0.1259; 0.0272]	0.21
LA/Ao ratio	0.045	0.002 [-0.0732; 0.078]	0.95
Fractional shortening (%)	0.038	-0.04 [-0.1131; 0.0385]	0.34
Ejection fraction (%)	0.048	-0.03 [-0.1054; 0.0454]	0.44
Model 2			
Left ventricular mass index (g/m²)[a]	0.193	0.08 [0.0017; 0.1562]	**0.046**
Relative wall thickness (cm)	0.061	0.04 [-0.0472; 0.1236]	0.38
E/A ratio[b]	0.166	0.03 [-0.0484; 0.1125]	0.44
E/é ratio	0.075	-0.003 [-0.0880; 0.0814]	0.94

|			
Mitral valve deceleration time (ms)[b]	0.015	-0.04 [-0.1307; 0.0441]	0.33
LA/Ao ratio	0.040	0.005 [-0.0814; 0.0912]	0.91
Fractional shortening (%)	0.050	-0.04 [-0.1226; 0.0491]	0.40
Ejection fraction (%)	0.056	-0.03 [-0.1150; 0.0562]	0.50

Abbreviation: CI, confidence interval; E/A ratio, ratio of mitral peak velocity of early (E) and late (A) diastolic filling; E/é ratio, ratio of mitral peak velocity of early filling (E) to early diastolic mitral annular velocity (é); LA/Ao, left atrial to aortic ratio.

Model 1: Each model included the following covariates: age; sex; ethnicity; socio-economic status; waist circumference; estimated glomerular filtrate rate; y-glutamyl transferase; cotinine.

Model 2: Each model included the following covariates: age; sex; ethnicity; socio-economic status; waist circumference; estimated glomerular filtrate rate; y-glutamyl transferase; cotinine; glucose; activity induced energy expenditure; high-density lipoprotein/triglycerides.

[a]Since left ventricular mass index already incorporates body composition, waist circumference was excluded.

[b]Additionally adjusted for heart rate; Bold values indicate p<0.05.

Discussion

In young healthy adults (aged 20-30 years) screened to be normotensive, we found 16.4% to have masked hypertension. Despite their young age, those with MHT had a 67% increased risk of having elevated LVMI compared to normotensives. These under-diagnosed, non-treated and unaware masked hypertensives are therefore at higher risk of developing hypertension-related organ damage as well as subsequent CVD [22].

Liu *et al.* was the first to associate MHT with increased LVMI in an elderly masked hypertensive population [2]. Since then, studies such as the Jackson Heart Study- a large population based study, have also reported LVMI to be higher in masked hypertensives as compared to normotensives, also in an elderly and hypertensive population [23]. Lurbe *et al.* in a study of 592 children ranging in ages from 6 years to 18 years, reported participants with persistent MHT or who progressed from masked to sustained hypertension to have higher LMVI (34.9 g/m$^{2.7}$) as compared to normotensives (29.2 g/m$^{2.7}$) [24]. Our findings are in alignment with these previous results as young healthy adults, who were masked hypertensive, presented

with a higher LVMI than normotensives (78.6 ± 15 vs 74.4 ± 16 g/m^2), independent of sex, age and ethnicity.

Following multiple adjustments ambulatory BP and LVMI remained high in the MHT group compared to normotensives. Moreover, 24-h BP and BP variability are stronger predictors of target organ damage when compared to clinic BP [3, 25]. The daily BP load (namely the percentage of pressures exceeding 135/85 mmHg during the day and 120/70 mmHg at night) and nocturnal hypertension (in which the expected nighttime dipping in BP is not seen) are risk factors of increased LVMI, with nocturnal BP being the strongest predictor of cardiovascular outcome [26]. In our study, 43% of MHT was diagnosed based on nighttime BP only, and this is supported by increased nighttime heart rate and non-dipping observed in masked hypertensives from our study. Both, elevated nighttime heart rate and non-dipping nighttime blood pressures, are features of increased sympathetic nerve activity [27, 28]. In addition, Grassi *et al.* reported increased bursts of sympathetic nerve activity in patients with elevated out-of-office BP, but normal office BP (MHT) [27]. Since a low BP within the normal physiological range is required for the adequate perfusion of organs during the night, the increased nighttime pressure will overload the cardiovascular system, causing a negative impact on the heart such as increasing left ventricular mass [29].

Increased left ventricular mass is due to the hypertrophy of existing myocytes rather than hyperplasia, since cardiomyocytes become terminally differentiated soon after birth [30]. The increase in mass is a compensatory mechanism to bear the extra load imposed by MHT, explained by the Laplace law (T= P x r / 2h) [25]. Sustained increased BP levels result in increased wall stress – which is a major determinant of myocardial oxygen demand and pump function. In order to normalise increased wall stress (afterload), left ventricular mass increases and subsequently minimises left ventricular dilatation and ejection fraction decline [25, 31].

In our study we observed similar ejection fraction between the young masked hypertensives and normotensives, confirming findings from Trachsel *et al.* [12] and Tadic *et al.* [14]. This could be because systolic function is normally preserved until advanced stages of

hypertension, and in these "apparently" healthy masked hypertensives, MHT is likely within its early phases. Hence, there were also no differences in diastolic function parameters between the two groups.

Our findings are useful to inform healthcare practitioners on characteristics that may aid in the early identification of young patients with MHT, since it remains impractical to perform ambulatory BP measurements to diagnose MHT in all young patients. In our study, the majority of young masked hypertensive adults were men, and those with MHT presented with an increased cardio-metabolic risk profile (elevated clinic blood pressure, abdominal obesity, glucose and low HDL-c) when compared to normotensives. When viewing the clinic BPs of MHT participants 22.1% had high-normal office BP (compared to 7.42% of NT participants), this increased risk profile flags the opportunity for physicians and healthcare providers to perform ambulatory BP monitoring. We postulate that individuals presenting with these several risk factors are susceptible to MHT and should be considered for screening by physicians.

The results of this study should be interpreted in the context of some limitations. This study is a cross-sectional study and therefore causality cannot be inferred. Despite these limitations there are also several strengths to our study. Since this sub-study forms part of the longitudinal African-PREDICT study, we will have the opportunity to later assess how MHT at baseline relates to future left ventricular structural and functional changes. Other strengths are that a rigorous protocol was followed during ABPM assessments, and that all echocardiography measures and analyses were performed by one specialist clinical technologist.

In conclusion, MHT is common among 20-30 year olds and is independently and positively associated with LVMI – a predictor of cardiovascular morbidity and mortality. We found no apparent left ventricular dysfunction in these young individuals, as MHT is still in its early stages. Our findings highlight the importance of early detection of MHT and effective treatment to avoid premature structural cardiac changes and subsequently increased risk for future CVD.

Acknowledgments

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Online supplementary data

Left ventricular mass independently associates with masked hypertension in young healthy adults: The African-PREDICT study

Running title: Masked hypertension and organ damage

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Condensed Abstract

It is unknown whether masked hypertension in young adults already translates to early organ damage. We evaluated this in young adults of the African-PREDICT study. We found masked hypertensives to have higher odds to present with increased left ventricular mass index (OR=1.67; p=0.031) compared to normotensives. In multivariable-adjusted linear regression analyses, left ventricular mass index positively and independently associated with masked hypertension (adj. R^2=0.193; β=0.08 [0.01; 0.16]; p=0.046). This study shows that 1 in 6 young adults have masked hypertension, and they present an increased risk to have a higher left ventricular mass index reflecting increased risk for future cardiovascular disease.

Table S1. Testing the interaction of sex or ethnicity for the relationship between masked hypertension and measures of left ventricular structure and function

	p value	
	Sex	**Ethnicity**
Left ventricular mass index (g/m^2)	0.94	0.13
Relative wall thickness (cm)	0.081	0.65
E/A ratio	0.32	0.99
E/é ratio	0.37	0.79
Mitral valve deceleration time (ms)	0.13	0.86
LA/Ao ratio	0.13	0.75
Fractional shortening (%)	0.72	0.88
Ejection fraction (%)	0.79	0.81

Abbreviations: E/A ratio, ratio of mitral peak velocity of early (E) and late (A) diastolic filling; E/é ratio, ratio of mitral peak velocity of early filling (E) to early diastolic mitral annular velocity (é); LA/Ao, left atrial to aortic ratio.

Table S2. Characteristics of participants stratified by ethnicity and sex

	Black men (n=152)	White men (n=165)	p value	Black women (n=242)	White women (n=215)	p value
Age n (%)	24.2 ± 3.03	25.5 ± 2.87	<0.001	24.6 ± 3.35	25.1 ± 2.89	0.11
Socioeconomic status			<0.001			<0.001
Low n (%)	96 (63.2)	26 (15.8)		130 (53.7)	41 (19.1)	
Middle n (%)	33 (21.7)	41 (24.9)		73 (30.2)	50 (23.3)	
High n (%)	23 (15.1)	98 (59.4)		39 (16.1)	124 (57.7)	
Anthropometric measures						
Weight (kg)	62.9 [48.4; 88]	85.1 [63.2; 112]	<0.001	65.7 [46.8; 97.1]	68 [50.9; 112]	0.11
Height (cm)	170 ± 6.81	179 ± 6.15	<0.001	159 ± 6.15	168 ± 6.34	<0.001
Body mass index (kg/m^2)	21.8 [17.4; 30.1]	26.7 [20.3; 35.9]	<0.001	25.9 [17.9; 37.1]	24.3 [18.3; 38]	0.002
Waist circumference (cm)	74.5 [63.3; 91.7]	89.3 [74.0; 114]	<0.001	78.0 [62.0; 103]	76.3 [63.4; 106]	0.13
Systolic blood pressure (mmHg)						
Clinic	122 ± 12.6	122 ± 9.43	0.55	113 ± 10.6	109 ± 11.1	<0.001
24-h	120 ± 8.27	124 ± 7.28	<0.001	112 ± 8.30	113 ± 8.75	0.30
Daytime	124 ± 8.50	128 ± 7.82	<0.001	117 ± 8.80	118 ± 9.40	0.071

Nighttime	111 ± 10.2	114 ± 9.17	0.006	105 ± 9.24	104 ± 9.25	0.35
Diastolic blood pressure (mmHg)						
Clinic	80.9 ± 8.85	80.5 ± 8.52	0.70	78.5 ± 8.16	75.5 ± 8.12	<0.001
24-h	69.5 ± 6	70.5 ± 5.73	0.11	68.2 ± 5.61	68.0 ± 5.64	0.81
Daytime	74.3 ± 6.44	75.1 ± 6.41	0.29	72.4 ± 6.19	73 ± 6.23	0.33
Nighttime	60 ± 7.40	61.2 ± 7.31	0.15	60.2 ± 6.43	58.4 ± 6.12	0.003
Heart rate (beats/min)						
Clinic	57.8 ± 8.00	63.5 ± 10.5	<0.001	69.3 ± 9.86	69.9 ± 11.1	0.55
24-h	68.2 ± 8.04	70.6 ± 9.87	0.023	81.0 ± 8.96	76.8 ± 10.0	<0.001
Daytime	72.7 ± 8.96	75.1 ± 10.8	0.028	85.0 ± 9.56	81.3 ± 10.8	<0.001
Nighttime	59.9 ± 8.66	62 ± 10.5	0.062	73.3 ± 10.1	68.4 ± 10.5	<0.001
Masked hypertension n (%)	27 (17.8)	59 (35.8)	<0.001	23 (9.50)	18 (8.37)	0.67
Non-dipping n (%)	78 (51.3)	60 (36.4)	0.009	115 (47.5)	68 (31.6)	<0.001
Left ventricular structure and function						
Left ventricular mass index (g/m^2)	82.9 ± 18.6	81.9 ± 15.5	0.59	66.6 ± 13.2	68.3 ± 14.8	0.20
Relative wall thickness (cm)	0.37 ± 0.07	0.37 ± 0.07	0.78	0.38 ± 0.07	0.34 ± 0.06	<0.001
E/A ratio	2.33 [1.49; 3.81]	1.95 [1.44; 2.74]	<0.001	2.11 [1.43; 3.21]	2.02 [1.36; 3.14]	0.079

E/é ratio	6.50 ± 1.28	6.05 ± 1.08	<0.001	6.78 ± 1.26	6.34 ± 1.10	<0.001
Mitral valve deceleration time (ms)	230 ± 49.7	229 ± 49.7	0.95	227 ± 45.4	233 ± 51.3	0.23
LA/Ao ratio	1.10 ± 0.14	1.08 ± 0.15	0.34	1.13 ± 0.15	1.11 ± 0.16	0.25
Fractional shortening (%)	36.7 ± 5.35	35.4 ± 4.27	0.013	37.9 ± 4.71	37.8 ± 5.04	0.89
Ejection fraction (%)	66.1 ± 6.87	64.3 ± 5.73	0.010	68 ± 5.76	67.5 ± 6.34	0.36
Biochemical markers						
Total cholesterol (mmol/L)	3.70 [2.78; 5.48]	4.75 [3.29; 6.64]	<0.001	3.77 [2.66; 5.35]	4.52 [3.18; 6.43]	<0.001
HDL-cholesterol (mmol/L)	1.29 ± 0.33	1.14 ± 0.30	<0.001	1.27 ± 0.33	1.54 ± 0.43	<0.001
LDL-cholesterol (mml/L)	2.26 [1.38; 3.87]	3.22 [1.97; 5.14]	<0.001	2.36 [1.26; 3.91]	2.80 [1.74; 4.43]	<0.001
Triglycerides (mmol/L)	0.79 [0.42; 1.58]	1.15 [0.55; 2.85]	<0.001	0.68 [0.36; 1.34]	0.88 [0.42; 2.13]	<0.001
Glucose (mmol/L)	4.30 ± 0.95	5.09 ± 0.61	<0.001	4.47 ± 0.75	4.73 ± 0.83	<0.001
eGFR (ml/min/1.73m^2)	118 ± 14.7	103 ± 16.4	<0.001	117 ± 15.3	108 ± 15.6	<0.001
Lifestyle factors						
AEE (kCal/kg/day)[a]	5.91 ± 2.84	4.30 ± 2.02	<0.001	7.04 ± 3.12	6.20 ± 2.90	0.010
y-glutamyl transferase (U/L)	27.7 [13.3; 82.8]	25.7 [12.6; 64.5]	0.24	22.7 [10.1; 62.7]	14.5 [7.40; 40.7]	<0.001
Self-reported alcohol use n (%)	101 (67.3)	109 (66.1)	0.81	123 (51.7)	116 (54.0)	0.63
Cotinine (ng/ml)	10.5 [1.00; 411]	5.90 [1.00; 365]	0.049	2.08 [1.00; 184]	2.29 [1.00; 265]	0.57

Former and current smoking n (%)	85 (55.9)	69 (41.8)	0.012	46 (19)	69 (32.1)	0.001
Night shift n (%)	11 (12.5)	15 (11.5)	0.81	26 (16.3)	4 (2.42)	<0.001

Abbreviations: E/A ratio, ratio of mitral peak velocity of early(E) and late (A) diastolic filling; E/é ratio, ratio of mitral peak velocity of early filling (E) to early diastolic mitral annular velocity(é); LA/Ao, left atrial to aortic ratio; HDL, high-density lipoprotein; LDL, low-lipid lipoprotein; eGFR, estimated glomerular filtrate rate; AEE, activity energy expenditure. Data presented as mean ± standard deviation or geometric mean [5th to 95th percentile intervals] for logarithmically transformed variables, or number of participants and percentages.

[a]n=594

Chapter 5

Concluding Remarks & Future Recommendations

1. Introduction

This is a summative chapter that interprets the main findings of this study. I will accept or reject the initial hypotheses made in Chapter 2, based on the results obtained in Chapter 4. I will also compare the main findings of this study against existing literature. Finally, conclusions will be made and I will make recommendations for future studies.

2. Interpretations and summary of key findings

It is well known from the literature that a relationship exists between masked hypertension (MHT) and left ventricular structure and function [1-3]. This relationship was mainly established in the elderly, clinic normotensive children and diseased populations (hypertensives, untreated masked hypertensives and diabetics) [4-6], but it is unknown if the same relationship exists for young healthy adults. Moreover, controversy in the literature circles around ethnic differences in the prevalence of MHT between black and white populations. Of note, ethnic differences in the prevalence of sustained hypertension has been established with a higher prevalence of hypertension in blacks [7, 8]. However, whether this applies to MHT, is still unclear. We therefore investigated the frequency of MHT in young black and white adults, and whether it associates with left ventricular structure and function in both population groups.

Hypothesis 1: No ethnic differences will exist regarding the frequency of MHT, but a higher frequency is expected amongst men.

In this study we found an ethnic difference regarding the frequency of MHT, with whites having a higher frequency (20.3%) compared to blacks (12.7%). This is in contrast with the findings from the Jackson Heart Study [8] and the Dallas Heart Study [9], which found blacks to have a higher prevalence of MHT than whites. However, both of these studies included elderly participants that were already taking medication for diabetes and hypertension. The occurrence of chronic diseases, such as hypertension and diabetes, form part of the exclusion criteria of the African-

PREDICT study, as the study aimed to evaluate potential risk factors contributing to cardiovascular disease development in young apparently healthy adults. The young age and healthy status of our participants could therefore have played a role in the contradicting findings. We also postulate that the overall increased cardio-metabolic risk present in whites (elevated clinic blood pressure, abdominal obesity, glucose, triglycerides and low high-density lipoprotein cholesterol) could have resulted in the whites to be more susceptible to MHT as compared to blacks [10, 11]. This may indicate that MHT is not necessary associated with ethnicity, as most but not all prior studies show no ethnic difference in the prevalence [12-14], but possibly associates with cardiovascular and lifestyle risk factors, especially increased adiposity [11, 15].

In addition, in our study MHT was predominant in men and these results are consistent with previous studies [4, 13].

I therefore reject the first part of the hypothesis specifying no ethnic differences in the frequency of MHT, since we showed frequency of MHT to be higher in white compared to black participants. I accept the hypothesis relating to the frequency of MHT to be higher in men, as our results confirmed this.

Hypothesis 2: Left ventricular mass and relative wall thickness will associate positively with masked hypertension.

In our group of young participants, we found that left ventricular mass index was positively associated with MHT, independent of a range of potential confounders. This confirmed previous studies in the elderly, clinic normotensive children and diseased populations such as sustained hypertensives [1, 5, 8]. We specifically found 1 in 6 young adults to have MHT. These participants presented with a 67% likelihood to have higher left ventricular mass as compared to normotensives, when adjusting for age, sex, ethnicity, socio-economic status, estimated glomerular filtrate rate, y-glutamyl transferase and cotinine. It should, however, be noted that MHT

presented a left ventricular mass index within the acceptable physiological range, namely below 50-102 g/m^2 in men and 44-88 g/m^2 in women.

The young adults included in our study were recruited with no self-reported chronic diseases and no known cardiovascular disease. We therefore speculate that due to their apparent healthy status and being in the early masked hypertensive phase, we found no association between relative wall thickness and MHT. This contradicts the findings from Liu *et al.* [1], as they found a positive relationship between relative wall thickness and MHT. Again, the difference in the results could be due to their inclusion of a sustained hypertensive population, possibly presenting with target organ damage such as left ventricular hypertrophy. The increased left ventricular hypertrophy, is a result of a compensatory mechanism on the increased pressure overload (MHT) exerted on the heart which increases wall stress. To normalise wall stress, left ventricular mass and relative wall thickness increases, that is classified as concentric hypertrophy [16-19].

I therefore accept the first part of the hypothesis confirming a positive association between MHT and left ventricular mass, but I reject the second part of the hypothesis suggesting a link between MHT and relative wall thickness in this young population.

Hypothesis 3: Adverse associations of systolic and diastolic function will exist with masked hypertension.

We found no relationship between left ventricular function (systolic and diastolic) and MHT. The lack of association between parameters of diastolic function and MHT are in alignment, but also contradicts the findings from the Masked Hypertension Study [20]. This study found no difference in E/A ratio or deceleration time between normotensives and masked hypertensives, but they found masked hypertensives to present with higher E/è. This is further supported by another cross-sectional study which included normotensive individuals, patients with MHT, and untreated sustained hypertensive patients [3]. The conflicting result on E/è ratio could be due to the

difference in the baseline inclusion criteria, as the Masked Hypertension Study included individuals that already present with Clinic Stage 2 Hypertension, but not on antihypertensive medication [20]. In our study, young adults were clinic normotensives. Our findings regarding a lack of association between systolic function and MHT, is supported by the literature [3, 21, 22]. Masked hypertensives were reported to have similar ejection fraction and fractional shortening as normotensives [3, 21]. The preserved ejection fraction is due to a compensatory mechanism involving an increase in mass to normalise wall stress - a major determinant of pump function caused by pressure overload [16, 17]. Again as previously mentioned, our population might be at the early stage of MHT and therefore present no functional changes, as shown by the preserved fractional shortening and ejection fraction on our results.

Therefore I reject my hypothesis proposing that an association between left ventricular function and MHT exist in young adults.

3. Limitations, chance and confounding factors

Participants from the African-PREDICT study were recruited in and around the Potchefstroom area in the North West Province. As defined in the inclusion criteria, these participants were young black and white adults that were apparently healthy, meaning that they were clinic normotensives, had no Human Immunodeficiency virus (HIV) or any other chronic diseases. Therefore, the results of this study do not reflect the whole demographic of the young South African population and the results cannot be generalised for all South Africans. Moreover approximately 57% of the black participants were from a low socio-economic background as compared to approximately 58% of white participants from a high socio-economic background. This may have caused biased results, as low socio-economic status is a known risk factor for hypertension [23]. However, since clinic hypertensives were excluded from this study, socio-economic status did not seem to affect the masked hypertensive status of individuals.

During the research measurements of the study, clinic blood pressure was assessed during a single study visit, but repeated three times. This is not in agreement with usual clinical practice guidelines to diagnose a patient with hypertension, where repeat clinic visits are required. For the purpose of the present study this is, however, not considered a weakness, since white-coat hypertension would be apparent in a single clinic visit, but not MHT. Furthermore, a strength of our study is that ambulatory blood pressure monitoring (ABPM) were performed thoroughly, only participants who were included had >70% of valid blood pressure measurements.

Due to the cross-sectional nature of this study, we could only ascertain the positive association between left ventricular mass index and MHT in young adults, and could not establish cause and effect. Our findings did allow us to postulate on the potential physiological mechanisms of the relationship of MHT with left ventricular mass index.

When multivariable logistic regression analyses were performed, we were unable to use clinical cut-off values for echocardiography measures, due to our young healthy population. We therefore used the 75th percentiles of echocardiographic measures as cut-off, which is a common alternative used in similar studies.

The possibility of chance findings should also be considered. When performing multiple correlations between variables, there is indeed a likelihood of chance findings. In our study, there is a low possibility of our finding being due to chance, as the same relationship between left ventricular mass and MHT was not only depicted in multivariable adjusted logistic regression, but also in multivariable linear regression after adjustments of different sets of covariates **(Table 1 below)**. An additional potential confounder that we considered is cardiac bundle branch block which associates with hypertension [24]. We decided to further exclude individuals with left and right bundle branch block and as shown in **Table 1** below, left ventricular mass again independently associated with MHT.

Table 1. Multivariable–adjusted logistic and linear regression confirming the association of left ventricular mass with masked hypertension

	Covariates	Left ventricular mass associates with masked hypertension
Multivariable-adjusted logistic regression	Age; sex; ethnicity; socio-economic status; estimated glomerular filtrate rate; y-glutamyl transferase; cotinine	OR: 1.67 [1.05-2.71 95% CI]; p=0.031
Multivariable-adjusted linear regression	Age; sex; ethnicity; socio-economic status; estimated glomerular filtrate rate; y-glutamyl transferase; cotinine	adj. R^2=0.194, β=0.09 [0.02; 0.16]; p=0.009
	Age; sex; ethnicity; socio-economic status; estimated glomerular filtrate rate; y-glutamyl transferase; cotinine; glucose; activity induced energy expenditure; high-density lipoprotein/triglycerides	adj. R^2=0.193, β=0.08 [0.002; 0.16]; p=0.046
	Exclude participants with left and right bundle branch block (n=55) Age; sex; ethnicity; socio-economic status; estimated glomerular filtrate rate; y-glutamyl transferase; cotinine; glucose; activity induced energy expenditure; high-density lipoprotein/triglycerides	Adj. R^2=0.188, β=0.08 [0.01; 0.15]; p=0.033

4. Recommendation for future studies

o The increasing burden of cardiovascular disease and hypertension in sub-Saharan Africa is a major concern [13]. Despite many epidemiological studies focusing on the burden of hypertension, these studies are only based on clinic blood pressures. Few studies report on MHT in the sub-Saharan region, particularly in young adults. In a Tanzanian elderly population, 55.7 % presented with MHT based on the 24-h ABPM [25]. Due to the difficulty in performing ABPM measurements in large populations, the South African hypertension guidelines recommends the use of ABPM on treated hypertensives that presents with persisting target organ damage [26]. However, our findings in young clinic normotensives already set the stage for future investigations on the burden of MHT in young adults in the sub-Saharan region.

o Our study had a very specific study design, but we also recommend large population-based studies including randomly selected individuals from the whole of South Africa. Such data would be important to ascertain the burden of MHT and related target organ damage, such as left ventricular structure and function. Large population-based studies can also evaluate ethnic differences in the frequency of MHT since conflicting findings exist.

o This study is a cross-sectional sub-study of the longitudinal African-PREDICT study. We will therefore be able to follow-up the participants to evaluate the progression or regression of MHT and how MHT will relate to changes in left ventricular structure and function over time. Since isolated nocturnal MHT is the strongest predictor of cardiovascular disease [27], it would be of interest to evaluate its effect on left ventricular structure and function in these young adults. Furthermore, we found masked hypertensives to be non-dippers, we also recommend that the contribution of non-dipping to possibly left ventricular structure and function impairment be evaluated in young adults.

o   There are other psychological and social factors that associate with MHT according to the literature, such as education level, work stress and marital status [28]. As these were not the primary focus of this study, we recommend future studies to evaluate psychosocial factors in the same population group to investigate whether the association between left ventricular mass and MHT would be affected.

5.5 Conclusion

Our study presents novel findings regarding the association between left ventricular mass and MHT in young adults. Our results suggest that 1 in 6 normotensive young adults are masked hypertensive and already present with an almost 2-fold risk of higher left ventricular mass compared to sustained normotensives. Overall, this study suggests that these young masked hypertensives are already at increased risk of future cardiovascular events.

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Appendices

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Articles in journals:

Zhou M-S, Schulman IH, Raij L. Vascular inflammation, insulin resistance, and endothelial dysfunction in salt-sensitive hypertension: role of nuclear factor kappa B activation. *J Hypertens* 2010; **28**:527–535

More than seven authors:

Palatini P, Reboldi G, Beilin LJ, Casiglia E, Eguchi K, Imai Y *et al.* Masked tachycardia. A predictor of adverse outcome in hypertension. *J Hypertens* 2017; **35**: 487-492

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> **Study title:** Masked hypertension and left ventricular structure and function in young black and white adults: The African-PREDICT
>
> **Study Leader/Supervisor:** Prof AE Schutte
> **Student:** NP Sekoba-29903904
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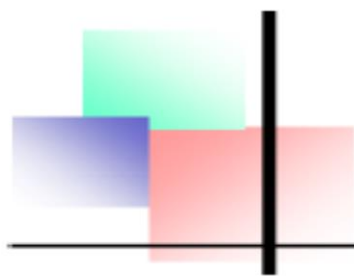
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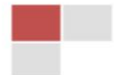
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