ORIGINAL ARTICLE

Masked hypertension and its associated cardiovascular risk in young individuals: the African-PREDICT study

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Hypertension prevalence is increasing globally, yet little is known about the occurrence of masked hypertension (MHT) in young, sub-Saharan African adults, and how it relates to elevated cardiovascular risk. The African-PREDICT study (recruitment based on normotensive clinic blood pressure (BP)) determined the frequency of MHT and its relationship with arterial stiffness and biochemical markers of inflammation and endothelial activation. We included men and women ($n = 352$), 20–30 years, screened for normotensive clinic BP (54% white, 40% men). Clinic BP, ambulatory blood pressure monitoring (ABPM), central systolic pressure, aortic pulse wave velocity (aPWV), augmentation index, anthropometry, physical activity and biochemical markers of cardiovascular risk were assessed (lipids, glucose, insulin, markers of endothelial activation and inflammation). Eighteen percent of the study population had MHT (60% white, 68% men). Those with MHT had increased adiposity, clinic-, ABPM- (24-h, day and night) and central-BP (within normal ranges), heart rate, aPWV and biochemical markers of cardiovascular risk, compared with normotensives (all $P < 0.05$). Using multivariable adjusted odds ratios, we found that MHT was associated with increased likelihood for higher aPWV (odds ratio (OR) = 1.567, $P = 0.010$), insulin (OR = 1.499, $P = 0.049$), monocyte chemoattractant protein-1 (OR = 1.499, $P = 0.026$), vascular cellular adhesion molecule (OR = 1.409, $P = 0.042$) and C-reactive protein (OR = 1.440, $P = 0.044$). In a young adult (supposedly healthy) cohort, the occurrence of MHT is alarming, especially since MHT further demonstrated elevated cardiovascular risk via increased adiposity, arterial stiffness, endothelial activation and inflammation. Detection of MHT is crucial to increase awareness of elevated cardiovascular risk, and to ensure the required lifestyle and/or pharmaceutical interventions.
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INTRODUCTION

Cardiovascular disease (CVD) is the main cause of death globally, and more than 80% of CVD deaths occur in low- and middle-income countries.[1] South Africa is a country undergoing rapid urbanization, and in a recent study conducted in six developing countries worldwide, South Africa had the highest levels of hypertension in adults over the age of 50 years.[2] Earlier detection and effective treatment of hypertension in this population are therefore imperative. Hypertension is primarily diagnosed by clinic blood pressure (BP) measurement, which does not allow for the detection of masked hypertension (MHT).

MHT is a risk factor for CVD and is a condition where a patient presents as normotensive in clinic, but is hypertensive when BP is measured over 24-h using ambulatory blood pressure monitoring (ABPM).[3–6] The more commonly known white coat hypertension is in contrast to MHT and results in patients being unnecessarily pharmaceutically treated for hypertension.[7] MHT is a concern as patients are less easily diagnosed and are therefore untreated and unaware of their elevated cardiovascular risk.[8] Studies conducted in white and Japanese populations identified MHT as an important cardiovascular risk factor[9,10] and suggested MHT to have a higher prevalence than white coat hypertension.[11]

The underlying pathology of MHT is not entirely understood. The prevalence of MHT has mostly been determined in diseased, older populations[12,13] and has not been determined in sub-Saharan African adults. It may therefore be of particular value to determine the frequency of MHT in young black and white adults, who are expected to be healthy and normotensive. Whether other cardiovascular risk markers besides BP are elevated in such a population is unknown. Factors such as arterial stiffness, lipids, markers of inflammation and endothelial activation are associated with increased cardiovascular risk, morbidity and mortality.[14–25] It may increase our understanding of

MHT to determine whether such markers are increased in young adult, masked hypertensives.

Therefore, we explored whether MHT occurs in young, black and white South Africans who were recruited on the basis of normotensive clinic BP. We reviewed several hemodynamic (peripheral clinic BP, ABPM BP, central systolic pressure, aortic pulse wave velocity (aPWV) and augmentation index (AIx)), biochemical (lipids, glucose, insulin, endothelial activation markers (intracellular adhesion molecules (I-CAM), vascular cellular adhesion molecules (V-CAM), monocyte chemoattractant protein-1 (MCP-1))) and inflammatory markers (interleukin-6 (IL-6), C-reactive protein (CRP), tumor necrosis factor-α (TNF-α) and reactive oxygen species (ROS))) of cardiovascular risk in participants with MHT compared with normotensive participants.

METHODS

Study population
Participants were recruited as part of the African-PREDICT (PRospective study on the Early Detection and Identification of Cardiovascular disease and hyperTension) longitudinal study. The aim of this project is to follow young, healthy, normotensive adults over a 20-year period in order to identify novel markers of early cardiovascular risk in an apparently healthy population. The current sub-study initially included cross-sectional data from the first 403 participants.

The study complied with all applicable requirements of the US and International Regulations, in particular, the Helsinki Declaration of 1975 (as revised in 2008), for investigation of human participants. The study was approved by the Health Research Ethics Committee of the North-West University (Potchefstroom Campus). All participants provided written, informed consent.

Active participant recruitment takes place on a continuous basis. Participants are invited from Potchefstroom and surrounding areas in South Africa via different routes, such as active contact via field workers, access through the workplace and advertisements by means of radio and local newspapers. Participants who are recruited firstly undergo screening to determine eligibility for participation in the African-PREDICT study. The participants therefore constitute a convenience or availability sample, stratified into different ethnic (black and white), sex and socio-economic class groups (low, mid, high). Of the 642 participants screened, $n = 403$ (63%) were eligible and took part in the primary project.

Young (20–30 years of age), apparently healthy, black and white men and women, with normal clinic BP (that is, $< 140/90$ mm Hg), no known CVD, not on any BP medication, no chronic disease (or treatment thereof), HIV-free, tuberculosis-free and not pregnant or breast feeding were recruited from the Potchefstroom area (in the North-West Province of South Africa).

Screening for eligibility of participation in African-PREDICT
Eligibility criteria, based on HIV status and BP, were assessed during a screening session that took place on a separate day, before the primary project day. HIV testing was performed using the South African Provider Initiated Counseling and Testing protocols, by trained counselors. HIV status was determined with the ABON HIV 1/2/O Tri-Line Rapid Test (ABON Biopharm, Hangzhou, China) using whole blood. If positive, the test was repeated with a First Response (PMC Medical, Nani Daman, India) rapid HIV test. If positive, participants were not eligible for the study.

BP eligibility was determined by BP measurement twice on each arm with a 5-min rest period between measurements, using a semi-automatic BP device (M3W-HEM7202, OMRON Healthcare, Kyoto, Japan) and appropriate sized BP cuffs. If the mean of four readings was > 140 mm Hg and/or 90 mm Hg, participants were not eligible to continue through to the primary African-PREDICT project. All screening measurements and primary project day measurements took place in the morning.

African-PREDICT primary project data collection

Anthropometric and physical activity measurements. Weight (kg) was measured to the nearest 0.01 kg (SECA electronic scales, SECA, Birmingham, UK), height (m) was measured to the nearest 0.1 cm (SECA stadiometer, SECA) and waist circumference (cm) was measured in triplicate using a non-flexible tape measure (Holtain, Crymych, UK), and recorded to the nearest 0.1 cm. The median of the three recordings was used in subsequent analyses. Trained anthropometrists conducted these measurements. Body mass index was calculated using the standard weight (kg)/height (m^2) calculation, and waist-to-height ratio was calculated using waist circumference (cm)/height (cm).

The combined heart rate (HR) and accelerometer ActiHeart (CamNtech, Cambridge, UK) device is a small, compact and non-invasive device that was worn on the chest by each participant for a period of 7 consecutive days, collecting data at 60 s epochs. The device was used in order to objectively capture Activity Energy Expenditure, an estimate of physical activity.

Cardiovascular measurements. With participants seated, clinic BP recordings were measured at the brachial artery, twice on each arm (DINAMAP, GE Healthcare, Buckinghamshire, UK), and a mean of the four readings was then used for all subsequent analyses. There was a 5-min rest period between each measurement, and appropriate sized BP cuffs were used.

We used validated CardioXplore devices (CardioXplore, MediTech, Budapest, Hungary) for collection of 24-h BP measurements, programmed to take recordings every 30 min during the day (0600 to 2200 hours) and every hour during the night (2200 to 0600 hours). The ABPM was fitted to each participant at approximately the same time every day (late morning), using an appropriate sized cuff, and as per the manufacturer's instructions. Only participants with $> 70\%$ of valid BP measurements, > 20 day measurements and > 7 night measurements were included in the final analyses.[26]

Both AIx and aPWV measurements were conducted using the SphygmoCor XCEL device (SphygmoCor XCEL, AtCor Medical, Sydney, Australia).[27] AIx was captured at the brachial artery pulse point using a brachial pressure cuff, and calculated using software-in-built pulse wave analysis. aPWV was captured at the femoral and carotid arterial pulse points. The femoral artery wave form was captured via an appropriate sized cuff placed around the thigh, and the carotid arterial waveform was captured simultaneously via applanation tonometry. The SphygmoCor XCEL device also produced a central arterial waveform that provided an estimated central systolic BP reading, obtained from the peripheral arterial wave form via the in-built generalized transfer function.[28]

Biochemical measurements. Fasted venous blood samples were collected from the brachial antecubital vein into serum SST tubes (γ-glutamyl transpeptidase (GGT), cotinine, lipids, insulin, I-CAM, V-CAM, IL-6, CRP, TNF-α and ROS), EDTA plasma tubes (MCP-1) and sodium fluoride plasma tubes (glucose). We conducted analyses for low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, triglycerides, glucose, high-sensitivity CRP and GGT (Cobas Integra 400plus, Roche, Basel, Switzerland). Cotinine (chemiluminescence method on the Immulite (Siemens, Erlangen, Germany)) and insulin (electrochemiluminescence method on the e411 (Roche)) were also assayed. I-CAM, V-CAM, MCP-1, high-sensitivity TNF-α and high-sensitivity IL-6 were assayed using Quantikine ELISA kits (R&D systems, Minneapolis, MN, USA). Serum peroxides as indication of ROS were determined by an improved assay system based on the principle of the derivatives of reactive oxygen metabolites test, which is recognized as an efficient method for evaluating oxidative stress in the body. This spectrophotometric method was performed on a Synergy H4 hybrid microplate reader (BioTek, Winooski, VT, USA). ROS levels are presented in Units, where 1.0 mg l^{-1} H$_2$O$_2$ represents one unit of ROS.[29]

Statistical analysis. We categorized participants according to their BP status. Based on normotensive screening BP $n = 403$ participants were recruited onto the African-PREDICT project, with $n = 7$ excluded as they did not have valid ABPM measurements, leaving $n = 396$. We included $n = 352$ in the current statistical analyses. The remaining 44 were excluded as on the primary project day they had elevated clinic BP; that is, they were identified as 'true hypertensive' ($n = 28$) or 'white coat hypertensive' ($n = 16$). These two cohorts were not included in further analyses as the size of the cohorts was deemed too small. See Table 1 for details.

The remaining participants were categorized as normotensive or MHT. Normotensive status was based on having a normal clinic BP (that is, <140 mm Hg systolic BP, and <90 mm Hg diastolic BP) and normal ABPM (that is, 24-h readings <130 and <80 mm Hg, daytime readings <135 and <85 mm Hg and night time readings <120 and <70 mm Hg). MHT status was classified as participants having normal clinic BP (<140 and <90 mm Hg), but an elevated ABPM (24-h SBP and/or DBP ⩾ 130/80 mm Hg; day SBP and/or DBP ⩾ 135/85 mm Hg; night SBP and/or DBP ⩾ 120/70 mm Hg). MHT was classified as being hypertensive either at 24-h, and/or day, and/or night.[26]

Statistical analyses were conducted using SPSS version 22 (IBM, Armonk, NY, USA). χ^2 analyses were conducted for categorical data, whereas independent samples *t*-test, and analysis of covariance analyses were used for analysis of continuous data. Normality of variables was tested using the Shapiro–Wilk test and visual inspection of histogram plots. Normally distributed data are expressed as the arithmetic mean and standard deviation. Skewed data were log transformed and the geometric mean and 5th and 95th percentiles are displayed (Tables 3 and 4). Adjusted odds ratio analyses were conducted, and data displayed in forest plots (Figure 1). As the study sample represents a young, healthy population, we were unable to use clinical cutoff values for odds ratio analyses as changes in pressure, stiffness and endothelial function are expected to be early sub-clinical changes for those at increased risk. Cutoff values used for the odds ratios were therefore determined as median splits of the cohort as a whole.

RESULTS

As indicated in Table 1, of the 352 participants included in our analyses, $n=290$ (82.4%) were normotensive by clinic BP and by 24-h BP and $n=62$ (17.6%) had MHT.

Table 2 demonstrates on which criteria participants were classified as MHT, indicating that the majority of classifications were based on hypertensive nighttime readings alone (52%), and that 24% were MHT according to all times (nighttime, daytime and 24-h).

In Table 3, we compared the profiles of the normotensive and MHT status groups. Although age and ethnicity did not differ between the groups, the MHT group consisted of significantly more men than the normotensive group (67.7% *vs.* 33.8%). The level of completed education between the two groups did not statistically differ; the majority in both groups having attained a college/university level of education. MHT participants were taller, had increased adiposity, higher clinic BP, 24-h BP and central BP, and aPWV (6.58 *vs.* 6.24 m s^{-1}; all $P \leqslant 0.001$). With regards to biochemical markers of cardiovascular risk, high-density lipoprotein-cholesterol was lower (1.17 *vs.* 1.38 mmol l^{-1}), and triglycerides (1.2 vs 0.92 mmol l^{-1}), glucose (4.62 *vs.* 4.30 mmol l^{-1}), insulin (12.77 *vs.* 10.13 uU ml^{-1}), MCP-1 (175 *vs.* 152 pg ml^{-1}) and I-CAM (185 *vs.*

Table 1 Blood pressure status based on clinic blood pressure readings and ABPM in all participants recruited to the primary African-PREDICT study with valid ABPM measures, $n=396$

	Ambulatory blood pressure status	
Clinic blood pressure status	*Normotensive*	*Hypertensive*
Normotensive	$n=290$ (33.8% men, 46.7% black)	$n=62$ (67.7% men, 40.3% black)
Hypertensive	$n=16$ (56.3% men, 81.3% black)	$n=28$ (71.4% men, 64.3% black)

Abbreviation: ABPM, ambulatory blood pressure monitoring.

Table 2 Number of participants fulfilling the criteria each MHT categorization

	MHT confirmed in n *(%),* n = 62
24-h ABPM only	1 (1.61)
Day ABPM only	4 (6.46)
Night ABPM only	32 (51.6)
24-h and day ABPM only	4 (6.46)
24-h and night ABPM only	6 (9.67)
Day and night ABPM only	0 (0)
24-h, Day and night ABPM only	15 (24.2)

Abbreviations: ABPM, ambulatory blood pressure monitoring; MHT, masked hypertension.
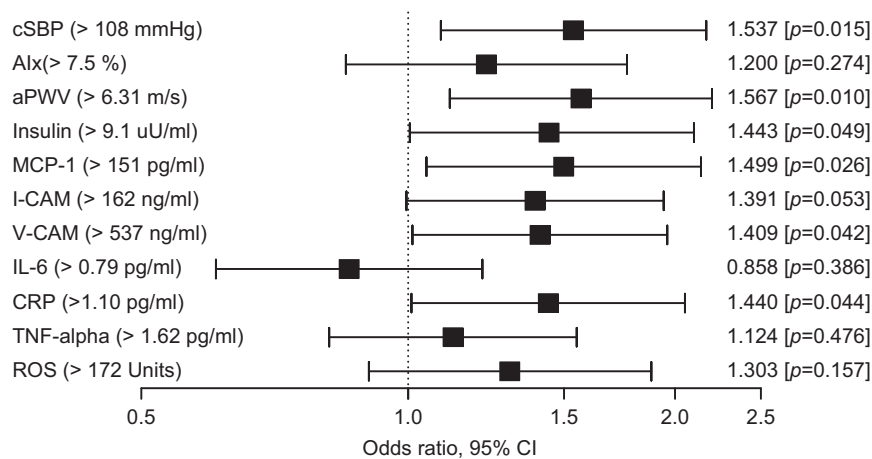

Figure 1 Adjusted odds ratios for having adverse central systolic blood pressure (cSBP), arterial stiffness and biochemical markers of cardiovascular risk in individuals with masked hypertension. Adjusted for age, sex, ethnicity, waist circumference, γ-glutamyl transpeptidase, cotinine and physical activity levels (augmentation index (AIx) additionally adjusted for height, aPWV additionally adjusted for MAP), $n=352$. aPWV, aortic pulse wave velocity; CRP, C-reactive protein; I-CAM, intracellular adhesion molecule; IL-6, interleukin-6; MCP-1, monocyte chemoattractant protein; ROS, reactive oxygen species; TNF-α, tumor necrosis factor-α; V-CAM, vascular cellular adhesion molecule.

Table 3 Descriptive characteristics of normotensive and masked hypertensive participants

Variable	Normotensive, n = 290 (82.4%)	Masked hypertension, n = 62 (17.6%)	P-value
Demographic variables			
Men, *n* (%)	*98* (33.8)	*42* (67.7)	<0.001
Age (years)	25.05 ± 3.13	24.87 ± 3.16	0.385
Black, *n* (%)	136 (46.9)	25 (40.3)	0.414
Socio-economic status by level of education			
High-school education completed, *n* (%)	99 (34)	24 (39)	0.226
College/university completed, *n* (%)	178 (61)	36 (58)	0.574
Anthropometric measures			
Weight (kg)	67.63 ± 14.39	84.66 ± 22.19	<0.001
Height (m)	1.67 ± 9.19	1.72 ± 9.35	<0.001
Body mass index (kg m^{-2})	24.28 ± 4.80	28.53 ± 6.90	<0.001
Waist circumference (cm)	76.92 ± 10.93	89.35 ± 16.70	<0.001
Waist/height ratio	0.46 ± 0.07	0.52 ± 0.09	<0.001
Cardiovascular measures			
Systolic blood pressure (mmHg)			
Clinic systolic blood pressure	113 ± 11	125 ± 9	<0.001
24-h systolic blood pressure	113 ± 7	128 ± 6	<0.001
Central systolic blood pressure	106 ± 8	113 ± 8	<0.001
Diastolic blood pressure (mmHg)			
Clinic diastolic blood pressure	76 ± 7	80 ± 6	<0.001
24-h diastolic blood pressure	68 ± 5	74 ± 5	<0.001
Pulse pressure (mmHg)			
Clinic pulse pressure	38 ± 7	44 ± 8	<0.001
24-h pulse pressure	46 ± 6	54 ± 8	0.006
Mean arterial pressure (mmHg)			
Clinic mean arterial pressure	88 ± 7	95 ± 6	0.006
24-h mean arterial pressure	83 ± 5	92 ± 4	0.006
Heart rate (b.p.m.)			
Clinic heart rate	65 ± 11	66 ± 10	0.668
24-h heart rate	75 ± 10	77 ± 12	0.298
Arterial stiffness			
Augmentation index (heart rate 75 b.p.m.; %)[a]	7.37 ± 7.65	8.07 ± 8.22	0.519
Aortic pulse wave velocity (m s^{-1})[b]	6.24 (6.15, 6.33)	6.58 (6.38, 6.80)	0.001
Lifestyle factors			
Gamma-glutamyl transpeptidase (U l^{-1})	23.39 (20.81, 25.96)	33.67 (24.16, 43.17)	0.041
Cotinine (ng ml^{-1})	45.67 (33.39, 57.96)	58.52 (27.88, 89.15)	0.586
Physical activity (kCal per day)	424 ± 199	437 ± 219	0.659
Biochemical markers			
HDL-cholesterol (mmol l^{-1})	1.38 ± 0.38	1.17 ± 0.38	<0.001
LDL-Cholesterol (mmol l^{-1})	2.74 ± 0.93	3.00 ± 0.86	0.050
Triglycerides (mmol l^{-1})	0.92 (0.86, 0.98)	1.21 (1.01, 1.40)	0.005
Glucose (mmol l^{-1})	4.30 (4.18, 4.42)	4.62 (4.41, 4.83)	0.007
Insulin (uU ml^{-1})	10.13 (9.38, 10.88)	12.77 (10.90, 14.64)	0.005
Monocyte chemoattractant protein-1 (pg ml^{-1})	152 (146, 158)	175 (157, 193)	0.009
Intracellular adhesion molecule (ng ml^{-1})	161 (153, 170)	185 (163, 207)	0.044
Vascular cellular adhesion molecule (ng ml^{-1})	566 (546, 87)	580 (541, 619)	0.482
Interleukin-6 (pg ml^{-1})	1.11 (0.95, 1.26)	1.15 (0.91, 1.39)	0.814
C-reactive protein (mg l^{-1})	2.80 (2.19, 3.40)	3.61 (1.73, 5.48)	0.193
Tumor necrosis factor-α (pg ml^{-1})	1.89 (1.72, 2.05)	1.99 (1.74, 2.24)	0.556
Reactive oxygen species (U)	189 ± 84	180 ± 65	0.322

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein.
Mean ± s.d.
Geometric mean and 5th and 95th percentiles displayed in brackets for the log transformed data.
[a]Additionally adjusted for height.
[b]Adjusted for mean arterial pressure and age.
Entries in italics denote P<0.001.

161 ng ml^{-1}) were higher in the MHT group (all $P<0.05$). GGT was higher in the MHT group, but there were no significant differences in physical activity or cotinine levels between the groups.

We repeated these analyses in Table 4, with outcome variables adjusted for age, sex, ethnicity, waist circumference, GGT, cotinine and activity energy expenditure. Following these adjustments, elevated levels for adiposity; BPs and aPWV (6.54 *vs.* 6.26 m s^{-1}, $P=0.020$) were confirmed in the MHT group compared with the normotensive group. Twenty-four- hour HR (79 *vs.* 75 b.p.m.) was also higher in the MHT group compared with the normotensive group. Following adjustments, MCP-1 (172 vs 153 pg ml^{-1}) was higher in the MHT group ($P=0.009$), whereas AIx (9.26% *vs.* 7.24%, $P=0.053$) and

Table 4 Comparison of normotensive and masked hypertensive groups following multiple adjustments

		Masked hypertension	
Variable	Normotensive (n = 290)	(n = 62)	P-value
Anthropometric measures			
Weight (kg)	68.10 ± 14.57	82.45 ± 14.95	<0.001
Body mass index (kg m^{-2})	24.20 ± 5.08	28.90 ± 5.21	<0.001
Waist circumference (cm)	77.17 ± 11.51	88.23 ± 11.81	<0.001
Waist:height ratio	0.46 ± 0.07	0.52 ± 0.07	<0.001
Cardiovascular measures			
Systolic blood pressure (mmHg)			
Clinic systolic blood pressure	114 ± 9	120 ± 10	<0.001
24-h systolic blood pressure	114 ± 6	124 ± 6	<0.001
Central systolic blood pressure	106 ± 8	111 ± 8	<0.001
Diastolic blood pressure (mmHg)			
Clinic diastolic blood pressure	76 ± 7	79 ± 7	0.004
24-h diastolic blood pressure	68 ± 5	73 ± 5	<0.001
Pulse pressure (mmHg)			
Clinic pulse pressure	38 ± 7	41 ± 7	0.009
24-h pulse pressure	47 ± 5	51 ± 6	<0.001
Mean arterial pressure (mmHg)			
Clinic mean arterial pressure	89 ± 7	93 ± 7	<0.001
24-h mean arterial pressure	83 ± 5	90 ± 5	<0.001
Heart rate (b.p.m.)			
Clinic heart rate	65 ± 10	68 ± 10	0.053
24-h heart rate	75 ± 9	79 ± 10	0.012
Arterial stiffness			
Augmentation index (heart rate 75 b.p.m.; %)[a]	7.24 ± 6.66	9.26 ± 6.80	0.053
Aortic pulse wave velocity (m s^{-1})[b]	6.26 (6.17, 6.36)	6.54 (6.33, 6.74)	0.020
Lifestyle factors			
Gamma-glutamyl transpeptidase (U l^{-1})	25.51 (22.56, 28.43)	24.98 (18.45, 31.51)	0.887
Cotinine (ng ml^{-1})	49.23 (37.41, 61.05)	41.13 (14.84, 67.42)	0.592
Physical activity (kCal per day)	433 ± 195	400 ± 196	0.283
Biochemical markers			
HDL-cholesterol (mmol l^{-1})	1.35 ± 0.21	1.33 ± 0.46	0.768
LDL-cholesterol (mmol l^{-1})	2.78 ± 0.86	2.83 ± 0.94	0.741
Triglycerides (mmol l^{-1})	0.96 (0.90, 1.02)	1.05 (0.92, 1.18)	0.225
Glucose (mmol l^{-1})	4.35 (4.25, 4.45)	4.48 (4.27, 4.70)	0.276
Insulin (uU ml^{-1})	10.61 (9.91, 11.31)	11.46 (9.88, 13.03)	0.251
Monocyte chemoattractant protein-1 (pg ml^{-1})	153 (147, 160)	172 (160, 185)	0.009
Intracellular adhesion molecule (ng ml^{-1})	164 (156, 172)	176 (157, 195)	0.266
Vascular cellular adhesion molecule (ng ml^{-1})	560 (540, 580)	604 (560, 648)	0.054
Interleukin-6 (pg ml^{-1})	1.13 (0.99, 1.27)	1.06 (0.75, 1.37)	0.722
C-reactive protein (mg l^{-1})	2.90 (2.29, 3.52)	3.26 (1.89, 4.63)	0.650
Tumor necrosis factor-α (pg ml^{-1})	1.89 (1.73, 2.04)	1.94 (1.61, 2.28)	0.764
Reactive oxygen species (U)	186 ± 74	193 ± 79	0.515

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein.
Mean ± s.d.
Adjusted for sex, age, ethnicity, waist circumference, γ-glutamyl transpeptidase, cotinine, physical activity levels (waist circumference, γ-glutamyl transpeptidase, cotinine and physical activity not individually adjusted for themselves).
[a]Additionally adjusted for height.
[b]Additionally adjusted for mean arterial pressure, geometric mean and 5th and 95th percentiles displayed in brackets for the log transformed data.

V-CAM (604 *vs.* 560 ng ml^{-1}) tended to be higher in the MHT group ($P = 0.054$).

Figure 1 displays the results of adjusted odds ratios for the likelihood of having increased central systolic BP, arterial stiffness or biochemical markers of cardiovascular risk in MHT. When compared with the normotensive group, participants with MHT had increased odds for having elevated central systolic BP (1.537, 95% confidence interval (CI) = 1.089–2.171), aPWV (1.567, 95% CI = 1.115–2.202), insulin (1.443, 95% CI = 1.005–2.101), MCP-1 (1.499, 95% CI = 1.049–2.141), V-CAM (1.409, 95% CI = 1.012–1.962) and CRP (1.440, 95% CI = 1.009–2.054).

DISCUSSION

Participants were primarily included in the African-PREDICT project based on their normotensive BP measurements at the screening stage of the project (that is, <140/90 mm Hg). It was therefore noteworthy to detect that almost 18% of this apparently healthy, black and white, 20- to 30-year-old cohort were hypertensive when assessed via ambulatory BP measurements, a condition termed MHT. The occurrence of MHT in our young cohort supports evidence that proposes that the prevalence of MHT is between 8 and 30% in populations classified as normotensive by clinic BP readings.[11,30] This population would not have been identified as hypertensive in the

current study if clinic BP solely had been assessed, and therefore would be unaware of being at increased risk of CVD development.

Andrikou et al.[31] have also previously demonstrated increased CRP and PWV levels in MHT participants compared with normotensives. Also, increased aPWV was observed in MHT of an 18- to 80-year-old age group[32] and brachial-ankle PWV was increased in a type-2 diabetic cohort.[33] Further MHT has been associated with inflammation, endothelial dysfunction, diabetes, chronic kidney disease, obstructive sleep apnea, increased physical activity, mental stress, smoking and alcohol consumption.[11] However, cardiovascular risk factors associated with MHT in young, otherwise healthy adults have been poorly explored, also in sub-Saharan Africa.

Despite the screening and clinic BP values for both groups being in the normotensive range, the masked hypertensives of the current study displayed higher BPs in all methods of measurement, namely, screening-, clinic-, ambulatory- and central systolic-BP, when compared with normotensives. Furthermore, adjusted odds ratios demonstrated that MHT was associated with increased risk for elevated levels of central systolic pressure, and also insulin. MHT was additionally associated with increased adiposity, as determined via body mass index, waist circumference and waist-to-height ratio, confirming findings from a Japanese population that demonstrated that waist circumference, body mass index and waist-to-hip ratio were all significant predictors of MHT.[34] We also observed an elevated 24-h HR in the MHT group, suggesting increased sympathetic nervous system activity, which may contribute to obesity-related hypertension.[35] Therefore, it is plausible that the observed increased adiposity in the MHT group may be associated with the development of MHT, potentially by regulation of insulin-[36] and HR-associated increases in sympathetic activation.[35] This is further supported by the observation that the majority of participants (52%) were categorized as MHT by their nighttime ABPM alone.[37]

Following adjustment for a number of potential confounders, large artery stiffness was higher in the MHT group compared with the normotensive group. Increased aPWV (independent of differences in MAP) in the MHT group suggests that early vascular remodeling has occurred, in which reduced elasticity of the arterial wall may have led to increased stiffness of the aorta. AIx (a surrogate marker of arterial stiffness) also tended to be higher in the MHT group ($P = 0.053$), thus suggesting augmented late central systolic pressure as a result of late return of the reflected wave because of increased stiffness of the artery. aPWV and AIx are both associated with increased morbidity and mortality[15,38–41] and are associated with the presence of other cardiovascular risk factors.[42–44]

As AIx is considered as a measure of global endothelial function,[45] we expected that markers of endothelial activation would also be elevated with MHT. Indeed, a prominent finding of our study was the elevated circulating levels of MCP-1 in MHT. Similarly, another marker of endothelial activation, V-CAM, also tended to be higher in the MHT group ($P = 0.054$). Furthermore, odds ratio analyses demonstrated that MHT was associated with increased risk for elevated levels of these two markers. Both factors activate the endothelium by promoting monocyte adhesion to the endothelial wall, and therefore facilitate the development of atherosclerosis.[46–49]

On top of the findings that MHT was associated with arterial stiffness and endothelial activation, we also found an increased odds for inflammation (CRP). Although CRP is an accepted index of overall inflammatory activity, the lack of difference in the inflammatory markers between the two groups may suggest that at this early stage of MHT development (young adults), inflammation may have a lesser role than endothelial activation. This may be supported by a study

conducted in an older (40–75 years), sedentary, pre-hypertensive African-American MHT cohort, where increased CRP levels were observed when compared with a 'true pre-hypertensive' control group ($n = 17$).[50]

The physiological mechanisms explaining the development of MHT are not well understood. Pickering et al.[3] hypothesized that that those with higher ABPM readings may be more physically active than those presenting as truly normotensive, however, we controlled for 7-day physical activity levels, and also found no difference between the two groups. Similarly, Mann et al.[51] suggested that smoking raises daytime ABPM readings, however, we controlled for cotinine levels, which should eradicate this effect, and also, cotinine levels did not differ between our two groups.

In this young adult population, a noteworthy contribution of our findings relates to those measures that were similar between the normotensive and MHT participants, namely serum lipids, glucose, the majority of inflammatory markers (IL-6, TNF-α), ROS, smoking behavior and physical activity levels. Our data suggest that these markers may not be useful markers in the prediction of MHT in this population, although this may be different in older populations. The current study demonstrated that MHT is associated with increased cardiovascular risk on a vascular level, which was specifically evidenced by increased endothelial activation and arterial stiffness. This increase in cardiovascular risk was also associated with increased adiposity. However, cause and effect cannot be established using our evidence because of the cross-sectional nature of the study, and therefore whether increased endothelial activation occurs before the development of MHT cannot be clarified.

In clinical practice in high-income countries, ABPM is typically conducted only in those who present as hypertensive in clinic, making the diagnosis of MHT difficult. A further contributing factor to the difficulty in MHT diagnosis is that in low- and middle-income countries ABPM is rarely used. Our study highlights the high prevalence of MHT occurring in young, seemingly healthy adults (We furthermore found no ethnic-specific difference in MHT frequency in young black and white individuals.). Effective methods of diagnosing MHT are vital, which will allow MHT patients to commence with the required pharmaceutical and lifestyle interventions. The ability to routinely detect MHT early in life would have a substantial beneficial impact by reducing the significant global economic burden posed by CVD development.

It is therefore important to devise a feasible method of diagnosing MHT. Fitting every individual with an ABPM device is not viable in low resource settings, but our findings support previous results[52,53] that MHT participants consistently have clinic SBP above 120 mm Hg. Therefore, for participants presenting in clinic with SBP ⩾ 120 mm Hg together with other hypertension risk factors (for example, obesity,[53] and family history of hypertension), ABPM is likely to be cost-effective. Although this remains unlikely in low- and middle-income countries, it may be more feasible than suggesting that clinics measure ABPM on all patients presenting with SBP greater than 120 mm Hg. Further to this, in low- and middle-income countries, home BP monitoring may be more viable than ABPM should low-cost validated devices be available. In the first instance, it is important to raise awareness of the phenomenon of MHT, as many medical and health practitioners may be unaware of its existence.

With regard to investigating MHT, a limitation of the current study is that we specifically recruited apparently healthy, young adults and therefore the data are not generalizable to all South African adults. Further, the study was cross-sectional and therefore causality cannot be inferred. However, the African-PREDICT project is longitudinal in

design, and therefore the opportunity to later assess how MHT at baseline relates to aging and future CVD does exist. Another limitation is the limited reproducibility of ABPM, as most recently demonstrated by Keren *et al.*[54] who demonstrated only a moderate correlation between ABPM measurements taken 14 weeks apart. To ensure the most accurate ABPM measurements in the current study, participants were familiarized with the clinic setting on a previous screening day. All operators of the ABPM were trained to fit the ABPM devices using an identical protocol.

In conclusion, we found that MHT was common (18%) in young, apparently healthy, black and white South Africans. This percentage may grossly underestimate population prevalence and is not generalizable to the whole South African population as the current data are based on apparently healthy participants younger than 30 years. However, a review conducted by Gorostidi *et al.*[53] demonstrated that MHT patients are more likely to be young. We found that MHT was associated with elevated cardiovascular risk, evidenced by increased adiposity, central pressure, large artery stiffness and endothelial activation. Our findings highlight the importance of early and accurate detection of MHT as a means of reducing the incidence of CVD, thereby reducing its global economic and social burden. Further studies are required in order to determine the most cost-effective method of identifying undiagnosed MHT cases, particularly in Africa.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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