**Review Article:**

**Recent advances in understanding hypertension development in sub-Saharan Africa**

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**Running Title:** Hypertension in black populations

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**Sources of Support:** South African Medical Research Council, National Department of Science and Technology and National Research Foundation (NRF). Any opinion, findings, and conclusions or recommendations expressed in this material are those of the authors, and therefore, the NRF do not accept any liability in this regard.
Abstract

Consistent reports indicate that hypertension is a particularly common finding in black populations. Hypertension occurs at younger ages and is often more severe in terms of blood pressure levels and organ damage than in whites, resulting in a higher incidence of cardiovascular disease and mortality. This review provides an outline of recent advances in the pathophysiological understanding of blood pressure elevation and the consequences thereof in black populations in Africa. This is set against the backdrop of populations undergoing demanding and rapid demographic transition, where infection with the Human Immunodeficiency Virus predominates, and where under and over-nutrition coexist. Collectively, recent findings from Africa illustrate an increased lifetime risk to hypertension from foetal life onwards. From young ages black populations display early endothelial dysfunction, increased vascular tone and reactivity, microvascular structural adaptations, as well as increased aortic stiffness resulting in elevated central and brachial blood pressures during the day and night, when compared to whites. Together with knowledge on the contributions of sympathetic activation and abnormal renal sodium handling, these pathophysiological adaptations result in subclinical and clinical organ damage at younger ages.

This overall enhanced understanding on the determinants of blood pressure elevation in blacks encourages (a) novel approaches to assess and manage hypertension in Africa better, (b) further scientific discovery to develop more effective prevention and treatment strategies, and (c) policymakers and health advocates to collectively contribute in creating health-promoting environments in Africa.
Introduction

A recent global analysis in 19.1 million participants indicated that blood pressure has on average decreased worldwide since 1975. However, during the past four decades, the highest blood pressures shifted from high income countries to the low income countries in sub-Saharan Africa. Unfortunately, current practices to detect and treat hypertension in Africa are overwhelmingly ineffective, evidenced by appallingly low awareness (27%), treatment (18%) and control rates (7%). These failing practices are possibly due to weak health systems, education and current antihypertensive treatment not being as effective in black populations.

A review paper in 2005 by Opie and Seedat on hypertension in sub-Saharan Africa described the classic salt-sensitive volume-overload low plasma renin phenotype. But they also highlighted that further studies in Africa are urgently needed, as this population could differ genetically and environmentally from African Americans. The Hypertension in Africa Research Team (HART) and other research centres throughout Africa have taken significant strides forward over the past decade in improving our understanding of hypertension development in Africa, beyond salt-sensitive volume-loading hypertension. In this review we will therefore provide an outline of recent advances in deciphering contributors towards blood pressure elevation and the consequences thereof in Africans. This is set against the backdrop of black populations simultaneously undergoing nutritional, epidemiological and demographic transition, where infection with the Human Immunodeficiency Virus (HIV) predominates; where famine, fertility rates and life expectancy fluctuate; and under- and over-nutrition coexist. Therefore, to counteract the rapidly increasing hypertension prevalence rates within a vast economically-driven continent, we urgently need a better pathophysiological understanding of hypertension in blacks to reach novel and alternative approaches in preventing, managing and treating hypertension in Africa.
Health behaviours and lifestyle exposures

Lifestyle and health behaviours remain the most important preventable cardiovascular risk factors, and this is also the case within Africa. With recent dramatic demographic transitions on the continent, adverse health behaviours are expected to escalate, with strong trends already evident.

An important aspect that was generally overlooked in the past, is the concept of lifetime risk applicable to the entire population from conception. Globally evidence indicates that the development of subclinical and sometimes clinical cardiovascular disease (CVD) results from early programming and lifetime exposure to cardiovascular risk factors. It is likely that lifestyle exposures during foetal life and childhood promote the development of vascular changes that launch the individual along the trajectory of so-called early vascular aging, in which an accumulation of vascular damage occurs already in early adulthood. Recent evidence from the longitudinal ‘Birth to Twenty’ study of urban black South African mothers and offspring shows that low birth-weight, combined with rapid weight gain in infancy, already produce elevations in blood pressure. While these changes translate into increased adiposity and blood pressure later in life, there appears to be a protective effect of upward socioeconomic status (SES) mobility on systolic blood pressure. These findings underscore the need for further research into lifetime risk and exposure to risk factors in Africa.

The nutrition transition

Advances in food technology have allowed the production of highly palatable, energy dense, low cost, ultra-processed foods, snacks and beverages that are increasingly appearing within the food supply in middle- and low-income countries. In Africa consumers are attracted to these products by their price, convenience, availability and taste, often as a result of heavy product marketing by companies, who in turn are attracted by the potential profits from the region alongside trade and investment liberalisation policies. As
consumption of ultra-processed foods (and fat, sugar and salt) increases, consumption of more traditional and nutritionally adequate diets is reduced, especially in poorer populations driven by the lower cost-per-kilojoule of processed alternatives. While changes are most pronounced in urban populations, rural populations are not immune to the nutrition transition. This was clearly demonstrated in rural areas from the Prospective Urban Rural Epidemiology (PURE) study in South Africa where added sugar intake more than doubled from 2005-2010. The net effect is reduced intake of nutrient dense foods such as fruits, vegetables, legumes and coarse grains with associated reductions in nutrients such as dietary fibre and potassium, concomitant with increased sodium-to-potassium ratio of the diet.

**Obesity**

The nutrition transition not only affects blood pressure, but also obesity rates. Within sub-Saharan Africa, individuals living in urban areas are at increased risk of being overweight or obese, with the largest increases in obesity observed in urban women with low SES. While physical inactivity inevitably plays a role in this, the nutrition transition also influences obesity levels in both urban and rural regions. The resultant overall obesity, but particularly abdominal obesity, was found to predict 5-year cardiovascular and metabolic risk in black South Africans. Obesity and hypertension are causally related, and also integrated with metabolic disturbances. Mechanistically we have also highlighted the contribution of obesity-related sympathetic over activity and adipocytokines to elevated blood pressure in black populations. When viewed in combination with the recent dietary and physical activity changes, plus the enhanced susceptibility to CVD proposed by the foetal origins of adult disease hypothesis, the rapid escalation of hypertension in African countries is perhaps not surprising.
Physical activity

The benefits of regular physical activity for blood pressure control are well established and recommended as part of antihypertensive therapy. However, in South Africa, 49% of women and 45% of men are estimated to be physically inactive, and these levels far exceed the estimated average (18%) for the African continent. Alarmingly these rates were also reported in South African children, where 50% of school children did not meet the daily recommended physical activity levels. Apart from elevated blood pressure linking to physical inactivity, an additional consequence is increases in adiposity. With reports indicating that rural populations have higher activity levels than urban dwellers, largely due to increased walking, cycling and more physically demanding jobs, the far-reaching consequences of rapid urbanisation for hypertension development become even clearer.

Alcohol and tobacco use

In an initial review of hypertension in sub-Saharan Africa in 2005, little mention was made of smoking and alcohol in the development of hypertension-related CVDs, with alcohol use being discussed primarily as a risk factor in high income groups. In the intervening years, and with economic transition, there has been a shift on the continent in smoking and alcohol consumption. Many African countries are finding tobacco products more affordable due to increases in income and purchasing power, with an estimated 20-50% of adult men smoking in Sierra Leone, Lesotho, the Seychelles, Burkina Faso, Côte d'Ivoire, Gabon, Gambia, Mali, Mauritania, Mauritius, Tanzania, Zambia and Zimbabwe, and tobacco use increasing in African youth. Taxes have had some success in reducing smoking prevalence in South Africa, although rates are still high, and worryingly 24% and 19% of 13-15 year old boys and girls respectively, are estimated as using tobacco.

Within South Africa, alcohol is the most commonly misused substance with high levels of reported binge drinking behaviour especially in youth, and excess alcohol use associated with hypertension. We found that South African adults reporting alcohol use had a 30%
increased risk of developing hypertension over five years. In Uganda, alcohol use was associated with a 64% risk, and in Angola with a 40% increased risk of developing hypertension. As we and others have demonstrated, alcohol abuse is implicated in arterial stiffness, metabolic disturbances, blood pressure elevation over time, as well as cardiovascular mortality. As such, it is crucial that more effective strategies be put in place to not only delay the onset of alcohol use, but to significantly change behaviours and societal acceptability of excessive alcohol use.

**Salt intake**

The Global Burden of Disease Study lists diets high in sodium as one of the ten largest contributors to disability adjusted life years, primarily through elevated systolic blood pressure. A recent systematic review examining salt intakes in sub-Saharan Africa and including data from 13 countries suggested that over 80% of adult populations consume more than the World Health Organization recommended 5g salt or 2g sodium each day with bread being a major contributor to salt intake. Within South Africa, high salt intakes are shown consistently across different age, gender and ethnic groups. There is some suggestion that black populations have a greater blood pressure benefit from salt reduction when compared to other ethnic groups, although these differences may be clinically insignificant and related to socioeconomic disparity rather than ethnicity. Salt reduction initiatives in the region have consistently shown small but significant reductions in blood pressure. South Africa appears to lead the way with implementation of legislation in June 2016 mandating maximum sodium levels in a comprehensive range of processed foods with further reductions planned for 2019. Estimates suggest considerable economic and health benefits of such a policy, whereas ongoing studies will determine whether the legislation will have the desirable effects on population salt intake and blood pressures.
Socio-economic status and health disparities

The African continent continues to experience some of the world’s highest levels of economic, health, gender and education inequity.\textsuperscript{50,51} Research in Africa confirms findings that the association between socioeconomic disparity and hypertension cannot only be explained by traditional risk factors such as obesity, smoking, alcohol use and physical activity.\textsuperscript{52} Much research on this topic has been conducted in African Americans, with less evidence available for blacks living within Africa. However, cross-sectional\textsuperscript{52,53} and longitudinal\textsuperscript{54,55} associations between socioeconomic status, emotional distress and hypertension are observed in Africa.

Blood pressure measurement and profiles

A systematic review on the burden of undiagnosed hypertension in Africa highlights that of those with hypertension, only 1 in 4 is aware of their hypertensive status.\textsuperscript{2} On this continent economic challenges and weak health systems barely allow for adequate clinic blood pressure assessment. But a recent study in Nigeria demonstrated that it would greatly benefit African countries to increase access to quality healthcare, as this was associated with a significant longer-term reduction in blood pressure in subjects at highest risk of CVD.\textsuperscript{3} Also, in Africa conventional office blood pressure measurement remains by far the most common method to determine blood pressure and manage hypertension. The recommendation for out-of-office measurements may therefore seem absurd. But it is only by reviewing 24-hour blood pressure profiles that specific features such as white-coat hypertension, masked hypertension and nocturnal dipping status can be detected. When viewing ambulatory blood pressure profiles in similarly-aged black and white South African school teachers from the Sympathetic activity and Ambulatory Blood Pressure in Africans (SABPA) study (Figure 1), it is clear that both black men and women exert significantly higher 24-hour, daytime, and nighttime systolic and diastolic blood pressures\textsuperscript{56} (as well as heart rate\textsuperscript{25}). Masked hypertension, referring to in-office normotension but out-of-office hypertension, carries similar cardiovascular risk to hypertension.\textsuperscript{57} We and others have
shown that masked hypertension is common in African populations,\textsuperscript{57} with prevalence rates of 18\% in healthy 20-30 year old black adults,\textsuperscript{58} 41\% of low-income South African adults (mean age 39 ± 9.7 years),\textsuperscript{59} and 14.4\% of Nigerians.\textsuperscript{60} These findings translate to a gross underestimation in the prevalence of hypertension in Africa, and encourage different approaches to determine out-of-office blood pressure (such as home monitoring), potentially in select populations.

Pathophysiological mechanisms of blood pressure elevation

\textit{Psychosocial stress, sympathetic nerve activity and neurogenic hypertension}

An urban lifestyle is characterised by demanding stress situations which may involve job stress, personal changes, marital problems, cultural differences and various others.\textsuperscript{53,61} The integrity of the physiological stress pathway, namely the hypothalamic-pituitary-adrenal cortex axis, is essential for an adequate defence response and cortisol secretion to determine the appropriate behavioural response to stress.\textsuperscript{62} Excessive, prolonged or inadequate cortisol responses will impair an individual’s adaptation to stress, with either up- or down-regulation in hypothalamic-pituitary-adrenal cortex axis activity.\textsuperscript{63,64}

Neurogenic hypertension refers to disturbed central neural control of subcortical areas regulating emotion, which may increase hypertension risk.\textsuperscript{65} Indeed, poor mental health was related to norepinephrine spill-over\textsuperscript{66} and essential hypertension in sub-Saharan African cohorts.\textsuperscript{52,53,65,67} While there is no generally accepted method of evaluating overall central and peripheral sympathetic nervous system activity,\textsuperscript{68} the probability of emotional stress preceding sympathetic activation and risk for hypertension has not been acknowledged. However, both acute and chronic stress responses are related to target organ damage in black adults,\textsuperscript{61,69} with accentuated responses in men coping defensively with social stress.\textsuperscript{65} In comparison to whites, the responses to both acute and chronic stress (\textit{Figure 2}) in black adults showed a profile of sympathetic activation and central neuro-endocrine control. Acute neural control demonstrated increased vascular responsiveness,\textsuperscript{69,70} myocardial ischemia\textsuperscript{54} and attenuated cortisol responses.\textsuperscript{64} Chronic neuro-endocrine control revealed chronic
depression, desensitised 24h heart rate variability and 24h urinary norepinephrine:creatinine responses. Chronic emotional stress and accompanying blood pressure increases to alleviate perfusion deficits, may exemplify neurogenic hypertension.

**Salt-sensitivity and volume-loading hypertension**

The suppression of the renin-angiotensin-aldosterone system (RAAS) due to volume-loading hypertension is common in Africans, and is evident from childhood. This phenotype guided Clinical Practice Guidelines for antihypertensive treatment in black populations to avoid medication directed towards the RAAS as first line treatment. Lower plasma renin activity and aldosterone were reported in normotensive and hypertensive black South Africans when compared to whites. We have also confirmed suppressed angiotensin I and II in black hypertensives compared to whites. This phenotype is characterised by elevated blood pressure, higher aldosterone-to-renin ratio (ARR), or low renin and low aldosterone. The ARR modifies the relationship between blood pressure and salt intake in Africans and African Americans, pointing to a role in salt-sensitive low renin hypertension. ARR relates to left ventricular hypertrophy in black children and adults, despite blacks having lower aldosterone and renin compared to whites. We also found that low plasma renin and renin reactivity to an acute stressor associated with markers of end-organ damage, such as urinary albumin excretion and carotid wall thickness, in blacks. Genetic polymorphisms in Africans confirm that altered renal sodium handling has a potent role in the development of salt-sensitive, low renin hypertension. Sodium retention and volume expansion remain some of the key role players in the development of hypertension in blacks.

**Arterial structure and function**

Within the concept of early vascular aging reside several pathophysiological mechanisms affecting the arterial wall – including in particular the endothelium, vascular smooth muscle cells and the extracellular matrix. With hypertension development these changes occur from
the microvasculature to the large conduit vessels. A brief overview is provided on observations in black populations.

- **Endothelial function**

One of the haemodynamic observations in sub-Saharan black adults,\textsuperscript{24,69} children\textsuperscript{67} and adult African Americans,\textsuperscript{88} is a higher vascular resistance compared to whites. Vascular tone and the regulation thereof depend largely on endothelial function.\textsuperscript{89} In Americans, black race was associated with digital artery endothelial dysfunction in men and women undergoing assessment of digital pulse amplitude response to forearm occlusion-induced hyperaemia.\textsuperscript{90} In healthy African Americans without known CVD risk factors, Ozkor \textit{et al}.\textsuperscript{91} investigated differences in vascular nitric oxide (NO) and endothelium derived hyperpolarising factor (EDHF) bioavailability. EDHF seemed preserved but NO bioavailability and sensitivity reduced in the vasculature in blacks compared to whites. Our findings in black South Africans with low SES support this, indicating blacks having lower serum L-arginine (a substrate for NO synthesis) than whites.\textsuperscript{92} Recent data also point to a balance between NO bioavailability and creatine kinase, where both the NO and creatine kinase systems share a common precursor in L-arginine.\textsuperscript{93} Creatine kinase was found to predict blood pressure in the general population, and also predicted the failure of antihypertensive therapy.\textsuperscript{94} On balance, we have found in black school teachers with a higher SES, an elevated NO synthesis capacity as reflected by higher L-arginine and lower asymmetric dimethylarginine.\textsuperscript{95} However, the increased oxidative stress and an up-regulated redox system observed in black teachers\textsuperscript{10,11} could counteract NO bio-availability. Furthermore, we found no link between creatine kinase and blood pressure or vascular resistance in these black teachers.\textsuperscript{96} Due to the complexities of physiological systems involved in NO bioavailability, further research in larger populations including different levels of SES, are needed to clarify the above findings.
Oxidative stress and inflammation

Both inflammation and oxidative stress play a pivotal role in the development of endothelial dysfunction by exerting pro-inflammatory actions and reducing NO bio-availability. Oxidative stress is defined as an imbalance between oxidants and antioxidants in favour of oxidants, and may lead to a disruption in redox signalling and macromolecule damage. Oxidative stress is closely related to various processes involved in the development of hypertension. Our studies in black South Africans found that increased oxidative stress relates to elevated blood pressure, subclinical atherosclerosis and arterial stiffness. Oxidative stress was also linked to various biological processes related to vascular tone, angiogenesis and haemostasis in blacks. Taken together, these findings suggest that oxidative stress plays a role in early vascular changes in blacks who are prone to the development of CVD. In this regard the glutathione system and especially the regulation of key enzymes such as glutathione peroxidase and glutathione reductase are important role players. But oxidative stress should not be viewed in isolation, as there seems to be a strong, two-way link between oxidative stress and inflammation, suggesting that oxidative stress may amplify the inflammatory process. In turn a sustained inflammatory response may lead to the overproduction of reactive oxygen species. We found low-grade inflammation to be more common in black than white South Africans, and that it was influenced by modifiable risk factors such as obesity, alcohol and tobacco use. Inflammatory markers were higher and increased also more prominently in black South Africans who developed hypertension over five years. Our findings thus support the notion of hypertension being an inflammatory disease. This concept is further strengthened by our finding that higher levels of inflammatory markers predicted both cardiovascular and all-cause mortality in Africans.

The microvasculature

Hypertension is closely related to microvascular structural and functional changes of target organs, in particular those with high perfusion rates such as the heart, kidneys and brain.
These changes include vasoconstriction, rarefaction, reduced vasodilatory reserve and in large arterioles, changes in wall-to-lumen ratio.\textsuperscript{113,114} The retina represents a unique site whereby direct visualisation of early hypertension-related microvascular changes can be observed.\textsuperscript{115} In the retinal microvasculature, small artery narrowing is related to hypertension and risk of incident hypertension, whereas vein widening related to atherosclerosis, atherosclerotic risk factors, risk of incident hypertension and independently predicted stroke.\textsuperscript{114,116-118} In 20-30 year old healthy blacks and whites from the African Prospective study on the Early Detection and Identification of Cardiovascular disease and Hypertension, (African-PREDICT), we found black ethnicity to be independently associated with retinal artery narrowing.\textsuperscript{119} In the older participants of the SABPA study, black teachers who displayed a worse cardiovascular profile, presented a smaller retinal arterio-venous ratio, with wider veins when compared to their white counterparts.\textsuperscript{120} Microvascular deterioration reflected by retinal vein widening in blacks was associated with a lack of nocturnal blood pressure dipping\textsuperscript{121} as well as chronic depression symptoms.\textsuperscript{71} In another microvascular bed healthy black South Africans were shown to display attenuated endothelium-independent microvascular function when compared to whites, suggesting possible differences in microvascular smooth muscle function.\textsuperscript{122}

\textbullet \ \textit{Arterial stiffness}

Carotid-femoral pulse wave velocity, the most accepted non-invasive method of determining arterial stiffness, is an independent predictor for all-cause and cardiovascular mortality, coronary events, as well as strokes, type 2 diabetes, and end-stage renal disease.\textsuperscript{123} Reports from both African Americans and black South Africans confirm increased arterial stiffness in black compared to white populations.\textsuperscript{124,125} It is as yet unclear whether increased stiffness in blacks is due to genetic predisposition, early life exposures or social disparities. Where early reports are limited in establishing a link between arterial stiffness and genetic predisposition,\textsuperscript{126} we have found increased arterial stiffness in blacks with low SES compared to whites with high SES.\textsuperscript{124} To counter SES, we included 6-8 year old black and
white boys from similar schools, and found increased arterial stiffness in the carotid-radial, carotid-dorsalis pedis and carotid-femoral regions, along with elevated diastolic pressure and peripheral vascular resistance in black boys. In the African-PREDICT study we excluded hypertensives, but included healthy black and white adults (20-30 years) with normotensive clinic blood pressure, and found similar ambulatory blood pressures and arterial stiffness, but elevated central systolic pressure in blacks. More evidence is needed to elucidate whether these findings are due to early life exposures or genetic predisposition.

• **Atherosclerosis**

Earlier studies from 1946, 1958 and 1963 unanimously reported that blacks had a low prevalence of atherosclerotic heart disease, but a high hypertension rate. Since then, Tibazarwa et al. have pointed to “a time bomb of cardiovascular risk factors in South Africa” which may have emerged due to rapid urbanisation. Endothelial dysfunction, together with excessive mechanical stress, as seen in a hypertensive milieu, are known to increase oxidative stress and vascular inflammation, contributing to the development of atherosclerosis. In young, healthy urban black adults with normotensive clinic blood pressure we recently found significantly increased markers of endothelial activation (cellular adhesion molecules and monocyte chemoattractant protein-1), reactive oxygen species and interleukin-6, when compared to white counterparts. In addition, endothelial activation markers associated independently with carotid wall thickness, only in black women. Regardless of these recent findings, sub-Saharan Africans remain far more likely to be diagnosed with heart failure, and far less likely to be diagnosed with coronary artery disease, independent of HIV infection. A possible explanation is the less atherogenic lipid profile (lower triglycerides, total and low-density lipoprotein cholesterol and higher high-density lipoprotein cholesterol) that is often seen in black compared to white populations.

However, with recent rapid epidemiological transition the proverbial time bomb is ticking.
Hypertension and end-organ damage

Renal function

Hypertension is the most common cause of renal dysfunction in blacks from sub-Saharan Africa, with consequent chronic kidney disease (CKD) being a major health burden.\textsuperscript{138} In Americans, the incidence of all-cause CKD was 2.7 times higher among African Americans compared to whites.\textsuperscript{139} The finer subclinical progression of renal function decline, in the form of endothelial damage and dysfunction at the glomeruli and consequent low-grade leakage of albumin, is often overlooked as a risk factor.\textsuperscript{140} Compared to whites, low-grade urinary albumin excretion was higher in sub-Saharan blacks at similar blood pressures, adjusted for age and body mass index (Figure 3).\textsuperscript{141} This supports data on African Americans showing a higher rate of kidney function decline compared to their white counterparts before the onset of CKD.\textsuperscript{139} In addition, urinary albumin excretion also seems to reflect general endothelial damage.\textsuperscript{142} In sub-Saharan Africans, we found that urinary albumin excretion associated with arterial stiffness,\textsuperscript{141} left ventricular hypertrophy (independent of blood pressure),\textsuperscript{143} and predicted all-cause and stroke mortality in non-diabetic, HIV-negative participants, independent of blood pressure and other covariates.\textsuperscript{144}

Cardiac structure and function

Aside from congenital cardiac abnormalities, normal cardiac geometry and function are largely impacted on by sex, ethnicity and body size.\textsuperscript{145,146} The Dallas Heart Study found African Americans to have increased left ventricular mass compared to whites, along with a 2-3-fold higher prevalence of left ventricular hypertrophy, independent of differences in body composition.\textsuperscript{147} Only two recent studies (Hypertension Genetic Epidemiologic Network (HyperGEN) and Coronary Artery Risk Development in Young Adults (CARDIA)) highlighted greater left ventricular size and lower left ventricular systolic and diastolic function in African American men compared to African American women, as well as white men and women.\textsuperscript{148,149} The Multi-Ethnic Study of Atherosclerosis reported on right ventricular MRI
findings, showing African Americans having lower right ventricular ejection fraction than whites, but which increased with older age. These findings suggest age-related ventricular stiffening leading to increasing right ventricular ejection fraction.\textsuperscript{150} In South Africa, at present, we lack sufficient data to investigate racial differences in cardiac structure and function, especially in the early stages of CVD development.

**Comorbidities**

Hypertensive African Americans exhibit a greater progression to end-stage renal disease, as well as heart failure, coronary heart disease, and stroke, than white counterparts.\textsuperscript{151} From a recent meta-analysis the overall prevalence of CKD was reported at 13.9\% in sub-Saharan Africa, with primary hypertension being the greatest risk factor.\textsuperscript{138} Although ischemic heart disease remains rare in most African countries,\textsuperscript{152} ischemic stroke incidence is more common as found in Mozambique, Nigeria, South Africa, Sudan, and Uganda.\textsuperscript{153} Severe heart failure and secondary valvular dysfunction are reported to present in the fourth decade of life in sub-Saharan Africa,\textsuperscript{154} with asymptomatic black hypertensives subjected to left ventricular systolic dysfunction associated with male gender, diabetes mellitus, and increased left ventricular mass.\textsuperscript{155} With changing lifestyles and increasing obesity rates, it is not surprising that in 2015 the International Diabetes Federation estimated that 3.85 million South Africans between the ages of 21 and 79 years have diabetes.\textsuperscript{156} Also unique to sub-Saharan Africa, the estimated incidence of new rheumatic heart disease cases aged above 14 years was 23.5 cases per 100 000 per annum.\textsuperscript{157}

**Human Immunodeficiency Virus**

Globally, sub-Saharan Africa is affected most by HIV and South Africa is the country with the highest number of people living with HIV accompanied by the largest antiretroviral treatment (ART) programme in the world.\textsuperscript{7} Besides cancer, CVD is the most frequent cause of death among HIV infected patients.\textsuperscript{158} The cardiovascular conditions most often reported in HIV infection in sub-Saharan Africa are pulmonary hypertension, cardiomyopathy and tuberculous pericarditis.\textsuperscript{159} Studies performed in populations from European descent found
HIV to be associated with endothelial dysfunction, increased arterial stiffness, hypertension, the metabolic syndrome, renal disease and carotid intima-media thickness. It is possible that findings may differ in sub-Saharan Africa where different ethnic groups, socio-demographics, a different HIV strain and ART programmes prevail. A systematic review including 29,755 patients from sub-Saharan Africa found that, despite the high prevalence of hypertension, HIV infection was associated with lower blood pressure, supporting our own findings. Furthermore, the prevalence of the metabolic syndrome in HIV infected populations was similar to the HIV-free population, with ART not contributing to the metabolic syndrome. In Cameroonianians, an association between HIV infection, the metabolic syndrome and arterial stiffness was reported. However, in South Africa we found that increased endothelial activation among HIV infected blacks was not accompanied by arterial stiffness or sub-clinical atherosclerosis. Even after five years and with the majority of HIV infected participants (73%) on first line therapy, the carotid-femoral pulse wave velocity (8.11 vs. 8.24 m/s, p=0.45) was similar to HIV free controls. Collectively, our results from a single population study in South Africa indicate that HIV infection does not increase CVD risk. However, this requires verification in large longitudinal studies in different African settings.

Conclusion

Black populations are consistently reported to have a higher prevalence of hypertension than whites – a main reason for the higher incidence of CVD and mortality in blacks. Collectively, recent findings from Africa illustrate an increased lifetime risk to hypertension from foetal life onwards, due to continuous exposure to demanding and rapidly developing socio-demographic environments. Captured within the concept of early vascular aging, black populations display early endothelial dysfunction, increased vascular tone and reactivity, microvascular structural changes, as well as increased aortic stiffness resulting in elevated central and brachial blood pressure during the day and night, when compared to whites. Together with knowledge on the contributions of sympathetic activation and abnormal renal
sodium handling, these pathophysiological adaptations result in early subclinical and clinical organ damage at younger ages.

This overall enhanced understanding on determinants of blood pressure elevation in blacks encourages (a) novel approaches to assess and manage hypertension in Africa better, (b) further scientific discovery to develop more effective prevention and treatment strategies, and (c) policymakers and health advocates to collectively contribute in creating health-promoting environments in Africa.

Such endeavours may include firstly to launch awareness campaigns and encourage the political will to enable every adult to know their blood pressure; secondly to ensure availability of effective low cost antihypertensive medication by piggy-backing on existing HIV healthcare infrastructure; thirdly to make healthy food choices (such as fruits and vegetables) easier and to discourage unhealthy food options (such as excess calories, salt, heavily processed foods), by introducing taxes for e.g. sugar to be used to subsidise healthy foods; fourthly to promote physical activity in daily living by ensuring safe and supportive environments; and finally to prioritise resource allocation to ensure quality healthcare facilities and resources to produce culturally relevant research regarding effective preventive and therapeutic options. By employing also in Africa the latest cutting-edge research on biomarkers and polyomics proven to predict hypertension and cardiovascular outcome (such as proteomics and metabolomics), precision medicine may have the potential to lead to novel strategies in both preventing and treating hypertension in Africa.
Acknowledgements

The authors of this paper, constituting the Hypertension in Africa Research Team, hereby thank the immense contributions of research support staff towards data collection, as well as input from collaborators within several challenging research projects performed in South Africa. Also, the participation of many volunteers in our studies is hereby duly acknowledged.

Conflict of Interest

The authors have nothing to declare.
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Figure Legends

Figure 1: Ambulatory blood pressure profiles of black and white South African school teachers during a normal working day.

Figure 2: Neuroendocrine control during acute mental stress (∆, delta change %);\textsuperscript{64,69,70,175} and chronic mental stress.\textsuperscript{54,65} hsTrop T, troponin T; NE:Cr, norepinephrine:creatinine ratio; HRVti, heart rate variability triangular index as a measure of overall cardiovascular risk. Adjusted for age, gender, waist circumference, physical activity, gamma-glutamyl transferase, cotinine and thyroid function for HRVti. * denotes P< 0.05; and ** denotes P< 0.01.

Figure 3: Albumin-to-creatinine ratio and 24h mean arterial pressure by ethnicity and category of 24h mean arterial pressure, adjusted for age and body mass index (adapted from Schutte et al.\textsuperscript{141}). Charted values are means and bars represent 95% confidence limits. * denotes P< 0.01; ns, non-significant for differences between black and white men.
Figure 2