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FACING EPIDEMIC HYPERTENSION IN SUB-SAHARAN AFRICA: REQUIREMENTS FOR BETTER BLOOD PRESSURE AND CARDIOVASCULAR RISK CONTROL IN A RURAL AREA OF THE DISTRIC OF NYARUGURU, RWANDA.

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Anno Accademico 2021/2022

Tra i medici, molti lo sono per i titoli,
pochi per i fatti.

Ippocrate

1. Introduction

1.1 Blood pressure

1.1.1 History of blood pressure and hypertension[1]

Early knowledge and measurements. In the Yellow Emperor's Classic of Medicine (first written approximately 200–400 BCE), the Yellow Emperor of China (approximately 2600–2700 BCE) was believed to have talked about the so called 'hard pulse disease', claiming that 'if too much salt is used in food, the pulse hardens', and suggested the use of venesection for treatment. Physicians in ancient Egypt (approximately 1500 BCE) and India (approximately 150 BCE) also noted the relationship between pulse quality and the development of afflictions of the heart and brain. Pulse also had an essential role in ancient Greek medicine, and its relationship with environment and disease was discussed at length by physicians including Hippocrates (460–370 BCE), Erasistratus (304–250 BCE) and Galen (130–210 CE). However, these physicians did not note the connection between apoplexy and high blood pressure or hardening of the pulse.

In 1628, William Harvey described the process of blood flowing out of the heart and then returning to the heart via arteries, peripheries, and veins. Nearly 300 years later, blood pressure was discovered, and a reliable method for its measurement was devised. Even before this technology was developed, the work of a few physicians, including Richard Bright and Frederick Akbar Mahomed, led to the first description of essential hypertension in the nineteenth century, for example, hypertension in the absence of renal disease.

The first accurate, direct measurement of human blood pressure was performed by the surgeon Faivre with the use of a mercury manometer during a limb amputation in 1856, with a reported arterial blood pressure of 115–120 mmHg. Devices for the indirect measurement of blood pressure (that is, to measure the counterpressure needed to stop the blood flow in an artery) evolved from the first sphygmograph to visualize pulse waves, invented by Karl Vierordt in 1855, to Samuel Siegfried Ritter von Basch's sphygmomanometer in 1880. In 1896, Scipione Riva Rocci invented an inflatable cuff

that compressed around the whole circumference of the arm to apply uniform pressure. The cuff size was later changed to 12 cm in 1901 from the original 5 cm, and it became the prototype of cuffs that continue to be used in modern devices.

In 1905, Nikolai Korotkoff, a Russian surgeon, reported a method that uses the tapping sounds detected through a stethoscope at different phases during the deflation of the cuff to determine the pressure at which blood flow was completely blocked, that is, SBP, and the pressure at which blood flow was no longer restrained, that is, DBP. Together, Korotkoff 's auscultatory technique and Rocci's cuff formed the basis of modern blood pressure measurement devices.

Blood pressure as a risk factor. The quantitative connection between high blood pressure and mortality was first revealed in studies with the use of insurance data at the beginning of the twentieth century. These data also revealed that blood pressure rises with age and is higher in those who have higher weight for their height. The Framingham Heart Study showed a greater risk of coronary heart disease in men and women with hypertension (defined as SBP ≥160 mmHg or DBP ≥95 mmHg) than in individuals with SBP <140 mmHg and DBP <90 mmHg. The study also showed an increased risk of CVD in those with high/normal blood pressure, that is, 130–139 mmHg for SBP and 85–89 mmHg for DBP, compared with those with optimal blood pressure, defined as SBP <120 mmHg and DBP <80 mmHg. The Prospective Studies Collaboration pooled 61 prospective observational studies with 1 million participants in Asia, Australasia, Canada, Europe, and the USA and found a doubling of the risk of ischemic heart disease and stroke with every 20 mmHg and 10 mmHg increase in SBP and DBP, respectively, starting from as low as 115 mmHg for SBP and 75 mmHg for DBP. The Asia Pacific Cohort Studies Collaboration found similar associations in Asian and Australasian populations. Based on observational studies, each 10 mmHg increase in SBP is associated with a 45% higher risk of ischemic heart disease and about a 65% higher risk of ischemic or hemorrhagic stroke in those aged 55–64 years. The relative risk is inversely associated with age.

The observational results were confirmed by data from clinical trials that lowered blood pressure. These trials included the VA Cooperative Trials, Multiple Risk Factor Intervention Trial (MRFIT), and those included in the Blood Pressure Lowering Treatment Trialists' Collaboration. Other trials, including the Systolic Blood Pressure Intervention Trial (SPRINT), and meta-analyses of trials further showed reductions in

CVD events but mixed results for cardiovascular and all cause mortality with intensive blood pressure lowering to levels below the conventional cutoff for hypertension of 140/90 mmHg, for example, SBP of 120–130 mmHg. However, most of the trials have been performed in Western populations, and trial evidence is especially scarce for Africa, Latin America, and South Asia.

1.1.2 Definition and classification[2]

Hypertension is defined as office SBP values ≥ 140 mmHg and/or diastolic BP (DBP) values ≥90 mmHg. This is based on evidence from multiple RCTs that treatment of patients with these BP values is beneficial. The same classification is used in younger, middle-aged, and older people, whereas BP centiles are used in children and teenagers, in whom data from interventional trials are not available.

Category	Systolic (mmHg)		Diastolic (mmHg)
Optimal	<120	and	<80
Normal	120–129	and/or	80–84
High normal	130–139	and/or	85–89
Grade 1 hypertension	140–159	and/or	90–99
Grade 2 hypertension	160–179	and/or	100–109
Grade 3 hypertension	≥180	and/or	≥110
Isolated systolic hypertension[b]	≥140	and	<90

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BP = blood pressure; SBP = systolic blood pressure.
[a]BP category is defined according to seated clinic BP and by the highest level of BP, whether systolic or diastolic.
[b]Isolated systolic hypertension is graded 1, 2, or 3 according to SBP values in the ranges indicated.
The same classification is used for all ages from 16 years.

Classification of office blood pressure and definition of hypertension grade.

1.1.3 Blood pressure measurements

1.1.3.1 Conventional office blood pressure measurement

Auscultatory or oscillometric semiautomatic or automatic sphygmomanometers are the preferred method for measuring BP in the doctor's office. These devices should be validated according to standardized conditions and protocols. BP should initially be measured in both upper arms, using an appropriate cuff size for the arm circumference. A consistent and significant SBP difference between arms (i.e. >15 mmHg) is associated

with major CV issues, such as aortic coarctation, or dissection, if in an acute onset. Where there is a difference in BP between arms, ideally established by simultaneous measurement, the arm with the higher BP values should be used for all subsequent measurements.

In older people, people with diabetes, or people with other causes of orthostatic hypotension, BP should also be measured 1 min and 3 min after standing. Orthostatic hypotension is defined as a reduction in SBP of >_20 mmHg or in DBP of >_10 mmHg within 3 min of standing and is associated with an increased risk of mortality and CV events. Heart rate should also be recorded at the time of BP measurements because resting heart rate is an independent predictor of CV morbid or fatal events, although heart rate is not included in any CV risk algorithm. The table summarizes the recommended procedure for routine office BP measurement. It is emphasized that office BP is often performed improperly, with inadequate attention to the standardized conditions recommended for a valid measurement of office BP. Improper measurement of office BP can lead to inaccurate classification, overestimation of a patient's true BP, and unnecessary treatment.

Patients should be seated comfortably in a quiet environment for 5 min before beginning BP measurements.
Three BP measurements should be recorded, 1–2 min apart, and additional measurements only if the first two readings differ by >10 mmHg. BP is recorded as the average of the last two BP readings.
Additional measurements may have to be performed in patients with unstable BP values due to arrhythmias, such as in patents with AF, in whom manual auscultatory methods should be used as most automated devices have not been validated for BP measurement in patients with AF.[a]
Use a standard bladder cuff (12–13 cm wide and 35 cm long) for most patients, but have larger and smaller cuffs available for larger (arm circumference >32 cm) and thinner arms, respectively.
The cuff should be positioned at the level of the heart, with the back and arm supported to avoid muscle contraction and isometric exercise-dependant increases in BP.
When using auscultatory methods, use phase I and V (sudden reduction/disappearance) Korotkoff sounds to identify SBP and DBP, respectively.
Measure BP in both arms at the first visit to detect possible between-arm differences. Use the arm with the higher value as the reference.
Measure BP 1 min and 3 min after standing from a seated position in all patients at the first measurement to exclude orthostatic hypotension. Lying and standing BP measurements should also be considered in subsequent visits in older people, people with diabetes, and people with other conditions in which orthostatic hypotension may frequently occur.
Record heart rate and use pulse palpation to exclude arrhythmia.

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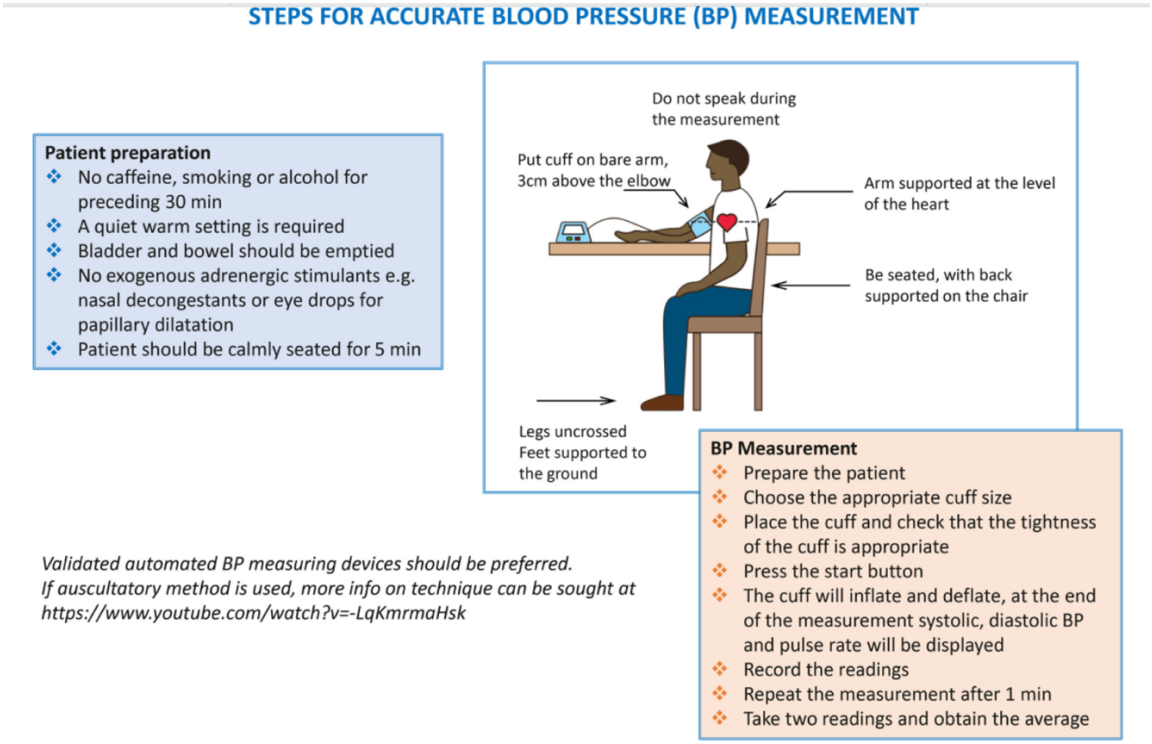
AF = atrial fibrillation; BP = blood pressure; DBP = diastolic blood pressure; SBP = systolic blood pressure.
[a]Most automatic devices are not validated for BP measurement in patients with AF and will record the highest individual systolic pressure wave form rather than an average of several cardiac cycles. This will lead to overestimation of BP.

Office blood pressure measurement.



Recommendations for blood pressure (BP) measurement, thresholds, and action required following appropriate office measurement. [3]

1.1.3.2 Out-of-office blood pressure measurement

Out-of-office BP measurement refers to the use of either HBPM or ABPM, the latter usually over 24 h. It provides a larger number of BP measurements than conventional office BP in conditions that are more representative of daily life.

1.1.3.3 Home blood pressure monitoring

Home BP is the average of all BP readings performed with a semiautomatic, validated BP monitor, for at least 3 days and preferably for 6–7 consecutive days before each clinic visit, with readings in the morning and the evening, taken in a quiet room after 5 min of rest, with the patient seated with their back and arm supported. Two measurements should be taken at each measurement session, performed 1–2 min apart. Compared with office BP, HBPM values are usually lower, and the diagnostic threshold for hypertension is >_135/85 mmHg (equivalent to office BP >_140/90 mmHg) when considering the average of 3–6 days of home BP values. Compared with office BP, HBPM provides more reproducible BP data and is more closely related to HMOD,

particularly LVH. There is also evidence that patient self-monitoring may have a beneficial effect on medication adherence and BP control, especially when combined with education and counselling. Telemonitoring and smartphone applications may offer additional advantages, such as an aid to memory to make BP measurements, and as a convenient way to store and review BP data in a digital diary and transmit them.

1.1.3.4 Ambulatory blood pressure monitoring

ABPM provides the average of BP readings over a defined period, usually 24 h. The device is typically programmed to record BP at 15 - 30 min intervals, and average BP values are usually provided for daytime, night-time, and 24 h. A diary of the patient's activities and sleep time can also be recorded.

A minimum of 70% usable BP recordings are required for a valid ABPM measurement session. ABPM values are, on average, lower than office BP values, and the diagnostic threshold for hypertension is >_130/80 mmHg over 24 h, >_135/85 mmHg for the daytime average, and >_120/70 for the nighttime average (all equivalent to office BP >_140/90 mmHg). ABPM is a better predictor of HMOD than office BP. Furthermore, 24 h ambulatory BP mean has been consistently shown to have a closer relationship with morbid or fatal events and is a more sensitive risk predictor than office BP of CV outcomes such as coronary morbid or fatal events and stroke. BP normally decreases during sleep. Although the degree of nighttime BP dipping has a normal distribution in a population setting, an arbitrary cut-off has been proposed to define patients as 'dippers' if their nocturnal BP falls by >10% of the daytime average BP value;

Category	SBP (mmHg)		DBP (mmHg)
Office BP[a]	≥140	and/or	≥90
Ambulatory BP			
Daytime (or awake) mean	≥135	and/or	≥85
Night-time (or asleep) mean	≥120	and/or	≥70
24 h mean	≥130	and/or	≥80
Home BP mean	≥135	and/or	≥85

BP = blood pressure; DBP = diastolic blood pressure; SBP = systolic blood pressure.
[a]Refers to conventional office BP rather than unattended office BP.

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Definitions of hypertension according to office, ambulatory, and home blood pressure levels.

however, the ‘dipping’ status is often highly variable from day to day and thus is poorly reproducible. The night-to-day ratio is also a significant predictor of outcome, and patients with a reduced night-time dip in BP (i.e. <10% of the daytime average BP or a night-to-day ratio >0.9) have an increased cardiovascular risk. Moreover, in those in whom there is no night-time dip in BP or a higher night-time than daytime average BP, there is a substantially increase in risk.

1.1.3.5 White-coat hypertension and masked hypertension

White-coat hypertension refers to the untreated condition in which BP is elevated in the office, but is normal when measured by ABPM, HBPM, or both. Conversely, ‘masked hypertension’ refers to untreated patients in whom the BP is normal in the office but is elevated when measured by HBPM or ABPM.

Although the terms white-coat and masked hypertension were originally defined for people who were not being treated for hypertension, they are now also used to describe discrepancies between office and out-of-office BP in patients treated for hypertension, with the terms masked uncontrolled hypertension (MUCH) (office BP controlled but home or ambulatory BP elevated) and white-coat uncontrolled hypertension (WUCH) (office BP elevated but home or ambulatory BP controlled), compared with sustained uncontrolled hypertension (SUCH) (both office and home or ambulatory BP are uncontrolled).

The white-coat effect is used to describe the difference between an elevated office BP (treated or untreated) and a lower home or ambulatory BP in both untreated and treated patients.

1.1.3.5.1 White-coat hypertension

Although the prevalence varies between studies, white-coat hypertension can account for up to 30 - 40% of people (and >50% in the very old) with an elevated office BP. It is more common with increasing age, in women, and in non-smokers. Its prevalence is lower in patients with HMOD, when office BP is based on repeated measurements, or when a doctor is not involved in the BP measurement. A significant white-coat effect can be seen at all grades of hypertension (including resistant hypertension), but the prevalence of white-coat hypertension is greatest in grade 1 hypertension.

Compared with true normotensives, patients with white-coat hypertension have increased adrenergic activity, greater prevalence of metabolic risk factors, more frequent asymptomatic cardiac and vascular damage, and a greater long-term risk of new-onset diabetes and progression to sustained hypertension and LVH. In addition, although the out- of-office BP values are, by definition, normal in white-coat hypertension, they tend to be higher than those of true normotensive people, which may explain the increased long-term risk of CV events reported in white-coat hypertension by recent studies after adjustment for demographic and metabolic risk factors.

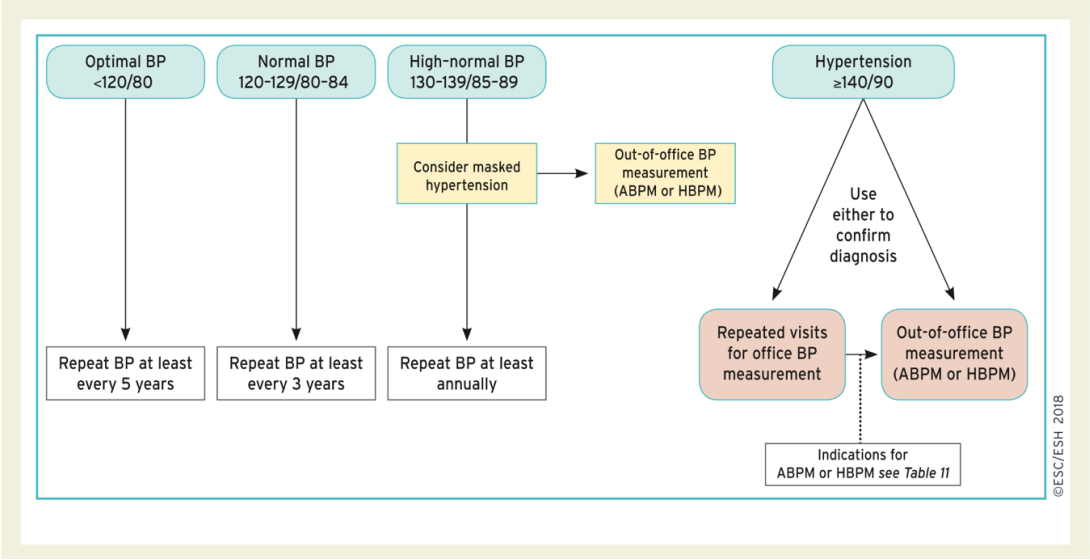
1.1.3.5.2 Masked hypertension

Masked hypertension can be found in approximately 15% of patients with a normal office BP. The prevalence is greater in younger people, men, smokers, and those with higher levels of physical activity, alcohol consumption, anxiety, and job stress. Obesity, diabetes, CKD, family history of hypertension, and high–normal office BP are also associated with an increased prevalence of masked hypertension. Masked hypertension is associated with dyslipidemia and dysglycemia, HMOD, adrenergic activation, and increased risk of developing diabetes and sustained hypertension.

1.2 Diagnosis

1.2.1 Screening for the detection of hypertension

Hypertension is predominantly an asymptomatic condition the is best detected by structured population screening programs or opportunistic measurement of BP. When structured population screening programs have been undertaken, an alarming number of people (>50%) were unaware they had hypertension. This high rate of undetected hypertension occurred irrespective of the income status of the countries studied across the world. All adults should have their BP recorded in their medical record and be aware of their BP, and further screening should be undertaken at regular intervals with the frequency dependent on the BP level. For healthy people with an optimal office BP (<120/80 mmHg), BP should be remeasured at least every 5 years and more frequently when opportunities arise. In patients with a normal BP (120–129/80–84), BP should be remeasured at least every 3 years. Patients with high–normal BP (130–139/85–89 mmHg) should have their BP recorded annually because of the high rates of progression of high–normal BP to hypertension. This is true also for people in whom masked hypertension is detected.



Screening and diagnosis of hypertension.

1.2.2 Confirming the diagnosis of hypertension

BP can be highly variable, thus the diagnosis of hypertension should not be based on a single set of BP readings at a single office visit, unless the BP is substantially increased (e.g. grade 3 hypertension) and there is clear evidence of HMOD (e.g. hypertensive retinopathy with exudates and hemorrhages, or LVH, or vascular or renal damage). For all others (i.e. almost all patients), repeat BP measurements at repeat office visits have been a long-standing strategy to confirm a persistent elevation in BP, as well as for the classification of the hypertension status in clinical practice and RCTs. The number of visits and the time interval between visits varies according to the severity of the hypertension and is inversely related to the severity of hypertension. Thus, more substantial BP elevation (e.g. grade 2 or more) requires fewer visits and shorter time intervals between visits (i.e. a few days or weeks), depending on the severity of BP elevation and whether there is evidence of CVD or HMOD. Conversely, in patients with BP elevation in the grade 1 range, the period of repeat measurements may extend over a few months, especially when the patient is at low risk and there is no HMOD. During this period of BP assessment, CV risk assessment and routine test are usually performed.

1.3 Pathophysiology [4]

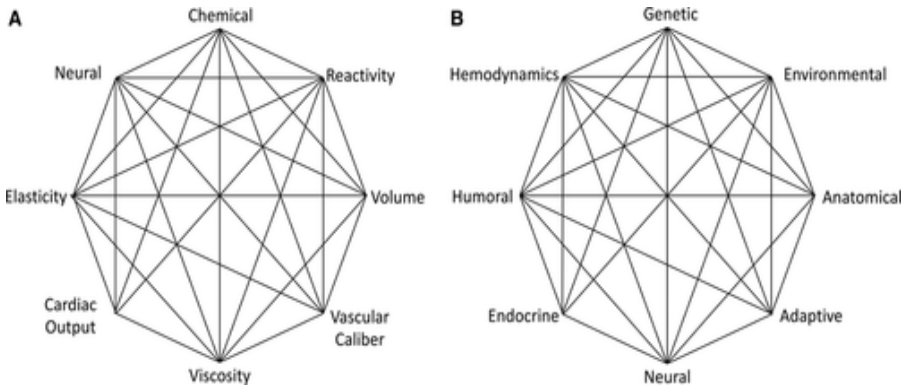
Clinical hypertension can be grouped into 2 broad categories. Primary (or essential) hypertension represents between 85% and 95% of human cases and has an unidentified cause. In contrast, secondary hypertension is caused by identifiable underlying conditions, including renal artery stenosis, pheochromocytoma, adrenal adenoma, or single-gene mutations. Historically, most patients were screened for secondary causes. However, it is now clear that this is not cost-effective and that in the absence of compelling clinical findings (abdominal bruit, hypokalemia, clinical symptoms of a pheochromocytoma) or a pressing need to improve treatment (drug-resistant hypertension) patients are generally treated without such an evaluation.

1.3.1 Pathophysiological/Historical concepts

Beginning with seminal observations by Tigerstedt, Franz Volhard, and subsequently refined and elegantly published by Goldblatt, it became apparent that the ischemic or under perfused kidney releases a substance or substances that can raise the BP in recipient animals. These early findings set the groundwork for Irvine Page and Braun Menendez in 1939 to report their discovery of a potent vasoconstrictor and pro-hypertensive agent isolated from renal extracts that they named hypertensin and angiotonin, respectively. They ultimately agreed to call it angiotensin.

Irvine Page is among the most prominent pioneers of hypertension research. In his initial experimental observations with Oscar Helmer, he discovered that when preparations of renin were exposed to plasma containing what he termed "renin activator" a pressor substance was formed that could raise BP up to 300 mm Hg. He named this substance "angiotonin." It would have been easy to assume that this elevation of BP was entirely due to intense vasoconstriction. However, his further observations suggested this was an inadequate explanation. In a classic article in 1949, he summarized evidence that hypertension could be mediated by the central nervous system, cardiovascular factors, endocrine factors, and perturbations of renal function. He provided evidence that the hypertension induced by acute injections of angiotonin could be reversed by ganglionic blockade with tetraethylammonium. In a subsequent study, Dr Page and colleagues reported that low rates of Ang II (angiotensin II) infusion had minimal or no effect on BP in the first hours after starting the infusion, but increased BP by 30 mm Hg 24 hours later. This increase in BP were exacerbated by tyramine (that releases norepinephrine from nerve terminals) and were blocked by guanethidine (that prevents norepinephrine release). Page concluded from these highly insightful studies that "angiotensin causes hypertension by an indirect action mediated by the central nervous system, an action independent of its vasoconstrictor action.". In his 1949 article, he chose to describe this multifactorial nature by the term "Mosaic," pointing out that "…many mechanisms are more or less involved. Elevated blood pressure is the resultant of multiple forces acting on the variety of tissues which compose the circulatory apparatus." In a subsequent review, Dr Page presented a now-iconic octagonal diagram that has been modified and often reproduced to illustrate his concept that hypertension is caused by multiple factors, including neural and chemical perturbations, alterations of vascular caliber and elastance,

cardiovascular reactivity, blood volume, and viscosity. Dr Page subsequently revised the Mosaic Theory to include more general terms; however, the principle of his Mosaic Theory has prevailed to the present day. It is fascinating to ponder that the factors composing his Mosaic Theory reflect an ongoing central discussion about the importance of the kidney (volume and cardiac output), the vasculature (elastance, vascular caliber, and reactivity), and the central nervous system (reactivity and neural).



The original (A) and revised (B) Mosaic Theories proposed by Page.

1.3.2 The role of the kidney and body fluid volumes in hypertension

The kidney is an important node in Dr Page's Mosaic Theory. Cardiac output is the product of heart rate and cardiac stroke volume. Stroke volume is dependent on venous return and is governed in large part by the kidneys and their modulation of volume homeostasis. As the renal pressure natriuresis mechanism regulates the body fluids and thereby exerted a primary role in setting the level of BP, whereas the central nervous system and vascular function, among others, provide important modulation.

The kidney has at least 4 major roles in hypertension. One is the production of renin, an aspartic protease that cleaves angiotensinogen to angiotensin I, which in turn is acted on by the ACE to generate Ang II. Renin is the rate-limiting step for activation of the circulating renin-angiotensin system (RAS) and its synthesis and secretion by the kidney is tightly regulated. Renin is initially synthesized as the inactive precursor prorenin, which is converted to active renin upon binding to the PRR (prorenin receptor). Under normal conditions, renin is produced almost exclusively by specialized juxtaglomerular cells of the afferent arteriole. It is released in response to a reduction in

perfusion pressure or delivery of sodium chloride to macula densa cells, or by an increase in sympathetic stimulation. Prolonged stimulation of the renal sympathetic nerves transforms a subset of vascular smooth muscle cells into renin-producing cells in the afferent arteriole. This transformation is governed by the transcription factor SRY-related HMG-box gene (Sox)-6. Although renin is normally released almost exclusively from the juxtaglomerular apparatus of the kidney, the proximal tubules can become an important site of renin production during oxidative stress or in response to increased glomerular protein filtration. Moreover, renin is a dual-purpose enzyme that both metabolizes angiotensinogen and acts as a complement C3 convertase. It has long been known that circulating levels of C3 predict the subsequent development of hypertension, likely by promoting innate and adaptive immune responses. Therefore, a role may yet emerge for improved direct renin inhibitors in the treatment of hypertension and for reducing complement C3 activation.

A second major role of the kidney in hypertension is to reset or alter the pressure diuresis and natriuresis. Although the mechanisms for pressure natriuresis are multifactorial, substantial evidence implicates increases in renal interstitial pressure and alterations of the sodium transporters, such as the NHE3 (sodium hydrogen exchanger 3) and the sodium-phosphate cotransporter isoform 2 in the proximal tubule. Acute hypertension retracts these from the luminal cell membrane to the base of the apical microvilli in the proximal tubule where they cannot participate in sodium reabsorption. Likewise, an increase in BP can relocate the thiazide-sensitive sodium chloride cotransporter in the distal tubule. However, during chronic hypertension, these transporters are translocated to the apical microvilli, where they enhance sodium reabsorption and likely sustain hypertension. The SGLT2 (sodium-glucose–linked transporter type 2) in the proximal tubule is also upregulated by Ang II acting on AT1 receptors during renovascular hypertension where it is functionally linked to NHE3 via the microtubule-associated protein 3 to enhance proximal Na^+ reabsorption during reactive oxygen species (ROS) stimulation. Perfusion of an SGLT2 inhibitor into the proximal tubule inhibits Na^+:H^+ exchange. Because NHE3 transports more Na^+ than SGLT2, this functional interaction between the two is likely to contribute to the surprisingly robust 27% inhibition of proximal Na^+ and fluid reabsorption by the SGLT2 inhibitor dapagliflozin in diabetic rats. This may underlie the reported effects of SGLT2 inhibitors to reduce the plasma volume in heart failure and the BP in hypertension. Shifts

in transporter location and function can be mediated by Ang II, inflammatory cytokines, loss of NO, and adrenergic stimulation. It is important to note that shifts in pressure natriuresis are often not reflected by overt changes in renal function as measured by usual clinical parameters, such as blood urea nitrogen, creatinine, or creatinine clearance. Moreover, renal Na^+ retention in hypertension is not usually accompanied by overt signs of fluid overload.

A third, recently recognized role of the kidney in hypertension is to modulate systemic sympathetic tone by generating reflex signals via renal afferent nerves. Approximately 90% of renal nerves are efferent nerves sending sympathetic signals to the kidney, thereby enhancing tubular sodium resorption, renin release, and vasomotor tone depending on the intensity of nerve traffic. However, a smaller proportion of renal nerves are afferents that generate signals from within the kidney and transmit them to the brain stem where they can initiate reflexes that promote increases in efferent sympathetic nervous system tone and induce hypertension. More recently, it has been recognized that the renal afferent nerves have a special role in salt-dependent hypertension. The ability of renal afferent nerves to initiate an increase in global sympathetic outflow might explain the pleiotropic effects of renal denervation. In Ang II–induced hypertension, renal efferent, rather than afferent nerves, seem to have a predominant role. Although the precise sites in the kidney where afferent nerves are activated remain undefined, recent studies have thrown light on some of the underlying mechanisms. A high-salt diet in the context of both acute or chronic causes the expected reduction in the circulating RAS but paradoxically activates the intrarenal RAS via increased ROS and activates renal afferent nerve traffic to reflexly increase BP.

A fourth important role of the kidney in hypertension is to serve as a site of immune activation. As Ang II–induced hypertension activates antigen-presenting dendritic cells in the kidney that migrate to secondary lymphoid organs to activate T cells which in turn return to the kidney. This process is blocked by renal denervation, suggesting that efferent renal nerves promote neoantigen formation in the kidney in hypertension. Single-cell sequencing has shown that the kidney, as opposed to blood vessels or the spleen, accumulates T cells with an oligoclonal T-cell receptor population, supporting the role of the kidney in antigen formation.

1.3.3 The role of the vasculature in hypertension

Several of the nodes in Dr Page's Mosaic diagram refer to potential vascular mechanisms, including vascular caliber, reactivity, elasticity, and, indirectly, cardiac output. Systemic vascular resistance is almost uniformly enhanced in adults with hypertension, and many common agents used for the treatment of hypertension are vasodilators. In addition to systemic autoregulation, which is a physiological response, it is now clear that there are long-term pathophysiological manifestations of hypertension that increase vascular tone and resistance.

There are at least 4 vascular perturbations that occur in and contribute to hypertension. The first is an enhanced milieu of vasoconstrictor hormones, including Ang II, catecholamines, and vasopressin, coupled with alterations in vascular function that promote vasoconstriction and diminish vasodilatation. Of particular interest are genes that modulate GPCR (G protein–coupled receptor) signaling, including the RGS (regulators of G protein signaling) proteins, that induce GTP hydrolysis to terminate G protein signaling. The RGS proteins 1 and 2 are linked to GPCRs that enhance responses to vasoconstrictors including thromboxane, Ang II, and norepinephrine. mRNA expression of RGS1 is attenuated by chronic Ang II infusion and suggested that hypertension leads to a loss of this important modulatory pathway. In contrast, RGS5 seems to have modest to no effects on BP by itself but activates RhoA stress fiber formation and a contractile phenotype of vascular smooth muscle. RhoA is a critical activator of Rho kinase that targets contractile proteins including the myosin light chain in vascular smooth muscle to promote vasoconstriction. Endothelial Rho kinase phosphorylates NO synthase on threonine 495 to inhibit NO production, which also increases vasoconstriction. The Rho kinase inhibitor Fasudil is approved for use in Japan and China for the treatment of cerebral vasospasm and pulmonary hypertension and has BP-lowering effects in genetic- and salt-induced forms of experimental hypertension.

Hypertension is also associated with impaired vasodilatation. For many years, it has been recognized that endothelium-dependent vasodilatation and NO signaling are reduced in hypertension. There are fundamental differences in the mechanisms underlying endothelium-dependent vasodilatation between larger conduit arteries, branch arteries, and resistance arterioles. Larger vessels predominantly employ NO, whereas smaller arteries and arterioles are also modulated by endothelium-dependent

hyperpolarization and vasodilator prostaglandins. In larger vessels, defects in NO synthesis and bioavailability include loss of critical cofactors for NO synthase, including L-arginine and tetrahydrobiopterin, inhibition of NOS (NO synthase) activity by asymmetrical dimethylarginine (ADMA), and oxidative inactivation of NO. It should be stressed that alterations of NO production extend beyond the vasculature and have implications for renal and central nervous system dysfunction in hypertension. In smaller arteries and arterioles endothelium-dependent vasodilatation is mediated by hyperpolarization, but the factors responsible for this have largely defied identification. In the past decade, there has been increasing interest in the role of direct communications or gap junctions that permit transmission of signals between the endothelium and vascular smooth muscle cells. Early studies using intracellular labeling showed polarized unidirectional movement of fluorescent dyes from the endothelium to adjacent smooth muscle cells. These dyes were shown to traverse MEJs (myoendothelial junctions) that were subsequently identified as holes in the internal elastic membrane lying between the endothelium and vascular smooth muscle. MEJs are particularly common in smaller arterioles and are sites of signaling events and signaling molecules, including calcium pulsars, the inositol 3 phosphate receptor, and calcium-sensitive potassium channels. Endothelium-dependent hyperpolarization is transmitted via MEJs directly to vascular smooth muscle cells. MEJs also facilitate the transfer of NO generated by NOS that is expressed at these junctions. The NO travels from the endothelium to the vascular smooth muscle where it regulates connexin43 to modulate the permeability of the MEJs. MEJs also contain hemoglobin alpha, which controls the passage of NO from the endothelium to the vascular smooth muscle cells in a redox-dependent fashion. Intriguingly, a peptide mimic that disrupts the binding of NO to hemoglobin alpha lowers BP abruptly in wild-type animals and reverses experimental hypertension caused by Ang II infusion. Importantly, the density of MEJs is reduced and their local inositol trisphosphate–stimulated calcium signals are blunted in mesenteric arterioles of spontaneously hypertensive rats, indicating that these signaling loci are deficient in hypertensive resistance vessels. In keeping with this, mice lacking the MEJ component connexin40 exhibit hypertension and reduced endothelium-dependent vasodilatation in response to the potassium channel activator SKA-31. Likewise, endothelial-specific expression of a mutant connexin40, which causes electrical impairment of gap junctions, leads to exercise-induced hypertension. Recently, it has been shown that chronic sympathetic stimulation in the setting of hypertension due to experimental chronic kidney

disease decreases the expression of connexin43, leading to disruption of MEJ function and enhanced vasoconstriction. These various lines of evidence strongly support the role of MEJs in modulation of microvascular tone and abnormalities in hypertension.

Perturbations of both microvascular and large vessel structure represent a second vascular contribution to hypertension. More than 60 years ago, Folkow et al proposed that vascular smooth muscle hypertrophy and concomitant narrowing of the arteriolar lumen increases systemic vascular resistance. This phenomenon has been detected in the retinal arterioles by fundoscopic examination in clinical hypertension where a reduced arteriole to venule ratio increases the odds of developing hypertension. This indicates that arteriolar remodeling can precede, and possibly predispose, to hypertension. The application of artificial intelligence and machine learning methods to quantitate parameters of retinal arterial morphology have further demonstrated that retinal artery morphology correlates with cardiovascular outcomes. There are multifactorial mechanisms of arteriolar remodeling in hypertension. These include the direct hypertrophic/growth–promoting actions of Ang II and catecholamines, oxidative signaling, and inflammatory cytokines released by immune cells. Many of these enhance the expression or activity of matrix metalloproteinases that promote cell migration, hypertrophy, and reorganization.

A related alteration of vascular function that likely contributes to hypertension is stiffening of large conduit arteries, and particularly the proximal aorta. A healthy aorta distends during systole and recoils in diastole. This leads to a reduction in the systolic pressure while maintaining diastolic pressure and perfusion. The aorta stiffens in common conditions, including aging, diabetes, obesity, and tobacco use, thereby reducing this critical Windkessel function. Aortic stiffening can be both a cause and a consequence of hypertension. Although the mechanisms by which aortic stiffening causes end-organ damage are not completely understood, a consequence is enhanced propagation of pressure into the microcirculation, leading to barotrauma in target organs, in part via increasing cyclical stretch of microvascular endothelial cells. Indeed, in an elegant analysis of the components of the pulse wave, an increased forward pressure wave was associated with an increased risk for incident cardiovascular disease.

Finally, there is an impaired vessel wall defense against thrombosis in hypertension that has been related to increased endothelial expression of tissue factor and

the vascular cell adhesion molecule 1. This enhances platelet-dependent leukocyte adhesion and is driven by thrombin factor XI and the platelet factor XI receptor. The thrombotic paradox of hypertension (the Birmingham paradox): although the blood vessels are exposed to high pressures in hypertension, the main complications of hypertension (stroke and myocardial infarction) paradoxically are thrombotic rather than hemorrhagic. Inhibition of factor XI in angiotensin-infused rats and mice prevents platelet thrombin formation, vascular leukocyte infiltration, endothelial dysfunction, and hypertension.

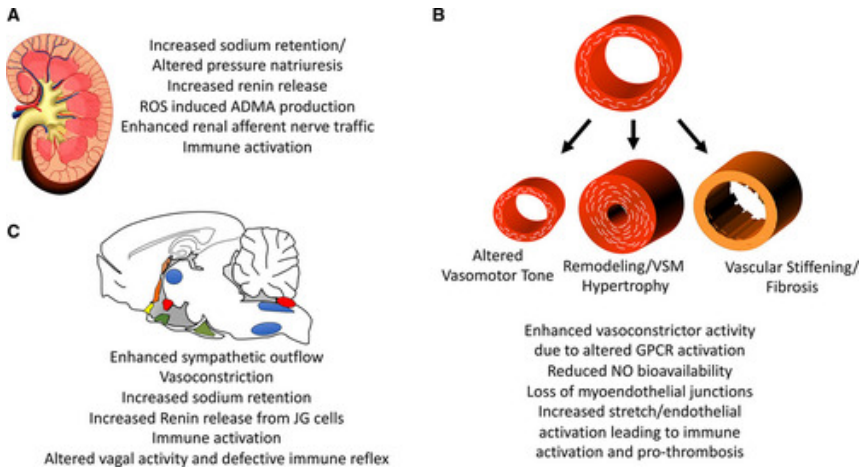
1.3.4 The central nervous system in hypertension

Dr Page's revised diagram included the term "neural." Indeed, Page demonstrated that Ang II caused hypertension predominantly by sympathetic neural activation. Measures of muscle sympathetic nerve activity, norepinephrine spillover, and heart rate variability have suggested that humans with hypertension commonly have increased sympathetic outflow and enhanced catecholamine mediated vasoconstriction. Ang II and ROS in the brain stem nuclei enhance vascular resistance by in part by inhibition of the microvascular endothelium-dependent hyperpolarizing factor that normally reduces vascular tone. In keeping with these central vascular effects, ganglionic blockade acutely lowers BP in humans with hypertension to a variable extent, particularly in those who are obese.

The many mechanisms whereby sympathetic tone modulates hypertension include enhanced vasoconstriction and vascular remodeling, renal renin production via beta 1 adrenergic receptors in the juxtaglomerular apparatus and enhanced renal sodium resorption and inflammation.

An important initiating site is the laminal terminalis, located anterior to the third ventricle, which contains the subfornical organ, the median preoptic eminence, and the organum vasculosum of the lamina terminalis. The subfornical organ and organum vasculosum of the lamina terminalis are circumventricular organs that have a poorly formed blood-brain barrier that permits blood-born Ang II and sodium to activate neuronal firing. Indeed, the organum vasculosum of the lamina terminalis is responsive to even modest increases in sodium to initiate salt-sensitive hypertension.

In addition to efferent signals promoting hypertension, there is ample evidence that afferent pathways are likewise involved. In addition to renal afferent activation, discussed above, afferent nerves from adipose tissue are triggered by a high-fat diet to reflexively increase BP and insulin resistance. Another source of afferent nerve stimulation is the heart. Infusion of saline into cardiac transplant recipients with no evidence of cardiac dysfunction failed to reduce their sympathetic nervous system activity, arginine vasopressin levels or their renin, angiotensin, and aldosterone levels and led to hypertension. This hypertensive response was linked to a failure to suppress Ang II during blood volume expansion and was prevented by angiotensin-converting enzyme inhibition.



Perturbations of the kidney (A), vasculature (B), and central nervous system (C) contributing to hypertension. *ADMA indicates asymmetrical dimethylarginine; GPCR, G protein–coupled receptor; JG, juxtaglomerular apparatus; ROS, reactive oxygen species; and VSM, vascular smooth muscle.*

1.3.5 Aldosterone, the mineralocorticoid receptor and their ubiquitous role in the mosaic theory

A major development since the initial Mosaic theory is the evolving understanding of aldosterone in hypertension. Aldosterone is produced by the zona granulosa cells of the adrenal gland in response to Ang II and elevations of extracellular potassium. Until recently, the sole effect of aldosterone was thought to enhance sodium reabsorption in the collecting duct, and aldosterone blockade was felt to predominantly promote diuresis. It has become obvious that the MR (mineralocorticoid receptor) is expressed in numerous organs and cells, including the heart, blood vessels, immune cells, and in the brain.

These myriad effects of the MR receptor are important because at least 5% of all cases of hypertension are due to primary hyperaldosteronism and this is likely much higher among those with resistant hypertension.

1.3.6 The role of ROS in hypertension

ROS likely contribute to almost each node of Dr Page's diagram. Superoxide and other related ROS can oxidatively inactivate NO and oxidize tetrahydrobiopterin, a critical cofactor for NO synthase. ROS can also enhance vasoconstriction and thereby alter vascular caliber and reactivity. ROS are important for vascular stiffening and for remodeling of microarterioles. In the kidney, ROS enhance renal sodium reabsorption and thus enhance volume and cardiac output. They have also been implicated in activation of matrix metalloproteinases and thus promote tissue remodeling. ROS likewise increase neuronal firing in critical brain centers, including the subfornical organ, and brain stem centers, thus altering neural control.

Although early studies emphasized the role of oxidative stress in vascular cells, the kidney and its vasculature develop oxidative stress with increased NADPH oxidase and reduced SOD (superoxide dismutase) activity both during Ang II infusion and during high salt intake. High salt intake enhances renal expression of NADPH oxidase and NOX2 and reduces SOD1 and SOD2, whereas Ang II infusion increases renal NADPH/$p22^{phox}$ and reduces SOD 3 expression. Renal ROS can activate renal afferent nerves, and increase renal and circulating levels of ADMA, by reducing its metabolism by dimethylarginine dimethylaminohydrolase and increasing its generation by protein arginine methyltransferase. Thus, an increase in circulating ADMA is one means whereby ROS in the kidney may enhance peripheral vasoconstriction. ADMA inhibits endothelial function and flow-mediated vasodilation and activation of the sympathetic nervous system during high salt intake could contribute to the failure of salt-sensitive subjects to reduce their peripheral vascular resistance during increases in cardiac output evoked by a high salt intake. In the kidney, the proximal tubular cells take up oxidatively modified albumin that induces a robust local activation of the RAS via NADPH oxidase, protein kinase C, NFκB (nuclear factor-κB), and AP-1 (activator protein 1). These together increase proximal tubular Ang II that initiates renal inflammation and fibrosis. This proximal tubule ROS pathway provides a potential link between hypertension, systemic oxidative stress, and proteinuria and the activation of the intrarenal RAS. These events

damage the kidney and can thereby perpetuate salt-sensitivity and worsening hypertension.

Therapeutically, scavenging ROS is not clinically employed, and there is evidence that high-dose vitamin antioxidants can be harmful, possibly because ROS can have important signaling function. Targeted scavenging of ROS or treatment with agents that inhibit untoward activation of ROS forming enzymes are viable future options. Indeed, one of the major benefits of Ang II blockade might be due to inhibition of ROS formation.

1.3.7 Inflammatory and immune mechanisms in hypertension

It is now recognized that virtually every type of immune cell, including those of innate and adaptive immunity, contributes to hypertension. These transmigrate into the interstitium of the kidney and blood vessels where they release potent cytokines, ROS, and metalloproteinases that modulate renal and vascular function and structure. It is likely that these mediators affect virtually every node of Dr Page's Mosaic diagram. A notable example is the cytokine IL-17A (interleukin 17A) produced by a subset of T cells, innate lymphocytes, histiocytes, and renal tubular cells. IL-17A affects renal tubular handling of sodium and seems to modulate pressure natriuresis. This cytokine stimulates vascular superoxide production, causes inhibitory phosphorylation of the endothelial NOS, and therefore, reduces the caliber of blood vessels. Over the long term, IL-17A promotes vascular fibrosis and impairs vascular elasticity. In contrast, regulatory T cells and anti-inflammatory cytokines, such as IL-10, have antihypertensive effects mediated, in part, by counteracting IL-17A.

There is substantial evidence that sympathetic outflow promotes immune activation in hypertension. Lesions of the forebrain that prevent sympathetic outflow reduce T-cell activation, whereas manipulations that increase sympathetic outflow promote T-cell activation. Recent data suggest that renal sympathetic tone modulates trafficking of immune cells to and from the kidney and the homing of memory T cells to the bone marrow, where they can be reactivated upon future hypertensive challenges. In the vasculature, T cells accumulate in the perivascular fat and adventitia of larger vessels in hypertension, likely via expression of chemokines, such as RANTES (regulated upon activation, normal T-cell expressed and presumably secreted) and MCP (monocyte chemoattractant protein)-1. This adventitial inflammatory response likely triggers

collagen deposition. There is also an immune reflex, whereby local tissue signals trigger a vagally mediated anti-inflammatory response.

Hypertension is associated with endothelial activation. It has long been recognized that the activated endothelium promotes rolling, adhesion, and transmigration of leukocytes. As monocytes transmigrate the endothelium, they are transformed into inflammatory macrophages and dendritic cells that emerge as activated monocytes with enhanced potential to produce cytokines and activate T cells. Endothelial cell stretch, oxidative stress, and loss of NO in hypertension can all enhance endothelial/leukocyte interaction and increase the endothelial activation of monocytes. Human monocytes activated in this way by the endothelium produce copious quantities of IL-6, IL-23, IL-1β, and stimulate autologous T cells potently. In addition, endothelial transmigration likely promotes myeloid cell accumulation in the corticomedullary junction of the kidney, where supraphysiological levels of sodium may provide a stimulus to activate monocytes.

1.3.8 Genetic influences

Genetic alterations are atop Dr Page's revised Mosaic diagram. Several single-gene mutations, including those responsible for Liddle syndrome, pseudohyperaldosteronism, aldosterone-producing adenomas, glucocorticoid remedial hypertension, and missense mutations of the mineralocorticoid receptor have been identified to be responsible for highly heritable Mendelian forms of hypertension. Although these single-gene mutations have provided insight into the pathogenesis of hypertension, they are rare and do not explain the high prevalence of familial hypertension commonly observed in the clinic. In contrast, single nucleotide polymorphisms that often occur in nonprotein coding regions of the genome and usually do not alter protein function are common. Genome-wide association studies in the past decade have identified >1000 single nucleotide polymorphisms that associate with hypertension. Although individual single nucleotide polymorphisms have small effects on BP, when multiple single nucleotide polymorphisms are analyzed as a polygenic risk score (PRS), they can account for as much as 13 mm Hg of BP variability.

1.3.9 Novel concepts related to salt and sodium intake

Dr Page's revised Mosaic Diagram included the environment, which includes diet, and in particular salt intake. There are numerous large epidemiological studies linking high levels of dietary sodium intake with risk for hypertension. Conversely, reducing dietary salt or administration of diuretic agents, such as thiazides, are effective treatments for elevated BP. In human populations, sodium-sensitivity, defined as an exaggerated change in BP in response to extremes of dietary salt intake, is a relatively common phenotype associated with increased risk for hypertension and cardiovascular events. Although salt-sensitive hypertension entails a renal defect in salt excretion, the increase in BP with salt intake is caused by increased peripheral resistance that requires a communication between the kidneys and the peripheral vasculature. Indeed, enhanced vasoconstriction and endothelial dysfunction, rather than a primary increase in renal Na^+ retention, can initiate salt-sensitive hypertension. Salt-sensitive subjects are unable to increase peripheral vascular resistance appropriately during a low salt intake or to reduce their peripheral vascular resistance during a high salt intake, thereby causing their BP to be unusually dependent on salt intake.

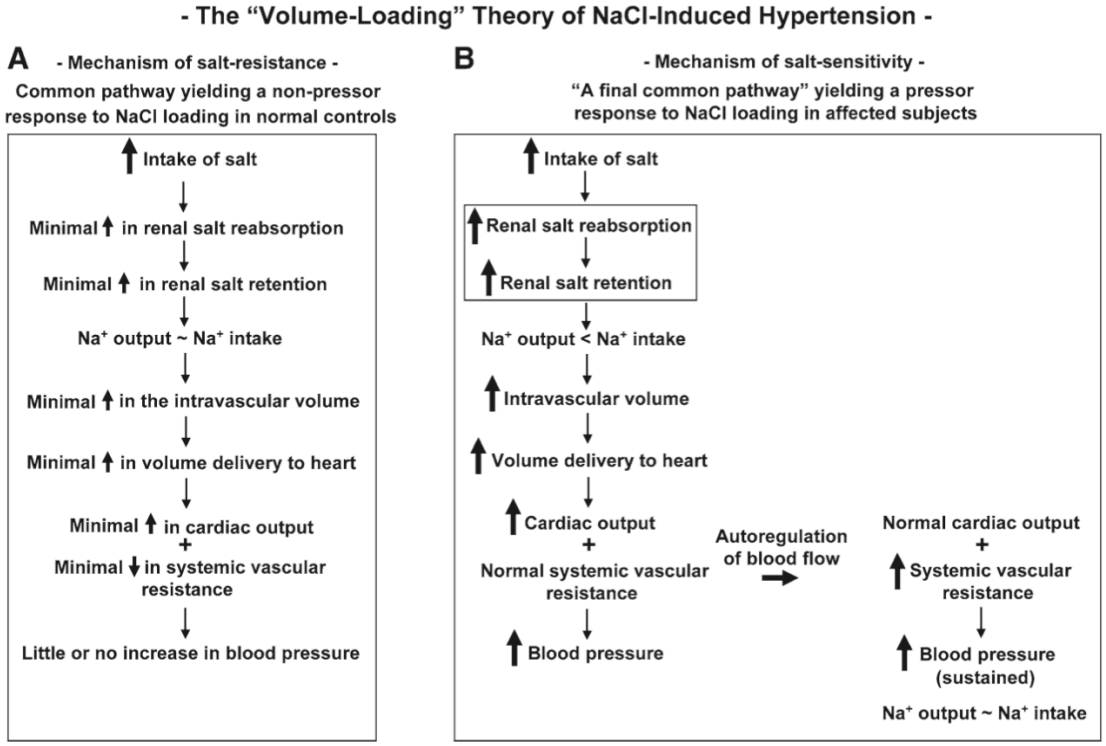
The impact of dietary sodium intake upon BP is complex, beyond the simple construct of intravascular volume expansion balanced by excretory functions of the kidney. For example, it is now apparent that during high salt feeding, sodium accumulates in the interstitium of the skin and other tissues where it may be stored at hypertonic concentrations in complexes with proteoglycans, acting as a reservoir and buffering the impact of sodium accumulation on intravascular volume and BP. This interstitial sodium storage can be visualized and quantified in humans using magnetic resonance imaging of the 23sodium isotope. Accumulation of sodium in tissues increases with high salt intake or aging and has been associated with hypertension and increased cardiovascular risk. In the subdermal space, sodium can also stimulate macrophages, triggering expression of TonEBP (tonicity-responsive enhancer-binding protein), a transcription factor regulating the expression of osmo-protective genes including VEGF (vascular endothelial growth factor)-C, a potent inducer of lymphangiogenesis. It has been suggested that these immunomodulatory actions of salt deposited in skin may have evolved to subserve a barrier function to prevent invasion by micro-organisms, but this may now be a maladaptive response.

Elevated concentrations of tissue sodium can also activate immune cells that contribute to hypertension. Modest elevations of sodium can stimulate T cells to produce the cytokine IL-17A which as mentioned above, promotes vascular remodeling, endothelial dysfunction, and renal sodium retention. Sodium entry via an amiloride-sensitive sodium channel can also drive dendritic cell activation and promotes transformation of human monocytes to a dendritic cell–like phenotype that produces cytokines like IL-6, TNF (tumor necrosis factor) α, and IL-1β. Upon entry of sodium into myeloid cells, calcium activation of the NADPH oxidase ensues leading to ROS formation and the generation of isolevuglandin adducts, which as discussed above act as neoantigens in these cells.

1.3.10 Salt sensitivity and salt-induced hypertension

Salt-sensitive subjects have an impaired renal ability to excrete a salt load that usually causes them to retain more sodium than normal salt-resistant subjects. The retention of abnormally large amounts of salt and water is held to cause abnormally large increases in sodium balance, blood volume, and a transient, abnormally large increase in cardiac output that contributes importantly to the hemodynamic initiation of increased blood pressure.

During the initiation of salt-induced hypertension, systemic vascular resistance is "normal" and pathogenically uninvolved in the initial pressor effect of salt. Abnormal systemic vascular resistance is held to be secondary only to increases in cardiac output and blood pressure caused by abnormal increases in renal retention of salt and water. This volume-loading theory, sometimes referred to as the autoregulation theory, also describes the sequence of events through which the phenomenon of abnormal pressure natriuresis is said to initiate and sustain salt-induced hypertension. Most theories of salt-induced hypertension share 2 core tenets: (1) Salt-sensitive subjects have a subnormal ability to excrete a salt load that causes them to retain more sodium than normal salt-resistant subjects, and (2) such an abnormally increased renal retention of sodium causes an abnormally large increase in cardiac output and thereby con- tributes importantly to the hemodynamic initiation of salt-induced increases in blood pressure. [5]



The volume-loading theory of the pathogenesis of NaCl-induced hypertension.

The critical pathogenic event in the initiation of the salt-induced increase in blood pressure is a subnormal decrease in systemic vascular resistance in response to salt loading: Without this vasodysfunction, a robust decrease in systemic vascular resistance, and not because they excrete sodium more rapidly, retain less sodium, and undergo smaller increases in cardiac output, begins within 12 to 24 hours of initiating salt loading in normal salt-resistant humans. Furthermore, in salt-sensitive subjects, the failure of systemic vascular resistance to normally decrease in response to increases in salt intake occurs before blood pressure increases above baseline. Thus, the abnormal vascular resistance response to salt loading cannot be a consequence of the salt-induced increases in blood pressure.

1.3.11 Microbiome as an emerging modulator of BP

Along with effects on fluid homeostasis and immune activation, sodium as a dietary constituent may promote hypertension by modifying gut microbiota. Indeed, many recent studies have highlighted the potential of the microbiome to influence BP. Advances in unbiased sequencing techniques have allowed precise identification and

assessment of commensal bacterial species in the gut that cannot be cultured, transforming understanding of the role of the microbiome in health and disease.

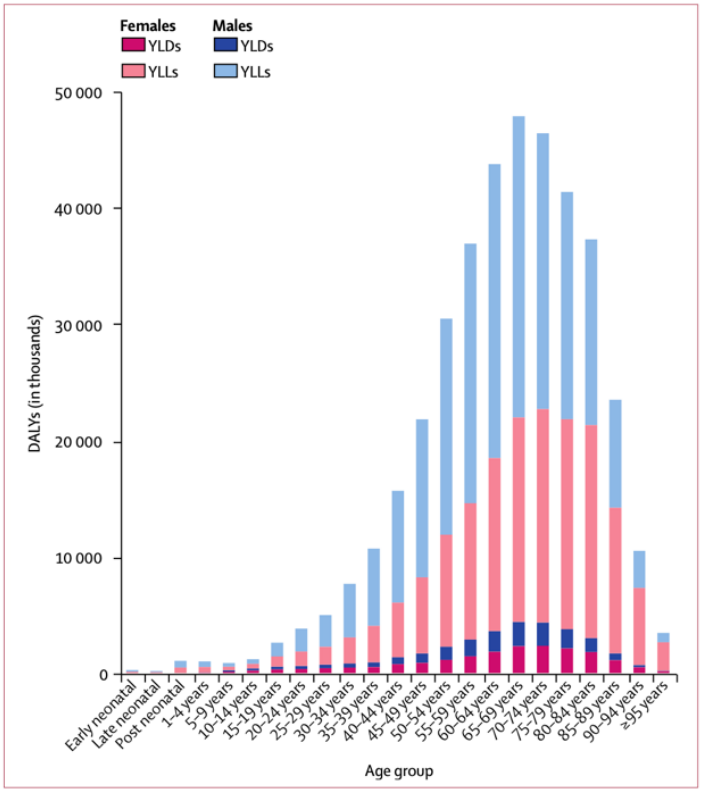
In healthy individuals, the gut microbiome is typically in a stable state of eubiosis and in relative equilibrium with the surrounding community. By contrast, significant alteration in the microbiome (dysbiosis) has been observed in range of disorders including hypertension. For example, in humans with hypertension and prehypertension, characteristic alterations in the microbiome have been observed. Fecal transfer from hypertensive mice to germ-free mice sensitizes the latter to hypertension, providing strong evidence for a role of the microbiome. In hypertension, alterations in the gut microbiome have been associated with inflammation, structural changes in the intestinal wall, and enhanced gut permeability. Altered intestinal permeability may facilitate egress of mediators, such as microbial products, hormones, and immune cells into the circulation where they can impact peripheral and central BP control mechanisms.

Along with associations between hypertension and gut dysbiosis, there is a direct relationship between diet and the composition of gut microbiota with potential to affect propensity for hypertension. For example, increased dietary salt intake causes significant alterations in the composition of microbiota and has been associated with accumulation of proinflammatory TH_{17} cells. Sodium is not the only dietary constituent with potential to impact BP through effects on the microbiome. Multiple studies have shown that diets enriched in fruit, vegetables, and fiber can lower BP and reduce risk for hypertension. Moreover, dietary fiber increases bacterial populations in the gut responsible for generating short-chain fatty acids through fermentation. In the human circulation, short-chain fatty acids are almost exclusively of microbial origin, and have been implicated as a key pathway whereby microbiota influence host physiology, perhaps through a family of nutrient-sensing GCPRs expressed in vascular smooth muscle cells, the autonomic nervous system and renal juxtaglomerular cells influencing renin release. Thus, the gut microbiome can influence BP control through pathways affecting many of Page's Mosaic components, raising the possibility that prebiotics and probiotics, antibiotics, and specific dietary formulations could be used to modify gut microbiome and its metabolites to prevent and treat hypertension.

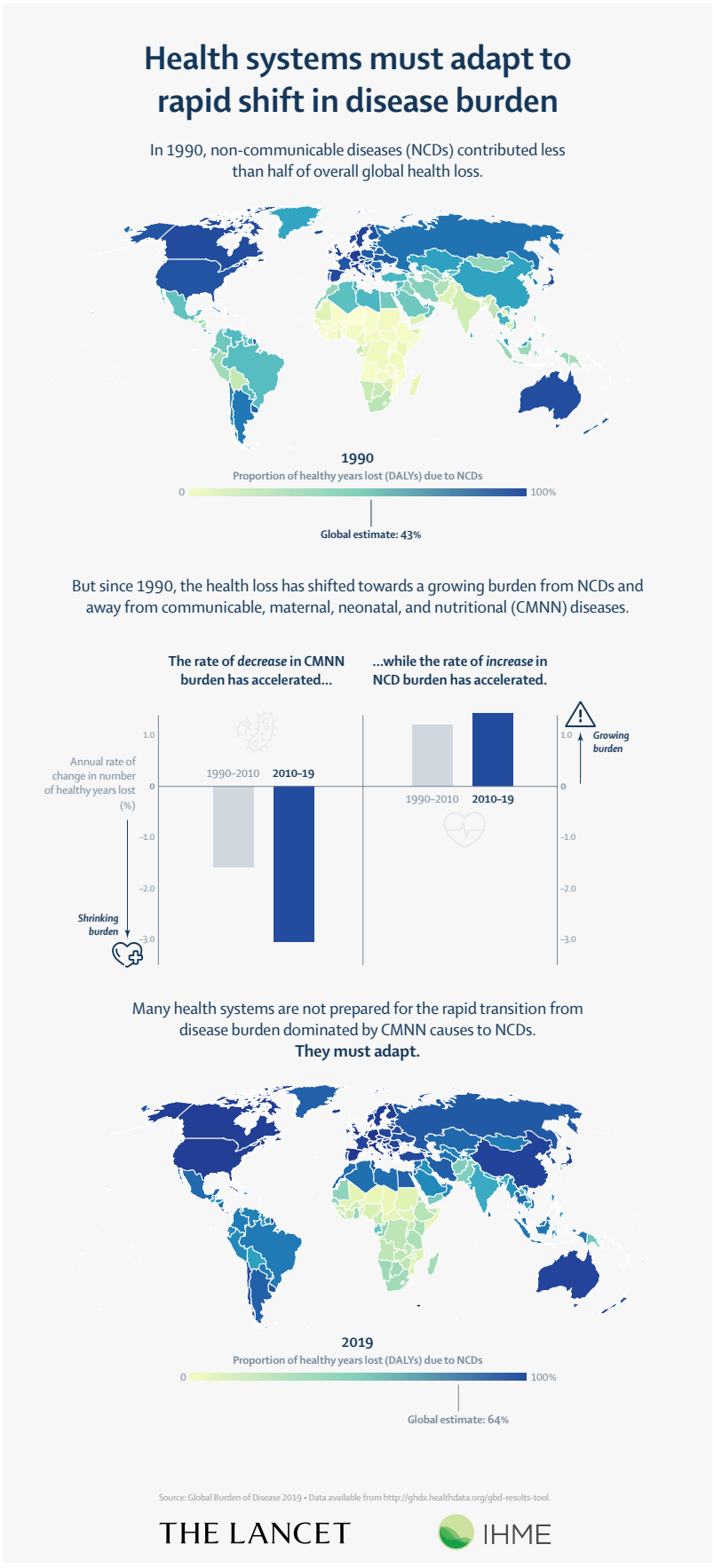
1.4 Non-Communicable diseases

For most populations, the last century has witnessed the most dramatic improvements in health in history. Life expectancy at birth has increased from a global average of 46 years in 1950 to 66 years in 1998.[6] The health status and disease profile of human societies have historically been linked to the level of their economic development and social organization. With industrialization, the major causes of death and disability, in the more advanced societies, have shifted from a predominance of nutritional deficiencies and infectious diseases to those classified as degenerative (chronic diseases such as cardiovascular disease (CVD), cancer, and diabetes). According to the WHO, chronic diseases, nowadays better known as Noncommunicable diseases (NCDs) tend to be the result of a combination of genetic, physiological, environmental, and behavioral factors. NCDs kill 41 million people each year, equivalent to 71% of all deaths globally.[7]

People of all age groups, regions and countries are affected by NCDs. These conditions are often associated with older age groups, but evidence shows that more than 15 millions of all deaths attributed to NCDs occur between the ages of 30 and 69 years. Of these "premature" deaths, 85% are estimated to occur in low- and middle-income countries. Children, adults, and the elderly are all vulnerable to the risk factors contributing to NCDs, whether from unhealthy diets, physical inactivity, exposure to tobacco smoke or the harmful use of alcohol.



Composition of DALYs by YLLs and YLDs, age group, and sex, 2019. [8]

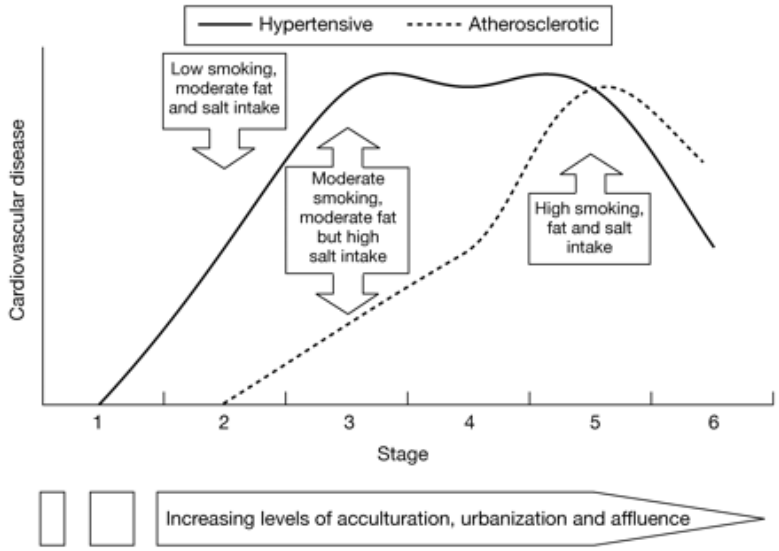


Lancet – NCDs – Global burden of disease 2019[9]

1.4.1 Epidemiological transition[10]

The theories on the health of populations in transition have developed with the groundbreaking contribution given to public health by Abdel Omran. In his essay of 1971 Omran conceptualizes with five propositions the theory of epidemiological transition in which degenerative and man-made diseases displace pandemics of infection as the primary causes of morbidity and mortality. The determinants of this transition, in his view, are ecobiological (interaction between biology and environment), socioeconomic, psychological, and medical (biotechnology and public health). Furthermore, Omran distinguishes between the 'Classical' transition (gradual and progressive from high mortality and high fertility to low mortality and low fertility) seen in England & Wales in the 19th century, the 'Accelerated' transition (faster decline in mortality rate) seen in Japan in the early 20th century, and the 'Contemporary' transition (slow and unsteady decline in mortality, but high fertility rates, thus rapid population growth) currently seen in developing countries. As the transition in the now developing countries is significantly influenced by medical technology, with the control of the traditional infectious diseases (e.g. diarrhea, malaria, and tuberculosis) and the decline in infant mortality rates, chronic diseases are becoming more prevalent.

An intriguing aspect of the epidemiology of vascular disease around the world is the consistent report that stroke is an important cause of morbidity, disability, and death in adults of black African origin, whether living in Africa, the Caribbean, US, or the UK. Six stages of the epidemiological evolution of patterns of cardiovascular disease among black people of sub-Saharan African origin have been suggested. The evolution is characterized by advancing acculturation, urbanization, and affluence with a progressive increase in salt intake, smoking habit, and saturated fat intake. The earlier stages (from 2 to 4) see the appearance of hypertension (and associated stroke) as the predominant form of cardiovascular disease whilst atherosclerosis (and associated ischemic heart disease) is predominant in the later stages (4 and 5). In stage 6, there is a decline in morbidity and mortality from vascular disease attributable to better prevention and management.



Stages in the epidemiological evolution of patterns of cardiovascular disease among people of sub-Saharan African origin.

Conceptually, the theory of epidemiologic transition focuses on the complex change in patterns of health and disease and on the interactions between these patterns and their demographic, economic and sociologic determinants, and consequences. At any given time, different countries in the world or even different regions within a country are at different stages of the epidemiologic transition. This transition can occur not only between different disease categories (e.g. deaths from childhood diarrhea and malnutrition giving way to adult chronic diseases), but also within a specific disease category (e.g. rheumatic heart disease of the young giving way to chronic coronary artery diseases of middle age or valve calcification, degeneration, and heart failure of the elderly).

For countries in the earliest stage of development, the predominant circulatory diseases are rheumatic heart disease, those due to other infections, and nutritional deficiency–related disorders of the heart muscle. Geographic regions experiencing this phase include Sub-Saharan Africa (SSA) and the rural areas of South America and South Asia (SA). During the second stage, as infectious disease burdens are reduced and nutrition improves, diseases related to hypertension, such as hemorrhagic stroke and hypertensive heart disease, become more common. During the third stage, as life expectancy continues to improve, high-fat diets, cigarette smoking, and sedentary lifestyles become more common. Noncommunicable diseases then predominate, with the highest mortality caused by atherosclerotic CVD, most frequently ischemic heart disease

and atherothrombotic stroke, especially at ages below 50 years. For most developing and middle-income countries, the increased incidence of CVD adds to the continuing burden of infectious, nutritional, and perinatal diseases, which has been termed the "double-burden". During the fourth stage, increased efforts to prevent, diagnose, and treat ischemic heart disease and stroke can delay these diseases to more advanced ages.

Previously the fourth stage was considered the "final" stage of the epidemiologic transition. However, a fifth stage should be added, where social upheaval or war breaks down existing social and health structures, leading to a resurgence of conditions seen in the first two stages. Diseases of the third and fourth stages persist. This regressive stage is associated with increased deaths due to both cardiovascular (CV) and non-CV causes such as infectious diseases, violence, and consequently a decrease in life expectancy.

1.4.2 Double burden of diseases

The burden of NCDs disproportionately affects populations in low- and middle-income countries (LMIC) where more than three quarters (77%) of global NCD deaths – 31.4 million – occur and health systems are weak. In LMICs, especially in Sub-Saharan Africa (SSA), hypertension is increasing rapidly because of rapid population growth, increased life expectancy and lifestyle factors.[11]

Research, however, shows that adequate blood pressure treatment and control can significantly reduce the first incidence of heart attack, strokes and recurrent strokes, heart failure, chronic kidney disease and premature death. However, limited access to health care is a barrier to preventing the epidemic of hypertension, diabetes and other cardiovascular diseases in the country is experiencing. There is a low level of awareness of hypertension and diabetes. In Africa, less than 30% of people living with hypertension are on biomedical treatment. Most people living with hypertension and diabetes are not on treatment because of limited access and cost of biomedical treatment. As a result, people living with NCDs healer shop which increases the risk of complications and mortality.

The most important imperative at the present time is to effectively blunt this growing epidemic of vascular disease. This epidemic of vascular disease is following the path characteristic of many other countries, with initial high rates of hypertension and vascular disease among the upper socioeconomic groups and then explosive epidemics of

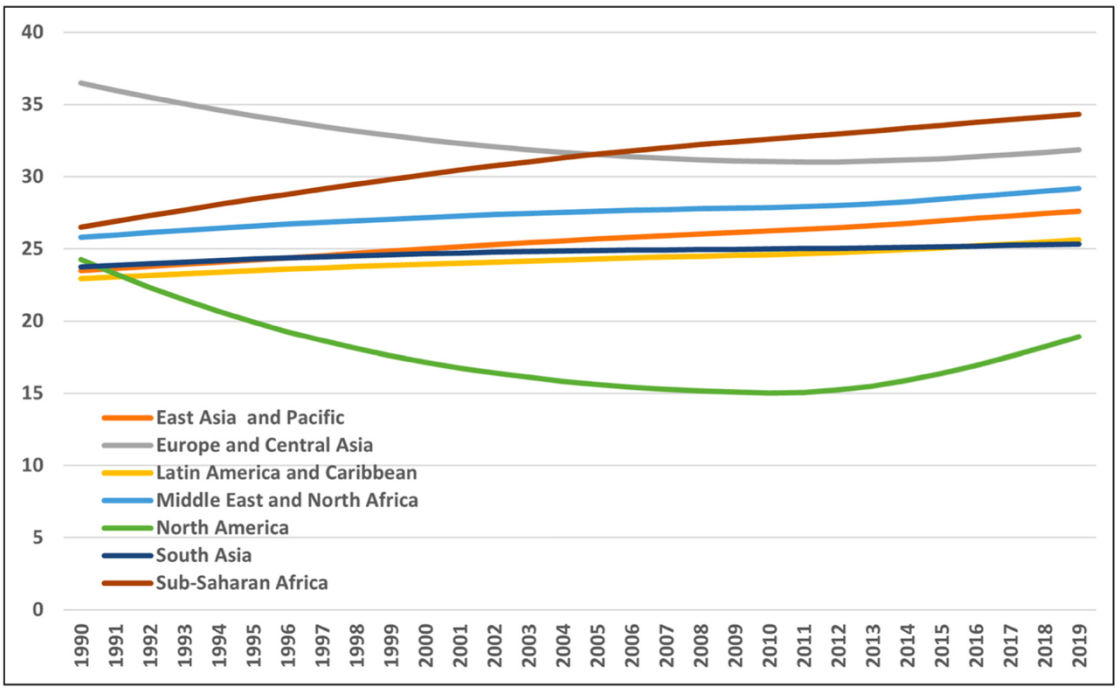
both hypertension and vascular disease among lower income populations.[12] The key variables that drive the epidemics are the greater use of processed foods, higher intake of calories, decreased physical activity leading to weight gain, and the reduction of foods high in potassium.

The epidemic, as noted, has begun in the upper social classes and in urban areas. Over time, the epidemic spreads to lower and rural socioeconomic groups. The increase in BP levels in the population is the primary concern. The risk of cardiovascular disease (CVD) is linearly related to BP levels and the increase in the average population BP levels will, over time, lead to an increase in stroke, kidney disease, and heart failure. The opportunity for successful public health primary prevention is greatly reduced by the time there is an obvious major epidemic of clinical CVD. Pharmacological and surgical therapies become the primary method of reducing the burden of disease, with substantial increasing cost and much greater disability.

The increasing prevalence of CVD, especially in the upper socioeconomic population, results in greater demand of high-cost health services in countries where the need for health services to deal with the problems of infectious diseases, malnutrition, pregnancy outcomes are in short supply. These high-cost health services for vascular disease shifts badly needed limited health resources from lower to upper socioeconomic groups. Increase in stroke, renal disease, and heart failure can also have a devastating impact on the better educated and potential national leaders and on the evolving political structures in these countries. This invisible epidemic is an under-appreciated cause of poverty and hinders the economic development of many countries.

1.4.3 Hypertension distribution

Elevated blood pressure is a leading preventable cause of CVD mortality and disease burden, globally and in most regions of the world. One of the global non-communicable diseases (NCD) target adopted by the World Health Assembly in 2013 is to lower the prevalence of raised blood pressure by 25% by 2025 compared with its 2010 level.[13]

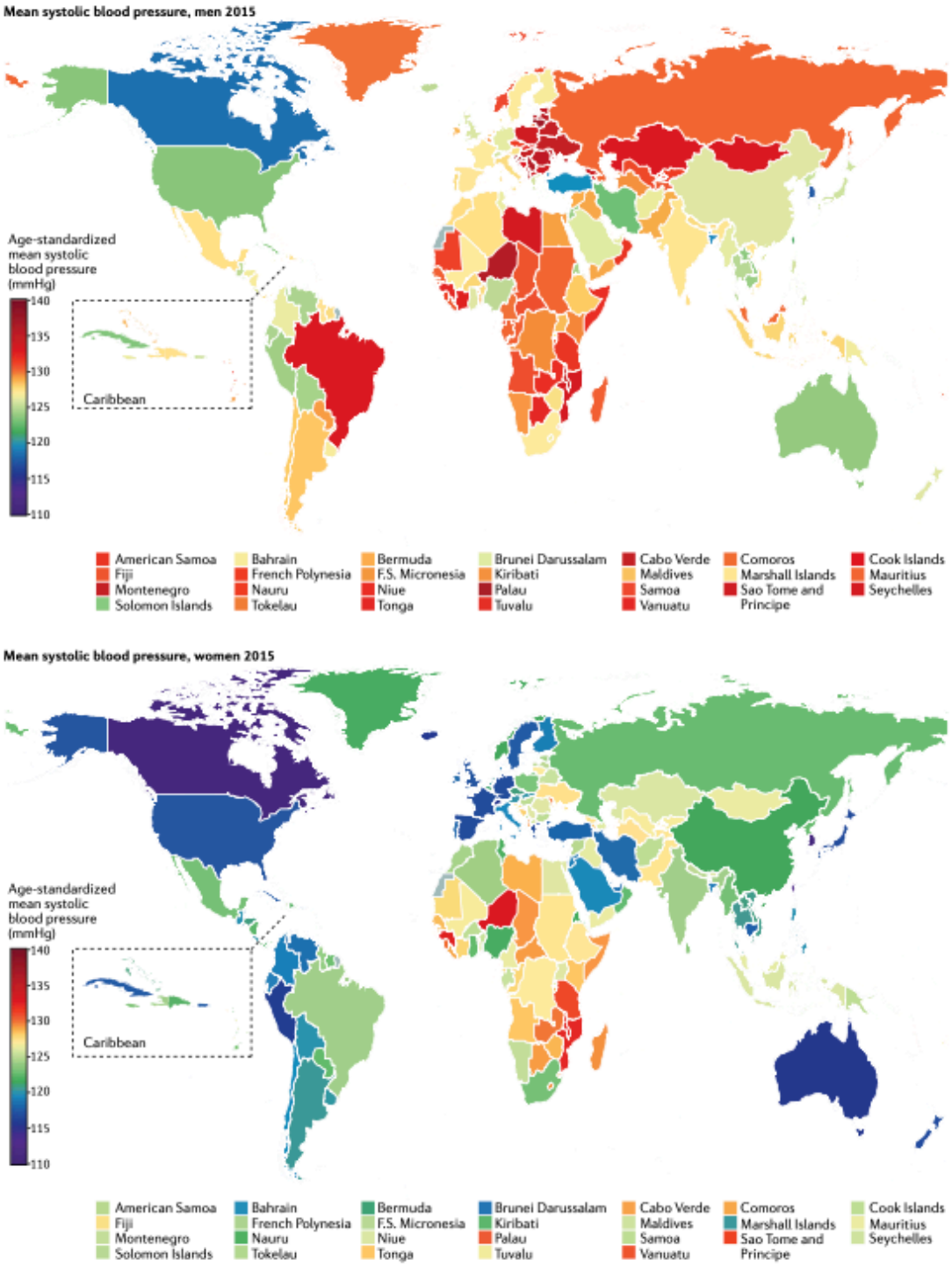


Trends in age-standardized summary exposure value of high systolic blood pressure, for the World Bank regions from 1990 to 2019.

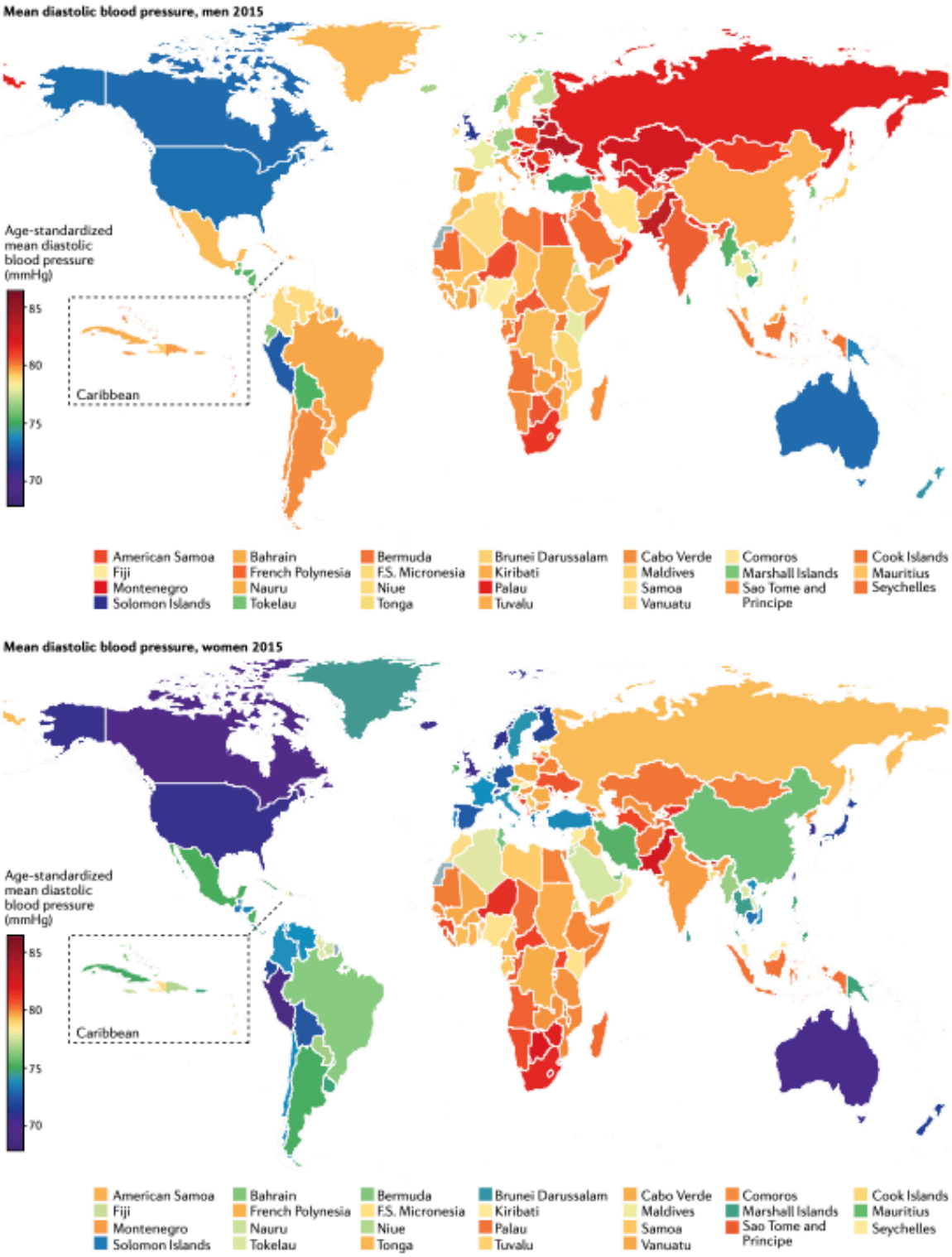
1.4.3.1 World

The global age standardized mean SBP in 2015 among men ≥18 years of age was 127.0 mmHg, largely unchanged since 1975. SBP declined slightly among women in the same period (from 123.9 mmHg to 122.3 mmHg). Trends in the age-standardized mean DBP, which was 78.7 mmHg for men and 76.7 mmHg for women in 2015, were similar. The age standardized prevalence of raised blood pressure declined globally in both sexes, from 29.5% to 24.1% among men and from 26.1% to 20.1% among women. Mean SBP and DBP declined substantially in the high income regions, from the highest in the world in 1975 to the lowest in 2015. The largest decline in mean SBP occurred in the high-income Asia Pacific region, by 3.2 mmHg and 2.4 mmHg per decade among women and men, respectively. The largest decline in mean DBP occurred in the high-income Western region: 1.8 mmHg per decade among women and 1.5 mmHg per decade among men. Mean SBP declined among women in Central and Eastern Europe, Latin America and the Caribbean and possibly in Central Asia, the Middle East and North Africa, albeit with larger uncertainty than in high income regions. Similarly, mean DBP decreased in women in these regions, but the reduction was smaller than in high-income regions. Men had little or no change in mean SBP or DBP in these regions. In contrast to these declines, mean SBP and DBP have risen among men and women in East, South and Southeast Asia,

Oceania and sub-Saharan Africa. The largest regional decrease in raised blood pressure was reported in the high-income regions, followed by Latin America and the Caribbean, Central and Eastern Europe, Central Asia, the Middle East and North Africa. Elsewhere, the age-standardized prevalence of raised blood pressure remained unchanged, despite rising mean blood pressure. South Korea and Canada had the lowest age standardized mean SBP in 2015 for both men (117–118 mmHg) and women (~111 mmHg). The highest mean SBPs in men were reported in countries in Central and Eastern Europe, Oceania, Central Asia and sub-Saharan Africa, with an age-standardized mean SBP reaching 137.5 mmHg (131.2–143.8 mmHg) in Slovenia. Women in countries in sub--Saharan Africa had the highest levels of mean SBP, surpassing 132 mmHg. Countries with the lowest mean DBP were Peru and several high-income countries, including Australia, Canada, New Zealand, Singapore and the UK. DBP was high throughout Central and Eastern Europe, South Asia and sub-Saharan Africa, with the age-standardized mean surpassing 85 mmHg in Lithuanian men. Australia, Canada, Peru, Singapore, South Korea, the UK and the USA had the lowest prevalence of raised blood pressure in 2015 for both sexes, with an age-standardized prevalence of <13% in women and <19% in men. At the other extreme, the age-standardized prevalence surpassed 35% among men in some countries in Central and Eastern Europe, including Croatia, Latvia, Lithuania, Hungary and Slovenia. The prevalence of raised blood pressure was >33% among women in some countries in West Africa.



Worldwide sistolic blood pressure. Age-standardized mean diastolic blood pressure by country in 2015.[1]



Worldwide diastolic blood pressure. Age-standardized mean diastolic blood pressure by country in 2015[1].

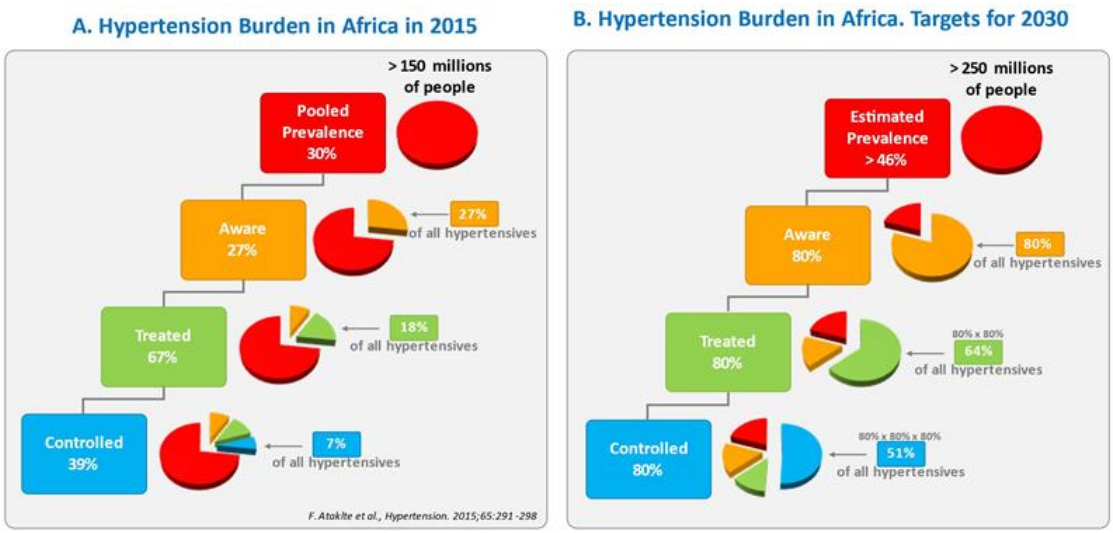
1.4.3.2 Africa[3]

In Africa, nearly half of those aged 25 years and above are hypertensive (>150 million adults), and an estimated 50 million adults have very substantively increased BP (>160/100 mmHg).
Hypertension prevalence significantly varies in different African countries. Africa now appears to have the highest prevalence of hypertension in the world, amounting to roughly 46% for both sexes combined in individuals over 25 years of age, with important regional differences. These differences in hypertension prevalence across regions may depend on different factors, such as methodological limitations of individual studies in terms of power and coverage, or real differences in hypertension mechanisms among different regions and between rural and urban settings. The latter include differences in age-adjusted prevalence of obesity as well as difference in socioeconomic, lifestyle, nutritional, and environmental risk factors, as well as in genetic factors. On such a complex background, the prevalence of hypertension in Africa has been estimated by separately considering the 140/90 mm Hg cut-off proposed by the ESC/ESH 2018 and the ISH 2020 hypertension guidelines, and the 130/80 mmHg cut-off proposed by the 2017 AHA/ACC Guidelines. In 21,512 individuals from different African countries, hypertension prevalence in males was 42.2% (41.3–43.1) and 58.2% (57.3–59.0), respectively, for the 140/90 and 130/80 mmHg cut-offs, while the corresponding figures were 41.8% (40.8–42.8) and 60.8% (59.8–61.8) in females. Thus, the burden of hypertension in Africa is substantially higher using the 2017 AHA/ACC BP cut-off as compared to the hypertension definition proposed by ESC/ESH and ISH guidelines. Moreover, hypertension prevalence in Africa is characterized by important regional differences and is significantly affected by sex-dependent differences, being significantly higher in women than in men.

Factor	Hypertension defined as ≥140/90 mm Hg n=21 512 Proportion (95% CI)	Hypertension defined as ≥130/80 mm Hg n=21 512 Proportion (95% CI)	P Value
Sex			
Male	42.2 (41.3–43.1)	58.2 (57.3–59.0)	<0.001
Female	41.8 (40.8–42.8)	60.8 (59.8–61.8)	<0.001
Age, mean ± SD	53.0 ± 11.2	51.1 ± 11.7	
<40 y	22.0 (20.7–23.4)	42.9 (41.4–44.6)	<0.001
40–44	29.5 (28.0–31.1)	49.1 (47.4–50.8)	<0.001
45–49	36.2 (34.6–37.8)	54.6 (52.9–56.2)	<0.001
50–54	44.6 (43.1–46.2)	62.5 (60.9–64.0)	<0.001
55–59	51.7 (50.1–53.4)	67.3 (65.7–68.8)	<0.001
60–64	65.9 (63.6–68.2)	76.9 (74.8–78.9)	<0.001
≥65	75.4 (73.3–77.3)	86.3 (84.6–87.8)	<0.001
Country			
Burkina Faso	16.4 (14.9–18.1)	30.7 (28.8–32.8)	<0.001
Cameroon	…	…	…
Ghana	45.9 (44.6–47.3)	60.7 (59.4–62.0)	<0.001
Guinea	…	…	…
Kenya	24.7 (22.9–26.5)	46.8 (44.8–48.8)	<0.001
Mozambique	34.1 (27.5–41.4)	53.9 (46.6–61.1)	<0.001
Namibia	25.0 (20.6–29.9)	45.5 (40.2–50.9)	<0.001
Nigeria	51.7 (50.3–53.1)	67.0 (65.7–68.4)	<0.001
South Africa	50.3 (48.9–51.6)	69.4 (68.2–70.6)	<0.001
Sudan	11.9 (7.8–17.9)	39.5 (32.4–47.1)	<0.001
Tanzania	…	…	…
Uganda	14.6 (10.4–19.9)	44.1 (37.6–50.9)	<0.001
Zambia	19.1 (14.4–24.8)	45.5 (39.0–52.0)	<0.001
Region			
East Africa	23.8 (22.2–25.5)	46.6 (44.6–48.5)	<0.001
Central Africa	…	…	…
North Africa	11.9 (7.82–17.9)	39.5 (32.4–47.1)	<0.001
Southern Africa	47.5 (46.3–48.7)	66.9 (65.8–68.1)	<0.001
Western Africa	43.3 (42.4–44.1)	58.2 (57.3–59.0)	<0.001
BMI (kg/m^2), mean ± SD	28.0 ± 17.2	27.4 ± 16.5	
Underweight (<18.5)	23.2 (21.3–25.1)	38.1 (35.9–40.3)	<0.001
Normal weight (18.5–24.9)	32.6 (31.6–33.5)	50.4 (49.4–51.4)	<0.001
Over weight (25.0–29.9)	50.1 (48.8–51.5)	68.5 (67.2–69.8)	<0.001
Obese (≥30)	60.0 (58.6–61.5)	76.6 (75.3–77.8)	<0.001
Overall crude proportion	42.0 (41.4–42.7)	59.3 (58.7–59.9)	<0.001
Age-adjusted proportion of hypertension	32.0 (30.9–33.0)	51.1 (49.6–52.5)	…

Differences in hypertension prevalence according to ESC/ESH and AHA/ACC cut-off.[14]

The higher prevalence of hypertension in urban areas compared with rural areas strongly implicates differences in lifestyle as an explanatory factor. Higher levels of obesity and increased salt and fat intake from consuming more processed foods and engaging in jobs with minimal physical activity are likely explanations for higher hypertension in urban populations. A systematic review and meta-analysis of 33 surveys involving 110 414 participants in Sub-Saharan Africa (SSA) with a mean age of 40 years showed that in 2015 average hypertension prevalence was 30% (27%-34%), varying widely across the studies and at different ages (range 15%-70%). Of those with hypertension, only 27% (23%-31%) were aware of their hypertensive status. Overall, about two-thirds of those diagnosed with hypertension were treated, accounting for 18% (14%-22%) of all hypertensive patients. Effective BP control was obtained only by 7% (5%-8%) of all individuals with hypertension.



Hypertension Burden in Africa in year 2015 and target changes proposed for year 2030.

SSA is among the regions of the world with lowest rates of hypertension detection, treatment and control and several countries in this region have seen little improvement in these outcomes over the past 30 years. Women have generally better detection, treatment, and control rates than men in both SSA and high-income countries. A possible explanation for higher detection among women is the increased chances of having blood pressure measured on contact with a health facility which usually occurs with pregnancy and related health conditions. Women probably accept more readily the diagnosis of hypertension even in the absence of symptoms and recognizing the need to stay healthy to support their families, are more willing to comply with treatment and get controlled. The generally low levels of detection, treatment, and control of hypertension reported emphasizes the difficulty in managing chronic health conditions that are usually not associated with symptoms and yet need lifelong management to ensure control. The need to change this situation is related to the high risk for disabling and life-threatening cardiovascular diseases (such as stroke) associated with hypertension also in Africa. In 2019 in North Africa high BP was the leading risk factor for death accounting for over a quarter (25.9%) of all deaths while it is the fourth leading risk factor accounting for more than 1 in 12 (8.8%) of deaths in Sub Saharan Africa. There were over 1 million cardiovascular deaths in Sub Saharan Africa in 2019. These findings emphasize the need for urgent implementation of appropriate strategies for hypertension diagnosis, control, and prevention.

1.5 Risk factors

1.5.1 Modifiable risk factors

1.5.1.1 Diet

Diet contributes to non-communicable diseases (NCDs) such as cancer, cardiovascular disease, and diabetes. Risk factors include diets low in fruits, vegetables, whole grains, nuts and seeds, fiber, milk, calcium, omega-3 oils, and polyunsaturated fatty acids; and high in sodium, red meat, processed meat, sweetened beverages, and trans fats.

Undernutrition – too little food – has long been a major concern in many low-income countries. Over the past 25 years, however, they are now facing the double burden of malnutrition which is characterized by the coexistence of undernutrition along with overweight, obesity or diet-related noncommunicable diseases (NCDs).

Body mass index (BMI) is a weight-to-height index commonly used to measure body fat. It is defined as a person's weight in kilograms divided by the square of his height in meters (kg/m^2).

Body Mass Index	***Classification***
< 18.5	Under Weight
18.5 - 24.9	Normal Weight
25 - 29.9	Over Weight
30.0 - 34.9	Obesity Class 1
35.0 - 39.9	Obesity Class 2
40 or above	Obesity Class 3

BMI ranges and classification.

Today, nearly one in three persons globally suffers from at least one form of malnutrition: wasting, stunting, vitamin and mineral deficiency, overweight or obesity and diet related NCDs. In 2014, approximately 462 million adults worldwide were underweight, while 1.9 billion were either overweight or obese. In 2016, an estimated 41 million children under the age of 5 years were overweight or obese, while 155 million were chronically undernourished. Nutrition-related factors contribute to approximately 45% of deaths in children aged under 5 years (mainly due to undernutrition), while low-

and middle-income countries are now witnessing a simultaneous rise in childhood overweight and obesity.

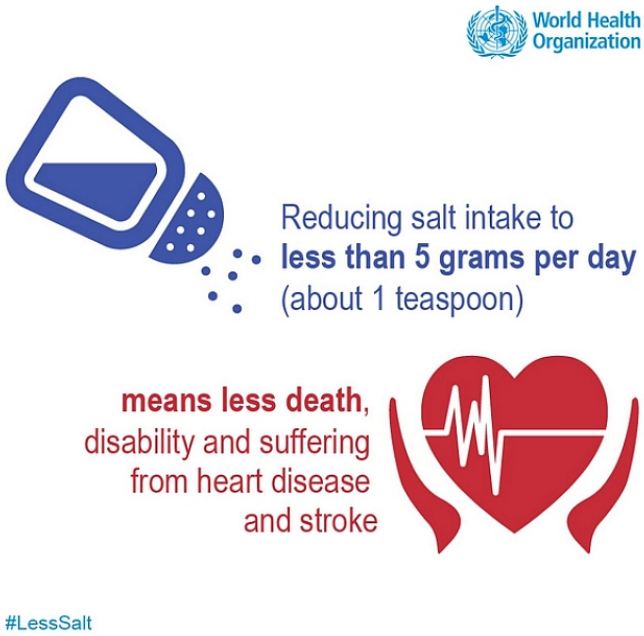
Nearly half of the world's 671 million obese population lives in 10 countries, of which 6 are LMICs. The causes of the double burden of malnutrition relate to a sequence of epidemiological changes known as the nutrition transition, the epidemiological transition, and the demographic transition. The nutrition transition describes the shift in dietary patterns, consumption and energy expenditure associated with economic development over time, often in the context of globalization and urbanization. [15]This change is associated with a shift from a predominance of undernutrition in populations to higher rates of overweight, obesity and NCDs. The epidemiological transition describes the changes in overall population disease burden associated with the increase in economic prosperity – with a shift from a predominance of infection and diseases related to undernutrition to rising rates of NCDs. Finally, the demographic transition describes the shift in population structure and lengthening lifespans. This sees a transformation from populations with high birth rates and death rates (related to the above transitions), with relatively high proportions of younger people, to populations with increasing proportions of older people (with age also being a risk factor for many NCDs).

In the last two centuries, these three processes have occurred slowly and in a near-linear fashion in most high-income countries. The nutrition transition, accompanied by and linked to the epidemiological and demographic transitions, has resulted in intergenerational, incremental, and controlled increases in population height and lifespans. The improved nutrition and higher caloric opportunity are associated with gradual increases in population health, but also a rise in overweight, obesity and NCDs. In low- and particularly middle-income countries, these processes have been accelerated – with the transitions described occurring over decades rather than centuries. This has resulted in intragenerational changes in diet quality and quantity for individuals and populations. This more rapid change has condensed these three transition processes, leading to a coexistence or overlap of overweight and undernutrition, or greater heterogeneity of nutritional status within populations. For example, this may result in obesity in individuals who experienced stunting as children, reflecting a changing food environment, diet and behaviors over interim decades; or obesity and micronutrient deficiency in a single household.

In general, the studies indicate that a double burden is not exclusive to urban areas and those with high income status, but also happens in rural areas and those with low-income status. Economic development, poverty, urbanization, and lifestyle changes are most suggested as reasons for this. This body of research is also pertinent to the developmental origins of adult disease (e.g. the Baker hypothesis, metabolic programming, thrifty phenotype, etc.), which helps explain the coexistence of high-prevalence undernutrition and obesity as well as lifestyle-related chronic diseases such as cardiovascular diseases and diabetes.

1.5.1.2 Salt intake

Excess sodium intake raises blood pressure, leading to hypertension, the principal preventable risk factor for stroke. Whereas ischemic heart disease predominates in high-income countries, stroke is the most important CVD in African countries. In 2005, 87 % of stroke death occurred in LMICs, rising to 94 % of stroke deaths in people under 70 years old.



The normal (physiological) requirement for sodium is likely to be between 0.1 and 1.0 g (2.5 g salt) daily. Recommended intake is less than 2.0 g sodium (5.0 g salt) for adults aged 16 and over, and this recommended maximum level of intake should be adjusted downwards in children ages 2-15 based on the energy requirements of children relative to those of adults.

Current global salt intakes are estimated at around 10 g/day. The sources of this dietary salt intake are split between salt from processed food and discretionary salt, which is salt that is added at home during cooking and at the table.

A meta-analysis reported that a reduction of ≈4.5 g of salt per day was associated with a decrease of 4.9 mm Hg of SBP and 2.7 mm Hg of diastolic BP among patients with

hypertension as compared with 2.0 and 1.0 mm Hg, respectively, among people with no hypertension. Food items like bread, meat and meat products, milk and dairy products, instant noodles, condiments, salted preserved foods, and bakery products contribute to high-salt diets in LMICs. Eating patterns are also changing in the African Region to less fruits, vegetables, and dietary fiber that are key components of a healthy diet. Fruits and vegetables contain potassium which is known to counter the negative effects of salt and contributes to reduced blood pressure.

In 2013, the World Health Assembly, the decision-making body of WHO agreed Global Action Plan for the Prevention and Control of Non-Communicable Diseases which encompasses nine global voluntary targets for the prevention and control of NCDs, which included a 30% relative reduction in the intake of salt by 2025.

1.5.1.3 Tobacco

Tobacco and hypertension are independent risk factors for CVD. Tobacco kills >8 million people a year, with the stark reality that over 80% of all tobacco users live in LMICs. With declining rates of tobacco consumption in HICs, the tobacco industry is shifting its focus to LMICs targeting the growing number of adolescents. So while tobacco consumption globally is decreasing, by 2025 the number of smokers in Africa is anticipated to rise by nearly 25 from 2010 levels. This is the largest expected increases in the world. Tobacco companies have strategically planned their expansion across Africa for over two decades, seeking to "aggressively and consistently" exploit these "profitable opportunities". To expand their consumer base, they target new prospective smokers in their promotional marketing, particularly women and younger groups. Over 80% of the 1.3 billion tobacco users worldwide live in low- and middle-income countries, where the burden of tobacco-related illness and death is heaviest. Tobacco use contributes to poverty by diverting household spending from basic needs such as food and shelter to tobacco.

The situation in Africa looks set to get worse. In 2013, about 77 million African adults smoked. If the tobacco industry is allowed to operate largely unregulated, this is expected to increase more than 7 times over to 572 million within the century. The economic, social, and public health ramifications of this growth would be unprecedented. It is not just public health that would suffer. The industry is responsible for up to 4% of

global deforestation - 12% in Southern Africa and, as of 2008, 600 million trees were being cut down to facilitate tobacco production every year. Tobacco leaf degrades the soil of more nutrients than many other crops, often making soil unviable to grow food essentials. Estimates suggest that if the land used to grow tobacco was instead used to cultivate food crops, 10-20 million people could be consistently fed.

In 2007, WHO introduced a practical, cost-effective way to scale up implementation of the main demand reduction provisions of the WHO FCTC on the ground: MPOWER.

The 6 MPOWER measures are:

- Monitor tobacco use and prevention policies
- Protect people from tobacco use
- Offer help to quit tobacco use
- Warn about the dangers of tobacco
- Enforce bans on tobacco advertising, promotion and sponsorship
- Raise taxes on tobacco.

1.5.1.4 Alcohol

Alcohol is one of the most frequently abused substances worldwide. Though the prevalence of current alcohol drinkers is high in HICs (67.3%) compared with upper middle (47.4%), lower middle (30.1%), and low-income (26.8%) countries, the prevalence of heavy episodic drinking is high in low-income (45.4%) and upper-middle-income (40.7%) and similar in lower-middle-income (37.7%) countries, as compared with HICs (38.7%).

The African Region is faced with a growing burden of harmful alcohol consumption and its disastrous effects. There is no other consumer product as widely available as alcohol that accounts for as much premature death and disability. Heart attacks, strokes and high blood pressure can develop from the harmful use of alcohol. Total alcohol per capita consumption in 2010 among male and female drinkers worldwide was on average 21.2 liters for males and 8.9 liters of pure alcohol for females.

WHO aims to reduce the health burden caused by the harmful use of alcohol and, thereby, to save lives, prevent injuries and diseases and improve the well-being of individuals, communities and society at large. In 2010, the Global Information System on Alcohol and Health (GISAH) has been developed by WHO to dynamically present data on levels and patterns of alcohol consumption, alcohol-attributable health and social consequences and policy responses at all levels. This resolution urges countries to strengthen national responses to public health problems caused by the harmful use of alcohol, calling to a 10% relative reduction in the harmful use of alcohol between 2013-2025.

1.5.1.5 Physical activity

Physical inactivity is one of the leading risk factors for NCDs. In the African Region, the prevalence of physical inactivity among adults is estimated at 22.1%. This corresponds to 223 million people who are at risk of developing. Furthermore, it is alarmingly high at 85.4% among in-school adolescents. Physical activity is a cost-effective intervention that is not effectively implemented by Member States in the African Region due to several challenges. Social, cultural and environmental barriers to physical activity include fear of violence and crime in outdoor areas, air pollution and cultural restrictions that particularly affect women and girls. Unplanned urbanization also limits the capacity of urban dwellers to adopt a more active lifestyle.

Physical inactivity and sedentary behavior are linked with several health conditions including cardiovascular diseases, cancers, diabetes, overweight, obesity and depression. Sedentary behavior is the lowest state of physical activity such as watching television or sitting at a desk. Physical inactivity is associated with 3.2 million deaths every year globally and over 200 000 deaths in the African Region. As physically inactive adults have a 20–30% increased risk of all-cause mortality, this represents over 55 million adults in the African Region being at increased risk of dying from conditions associated with physical inactivity.

In low-income countries, ownership of all three common household devices; a television, a car and a computer were associated with a 31% decrease in physical activity. With these economic transitions, eating patterns are shifting towards energy-dense, nutrient-poor diets, and sedentary behavior is spreading, contributing to increased rates

of overweight and obesity in urban settings. The rural populations who perform manual and labor-intensive occupational activities such as farming are more physically active than their urban counterparts who engage in more sedentary behavior.

The World Health Organization (WHO) has developed Global Action Plan for Physical Activity (GAPPA) 2018–2030: more active people for a healthier world, to guide Member States in the planning and implementation of physical activity interventions tailored to their specific needs and socioeconomic contexts. It has set targets and milestones to be achieved:

1) by 2022:

-80% of Member States have developed a national action plan on physical activity.

-80% of Member States have conducted a communications campaign to raise awareness on physical activity and its benefits.

2) by 2026:

-A 10% relative reduction in the prevalence of insufficient physical activity among adults aged over 18 years and adolescents aged 11–17 years.

3) by 2030:

-A 15% relative reduction in the prevalence of insufficient physical activity among adults aged over 18 years and adolescents aged 11–17 years.

1.5.2 Non-modifiable risk factors

1.5.2.1 Epithelial sodium channel and Baker hypothesis

The aldosterone sensitive ENaC is the final regulator for sodium balance in the kidney. Sodium reabsorption is determined by the number of ENaCs expressed on the internal cell surface of the collecting duct.[16] Under physiological circumstances, ENaC expression is promoted by aldosterone, and internalized and degraded by neural precursor cell expressed, developmentally downregulated 4 (NEDD4), an ubiquitin E3 ligase protein. Liddle's syndrome is caused by mutations of subunits of the epithelial sodium channel that result in increased sodium-channel activity in the distal renal tubule with excess sodium reabsorption, as NEDD4 is unable to bind and degrade the ENaC

effectively. ENaC is an attractive candidate gene in black people with primary hypertension as more common single-nucleotide polymorphisms (SNPs) may result in hypertension with the 'Liddle phenotype' of low-renin/low-aldosterone hypertension without causing overt Liddle syndrome. High blood pressure in these patients responds well to reduction of salt intake or to amiloride, which acts specifically to reduce the activity of the abnormal channels.

The clinical features of Liddle's syndrome overlap with those of some patients with essential hypertension. In particular, black patients with hypertension are known to be sensitive to changes in salt intake and have low plasma renin activity. Therefore, it is possible that this sodium-channel mutation in patients with essential hypertension could contribute to the rise in blood pressure by increasing renal tubular sodium reabsorption. Therefore, Baker et al. examined the frequency of the T594M point mutation, the most commonly identified sodium-channel mutation, to see if it occurred more frequently in hypertensive than in normotensive black people.

The association of SNPs in the ENaC with hypertension in blacks was first described by Baker et al. in London, who described an association with the T594M SNP of b-chain.[17] Indeed, in hypertensive individuals we found the plasma renin activity to be significantly lower in patients with the T594M variant than in individuals without the variant. This suggests that possession of the T594M variant is indeed associated with sodium retention and is consistent with a role for the T594M mutation in the development of high blood pressure. The effects of the T594M variant on blood pressure may be modulated by other genetic or environmental factors. The degree of suppression of aldosterone in response to increased sodium reabsorption in patients with the T594M variant may be one additional factor which determines the blood pressure in these patients. Therefore, according to Baker, the T594M variant may increase sodium-channel activity and could raise blood pressure in affected people by increasing renal tubular sodium reabsorption. These findings suggest that the T594M mutation could be the most common secondary cause of essential hypertension in black people identified to date.

1.5.2.2 Genes controlling the renin-angiotensin-aldosterone system

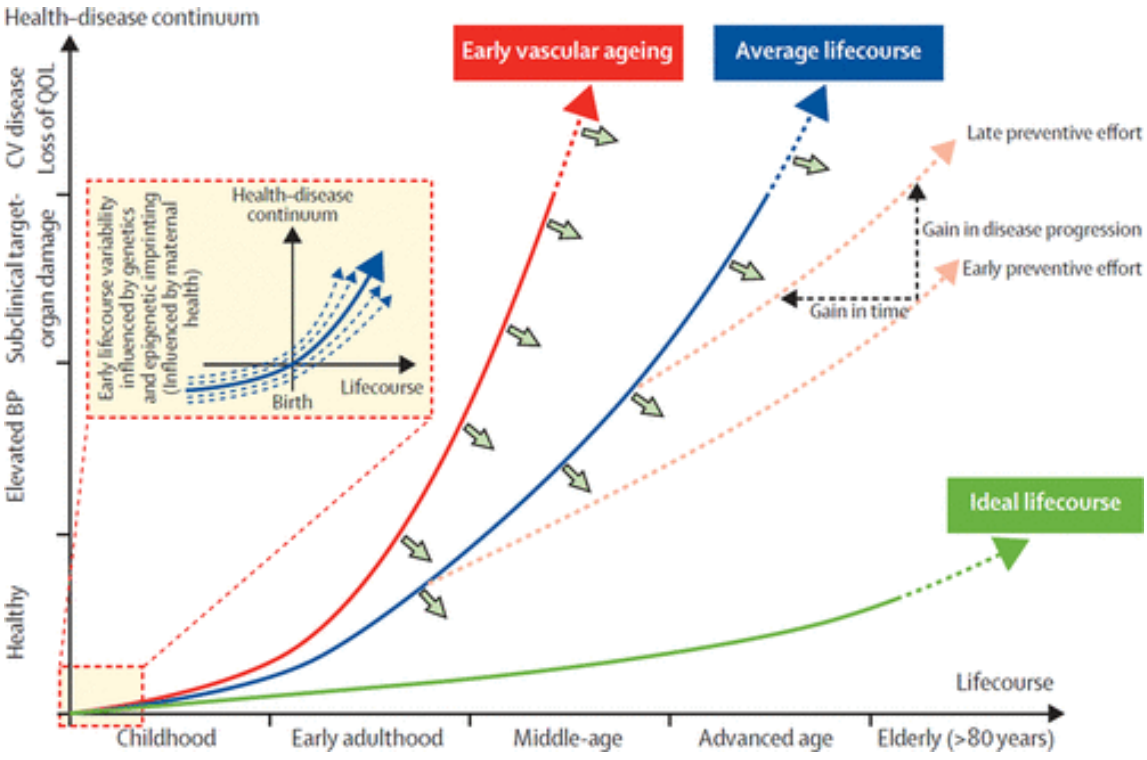
Although it is renin and not angiotensinogen that is normally thought to be rate limiting for the renin-angiotensin-aldosterone system (RAAS) and hence, the major

switch-on signal, abnormalities in the angiotensinogen gene may be important, especially in the presence of low plasma renin activity. Polymorphism of the aldosterone synthase gene, CYP11B2, is linked to a higher initial systolic BP in previously untreated black South Africans.

1.5.3 Emerging risk factors[18]

1.5.3.1 Low birth weight

Epidemiological studies have examined the association between low birth weight and adult BP. The global prevalence of low birth weight in 2015 was estimated to be 14.6% (12.4–17.1). The prevalence in Sub-Saharan Africa was slightly lower than the global estimate at 14.0% (12.2–17.2). Low birth weight affects kidney structure and function, is associated with an increase in large artery stiffness, a reduction in the size of the aorta, and an increase in aortic wall thickness, which may result in early vascular aging. There is a cyclical relationship between hypertension and endothelial dysfunction—worsening of one may lead to worsening of the other.



Early-life effects and preventive efforts across the life course to manage raised blood pressure (BP).

The mechanisms by which low birth weight affects BP are complex and involve nutrition, inflammation, glucocorticoids, and epigenetic changes. It is, therefore, of paramount importance to improve nutritional quality during the first 1000 days of life, spanning from pregnancy to approximately age two, as it has far-reaching effects for future cardiovascular and metabolic health, cognition, and socio-behavioral development. These putative risk factors, including low socioeconomic status, poor growth, shorter leg length, poor diet, and obesity, are strongly associated with chronic diseases in adult life and of increasing relevance in LMICs.

1.5.3.2 Stunting

Stunting is defined by an abnormally low height relative to a group of children of the same age and sex who have grown up under conditions that do not restrict growth. As conceptualized by UNICEF, the underlying causes are household food insecurity, inadequate care, poor sanitation, and lack of access to adequate health services. However, the true basic causes are poverty, unemployment, and limited access to all forms of capital, commonly conditioned by social, economic, and political contextual factors.

The concept that the intrauterine periods and the first 2 years of postnatal life are critical for preventing malnutrition; once stunting is established, the lost length typically persists unless there are substantial delays in bone age maturation. This is observed in selected specific nutritional deficiencies such as in zinc deficiency.

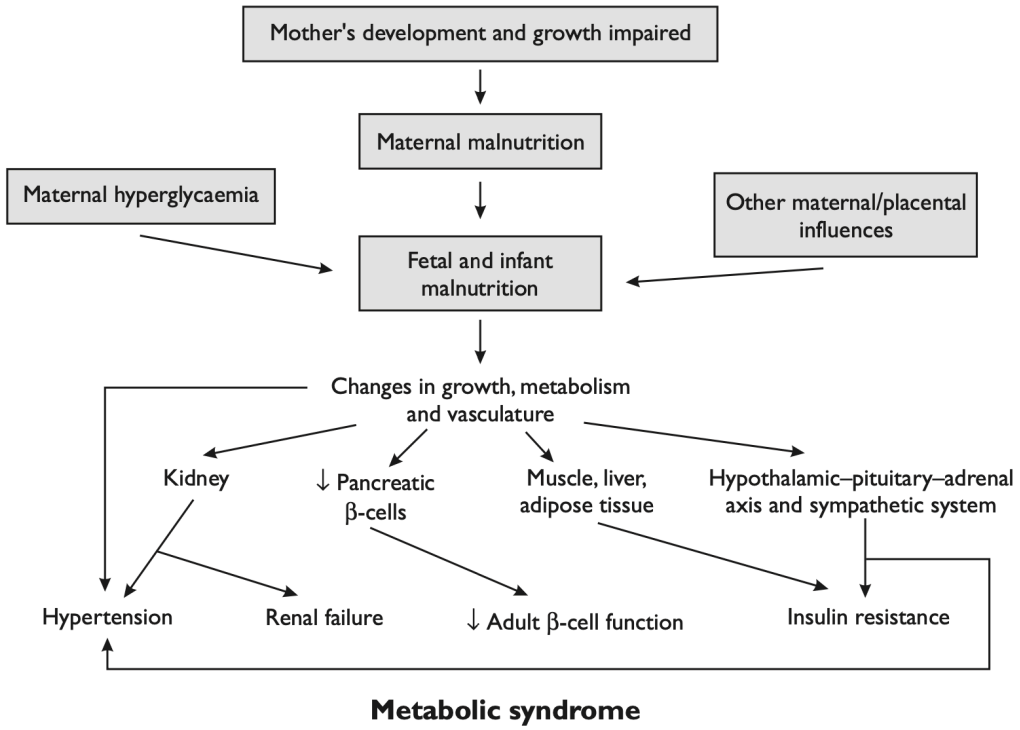
The effect of stunting is not only restricted to the first few years of life but extends throughout childhood and beyond. Stunting has been associated with lower school performance, poorer attention in class, greater grade repetition, higher drop out of school, and lower graduation rates likely due to the lack of stimulus from deprived environments as well as the persistence of functional and behavioral damages. Long-term consequences of stunting have been documented in terms of lower earnings and family income, which affect men and women. In terms of long-term body composition, birth length has been positively associated with attained adult height and fat-free mass. It has been suggested that stunted children would have a higher predisposition to develop obesity and metabolic complications later in life due to decreased energy expenditure.

Furthermore, it is likely that the detrimental effects of the nutrition transition in developing countries will be amplified due to this transgenerational transmission of risks. Altogether, these results emphasize the need to assess the consequences of stunting not only in early life but as part of a cumulative life-course perspective. Stunting may exacerbate poverty, perpetuating the vicious cycle as vulnerability to malnutrition and disease grows. From a population perspective, the evidence summarized here shows that stunting in early life has negative effects not only on children's health and educational performance but in the added burden of disease across the life course it imposes, affecting health expenditures and reducing overall productivity. Thus, the total cost of undernutrition is a function of higher health care spending, inefficiencies in education, and lower productivity.

1.5.3.3 DOHaD paradigm/Thrifty phenotype/Barker hypothesis

Over the past decades, a body of epidemiologic evidence has shown that early-life conditions influence patterns of growth, body composition, and later risk of noncommunicable chronic diseases (NCDs). Associations between low birth weight (considered a proxy of intrauterine and perinatal environmental conditions) and diabetes, elevated metabolic risk and blood pressure, and higher cardiovascular disease (CVD) risk and mortality were originally described in European countries in the 1950s but have been now replicated in almost all settings including those of developing countries.

The thrifty gene hypothesis, proposed by James V Neel in 1962, has been postulated to be a factor in promoting selective survival, over generations, of persons who encountered an adverse environment of limited nutritional resources. Hales and Barker later challenged this theory and proposed that the fetus which experiences suboptimal nutritional uptake during intrauterine development, may lead to reprogramming of fetal genes that subsequently alters fetal structure, function as well as metabolic changes. This hypothesis is called the FOAD (Fetal origin of adult disease) or thrifty phenotype or Barker's hypothesis or "developmental origins of adult health and disease" hypothesis (DOHAD)[19] .



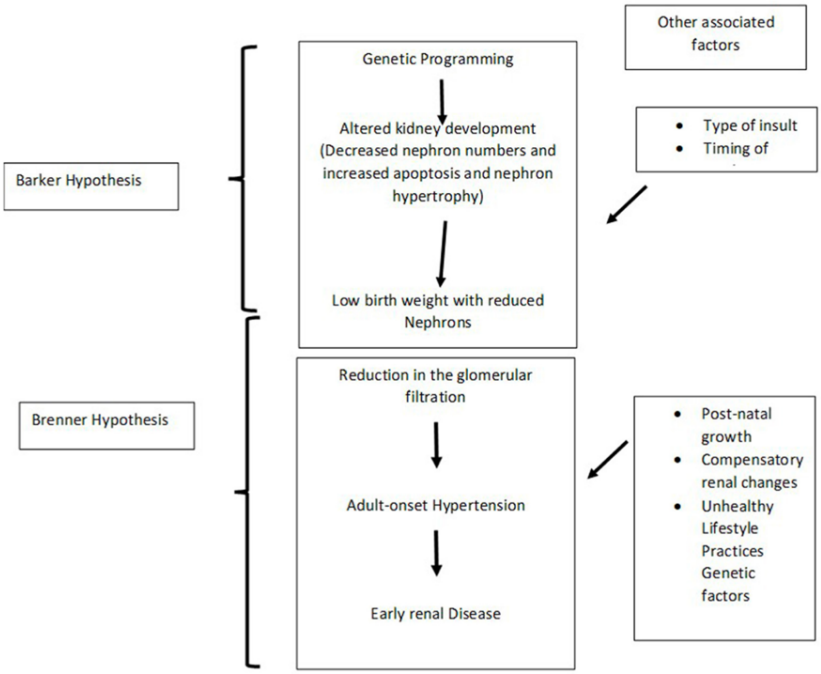
An updated diagram of the thrifty phenotype hypothesis.

The thrifty phenotype hypothesis proposes that the epidemiological associations between poor fetal and infant growth and the subsequent development of type 2 diabetes and the metabolic syndrome result from the effects of poor nutrition in early life, which produces permanent changes in glucose-insulin metabolism.[20] The central element is that poor fetal and infant nutrition are the insult that drives the process. World-wide, the most important cause of malnutrition in early life is maternal malnutrition (Barker hypothesis). However, other influences, maternal and placental, may also be involved in considering the downstream effects of poor fetal nutrition, poor development of pancreatic b-cell mass and function (including islet of Langerhans vasculature and possibly innervation) were key elements linking poor early nutrition to later type 2 diabetes. Fetal malnutrition led to insulin resistance and thereby set in train mechanisms of fetal nutritional thrift, which had a differential impact on the growth of different organs, with selective protection of brain growth. Altered growth permanently changes the structure and function of the body. A poor functional capacity for insulin secretion would not be detrimental to individuals who continued to be poorly nourished and remained thin and, therefore, insulin sensitive. Glucose intolerance would be triggered by a positive calorie balance because of increased

food intake and decreased energy expenditure leading to obesity. The combination of malnutrition during fetal life and infancy followed by overnutrition in childhood and adult life characterizes populations undergoing the transition from chronic malnutrition to adequate nutrition.

The famine in western Holland began abruptly in November 1944 and ended abruptly with the liberation of Holland in May 1945. Because of its brief duration, the Dutch famine provides information about the effects of fetal undernutrition at different stages of gestation. It seems that famine exposure in early gestation led to disturbance of lipid metabolism while in mid and late gestation it led to disturbance of glucose-insulin metabolism.

According to the FOAD hypothesis, a mismatch between fetal life and neonatal life leads thereby to an increased risk for cardiometabolic diseases.[21] Hence low birth weight, which is a surrogate marker of poor fetal growth, is linked to hypertension, diabetes, obesity, and insulin resistance. In addition, a disproportionate catch-up fat growth, in comparison with lean body mass, is one of the major driving factors for the development of cardiometabolic problems among adults with LBW.

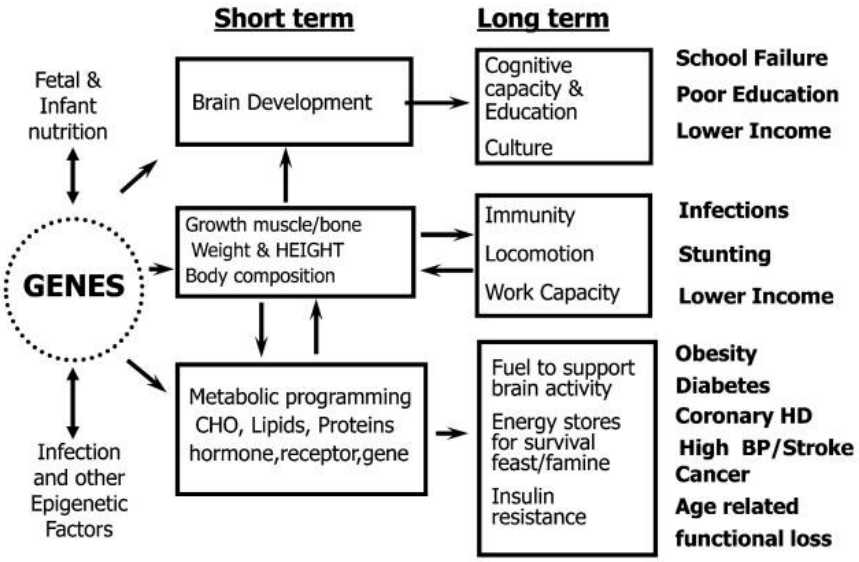


Integration of the Barker and Brenner hypothesis.

There are several mechanisms that have been proposed for the association between low birth weight and hypertension. One proposed mechanism was that an increased pressure in fetal circulation, as a compensatory mechanism in maintaining placental perfusion, might persist even after birth. Another mechanism that has been proposed: intrauterine growth retardation causing low birth weight may lead to accelerated postnatal growth and thereby, an accelerated rise in blood pressure. This was shown in both mothers with and without hypertension during pregnancy. A two-hit hypothesis explain the link between low birth weight and hypertension as due to the reduction in the number of nephrons and a subsequent decline in glomerular functions and a high intake of salt when compared to the western population. The reduced critical mass of nephrons imposes immense workload on the individual nephrons by increasing hyperfiltration. Furthermore, glomerular sclerosis in adult life causes nephron death, thereby initiating a vicious cycle and thereby resulting in end stage renal disease. Moreover, obesity increases renal filtration load, and the associated insulin resistance further augments the workload on the kidneys. Hence, the imbalance between the triad of low birth with progressive weight gain, reduced nephron mass and an increased load on the kidneys and its related sodium homeostasis induces an early onset hypertension in those born with LBW.

It has become increasingly apparent that the response to fetal malnutrition entrains not only (presumably advantageous) selective preservation of key organs but also metabolic adaptations of advantage for postnatal survival. Thus, the thrifty phenotype is not only thrifty with respect to antenatal life, but also in relation to the use of poor nutritional resources postnatally. The poorly nourished mother essentially gives the fetus a forecast of the nutritional environment into which it will be born. The adaptations only become detrimental when the postnatal environment differs from the mother's forecast, with an overabundance of nutrients and consequent obesity. This underlying susceptibility given by the "mismatch" between early and later environment may explain the earlier onset and higher severity observed in the presentation of NCDs in developing countries. Given that several developing countries are presently experiencing an important maternal obesity epidemic, which is associated with obesity and NCDs such as diabetes, blood pressure, and lipid disorders in offspring, and the potential for this transgenerational transmission of risk is of concern because it predicts a significant increase of obesity and NCDs for these countries in the near future.[19] Thus, it makes sense

to believe that the DOHaD paradigm applies more to the actual nutritional situation of developing countries in which patterns of the population's behaviors are rapidly changing than to that of developed countries in which changes have taken place at a slower pace.



Short- and long-term consequences of nutrition-gene-environment conditions in early life on relevant health and disease outcomes.

For instance, the salt-sensitive person whose forefathers thrived despite a limited supply of salt reacts to a salt-enriched diet with high blood pressure. Similarly, an insulin-resistant individual whose ancestors may have survived because a relative lack of insulin sensitivity in the skeletal muscle ensured adequate blood glucose levels for the brain in conditions of limited calorie intake and demanding physical challenges may now respond to a high-calorie diet and a sedentary lifestyle with varying degrees of glucose intolerance and hyperinsulinemia.

Therefore, differences in demographic profiles, environmental factors, early childhood programming influences as well as differences in gene frequency or expression can all contribute to variations in CVD between different populations. The challenge of preventing CV diseases lies in identifying and addressing the components most relevant to each community at their present and projected levels of the epidemiologic transition.

1.5.3.4 Exposure across life

A multitude of environmental, metabolic, and endocrine effects can cause IUGR (intrauterine growth-restriction) and SGA (small for gestational age). Recently, genes in

SGA infants, which are related to B cell development, metabolism, and obesity, were found to be hypomethylated compared to those in non-SGA infants. Thus, DNA methylation profiles may prove to be a useful diagnostic tool if epigenetic changes are indeed the key mechanism underlying DoHAD and the pathogenesis behind SGA.[22]

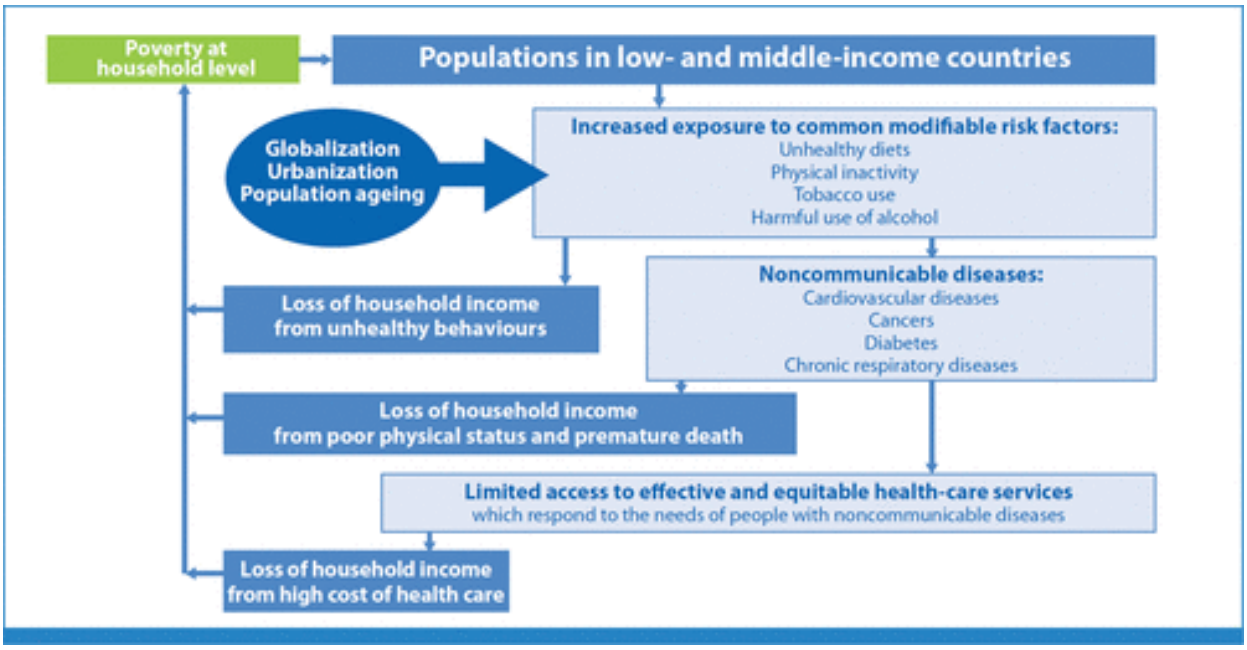
Every cell in the human body and in the developing embryo has a unique epigenome, which determines which genes are expressed and by how much. Epigenetic modifications encompassing the epigenome can be relatively stable while transmitting from one cell generation to the next. DNA methylation, histone modifications, genomic imprinting, chromatin remodeling, and non-coding RNA are all mechanisms for epigenetic modifications. Methylation to nucleotide bases at cis- acting elements, such as promoters or enhancers, cause DNA conformational changes that prevent the binding of trans-acting factors which initiate gene expression. Histone modifications can alter the charge differential between the histone tail and DNA double helix and, thus, change in chromatin compaction.

Excess or deficits in nutrients, hormones, or metabolites may trigger changes in DNA or histone methylation, which in turn suppresses or enhances gene expression; in addition, changes in small noncoding RNA activity act by modulating gene expression.

1.5.3.5 Environmental factors [23]

1.5.3.5.1 Social and commercial determinants of health

Social determinants include the causes of the causes of health inequality. These are the unequal conditions in which people are born, grow, live, work, and age. These unequal conditions depend on a person's socioeconomic status, sex, ethnicity, and disability. Social determinants influence the distribution of risk factors for hypertension, such as unhealthy diets, physical inactivity, and tobacco and alcohol consumption.[18]People in the low socioeconomic groups in LMICs are more likely to consume unhealthy diets and use tobacco and alcohol. People in poor neighborhoods are also more likely to be exposed to air pollution—an emerging risk factor for hypertension. Once diagnosed with hypertension, people with low socioeconomic status are less likely to afford out-of-pocket expenses for antihypertensive medication, leading to uncontrolled hypertension and early development of complications.



Relationship between poverty and noncommunicable diseases.

More recently, it has also been established that unhealthy behaviors are often influenced by commercial determinants of health, namely "strategies and approaches used by the private sector or select industries to promote products and choices that are detrimental to health." Large corporations selling unhealthy foods and tobacco often target consumers including children, public health professionals and organizations, researchers and research organizations, civil society, national governments, and even United Nations through their activities and earn profits at the expense of the health of individuals and societies.

1.5.3.5.2 Green space and pollution

Environmental factors such as green space (eg, the amount of tree canopy), pollution, and urbanization are strongly associated with raised BP. Between 2001 and 2018, LMICs have had the most extensive urban expansion and the highest urban population growth compared with HIC. Environmental pollution includes water, noise, light, and notably air pollution. Air pollution is 17× greater in cities of LMICs compared with that in North America and Europe. The prevalence of hypertension among people exposed to >30% green space was 1.9 percentage points lower compared with those who were exposed to 0% to 4% green space. The effect of green space on hypertension can be

explained by a multitude of factors including reduction in exposure to environmental stressors such as air pollution, heat, and noise.

Polluted air contains particulate matter of different sizes, of which $PM_{2.5}$ is particularly important. The particulate matter in the lungs leads to pulmonary oxidative stress and inflammation initiated by the release of cytokines, activated immune cells, and vasoactive molecules. The soluble constituents in the inhaled polluted air can cross the alveolar membrane reaching the bloodstream and directly affecting the vascular endothelium resulting in vasoconstriction and arterial stiffness. Particulate matter can also stimulate the autonomic nervous system resulting in sympathetic nervous system–mediated arterial vasoconstriction. Reducing the $PM_{2.5}$ level to recommended standards was estimated to potentially decrease the prevalence of hypertension by 15%.

1.5.3.5.3 Urbanization

With the rapid migration of vast populations from rural to urban areas in most LMICs, it is now clear that the confluence of several exposures accompanying urbanization is conducive to the rapid development of hypertension. Urbanization leads to a nutrition transition (consumption of foods high in fat, salt, and sugar and low in fruits and vegetables), a decrease in physical activity, adoption of a sedentary lifestyle, greater access to tobacco, alcohol, and other unhealthy substances, and exposure to an environment characterized by pollution (air, water, light, and noise), stress, and a lower number of green spaces. Understanding these pathways is essential to develop and implement interventions to prevent and curb hypertension development in this rapidly growing population.

In addition to increased migration of individuals from rural to urban areas, rural areas are themselves also being transformed.[6] For example, increased mechanization in agriculture and increased use of automobile and bus transportation in rural areas are leading to a decrease in physical activity. Concomitantly, global influences (via television or increased availability of processed food) on lifestyles perceived to be desirable or modern are changing the types of food consumed in both urban and rural areas.

Percentages of Individuals Living in Urban Settings in 1970 and 2025			
Region	**1970**	**1994**	**2025**
World	36.6	44.8	61.1
Developed countries	67.5	74.4	84.0
Economies in transition*	25.1	37.0	57.0
Developing countries	12.6	21.9	43.5
***Current term for Eastern Europe.**			

Therefore, variations in CVD rates between different parts of the world reflect interactions between genetic susceptibility and marked environmental changes usually secondary to urbanization, increasing affluence, and a range of other influences from early childhood to adulthood.

Percentage of individuals living in urban settings between 1970 and 2025.

1.5.3.5.4 HIV

Over the past 20 years, HIV has become a manageable chronic illness for people who can be tested and treated. Interventions such as antiretroviral therapies (ART), prophylaxis, and prevention of mother-to-child transmission have been successful.[24]

A relationship between higher systolic blood pressure and duration of HIV has been reported in HICs. In the Multicenter AIDS Cohort, Seaberg et al. noted that the odds of developing systolic hypertension among men followed between 1984 and 2003 was greatest after 5 years or more of ART (OR 1.7, 95% CI 1.34-2.16). The effect is greatest for protease inhibitor (PI) and non-nucleoside reverse transcriptase inhibitor (NNRTI) based regimens, but it may also be mediated through metabolic derangements.

The prevalence and severity of hypertension among HIV+ individuals in LMICs is only recently gaining attention. Studies from Kenya and Uganda describe hypertension prevalence rates between 11% and 28% among HIV+ individuals, and men are disproportionately affected. CD4 count is positively correlated with hypertension, especially among younger individuals. Clearly, there is a great need for prospective data to establish the relationship between hypertension, HIV infection, and ART in LMICs.

1.6 What to do [3]

1.6.1 Integrating chronic conditions care

In recent years there has been a sharp rise in the prevalence of diabetes and hypertension in Africa, where these two conditions account for around 2 million premature adult deaths annually. Despite the availability of effective treatments for diabetes and hypertension, only 10% to 20% of persons living with these conditions are under regular care, which is mainly due to lack of effective health care services, which emphasizes the need of approaches aimed at increasing access to health services for the management of diabetes and hypertension in Africa. This represents a major public health challenge in Africa, where health care is mainly organized to deal with acute infections, with limited experience in management of chronic diseases, except for HIV infection which requires long- term management. In Eastern and Southern Africa 83% of people affected by HIV infection are in regular care, with 90% of these virally suppressed. In fact, HIV- associated mortality has been markedly reduced from >2 million to less than half a million per year. Similar levels of retention and control should thus be achieved also for hypertension and diabetes, to obtain a significant reduction in mortality needed to meet the Sustainable Development Goals. One possible explanation for the success in fighting HIV is related to the early organization of HIV services in stand-alone clinics in most African countries as soon as effective antiretroviral drugs were made available. African health systems should consider re-organizing their services to manage hypertension and diabetes in a similar way. Managing multiple chronic conditions in the same clinics could optimize use of health care resources, allowing the application of what was learnt in HIV treatment programs to control hypertension and diabetes. There is some theoretical concern that integrating care of HIV with that of other chronic diseases might deter patients with diabetes and hypertension from seeking care due to fear of contact with patients affected by HIV infection or perceived to have HIV. In Tanzania and Uganda, Birungi et al conducted a cohort study (MOCCA [Management of Chronic Conditions in Africa]) to evaluate a program based on integrated care for HIV infection, diabetes, and hypertension in terms of feasibility, acceptability, retention, treatment and control of high BP and diabetes. Integrating care for HIV infection, diabetes and hypertension achieved high levels of retention for people living with diabetes or hypertension in Africa. This improvement was not at the expense of HIV control, as

retention in all 3 groups of people with single conditions was similar, and the proportion with an HIV viral suppression was close to 90%. Thus, the study suggests that an integrated approach could achieve excellent retention for diabetes and hypertension. Achievement of high retention rates improved BP and glycemia control. However, it still was associated with a high percentage of patients continuing to have uncontrolled BP and glycemia, in contrast to the situation with HIV for which most patients continued to have excellent control of viraemia. The importance of exploring the possible integration of HIV and hypertension management is related to the evidence that SSA is affected by the highest burden of infectious diseases worldwide, including 70% of global HIV burden. Antiretroviral therapy has led to the reduction in new HIV infections, a decrease in deaths due to HIV/AIDS, and dramatic improvement in the survival and quality of life among people living with HIV (PLWH). The importance of providing integrated care covering both HIV and noncommunicable diseases (NCDs), such as hypertension is emphasized as PLWH are at increased risk of NCDs, in particular CVD, and both HIV infection and antiretroviral therapy are involved in determining the increased prevalence of CVD among PLWH.

1.6.2 Salt consumption

Given that currently there are limited effective strategies and resources to screen and control hypertension in Africa and other LMICs, a major paradigm shift is required to reduce the burden of hypertension related death and disability at a population level. The way to this paradigm shift was clearly outlined by the 2017 Pan African Society of Cardiology roadmap to reduce the burden of hypertension in Africa but received very little political attention so far. Several acknowledged risk factors would need to be adequately managed also in Africa to face this situation, including unhealthy diet (with high salt and low fruit and vegetable intake), physical inactivity, tobacco and alcohol use, and obesity. Among the interventions to be implemented to reduce the burden of hypertension in African countries, a great emphasis must be given to salt reduction policies. Indeed, roughly 30% of hypertension prevalence can be associated to high dietary sodium worldwide. In addition, those of Black ancestry may have greater increases in BP when excess salt is consumed. This emphasizes the need of effective and early intervention in young people before permanent harm occurs.

1.6.3 Hypertension in pregnancy

Another important problem to face in relation to uncontrolled hypertension is the high mortality in child- bearing women due to preeclampsia. Maternal mortality is high in LMIC. SSA is the most affected region, with 66% of maternal deaths, with hypertensive disorders during pregnancy being identified as the second leading cause, after hemorrhage, of maternal and perinatal death, accounting for 14% and 27.1%, respectively. According to the World Health Organization (WHO), 16% of maternal deaths in SSA are attributable to hypertensive disorders during pregnancy, with preeclampsia and eclampsia being the leading causes. The incidence of preeclampsia ranges from 3% to 5% and can reach 10%, being higher in LMIC. Cardiovascular risk factors have been reported to be involved in the onset of preeclampsia. This may represent a problem in Africa, in particular in SSA, where women have been reported to be characterized by a high prevalence of cardiovascular risk factors. According to a review of available studies, the most prevalent ones are hypertension (29%), diabetes (7%), overweight (35%), obesity (11%), alcohol consumption (13%), tobacco (2%). Chronic hypertension can increase the risk of developing preeclampsia during pregnancy by 3- to 10-fold.

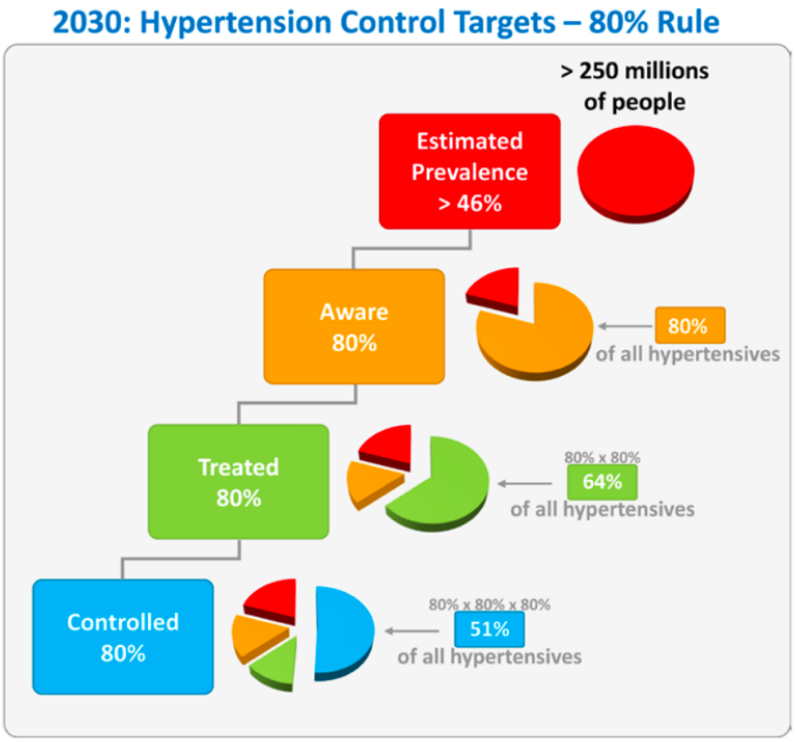
Facing this situation in Africa requires urgent implementation of several actions. These include: (1) extensive implementation of the WHO HEARTS technical package (made by modules spanning healthy-lifestyle counselling, evidence-based treatment protocols, access to essential medicines and technology, risk-based CVD management, team-based care, and Systems for monitoring); (2) engagement to aim at health-promoting environments through salt-reduction policies and sugar and alcohol tax; (3) implementation of cost-effective screening and simplified treatment protocols to over-come treatment inertia by physicians and poor patients' adherence to prescribed treatment; (4) decentralization of hypertension care of the primary health care systems and communities to increase the access to care, within a context of integrated care, while ensuring competencies to enhance care of conditions for which LMIC cannot afford to promote verticalized care.

1.6.4 WHL - Call to action

The recent call to action proposed by the World Hypertension League aims to stimulate all African countries to fight hypertension by adopting the proposed solutions and to achieve the following 3 goals in Africa by 2030:

1. Eighty percent of adults with high BP in Africa are diagnosed. This would mean an almost 3-fold improvement from current awareness rate and could be obtained though: (1) Expansion of the scope of practice, skill and capacity of community health workers, public health practitioners, nurses, and pharmacists and trained lay people to screen for, diagnose and treat hypertension. (2) Empowerment of all adults to take responsibility for their health and wellbeing, seeking for BP screening, treatment, and control and adopting healthy lifestyle under supervision and according to agreed protocols and referral systems. The final step in this direction is to have BP measured accurately and regularly in all adults in Africa.

2. Eighty percent of diagnosed hypertensives, that is, 64 % of all hypertensives, are treated. This would mean a 3.5-fold improvement from current rate. To achieve this ambitious target, countries should implement patient-friendly and health system-sustainable models of care, including task sharing and multi-month pills refills for stable patients. Prices of antihypertensive medicines can also be reduced through increased demand, local production, and quality control, consolidating treatment algorithms and price negotiations.



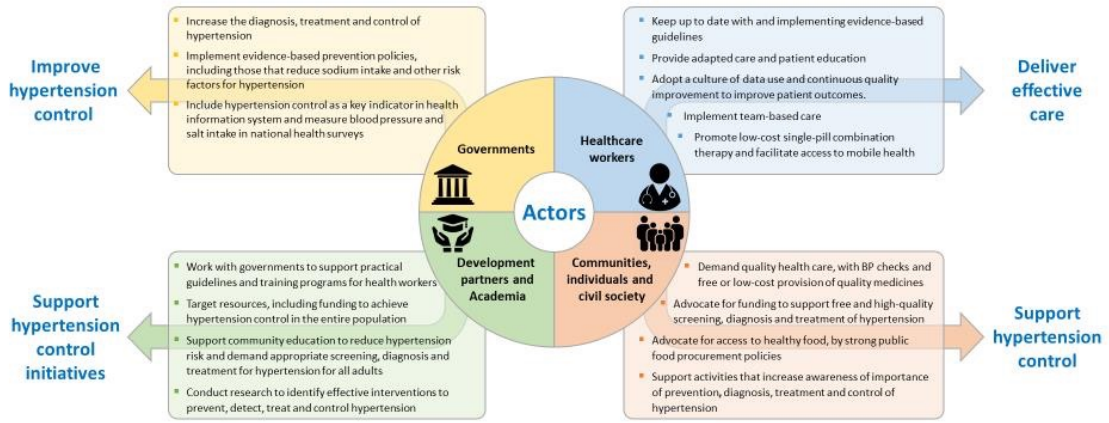
Target changes proposed for year 2030 by WHL.

3. Eighty percent of treated hypertensive patients, that is, 51.2% of all hypertensives, are controlled. This would mean a ≥7-fold improvement from current rate (7%).

As an intermediate step, by 2025 the current awareness, treatment and controlled rates are doubled. This would mean a shift from 27% to 54%, from 18% to 36%, and from 7% to 14%, respectively.

These very ambitious goals have been set in order to urge African countries to implement all necessary changes in health care management that might lead to an improved prevention and control of NCDs and to a quick reduction in the level of cardiovascular risk associated with hypertension.

The implementation plan is critical. To achieve the above listed aims, we thus call on individuals and organizations from government, private sector, health care and civil society in Africa, and indeed on all Africans, to undertake high priority actions to improve the detection, diagnosis, management, and control of hypertension, to be considered the leading preventable killer in Africa.



Specific actions to implement, to improve hypertension control in Africa.

1. Actions for African governments to improve hypertension control in their populations:

1.1 Increase the diagnosis, treatment, and control of hypertension. This should be achieved through the following actions:

(a) Adopt a robust national strategic plan for NCD that prioritizes and calls for resources for effective hypertension prevention and control. In this regard, politicians charged with prioritizing resource decisions related to malaria, HIV, or hunger due to poverty, should also address the silent killer, that is, hypertension, which is a major contributor to burden of illness in Africa.

(b) Issue appropriate orders and define health facilities reference staff, to ensure that BP measurement, diagnosis of hypertension, and management as per protocol is an essential service of primary health care and in ongoing programs such as HIV and tuberculosis. Allow nonphysician health providers with adequate education and training to diagnose and manage hypertension, under supervision and according to agreed referral systems.

(c) Ensure accurate measurement of BP at all routine adult clinic visits at all levels of health care and using all other opportunities such as markets, religious congregations, social events, vaccinations, political events, population census, elections etc, supported by massive awareness campaigns.

d) Develop and implement hypertension diagnosis and treatment guidelines by adopting the WHO's HEARTS package.

(e) Ensure all hypertension medicines included in national guidelines are on the national essential medicines list are procured from quality-assured providers and are available free of cost or at affordable cost, at all health facilities.

(f) Introduce regulations to ensure procurement of BP measurement devices that are validated for accuracy according to WHO recommendations.

(g) Integrate hypertension detection, treatment, and control within existing health services, such as HIV care or diabetes care units and indeed in all health facilities.

(h) Make care patient-friendly, by decentralizing care and treatment of stable patients to the primary care level and supporting visit spacing and extended drug refills for stable patients.

(i) Promote availability of low-cost single-pill combination therapy.

(j) Adopt strategies to improve access to care. Mobile-health, telehealth, decentralization of care to the bottom of health systems may be different options in different contexts.

1.2 Implement evidence-based prevention policies, including those that reduce sodium intake and other risk factors for hypertension, such as:

(a) Design and implement regulations requiring packaged foods to include easy-to- interpret front of package labeling, such as warning labels, that enable consumers to avoid foods high in sodium and other unhealthy ingredients.

(b) Adopt sodium targets for different categories of packaged food.

(c) Enact public food procurement policies to address dietary risk factors for hypertension and CVD, by establishing nutritional standards.

(d) Support public health awareness campaigns on salt intake reduction, including through mass media campaigns aimed at educating people not only to control the salt content in packaged food, but also to avoid adding too much salt during cooking in foods such rice and other staple foods and to increase use of low sodium salts (that have some of the sodium replaced by potassium).

(e) Scale up tobacco and alcohol control, following the WHO's MPOWER and SAFER frameworks.

(f) Promote physical activity, including provision of safe environments and incentives for exercise. Education on the favorable effects of regular physical exercise should be provided.

(g) Scale up obesity control across the life course through education, exercise, and diet.

(h) Establish intersectoral collaboration with the agricultural, food industry, educational and private sectors to control the food value chain and make healthy food avail- able at homes, schools, and at work.

1.3 Include hypertension control as a key indicator in health information system and measure BP and salt intake in national health surveys.

(a) Annually monitor and report the detection, treatment, and control rates of hypertension, with a clear target of improvement by 2025, and 2030 using the WHO stepwise surveillance approach in all countries and ensuring that health information systems are in place and. where applicable. that they are inclusive of NCD indicators, which are lacking in most LMICs.

(b) Initiate and fund national hypertension programs.

2. Actions for all African health care workers to deliver effective care:

(i) Keep up to date with and implement evidence- based screening, diagnosis, and treatment guidelines. In particular, health care providers should be taught the correct procedures for BP measurement in the office, at home and over the 24 hours as outlined in the American Heart Association/American College of Cardiology BP measurement guidelines and in the ESH Practice BP measurement guidelines. Implementing accurate BP measurements was also recommended by the Pan-African Society of Cardiology task force on hypertension which in 2018 published a roadmap for better hyper- tension control in Africa. Their practical recommendations for accurate BP measurement.

(ii) Provide patient-friendly and culturally adapted care and hypertension patient education and empowerment.

(iii) Adopt a culture of data use and continuous quality improvement to improve patient outcomes.

(iv) Implement team-based care and promote task shifting to lower levels of care.

(v) Promote availability of low-cost single-pill com- bination therapy and facilitate easier access to telehealth and mobile health.

(vi) Promote and standardize the role of pharma- cists in both measuring BP and in being part of the team providing hypertension treatment. This possibility deserves a special mention, given that in many regions of Africa, health facilities are often distant, difficult to reach and poorly resourced, while it is easier to find a pharmacy in every village.

3. Actions for African communities, individuals, and civil society to support hypertension control:

(i) Demand quality health care, including BP checks for at least for all adults at clinic visits and the free or low-cost provision of quality medicines to reach hypertension control. Communities should create demand for high quality hypertension services, favoring the organization of a supply and demand model for hypertension services in Africa. Moreover, given that most of the rural SSA population will not go to a clinic nor will be available for any other form of routine medical visits unless they are seriously sick, rural community based know your numbers of campaigns or outreach should be organized, with health care personnel going to the community door-to-door to measure BP, weight and other relevant clinical parameters, and providing training and education at the same time.

(ii) Advocate for adequate resourcing and funding (including from implementation partners, donors, insurance companies, etc) to support access to free and high-quality screening, diagnosis, and treatment of hypertension to all who need it.

(iii) Advocate for policies that support access to healthy food, such as strong public food procurement policies for schools, hospitals, and public workplaces.

(iv) Support activities that increase community awareness of the importance of sodium reduction and obesity prevention to prevent hyper- tension and the importance of early diagnosis, treatment and control of hypertension, and the disastrous consequences of uncontrolled hypertension. Given that rural adult population in SSA are not as well educated, health care officers should consider the possibility of using school going children as a means for education or outreach to their parents and grandparents.

(v) Support the diffusion of community-based organizations focused on hypertension, as done for HIV.

(vi) Provide feedback to government and health care workers as to the needs of the community and the quality of services provided

4.Actions for African development partners and academia to support hypertension control initiatives:

(i) Work with governments to support the design and implementation of simple, practical evidence-based policies, guidelines and programs, and regulated initiatives such as those on salt reduction, as well as courses and training and certification programs for health workers. Academic institutions and associated health care investigators should specifically play a major role in developing and or adapting guidelines balancing best evidence and local resources.

(ii) Target sustainable resources, including the proposal to have government officers in charge of health care management examine innovative funding platforms (e.g. taxation on unhealthy foods, alcohol, and tobacco) to achieve hypertension control in the entire population.

(iii) Support community education to enable individuals and communities to take action to reduce their hypertension risk and demand appropriate screening, diagnosis, and treatment for hypertension for all adults.

(iv) Conduct focused implementation research on hypertension to identify effective, scalable interventions to prevent, detect, treat, and control hypertension. This should be done also following the example of a few intervention trials specifically focused on the best treatment to be implement for black African patients.

(vi) Academia should also play an important role and collaborate with local governments in organizing education programs for health care personnel focused on hypertension. This should be done starting from the time of their initial training through the process of continuing medical education up to postdoc educational activities, with the aim to keep health care workers constantly updated on progress in knowledge. Also in this perspective, academia should collaborate with government in targeting resources to constantly promote continuous education programs.

1.7 Rwanda

1.7.1 Geography

Rwanda is located in central Africa, immediately south of the equator between latitude 1°4' and 2°51'S and longitude 28°63' and 30°54' E. It is a country of hills, mountains, forests, lakes, laughing children, markets of busy people, drummers, dancers, artisans, and craftsmen. Rwanda, also known as “Land of Thousand Hills”, manages to squeeze endless hills and 13 million people into a surface area of 26,338 square kilometers, being landlocked by Uganda to the north, Tanzania to the east, the Democratic Republic of the Congo to the west, and Burundi to the south. Rwanda forms part of the highlands of eastern and central Africa, with mountainous relief and an average elevation of 1,700 meters. However, there are three distinct geographical regions. Western and north-central Rwanda is made up of the mountains and foothills of the Congo-Nile Divide, the Virunga volcano range, and the northern highlands. This region is characterized by rugged mountains intercut by steep valleys, with elevations generally exceeding 2,000 meters. The divide itself rises to 3,000 meters at its highest point but is dwarfed by the volcano range, where the highest peak, Mount Karisimbi, reaches 4,507 meters. The Congo-Nile Divide slopes westward to Lake Kivu, which lies 1,460 meters above sea level in the Rift Valley trough.

Because of its elevation, Rwanda enjoys a temperate, sub-equatorial climate with average yearly temperatures around 18.5°C. The average annual rainfall is 1,250 millimeters, occurring over two rainy seasons of differing lengths that alternate with one long and one short dry season. Although Rwanda enjoys more or less constant temperatures, the climate is known to vary from year to year, with extreme variations in rainfall sometimes resulting in flooding or, more often, drought. These extremes have a profound impact on agricultural production.

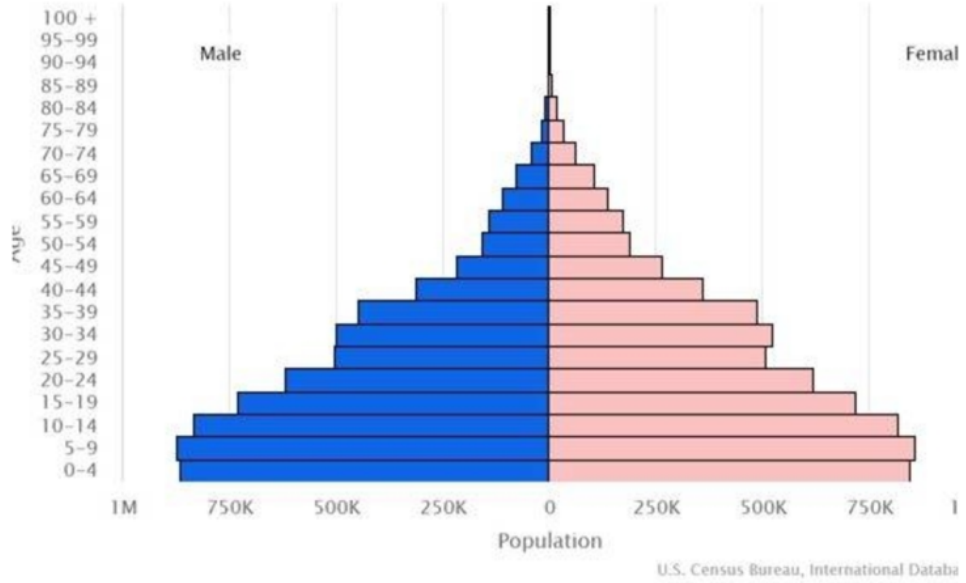
1.7.2 Population

Rwanda is divided into four geographically based provinces North, South, East, and West and the City of Kigali. The lower administrative areas consist of 30 districts, 416 sectors, 2,148 cells, and 14,837 villages.

Rwanda is one of the smallest but most densely populated countries in Africa. The population is still growing, from once 2.1 million in 1950 to 13.1 million in 2021. The population increased from 4,831,527 in 1978 to 7,157,551 in 1991 and 8,128,553 in 2002 before reaching the 2012 total of 10,515,973. Thus, the population more than doubled between 1978 and 2012.[25] The increase was essentially due to rapid population growth, which remains high despite the progressive decreases in the natural growth rate and the total fertility rate. In fact, according to census estimates, the natural growth rate was 2.6 percent between 2002 and 2012 and 3.1 percent between 1978 and 1991.

Population pyramid is wide at the base, narrowing rapidly as it reaches the upper age limits, an indication of a population with high fertility. Although the base of the pyramid (age 0-4) remains large, it is narrower than the bars for the age group 5-9. In

addition, there is a notable gender imbalance: there are 89 males for every 100 females in the total population.



Rwanda population distribution.

0-14 years: 39.95% (male 2,564,893/female 2,513,993)

15-24 years: 20.1% (male 1,280,948/female 1,273,853) 25-54 years: 33.06% (male 2,001,629/female 2,201,132)

55-64 years: 4.24% (male 241,462/female 298,163) 65 years and over: 2.65% (2020 est.) (male 134,648/female 201,710)

The shape of the pyramid gradually evolves over time based on fertility, mortality, and international migration trends.

The population is largely rural: according to the RPHC4, almost 84 percent of the country's residents live in rural areas. Among the total urban population, 49 percent live in City of Kigali, the capital of the country. Also, the population is essentially young, with 43.4 percent of all Rwandans under age 15 according to the RPHC4.

1.7.3 History

A Rwandan kingdom increasingly dominated the region from the mid-18th century onward, with the Tutsi monarchs gradually extending the power of the royal court

into peripheral areas and expanding their borders through military conquest. While the current ethnic labels Hutu and Tutsi predate colonial rule, their flexibility and importance have varied significantly over time. The majority Hutu and minority Tutsi have long shared a common language and culture, and intermarriage was not rare. The Rwandan royal court centered on the Tutsi king (mwami), who relied on an extensive hierarchy of political, cultural, and economic relationships that intertwined Rwanda's ethnic and social groups. Social categories became more rigid during the reign of Rwabugiri (1860-1895), who focused on aggressive expansion and solidifying Rwanda's bureaucratic structures. From 1895, an era of colonialism began, with the Germans being the first (1895-1916). During World War One, the country was occupied by Belgian troops, who in 1923 were granted by the League of Nations to govern Rwanda-Urundi. European explorers and missionaries frequently labelled Rwandan Tutsis as a "superior race natural born leaders". Colonial-era documents described Hutus as short, stocky, dark skinned and wide-nosed, as opposed to Tutsis, who were presented as tall, elegant, light-skinned and thin-nosed.

From 1922 until its independence in 1962, Rwanda was part of the Belgian colony Ruanda-Urundi (comprising present Rwanda and Burundi). In 1961 elections, the first government's Prime Minister was Grégoire Kayibanda, founder of the Parmehutu, a party for the emancipation of the Hutu. A year later, Rwanda gained independence, becoming a highly centralized, repressive state with a single-party system. The regime was characterized by the persecution and ethnic cleansing of Tutsis, excluding Tutsis from prominent careers and implementing education quotas. A Hutu Power ideology emerged, grounded in the Hamitic Hypothesis, in which Tutsi were recognized as foreigners to Rwanda, rather than an indigenous ethnic group. In addition to ethnic divisions, the Kayibanda regime created regional divisions which contributed to the coup d'état by Major General Juvénal Habyarimana in 1973. [26]Over 700,000 Tutsis were exiled from our country between 1959-1973 as a result of the ethnic cleansing encouraged by the Belgian colonialists. The refugees were prevented from returning, despite many peaceful efforts to do so. Some then joined the Rwandan Patriotic Front (RPF). The RPF were intent on re- establishing equal rights and the rule of law, as well as the opportunity for refugees to return. Among the new political parties, the opposition party Mouvement Démocratique Républicain (MDR) was formed. It had both extremist and moderate Hutu members, some of whom were later singled out for extreme violence.

Habyarimana's MRND was responsible for establishing the Interahamwe, a flamboyant and potentially dangerous Hutu youth militia that gained enormous popularity. Advocating Hutu Power and "Hutu-ness" at the expense of Tutsi lives, their message was reinforced and spread by an extremist media. By 1990 the genocidal ideology of Hutu Power had been perfected. On October 1, 1990, the Tutsi-led RPF launched its attack on Rwanda from Uganda, beginning the civil war. This fear was used to construct all Tutsis, regardless of their affiliation with the RPF, as enemies of the state. Tutsi in Rwanda began to suffer ever more intense waves of persecution from 1990. Tutsi men and women were jailed and tortured. Waves of massacres acted as a precursor to the genocide. The persecution, though barely recognized by the outside world, was an early indication of what was to come.

A cease-fire was negotiated and signed between Habyarimana and the RPF in July 1992 from which came an agreement. In 1993, the Rwandan Government and RPF signed an agreement known as the Arusha Peace Accords. Rwanda was to have a transitional government leading to a democratically elected government. Habyarimana and his political allies did not want the Arusha Accords to work. The transitional government was not established. Habyarimana and his extremist allies saw it as surrender to the RPF.

On the 6th of April of 1994, President Juvenal Habyarimana and President Cyrien Ntaryamira of Burundi were flying into Kigali, when at 20:23 the plane was shot down on its approach to Kigali airport. The assassination was blamed on the Tutsi minority. By 21:15 roadblocks had been constructed throughout Kigali and houses were being searched. Shooting began to be heard within an hour. Genocide was instant. Roadblocks sprang up right across the city with militia armed with one intent to identify and kill Tutsi. At the same time, Interahamwe began house-to-house searches. The people in the death lists were the first to be visited and slaughtered in their own homes.

After mid-May, the killings began to slow. The RPF gradually took back significant parts of the country, and by July, the RPF pushed the sitting government out of the country. As the RPF began to move in on Kigali and engage the Rwandan army in an attempt to gain control and stop the genocide, the crisis was described as 'civil war' or 'ethnic strife' by commentators. There was no ethnic war. On 4th July 1994, Kigali fell to the RPF. The RPF forced the Hutu army and militias into the Democratic Republic of Congo. As a result, the genocide and civil war ended in mid-July.

The genocide resulted in the deaths of over a million people. But death was not its only outcome. Tens of thousands of people had been tortured, mutilated, and raped, tens of thousands more suffered machete cuts, bullet wounds, infection, and starvation. There was rampant lawlessness, looting and chaos. The infrastructure had been destroyed, the ability to govern dismantled. Homes had been demolished, belonging stolen. There were over 300,000 orphans and over 85,000 children who were heads of their household, with younger siblings and/or relatives.

As the genocide neared its end, chaos reigned across the country. People were fleeing for different reasons. Perpetrators were on the move to avoid capture by advancing RPF troops. Victims were on the move towards RPF-liberated zones. Large numbers of Hutus fled across Rwanda's borders in fear of revenge killings. Refugee camps were set up in Burundi, Tanzania, Uganda and Zaire. The number of refugees was over 2,000,000. It was estimated that over two thirds of the population of Rwanda was displaced, fleeing out of guilt, fear, or confusion, or held hostage.

The International Criminal Tribunal for Rwanda (ICTR), based in Arusha, Tanzania, was established by the UN Security Council in its Resolution 955 of November 8th, 1994, to prosecute high-level organizers of the genocide. After nineteen years the Tribunal had completed 75 cases with 12 acquittals and 16 cases pending appeal. In other countries, genocide suspects are being prosecuted under the principles of universal

jurisdiction. Some accused are being returned to Rwanda for trial. Many suspected perpetrators, however, remain free in their host countries.

After serious deliberation, the government initiated Gacaca (meaning 'grass'), a community restorative justice system which evolved from a mix of traditional and modern approaches. Officially launched in 2002, Gacaca brought together survivors, perpetrators and witnesses before locally chosen judges to establish truth about what happened in the genocide and to determine consequences for perpetrators. Over ten years, more than 1.9 million cases - including 1,200 alleged genocide organizers, instigators, and supervisors – were tried in over 12,000 community-based courts.

After the Genocide, the RPF organized a coalition government similar to that established by President Juvénal Habyarimana in 1992. The Broad-Based Government of National Unity's fundamental law is based on a combination of the constitution, the Arusha accords, and political declarations by the parties. The MRND party was outlawed.

In 2000, Vice President Kagame ousted President Bizimungu, a Hutu. He took over the presidency disregarding the transitional constitution. Rwanda held its first post-genocide presidential and legislative elections in August and September 2003. Paul Kagame (leader of the RPF) received 95% of the vote in the national election which had a voter turnout of 96%. The Coalition, which includes the RPF, received 73% of the vote, formalizing President Paul Kagame's de facto role as head of government. This and the involvement in the eastern DRC drew growing ire from major international supporters and donors. To reassure these critics, but also to gain legitimacy among its citizens, the government decided to customize the constitution and to elaborate a vision of its socioeconomic future. Kagame won reelection in 2010, and again in 2017 after changing the constitution to allow him to run for a third term, which will run through to 2024.

1.7.4 Genocide aftermath

The government that took power in July 1994 faced enormous challenges. Government coffers had been emptied, ministries had been sacked, and vehicles stolen or destroyed. The economy was at a standstill, and the country's human capital had been devastated. Many of Rwanda's surviving trained personnel had fled the country and feared returning. Survivors of the genocide were destitute and traumatized. [27]

The genocide decimated healthcare infrastructure such as hospitals, clinics and laboratories and generated a mass exodus of skilled medical personnel. Erratic power supply compromised blood safety, data management and drug storage. Nearly 80% of physicians had either been killed or had fled the country. Those who remained were so traumatized, they were in no position to care for others.

During the first two years after the genocide, 800,000 former Rwandan exiles, mostly Tutsi, returned to Rwanda from neighboring countries (Uganda, Burundi, Tanzania, and Zaire), and from Europe, North America, and elsewhere in Africa. Settling mainly in Rwanda's two main cities, Kigali and Butare, and in areas in the east (Kibungo, Byumba, and the new prefecture of Umutara), these returnees frequently occupied houses left empty by owners who died or fled to other parts of Rwanda or to refugee camps in neighboring countries.

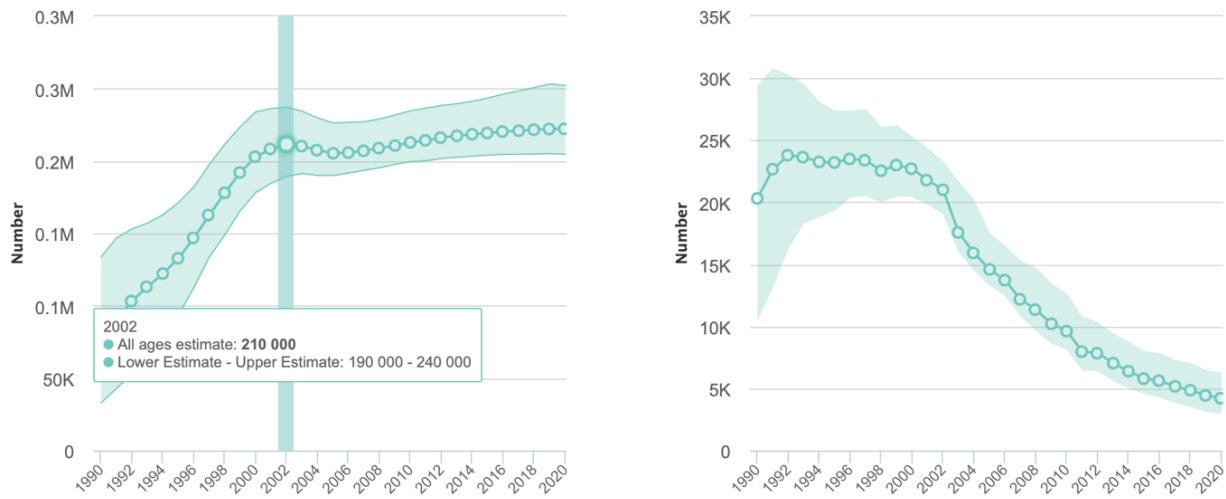
During November and December 1996, close to half a million Hutu refugees, who had fled during or after the genocide, returned to Rwanda en masse from Zaire, with smaller numbers returning gradually in subsequent months.

1.7.4.1 HIV weaponization

Rape was systematically used as a genocidal weapon against the Tutsis, with an esteem of 250000 to 500000 of victims. It is generally admitted that perpetrators intentionally infect their victims with the diseases, which in turn makes diseases like HIV and AIDS their own weapons of war. A study in 2001 revealed that 70% of rape survivors from the Rwandan genocide were HIV-positive. [28]Transmission of the virus spread with millions of people fleeing for refuge in and out of Rwanda in the years that followed the genocide, making it difficult for authorities to detect and control the spread of new infections.

Sexual violence during war creates multi-fold challenges for survivors: shame and stigma, psychological trauma, and access to medical treatment. Several women began to show signs of the disease between 1999 and 2002, which is consistent with the time for HIV to lead to AIDS, estimated between three and 10 years.

While immediate health priorities were focused on providing food, clean water, and treating sicknesses such as diarrhea and malaria, President Paul Kagame in 2000 recognized that curbing the spread of the virus was a national priority. Supported by donor funding, screening and treatment centers were established across the country, providing free access to anti-retroviral drugs to all patients. According to UNAIDS, new HIV infections in Rwanda dropped by 20% between 2010 and 2017 from 9,300 to 7,400. AIDS-related deaths almost halved in the same period, from 6,000 to 3,100, largely due to the provision of medication.



AIDS-related deaths and coverage of people receiving ART

1.7.4.1.1. Metabolic consequences of HIV treatment

Body composition and metabolic abnormalities associated with body fat redistribution (BFR) (central adiposity and/or peripheral lipoatrophy), glucose and lipid abnormalities, and hypertension have been reported in approximately 20–60% of HIV-positive (HIV^+) patients receiving highly active antiretroviral therapy (HAART).[29] Although treatment with potent HAART has improved the morbidity rate and well-being of HIV^+ patients accessing these therapies, HAART-and HIV-related complications have been associated with increased cardiovascular disease (CVD) and diabetes risks. Framingham risk equations suggest increased risk for myocardial infarction and greater than a 20% increase in 10-year CVD risk in HIV^+ patients receiving HAART compared

to age-matched controls. Therefore HAART-treated HIV-infected patients represent an emerging population with increased risk for CVD and diabetes.

As HAART becomes more accessible to HIV-infected people in resource-limited regions of the world, and their quality of life improves, the challenge is how to manage HIV- and HAART-related metabolic syndromes. Subsequently, there is a growing concern that CVD and diabetes risks, the main causes of morbidity and mortality in the developed world, may emerge, along with infectious diseases, as significant health concerns in HIV^{+} individuals in sub-Saharan countries.

1.7.4.2 Orphanage

During the 1994 war, Rwandan children — both Tutsi and Hutu — experienced severe and traumatic losses for which they lacked the life experiences and skills to cope adequately. Many such children observed violent events, witnessed the death of family members and friends, lost their homes and material possessions, or were displaced to other locations within and outside the country.

By the end of the war, many children had become orphans. In subsequent years, many other children became orphans when their parents died from war wounds, from ongoing rebel insurgencies, or from diseases, including AIDS.

In 1999, there were about 270,000 orphans in Rwanda. Since then, it has been estimated that at least 45,000 households in Rwanda are headed by orphaned children; it is further estimated that about 90 per cent of these households are headed by orphaned girls.

1.7.4.3 Food scarcity

In 1999, five years after the genocide, the World Bank estimated that 70 percent of the population in Rwanda was living below the poverty line.[30] Housing remains a serious problem. An estimated 300,000 people, many of them women, still need housing.

Without sufficient land, rural mothers heading a household with small children could not hope to provide the basics for the children. Food insecurity was an immediate

issue.[31] WFP set out to assess food needs and the Consultative Group on International Agricultural Research (CGIAR) launched the 'Seeeds of Hope' rescue plan.

Agricultural biodiversity, one of Rwanda's most important economic resources, is linked to topography; linked to the fact that the country's food growing are as range from the (cooler) high altitude zones in the West to the (warmer) low altitude zones in the east.

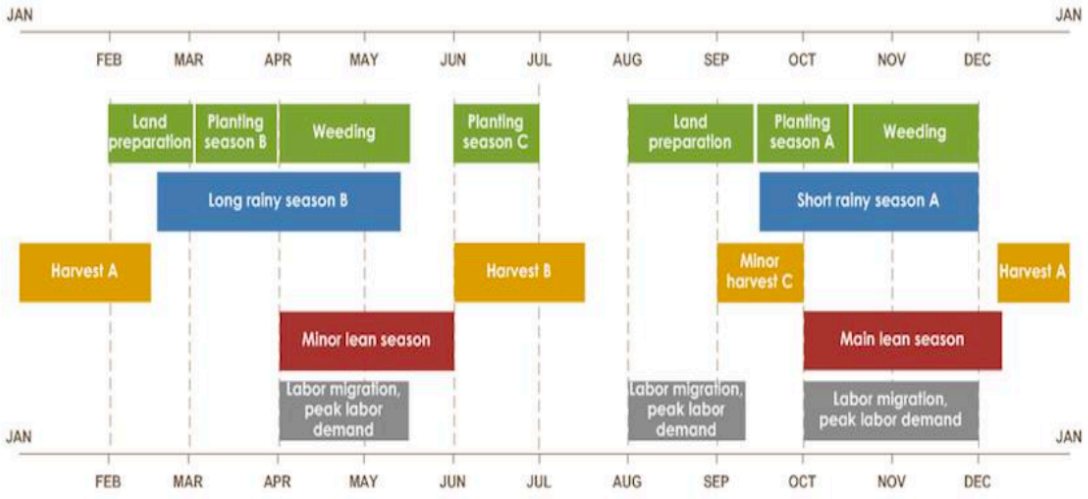
Rwanda has three growing seasons:

-season A, from September to January. Beans, sorghum (at high altitude) and maize are the main crops

-season B, from February to July. Sorghum (grown at mid- and low-altitude) is the main crop but beans and maize are also prominent.

-season C, from July to September. Although this is the dry season, cultivation in the low-lands and valley bottoms is possible, especially for sweet potatoes.

Root and tuber crops (sweet potato, potato, cassava, taro/Colocasia) are cultivated year-round.[32]



Seasonal calendar.

Harvest and seed losses, for beans as well as sorghum, feature prominently in reports on the agricultural devastation after 1994. Not only were about half the farmers away from home, but there was also a tremendous shortage of seeds and tools. The lost seeds, animals, and tools had to be replaced; the lost farmers, where they were still alive, had to return from the refugee or IDP camps. The return of the refugees was essential for revitalizing the agricultural sector. Throughout August 1994, there were reports of near-

total harvest failure, anarchy, and devastation. Virtually, all of Rwanda's seed supply has been eaten by famished citizens or destroyed during the fighting.

According to the WF, prices of beans and cereals have more than doubled since the beginning of the year, reflecting more the scarcity of supplies than strong effective demand. In the case of roots and tubers, prices had increased by more than 200 percent, also reflecting the preference for cheap sources of food. Other evident indicators of the food difficulties faced by the population were the low prices of livestock, that farmers sell to obtain resources to buy food, and the widespread evidence of premature harvesting of roots and tubers.

The famine was averted in the aftermath of the war and genocide had much to do with the international 'seeds of hope' effort, but also through the efforts of the people of Rwanda themselves and through efforts by the RPF who, aided by UNICEF and the Catholic Relief Service CRS, mobilized the population for the purpose of harvesting and planting. Farmers' individual effort to procure the right seed for their farms went unrecorded yet contributed in no small way to the aversion of famine conditions. Farmers had been resilient and resourceful, knowing full well how to get by under difficult circumstances.

1.7.4.4 PTSD

Post-Traumatic Stress Disorder (PTSD) is defined as a mental illness that people develop after experiencing a life-threatening event, like combat, a natural disaster, a car accident, or sexual assault. PTSD is mainly characterized by flashbacks, nightmares, avoidance, numbing and hyper-vigilance. It originates from the maladaptive persistence of appropriate and adaptive responses, which occur during traumatic stress, and therefore a variety of reactions may be observed after major trauma. The 1994 genocide against ethnic Tutsi resulted in a substantial burden of mental health disorders including PTSD in the Rwandan population, especially among genocide survivors.

The clinical manifestations of PTSD may reflect enduring changes in the stress-related neurobiological structures and systems. Indeed, changes in the activity of the hypothalamus-pituitary-adrenal (HPA) axis, the main stress regulatory system, are

induced by exposure to severe stressors and dysfunction of the HPA axis activity is a well-characterized feature in PTSD.

The genocide has having also crucial physical and psychological consequences on the following generations. Exposure to extreme stress, lack of adequate prenatal care, and poor nutrition throughout gestation can affect fetal development, including reducing fetal growth rate and shortening gestation length. Postnatal exposure to stress from lack of adequate mother-child attachment, abandonment, various forms of abuse, parental poverty, and lack of access to essential health care and food further increase hardship in infancy and early childhood.

Early-life stress has been shown to interfere with gene expression by altering DNA methylation patterns at multiple genes including GR. Early-life adversity is associated with both hypomethylated and hypermethylated promoters, suggesting that active DNA methylation and demethylation may result from social stressors during early development. Exposure to stressors during fetal development or in early infancy is associated with an upregulation of genes involved in the hypothalamic-pituitary-adrenal (HPA) response to stress and a downregulation of genes that exert a dampening effect on these pathways.

The HPA response to stress involves neuronal activation within the hypothalamus, which triggers the release of corticotrophin-releasing factor (CRF) and vasopressin (Avp). CRF and Avp then stimulate the release of adrenocorticotropic hormone from the pituitary. The adrenocorticotropic hormone then stimulates the release of glucocorticoids from the cortex of the adrenal gland. Negative-feedback regulation of the HPA axis, generally achieved through the activation of glucocorticoid receptors (GRs) in the hippocampus, is also impaired in prenatally stressed offspring, and this impairment may account for the prolonged levels of stress-induced adrenocorticotropic hormone and corticosterone.

Arterial blood pressure is the product of cardiac output and total peripheral vascular resistance. Several physiological and neurohormonal mechanisms regulate cardiac output and/or peripheral resistance and contribute to maintain the homeostasis of arterial blood pressure. These mechanisms involve several organ systems including the kidney and the cardiovascular, nervous, endocrine, and immune systems. Both

exaggerated and diminished cardiovascular reactivity to acute psychological stressors have serious consequences for health.

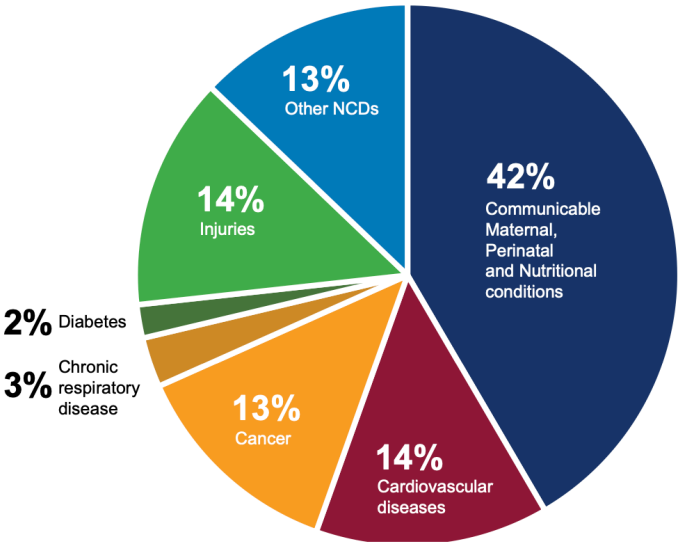
The "reactivity hypothesis" has two basic forms: the individual difference or personality approach, which suggests that people who show exaggerated cardiovascular responses to stress are at increased risk of developing cardiovascular disease, and the situational or social psychological approach, which suggests that circumstances which give rise to unusually large responses are those that put people at risk of disease. Exaggerated reactions are associated with the development of hypertension, markers of systemic atherosclerosis, and cardiovascular disease. Blunted or low reactivity is related to depression, obesity, and a range of addictions.

1.7.5 Health background

The National Strategy and Costed Action Plan for the Prevention and Control of Non-Communicable Diseases in Rwanda 2020-2025 will guide the national response to NCDs in Rwanda over a period of five years. This national strategy will fulfil Rwanda's commitment to delivering Sustainable Development Goal 3: Ensure healthy lives and promote well-being for all at all ages, and, more specifically, target 3.4: By 2030, reduce by one-third premature mortality from NCDs. [33]

People with NCDs often suffer from two or more conditions, such as diabetes and hypertension (HTN), which are closely linked. NCDs are also interconnected to, and interact with, communicable diseases. Health systems must therefore increasingly manage patients living with NCDs as well as communicable diseases. For example, antiretroviral drugs allow people with HIV to live longer, putting them at risk of developing NCDs.

The burden of NCDs in Rwanda has increased tremendously over the years. In 2018, the Institute for Health Metrics and Evaluation (IHME) noted that NCDs are significant contributors to health loss in Rwanda, accounting for 35 percent of DALYs in 2016, up from 16 percent in 1990.



WHO estimates from 2016 show that NCDs accounted for 44 percent of total annual mortality in Rwanda, with CVDs and injuries the single largest shares of NCD-related mortality (both 14%), followed by cancers (13%), CRDs (3%), diabetes (2%) and other NCDs (13%).

Disease prevalence in Rwanda.

1.7.5.1 Hypertension

A countrywide population-based survey showed HTN prevalence at 15.9% (16.8% for males and 15% for females), of which only 22% were diagnosed. Therefore, the largest share is not only unaware but also is not under treatment. The aim is to increase the coverage rate of around 5.4 percent to 20 percent by the year 2025. It is estimated that 1,188,142 people between the age of 15 and 64 are living with HTN in Rwanda. The percentage of DALYs lost because of hypertension was 2.81%, whereas mortality caused by hypertensive heart disease was 1.82% in 2017.

1.7.5.2 Alcohol consumption

In Rwanda, the overall prevalence of alcohol drinkers is estimated at 41.2 percent (males 52%, females 31.4%). Alcohol consumption is highest in semi-urban areas (44.7%), followed by in rural residences (43.1%) and urban residences (29%).

Locally produced alcohol is affordable and accessible to a large majority of the Rwandan population. Despite high taxation on commercially produced alcoholic drinks, the population's large-scale consumption of locally brewed alcohol poses several

challenges for alcohol control in Rwanda. There is a need to increase awareness in the general population on the harmful use of alcohol, as there is currently no significant media outreach focused on raising awareness of alcohol abuse.

Urwaga,[34] which is the oldest and most popular Rwandan traditional alcoholic beverage, is an artisanal banana beer made from the fermentation of the Musa acuminata variety of bananas that is very popular in the area of Kivu Lake, in the Kibungo region of western Rwanda and the neighboring Democratic Republic of Congo as well as in regions neighboring South-Kivu. The production, which is mainly domestic, annually counts of 700 million liters and an average consumption per capita of about 1.2 liters per day.

1.7.5.3 Diet

Overall fruit and vegetable consumption in Rwanda is very low.
In Rwanda's STEPS 2012-2013:
- 99.6% of the population consumed less than five servings of fruit per day and
- 99.3 % consumed less than five servings of vegetables per day.

It is also important to highlight the low diet diversity found generally in the diet of the Rwandan population. A national Nutrition, Market and Gender survey by the Rwanda Agriculture Board in 2015 found that women of reproductive age have an unbalanced diet. A food consumption survey using a 24-hour recall method revealed that there were few consumers (≤5%) of colored vegetables (rich in Vitamin A), eggs, fish, and meat. It also found that fat consumption was insufficient, and that their diet was largely composed of carbohydrates.

The consumption of salt in Rwanda is not documented.

1.7.5.4 Smoking habit

Tobacco use kills over 2,000 people a year in Rwanda, according to the Tobacco Atlas report. In Rwanda, adult tobacco smoking prevalence stands at 12.8 percent with variations in age and sex. Male smokers accounted for 19.1%, while females accounted for 7.1%. The majority of male smokers (17%) are in the lower-income category, while most male smokers, 14.4%, are from the Southern Province of Rwanda.

Smoking prevalence also varied by residence with the highest prevalence reported in rural areas (13.5%), followed by semi-urban (12.0%) and urban areas (9.7%).

Rwanda is a tobacco growing country, although it is not a major agricultural product in Rwanda. Yet it has been seen as an attractive crop for poor rural farmers in Rwanda because of its low startup costs.

1.7.5.5 Physical activity

In Rwanda, 61.5% of the population have high levels of physical activity; 25.2% moderate levels and 13.3% have low levels of physical activity. People residing in semi-urban and rural areas have higher levels of physical activity than urban dwellers (semi-urban 68.2%, rural 64.4% and urban 42.8%).

In 2014, MoH, in collaboration with the Ministry of Sports and Ministry of Local Government, introduced a 'Sports for All' initiative across Rwanda. For example, in May 2016, the City of Kigali, Rwanda's capital, launched a 'Car Free Day', aimed at encouraging people to engage in regular physical activities to prevent NCDs. It started as a once-a-month idea, and now takes place twice a month in Kigali and has been extended to other districts. In addition to promoting physical activity, it also serves as a platform for NCD awareness and screening.

Since the initiative started in 2016, 48,782 people have been screened for NCDs. Among those screened, 23.7% were found to have high blood pressure, 9.4% had high blood sugar and 11% were obese.

1.7.5.6 Overweight and obesity

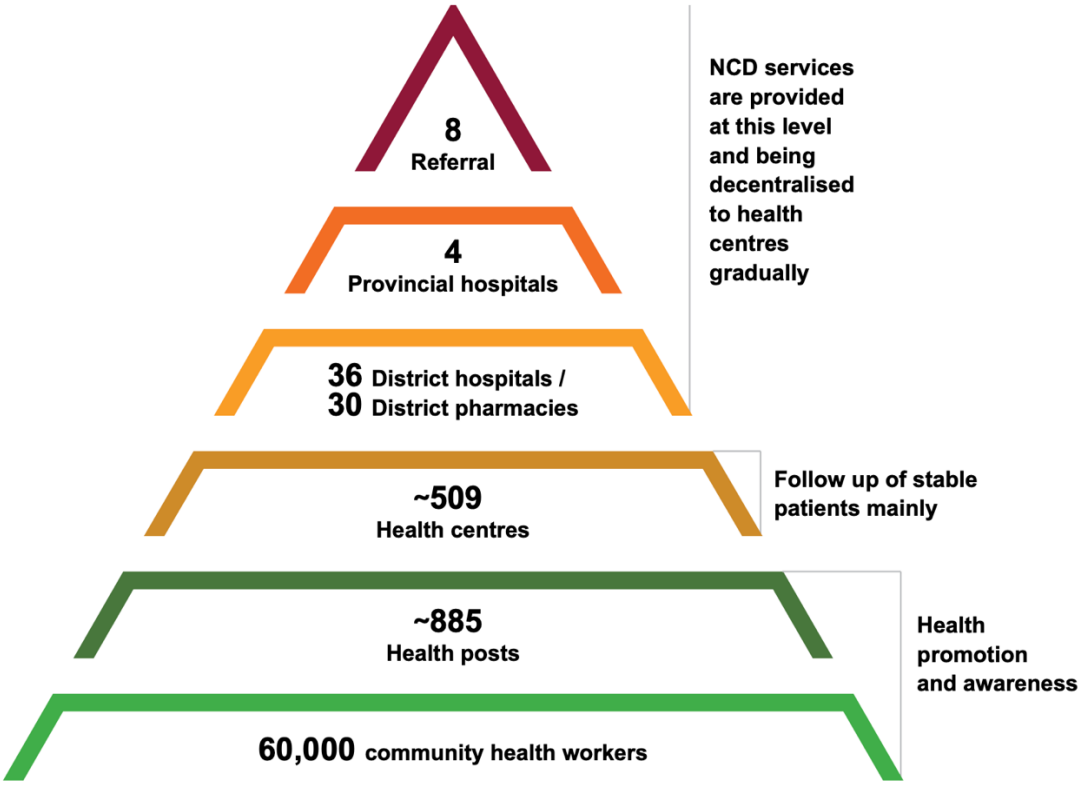
2.8 percent of Rwanda's population are obese, 14.3 percent are overweight and 7.8 percent are underweight. Obesity is most prevalent in the age group 35-54 and among females (4.7%). Furthermore, the prevalence of obesity is more predominant in urban areas (10.2%), and Kigali specifically (7.7%). 36.8 percent of women were overweight or obese in urban areas, compared to 16.8% in rural areas.

1.7.5.7 Environment, occupation and nutrition

Environmental, occupational, and nutritional risk factors like indoor pollution, agrochemicals, aflatoxins and asbestos exposure have been recognized regionally and internationally as risk factors contributing to increased NCD-related morbidity and mortality. More research into this burden for Rwanda will be generated over the course of the next five years.

1.7.6 Health care system

NCD services in Rwanda are provided through a mix of public and private systems.



Structure of Rwanda health care system.

The journey of individuals with a NCD starts in their local community, through contact with community health workers who link the patient to a health facility. Each level of health facility treats patients according to its package of services, and each level of care then refers patients who need advanced management upward through the various levels.

District hospitals receive suspected HTN, DM, CRD cases from health centers to confirm diagnosis, provide treatment, and identify possible complications. Some are then managed at this level, and others with more severe diseases are escalated to upper-level hospitals. Stable patients on medication are referred to health centers to continue follow-up care.

All district hospitals and health centers are meant to provide the minimum WHO Package of Essential NCD Interventions (PEN). This includes health education, screening, referral, and treatment. However, effective access to these services is limited due to a lack of availability, either because of funding limitations, insufficient staffing, or delays in the supply chain.

There are currently pilot services taking place in 79 health centers across five districts, diagnosing and initiating the treatment of non-complicated NCD cases. Lessons learned in these pilot sites will inform the scale-up of services to remaining district hospitals and raise the capacity of health centers to provide PEN.

To ensure the quality of NCD services, training manuals for various health cadres were developed and disseminated. All health centers therefore have at least one nurse trained in early detection and management of NCDs. Health centers have initiated NCD clinics to treat HTN, asthma and DM. By 2017, all of Rwanda's 42 hospitals had established NCD clinics, providing management and care of NCDs. In addition, diagnosis, and treatment protocols for major NCD diseases were developed and distributed to health facilities.

1.7.7 Mabawa[35]

Mabawa association was formally funded on January 28th, 2004, by a group of friends led by Katrine Keller. However, they were already giving financial and practical support since 1998 to the city of Bukavu, in South Kivu, Congo R.D.C., which was dramatically devastated by guerilla, floods of Rwanda genocide refugees, and a cholera epidemic. In 1999, they financed a school in the small village of Bwegera, located on the Rusizi plain, on the border with Burundi and Rwanda. Not without difficulties due to the ongoing civil war, the school, which is nowadays financially independent and locally well-renowned, was built and provided with teachers' salaries, teaching materials, uniforms, and maintenance of facilities. After a severe flood, which occurred in 2021, the school was completely rebuilt with the help of Mabawa, currently welcoming 361 students and 10 teachers, while supporting 81 scholarships with excellent results.

Poster of school project in Congo.

With unused funds from Bwegera, Mabawa arrived in Nyamyumba almost by accident. It is an "umudugudu" (community village) built as a matter of urgency by the Rwandan government (1995) to provide a home for a community of about 500 survivors of the Genocide (1994).

Despite the gradual reconstruction of the country, the isolation and abject poverty in which they found themselves had led them to a state of complete hopelessness.

Struck by the stark contrast between the serene beauty of the landscape and the harsh reality faced by the inhabitants, the choice of Nyamyumba for the construction of the school with unused funds from Bwegera was the spark that would start it all.

This small project marked the beginning of a lasting relationship between Mabawa and Nyamyumba: an experience that would change the lives of the villagers, who, thanks to Mabawa, regained the will to live they had lost.

Nyamyumba school campus.

Throughout the years, Mabawa has strived to meet every day needs and basic necessities in order to provide long-term decent living conditions. Indeed, thanks to the local workforce, plenty of facilities have been put up: a middle school and pupils' accommodations, such as a kitchen, a refectory, and dormitories in 2005, in conjunction with the renovation of the existing primary school. A kindergarten for 70 children was built to keep under-school age children safe and away from wandering the village, and a nursery as well are available since November 2011. An aqueduct provides potable water to the whole village since June 2005, while secondary junior and senior schools alongside four computer rooms (2019), a library (2022), and 3 laboratories (2018-2020) of physics, biology and chemistry have been added to the campus where teachers' residence can also been found. By the end of 2020, a sports field had finally realized. Still more projects are on their ways, such as a boundary wall for ensuring security to students, and friendly toilets to promote menstrual health management, which is set into the broad project of women's empowerment.

From November 2005 to January 2020, 114 houses have been built. Each one is composed of 4 rooms, the outdoor kitchen and the latrine. Each family also receives beds, benches and small furniture. With a microcredit families can also install electricity or add a mat ceiling. Microcredits, which are repayable loans starting from $100, have promoted small businesses, seamstresses, carpenters, small livestock breeders, a bakers', and beekeeping cooperative, as well as a terrace cooperative for terracing hectares of hillsides for potatoes, maize, beans, and wheat crops.

Pygmies-Batwa, 1% of the Rwandan population, in centuries-old tradition, have been helped too. They used to live in the forests as gatherers and hunters, because of discrimination and marginalization. Mabawa played a crucial role in their integration in the community building houses and ensuring school attendance, providing a cow to each family, and constructing radical terraces for harvests.

A health care center also is located in the village. The Nyamyumba medical dispensary was built in 1998 by a German foundation. It depends on the local hospital of Munini and the Minisanté (Health Ministry) and is managed by nurses and assistants. Mabawa finances the weekly presence of doctors for specialist care in the facilities it has installed. Today it serves 14,925 people from the surrounding areas.

Original health center plate.

Since 2005, in addition to the construction of recent facilities, Mabawa has been supplying medicines, supplies and various medical equipment: autoclave, electronic microscope, ultrasound scanner, EEGigraph, tensiometers, electrocardiograph, etc.

Nyamyumba health center.

The construction of a basic dental clinic took place in 2012. A dentist from Butare University's Medical School is present at the clinic bi-weekly or as required by the patient load.

Obstetrics and Neonatology was supported in various ways since 2005. In 2015, it became one of Mabawa's main areas of focus. Today, the facilities provide consultation rooms, delivery and hospitalization rooms and an analysis laboratory. In early 2018, a crucial turning point was the arrival of the ultrasound scanner for pregnancy examinations. The use of the scanner has since saved lives, helping to avoid the still too frequent complications occurring during pregnancy and childbirth often undetectable without ultrasound.

Between 2014-2017, Angela Casadei, a technician in neuro-physiopathology working at the Civic hospital of Lugano, collaborated, and established with Mabawa, a new « Epilepsy project » at the Nyamyumba health center already serving a population of 14,925 people. Mabawa equipped the epilepsy department with an EEGigraph and Telesphore Vuguzigame, head of neurology at the hospital of Munini was assigned to the project.Trained by Angela, he quickly became very competent. Since 2014, Professor Fidèle Sebera, head of the Neurologic Department at the Ndera hospital in Kigali, is our "Tutor" who follows with great passion and interest the project. He spends two days a month in Nyamyumba to monitor the daily work routine and analyze the more complex cases. A consulting room for the diagnosis and treatment of epilepsy was built adjacent to the dental care room and is in use since May 2017 as before the patients were treated in the dental practice waiting room. The epilepsy project is constantly evolving and improving services and diagnostic capabilities for patients. From January to October 2020, 500 patients were seen of which 256 diagnosed as epileptic.

2. Aim

Non communicable diseases (NCD) are becoming overwhelmingly predominant in African countries. Arterial hypertension and cardiovascular diseases (CVD) are the leading ones among chronic illnesses. Hypertension is an important public health challenge worldwide as the up-to-date Call to action from WHL (World Hypertension League) overwhelmingly reminds. Information on the burden of disease from hypertension is essential in developing effective prevention and control strategies. In spite of the relatively limited evidence base, it is clear that hypertension is a major public health problem in SSA, particularly in urban areas. However, levels of detection, treatment, and control are worryingly low, suggesting that high levels of adverse effects such as stroke, heart failure, and renal failure will become apparent in the years to come. Conversely, the magnitude of hypertension in African rural regions is mainly neglected because of a lack of studies locally conducted.

Strikingly, these trends can equally be observed in urban as well as rural settings, although studies carried out in rural African regions are few. Therefore, on the ground of a strikingly evidence of considerable under-diagnosis, treatment, and control, a project for an epidemiological study in a rural area has been presented and approved by the Rwandan National Ethics Committee with these aims:

-Primary end-point: detection of hypertension prevalence in a rural population.

-Secondary end-point:

-improving local knowledge and competence of medical and health care personnel in blood pressure management;

- improvement of the health infrastructure dedicated to the control of hypertensive patients (equipment and data management system);

-highlighting associated cardiovascular risk factors and raising individual awareness and commitment to healthy lifestyles and therapy.

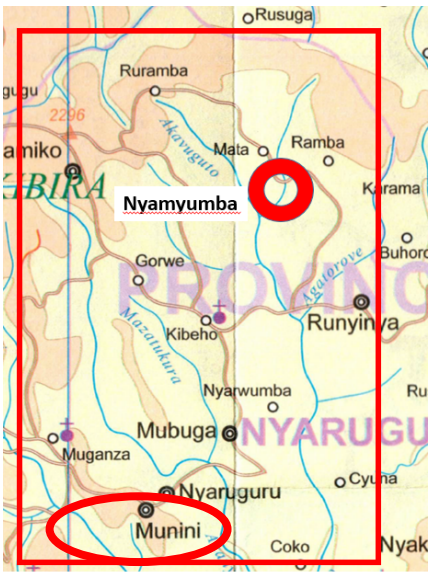
The Hypertension Project, sent as an oral communication to the 19th European Congress of Internal Medicine (ECIM) to be held virtually from March 18-20/2021 has been accepted and presented by Dr. Franco Muggli.

The project is currently on-going, being carried out under the auspices of the World League of Hypertension and the Swiss Society of Hypertension, in close collaboration with the Faculty of Biomedical Sciences of the University of Lugano, the Faculty of Medicine of the University of Zurich and Milano - Bicocca.

3. Materials and methods

3.1 Study design

It is a cross-sectional study that stemmed from the surprising data of BP measurements that have been collected during the screening.



Nyaruguru district map.

The study focused on identifying the rate of high blood pressure and related risk factors in the rural District of Nyaruguru – Mata Sector, in southern province of Rwanda. An assessment of the incidence of hypertension in a group of patients at the Nyamyumba Medical Centre took place when Dr. F. Muggli joined the team in October 2017.

The District hospital of Munini was equally involved, using the same validated device for measurement of BP. During the hospital screening, height and weight were taken and we had information on multiple risk factors including dietary habits, salt consumption, drinks, such as soft drinks and alcohol, then smoking habit, number of sleep hours, on-going therapy for hypertension and/or diabetes, pain killer assumption.

HYPERTENSION & CARDIOVASCULAR RISK PROJECT

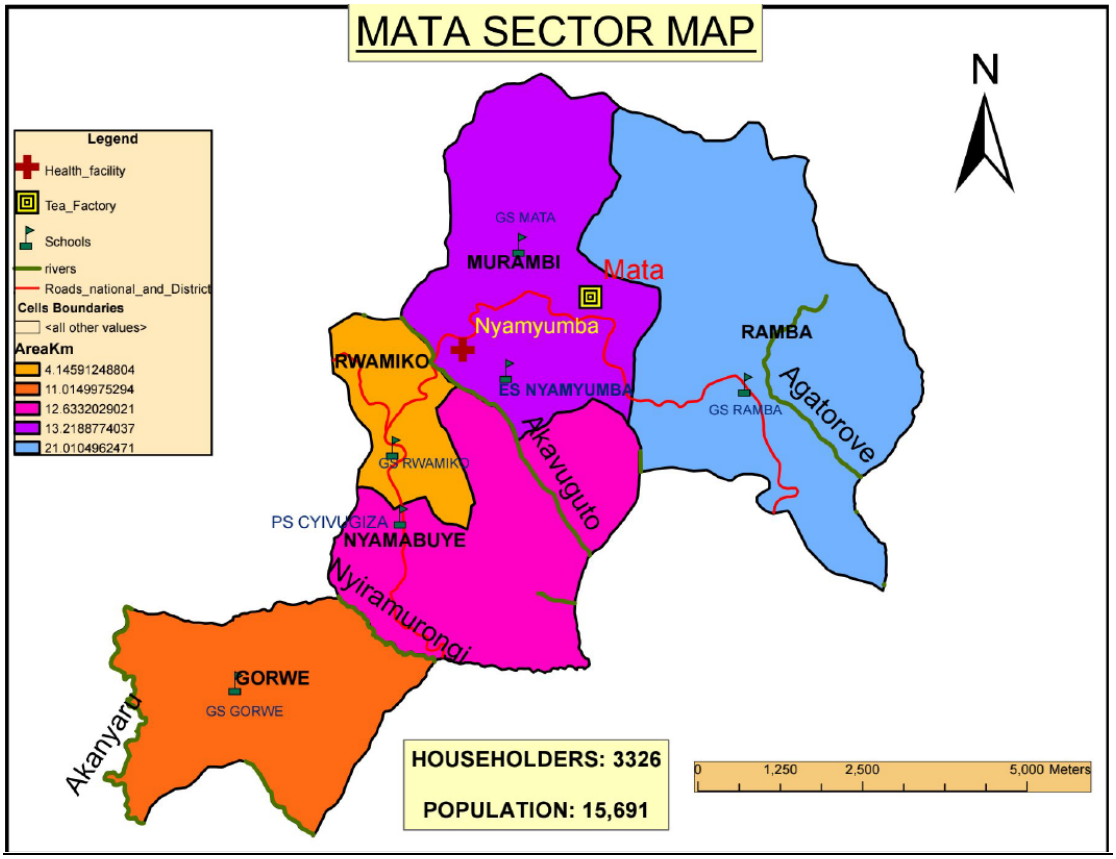
Name	[illegible] Triphine		
Date of birth	1961		
Gender	☐ M ☒ F		
Height	158		
Weight	49		
Waist circumference			
Blood pressure 1	Sist. 181	Diast. 101	Pulse 73
Blood pressure 2	Sist. 174	Diast. 102	Pulse 71
Blood pressure 3	Sist. 173	Diast. 106	Pulse 69
Age of parents (if alive)	No parents		
Cause of death (if dead)			
How do you feel? Good/not good?	Good		
Are you on medical care? Why?	Yes		
Do you take any drugs ? Why? Name and dosage:	NO Unknown of disease		
Walking 15 min without shortness of breath (SOB)?	No problem		
Dietary habits:			
Adding salt to food?	Yes		
Usual daily food?	beans, patatoes		
Usual daily drinks: water, soft drinks, coffee, tea, beer...	water		

DATE [illegible]

Screening at Munini Hospital and sample of visit report.

Surprisingly, it was found that the measured pressure values at the Health Centre as at Munini Hospital both showed an incidence of abnormal values of BP in a high number of cases.

For this reason, it was decided to intervene with a structured and scientifically validated project that provided a phase of screening and subsequent diagnosis and treatment, encompassing the entire local sector rural area (over 15,000 people).



Mata sector map.

3.2 Population

Study participants were voluntarily tested for BP, moving village to village with community health care workers taking blood pressure. To be more specific, eligible participants were considered subjects of both sexes aged ≥18 years living in the rural area of the District of Nyaruguru. Having said that, subjects with intolerance to specific classes of hypertensive drugs or any allergies; contraindication for certain antihypertensive drugs, subjects who are unable to comply, and those with any severe disease that were already known or that would have been diagnosed by chance, were excluded. They were instead referred to the Hospital (the BP will be treated there).Over a period of time from February to July 2020, they managed to measure blood pressure values of more than 7,000 inhabitants.

Community health care workers during the screening in a local village.

3.3 Data collection and approach

Eligible participants were identified by name, sex and age. Subsequently, physical measurements of blood pressure, height, weight were performed.

The study shows several strengths. Firstly, it was conducted in sites in rural Africa selected to represent remote areas of SSA. Few previous studies have managed to collect information to characterize prevalence and risk factors of HTN in such settings. Moreover, data were collected with the same automated devices and standardized

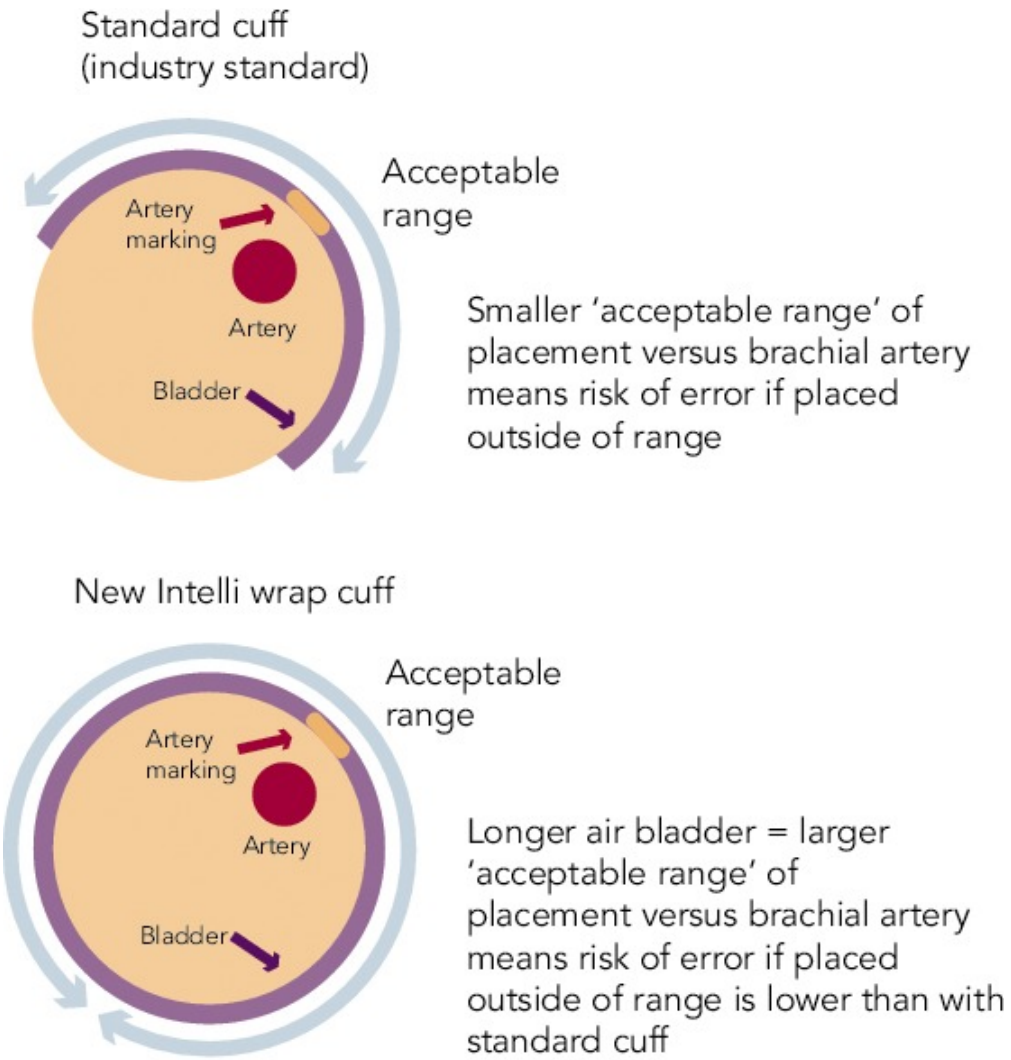
protocols across all settings in an effort to minimize measurement errors and bias associated with training multiple research teams in the use of manual sphygmomanometers.

OMRON oscillometric device.

Indeed, under the close and valuable collaboration of Alice Umulisa, a respected public health worker and crucial on-site partner and nurse of the study, local health care workers have been trained about hypertension and its accurate measurement according to the aforementioned guidelines of WHL. Furthermore, each of them has been provided with a validated automated oscillometric device (OMRON M7 Intelli IT-HEM-7322T-E).

Training of community health care workers.

The Intelli wrap cuff technology features a longer inflatable area within the cuff that wraps all the way round the arm. This reduces pressure loss on the brachial artery, increasing the 'acceptable range' of placement and thus reducing the impact of cuff placement on accuracy.



Intelli technology.

Incorrect positioning of a conventional cuff significantly affects BP measurement results, with the greatest overestimation of BP when the bladder center is displaced by 90° laterally or by 180° compared with the correct position. When the Intelli Wrap cuff is used, there is no significant effect resulting from cuff position. BP values obtained with the oscillometric device tend to be lower than those obtained by reference method because of relative under cuffing with the mercury device equipped with standard size cuff in subjects with a large arm circumference.

Blood pressure was measured after the participant rested for at least 3 minutes. BP was taken in a home setting, preventing subjects from being in a medical, potentially stressor, office. The white-coat effect was adequately mitigated, taking patients BP in the comfort of their households by a community member yet trained.

3.4 Definition and measurement of variables

High blood pressure

High blood pressure was defined as a systolic blood pressure of more than or equal to 140 mmHg. An automated blood pressure machine (OMRON M7 Intelli IT-HEM-7322T-E) was used to obtain the blood pressure readings. Three readings were taken 3–5 min apart after 3 min rest of the survey participant. As recommended by WHO, the average of the last two readings were calculated and used as the final blood pressure measurement.

Body mass index

BMI was expressed as weight in kilogram/height in square meters (kg/m^2). Height and weight were measured using respectively a centimeter and a common scale for weighing people in kilograms. The survey participants were measured without shoes and wearing only light cloths. Respectively, height and weight were measured to the nearest whole centimeter and 0.1 kg. BMI was classified as ≤ 18.5 kg/m^2 (lean), 18.5– 24.9 kg/m^2 (normal), 25.0–29.9 kg/m^2 (overweight), and ≥ 30 kg/m^2 (obese).

3.5 Statistical analysis

Continuous variables were expressed as median and interquartile range, whereas categorical variables were expressed as percentages.

For statistics, the Mann-Whitney-Wilcoxon test (rank sum test for two independent samples) and the Fisher exact test were used. A P-value of <0.05 was considered to evaluate statistical significance.

Statistical analysis was conducted with the support of Dr. Dragana Radovanovic using software Data Analysis SPSS.

4. Results

Among Mata Sector, the population counts approximately 15000 inhabitants. The total number of screened subjects were 7336. The average age of study participants was 32 years, and a similar number of males - 3301 (45%) - and females – 4035 (55%) - were enrolled.

Considering SBP ≥ 140 mmHg and DBP ≥ 90 mmHg for the diagnosis of hypertension, 6694 (91%) had normal BP, while 642 subjects (9 %) showed high BP values. The female to male ratio, body weight, and height were similar in hypertensive and normotensive subjects. Heart rate and body mass index were slightly but significantly higher in hypertensive than in normotensive subjects. Nonetheless, the prevalence of body mass index ≥25.0 kg/m^2 was similarly low (11.9% vs 11.5%) in hypertensive and normotensive subjects.

The most relevant difference between hypertensive and normotensive subjects was the age: 52 [35-65] years old vs 32 [21-45] years old (p<0.001).

	All	Normotensive	Hypertensive	P-value
N	7336	6694	642	
Age, years	32 [21-47]	32 [21-45]	52 [35-65]	<0.001
Females: Males, N	4035 : 3301	3682 : 3012	353 : 289	0.999
Blood Pressure, mmHg				
Systolic	118 [110-128]	117 [109-125]	149 [144-158]	
Diastolic	75 [69-81]	74 [68-80]	89 [82-95]	
Heart rate, b/m	77 [68-86]	77 [68-86]	81 [71-90]	<0.001
Body weight, kg	56 [50-62]	56 [50-62]	56 [50-63]	0.33
Height, m	1.62 [1.56-1.68]	1.62 [1.56-1.68]	1.61 [1.56-1.68]	0.53
Body mass index				
kg/m^2	21.2 [19.5-23.1]	21.2 [19.5- 23.1]	21.5 [19.7-23.4]	0.028
≥25.0 kg/m^2	849	772	77	0.698

Table 4.1 – Clinical data in subjects with normal or increased blood pressure.

Heart rate was similar in females and males with hypertension. The age (by about 21 years), systolic (by about 5 mmHg) and diastolic (by about 4 mmHg) blood pressure, the body mass index (by about 0.3 kg/m^2) and the prevalence of BMI ≥25.0 kg/m^2 were significantly higher in females than in males with hypertension.

	Females	Males	p-value
N	353	289	
Age, years	58 [45-67]	37 [28-61]	<0.001
Blood Pressure, mmHg			
Systolic	152 [144-162]	147 [143-154]	<0.001
Diastolic	91 [84-97]	87 [80-93]	0.001
Heart rate, b/m	81 [71-91]	81 [70-89]	0.3932
Body mass index			
kg/m^2	21.6 [19.8-23.8]	21.3 [19.5-23.0]	0.0221
≥25.0 kg/m^2	55	22	0.0022

Table 4.2 - Characteristics of females and males with hypertension.

5. Discussion

5.1 Hypertension in rural area

In this study, we found that hypertension is prevalent in rural SSA, emerging as a critical and potential disabling health condition as in urban areas.

Several researchers have investigated the prevalence of HTN in various parts of Africa, including SSA. However, they focus their attention on urban and peri-urban areas. Furthermore, if they target rural settings, they used different criteria for classification of HTN, making comparisons difficult.

Urban African dwellers are becoming extensively exposed to western lifestyles. In African cities, many people have service and office jobs, and mobility has become less energy-intensive owing to shorter travel distances and the use of cars and buses. Furthermore, urban markets where fresh produce is sold are increasingly replaced by commercially prepared and processed foods from transnational and local industries and street vendors. These effects are exacerbated by limited time and space for cooking healthy meals and possibly perceptions of large weight as a sign of affluence. At the same

time, health care facilities are improving diagnosis and long-term management of this rapidly raising number of NCDs. Thanks to effective and widespread educational campaigns, individuals' awareness has significantly improved.

Conversely, the need for active surveillance, and the identification and treatment of hypertensive patients in rural areas are crucially needed as demonstrated by the HTN status observed in this study.

A study of a socio-economically advantaged rural area of Tanzania reported prevalence of 41 and 39% among males and females aged 35–54 years and 54 and 61% among males and females aged 55 and older. To our knowledge, no study reports HTN prevalence exclusively among poor rural populations in SSA. Our study settings of Nyamyumba – Mata Sector strengthens the evidence for prevalence of HTN (9%) (Table 4.1) and its importance as potential cause of significant morbidity and mortality in this population. Investigations of previously reported relationships between childhood undernutrition and adulthood HTN, and potential mechanisms related to impaired energy expenditure regulation, fat deposition and susceptibility to insulin resistance are needed in this population.

Rural residents seem to develop HTN regardless to their gender (Table 4.1). Indeed, the number of hypertensive males and females was similar ($p=0.999$). With regards to aging, it seems to be a non-modifiable risk for developing HTN also in rural areas (Table 4.1) with hypertensive people being 21 years older than normotensive people ($p<0.001$). Strikingly, hypertensive women were older than men (Table 4.2), suggesting the beneficial role of estrogens in cardiovascular protection until menopause. Further studies on the association between HTN and menopause in rural setting should be performed.

Moving to modifiable risk factors (such as weight), no relevant difference ($p=0.33$) was reported among normotensive and hypertensive people (Table 4.1), as well as in relation to BMI ($p=0.028$). 89% of screened population had a BMI ≤ 25 kg/m^2, while just 1% of subjects with BMI ≥ 25.0 kg/m^2 was hypertensive. This overwhelmingly suggests that overweight and obesity, which are increasingly spreading in African cities, are not common in African rural areas. Moreover, overweight and obese people develop HTN only in a tiny minority of cases, although our understanding of dietary patterns is

limited and further evaluation of the role of dietary habits (both macro- and micronutrient intakes) in the etiology of HTN in SSA using standardized tools is crucial.

These results highlight the impending need of broad and thorough works aimed to understand real, local, and emerging risk factors for developing HTN in rural settings. The influence of salt intake and alcohol consumption on blood pressure deserve, in my opinion, to be specifically addressed.

5.2 Raise awareness

More studies in rural SSA area should be conducted in order to gather an update health picture of these communities in relation to the epidemiological and transgenerational transition that they are rapidly facing.

This would urge governments to put into practice prompt and effective policies to effectively tackling this rapidly spreading epidemic.

At the same time, campaigns of health prevention and education should be carried out. Simple, practical, and stick to the context advice should be given about daily habits, such as food choices, salt and alcohol consumption, in order to tackle major and modifiable risk factors related to the development of high BP. Prevention of CVD and reduction of its risk factors through lifestyle changes including nutritional and other health interventions in developing countries, particularly in SSA, are receiving timely consideration. Sensibilization campaigns, such as the World Hypertension Day – 17/05, community-based BP measurements and screening at gathering places, such as churches and schools, seem to be effective in reaching out an extensive number of people while promoting conscious behaviors and regular access to health care.

5.3 Health care community workers

People living in rural areas are frequently far away from health care centers, which tend to be the first level of medical care available. Furthermore, as awareness about health issues is still fairly low, a large number of them have never got access neither to these nor to more developed health facilities. Involving local, trained animateur de santé has revealed a winning call to let these people meet some health care assistance. This approach seems not only to boost subjects' health sensibility, but also to ensure high involvement, leveraging on building a robust relationship between patients and health care providers, which is widely renowned to be essential for catching and retaining patients.

A community health care worker measures home blood pressure.

5.4 Planning future strategies

According to our and similar data of disease prevalence, the attention of national health care systems should be drawn to compelling emerging issues, such as hypertension, which can be effectively controlled and treated in order to prevent worst and more economically demanding consequences. Stroke, which is one of the harsh consequences of uncontrolled HTN both on the national system and on families, is on the increase with Westernization of African cities, with the rate of stroke disability approaching that in high-income countries. Of note, a large percentage, between 30% and 50%, of stroke mortality occurs in those inadequately treated for hypertension.

If governments are committed to allocate resources for the early diagnosis and treatment of chronic disease, both their population and health care systems will benefit. They should rapidly join the WHL – Call to Action and integrate its numerous suggestions in their national health programs, undergoing a drastic renovation of their health care

delivery in order to successfully meet the worldwide objectives in curbing NCDs spread. Promising research efforts highlight that successful interventions are feasible in LMICs. These include creation of health-promoting environments by introducing salt-reduction policies and sugar and alcohol tax; implementing cost-effective screening and simplified treatment protocols to mitigate treatment inertia; pooled procurement of low-cost single-pill combination therapy to improve adherence; increasing access to telehealth and mHealth (mobile health); and training health care staff, including community health workers, to strengthen team-based care.

5.5 Limiting factors

Some limitations of our study deserve mention. In this cross-sectional study, we measured blood pressure among participants at one point in time. This may lead to misclassification of HTN status. Residual confounding by unmeasured variables and misclassification of measured confounders is a possibility. We had crude measures of dietary intake (frequency) and physical activity (work related) determined from participants using questionnaires. Finally, our study evaluated eastern rural Africa and study findings may not be generalizable to other parts of rural Africa where populations may have different disease and risk factor distribution.

6. Conclusion

We found that HTN is common in rural SSA, despite being neglected and underestimated for years. We also observed associations of non-modifiable (age) and modifiable (BMI, physical activity, and dietary intake) risk factors with HTN in this population. HTN should be carefully prevented with effective and locally feasible interventions in conjunction with raising awareness in individuals. Future studies that evaluate trends in risk factors and CVD morbidity and mortality (longitudinal studies), associations of risk factors with disease in similar populations and barriers to health care for CVD are needed. Information from such studies may enhance the primordial, primary, and secondary prevention of HTN and CVD in rural Africa. Furthermore, common cut-off for the definition of hypertension should be shared by ESC/ESH and AHA/ACC in order to extensively collect worldwide comparable data about hypertension prevalence

and treatment effectiveness. Governments should rapidly plan a capillary screening of NCDs, such as high BP, in order to be aware of their prevalence. Providing effective and early strategies of management, it would release the strain of chronic treatment and invalidating health consequences on the national health system. As the blood pressure trajectory continues creeping upward in LMICs, contextual research on effective, safe, and cost-effective interventions is urgent. New emergent risk factors require novel solutions. Lowering blood pressure in LMICs requires urgent global political and scientific priority and action.

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Acknowledgements

I am profoundly thankful to Prof. Gianfranco Parati for introducing me to this illuminating and stimulating project as it enabled me to broaden my medical horizons while gathering unforgettable everyday-life experiences and human relationships. His indisputable and renowned competence and restless dedication go beyond any physical borders as his commitment to pass them down to young students and doctors.

My endless thanks to Katrine Keller for welcoming me in the huge and colorful family of Mabawa Association and Nyamyumba village. I sincerely admire what she has done for these fantastic people and her persistent commitment to help them, combining strong determination with big heart .

I can't find enough words to express my gratitude to Dott. Franco Muggli. Working side by side was for me dramatically useful and motivating, putting me in the frontline of a study project in an unknown and peculiar setting. All what I learned and experienced has left a permanent sign in my growth both as a budding doctor and as a person. His persistently helpful and listening attitude towards local patients as well as Swiss ones is admirable and a precious example.

Sincere thanks to Dott. Mario Bianchetti for his invaluable help in optimize and finalize my work, with appreciated and invaluable suggestions, and insightful comments that I will retain for my future career. His cheerful attitude yet rigorous and professional at the same time supported me in the toughest, convulsive moments.

To all you doctors that supported me in this journey, I hope to become as dedicated, competent, and committed to patients and work as you are, with ever-lasting passion, enthusiasm and motivation to learn and improve people's lives.

Special thanks to Alice, Benita and Clara, wonderful friends and formidable co-workers, for how we greatly did the job, addressing unpredictable inconveniences too, and for all laughter, and funny and memorable time we enjoyed together.

To all Mabawa members, especially Leon, thank you for making me feel as a family member and for the regard, friendship, and love that you unconditionally showed to me.

Lastly, I have to express huge thanks to my beloved family, my parents and my brothers, for waiting on my coming back home while constantly supporting me from far.

Wholehearted thanks to you all for be by my side, you are and will always be in my heart.