High blood pressure and associated risk factors as indicator of preclinical hypertension in rural West Africa

A focus on children and adolescents in The Gambia

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Abstract

Hypertension is fast becoming a major public health problem across sub-Saharan Africa. We sought to determine the prevalence of high blood pressure (BP) and associated risk factors as indicator of preclinical hypertension in a rural Gambian population.

We analyzed data on 6160 healthy Gambians cross-sectionally. Attention was given to 5 to <18-year olds (N = 3637), as data from sub-Saharan Africa on this young age group are scarce. High BP was defined as systolic blood pressure (SBP) above the 95th percentile for age-sex specific height z scores in <18-year olds employing population-specific reference values. Standard high BP categories were applied to ≥18-year olds.

In <18-year olds, the multivariable analysis gave an adjusted high BP prevalence ratio of 0.95 (95% confidence interval [CI] 0.92–0.98; $P = 0.002$) for age and 1.13 (95% CI 1.06–1.19; $P < 0.0001$) for weight-for-height z score (zWT-HT); sex and hemoglobin were not shown to affect high BP. In adults age 1.05 (95% CI 1.04–1.05; $P < 0.0001$), body mass index z score 1.28 (95% CI 1.16–1.40; $P < 0.0001$), hemoglobin 0.90 (95% CI 0.85–0.96; $P < 0.0001$) and high fasting glucose 2.60 (95% CI 2.02–3.36; $P < 0.0001$, though the number was very low) were confirmed as risk factors for high BP prevalence; sex was not associated.

The reported high BP prevalence and associated risk factors in adults are comparable to other studies conducted in the region. The observed high BP prevalence of 8.2% (95% CI 7.4–9.2) in our generally lean young Gambians (<18 years) is alarming, given that high BP tracks from childhood to adulthood. Hence there is an urgent need for further investigation into risk factors of pediatric high BP/hypertension even in rural African settings.

Abbreviations: BP = blood pressure, BCCG = Box-Cox Cole and Green distribution, BMI; zBMI = body mass index; body mass index z-score, BPCE = Box-Cox Power Exponential distribution, DBP = diastolic blood pressure, DFID = Department for International Development, GAMLSS = generalized additive models for location, scale and shape, g/dL = grams per decilitre, high-BP = high blood pressure, KEMReS = Keneba Electronic Medical Records System, kg/m^2 = kilogramm per meter squared, KWDSS = Kiang West Demographic Surveillance System, KWLPS = Kiang West Longitudinal Population Study, LMIC = low- and middle-income country, min = minutes, mmHg = millimeter of mercury, mmol/l = millimoles per litre, MRC = Medical Research Council, WT-HT; zWT-HT = weight-for-height; weight-for-height z score, P = P value, SBP = systolic blood pressure, WHO = World Health Organization, Y = years.

Keywords: adolescents, gambia, high blood pressure, population prevalence, pre-clinicalhypertension, risk factors, west Africa

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1. Introduction

Cardiovascular diseases are an increasing major public health issue worldwide, a trend occurring at an alarming rate in low- and middle-income countries (LMIC), with the morbidity burden rising sharply.[1–3] High blood pressure (BP) and clinical hypertension are major risk factors for cardiovascular diseases (ischemic cardiomyopathy, stroke, and heart failure) and chronic kidney disease,[4] and a leading cause of mortality world-wide.[1,2,5] According to the WHO, 1 billion people (i.e., 40% of people aged 25 years and above) are living with hypertension with the prevalence highest in the African Region at 46%.[1] It is a challenging task to compare hypertension prevalence in sub-Saharan Africa from published data owing to both the scarcity, especially in younger age groups, and the heterogeneity of studies, with the prevalence of hypertension varying extensively between and within studies.[6] As an example, national prevalence rates range from 15.9% in Eritrea[7] to 39.6% in the Seychelles.[8] The prevalence of hypertension may also be affected by locality. In a study in Nigeria, the prevalence was significantly higher among urban (32.7%) compared to rural dwellers (12.9%).[9] However, such differences are less marked in other countries like Ghana being respectively 33.4% and 27.0%[10] and Ethiopia being

respectively 10.1% and 9.7%.[11] Hypertension may go undiagnosed for years largely because of the absence of severe clinical symptoms resulting in serious complications.[12] There is also growing evidence suggesting that hypertension in adulthood has its roots in childhood and adolescence.[13] This necessitates population-based screening for early detection of those with high (BP) and hypertension across all age groups. To date, data on high BP/hypertension in children and adolescents in sub-Saharan Africa are only available from a few sites including South Africa, Nigeria, Congo, Uganda, and Ghana.[14–19] The majority of these are set in urban areas where the epidemiological transition from communicable to noncommunicable disease (including cardio-vascular diseases) is more advanced, with less active and unhealthier lifestyles compared to rural areas.

There is a paucity of data on hypertension and its related risk factors in The Gambia. Indeed, population-based studies with a comparison between urban and rural sites were published 10 to 20 years ago, when the nationwide prevalence of hypertension was found to be around 24% in adults, with slightly lower rates in rural areas.[20–22] A more recent study including urban adults from The Gambia and Sierra Leone reported a much higher overall prevalence of 44.8%.[23] This may be because of the speed at which the epidemiological transition is occurring. There is no large comprehensive recent study on hypertension including pediatric hypertension in Gambia or elsewhere in rural Africa as far as we are aware. The present study was carried out to investigate the prevalence of high BP and associated risk factors for hypertension in >6000 healthy rural Gambians aged 5 years and older. We gave particular attention to <18-year olds, as data on this age group are very scarce and has to our knowledge not previously been reported in a systematic manner in this rural sub-Saharan setting. High BP tracks from childhood to adulthood and raised BP in this younger age group can be viewed as indication of preclinical hypertension, which may lead to substantial negative health consequences later in life.

2. Materials and methods

2.1. Study population and data sources

This study was conducted within the Kiang West Longitudinal Population Study (KWLPS) cohort in The Gambia,[24] which captures >14000 residents across 36 villages within the rural Kiang West District, served by the Medical Research Council (MRC) Keneba field station. Relevant data for these analyses primarily originated from the Keneba Biobank (http://ing.mrc.ac.uk/home/research-areas/the-keneba-biobank/), with BP, anthropometric and hematological measures, and questionnaire data collected between May 2012 and October 2014. Demographic and clinical data were available via linkage with the Kiang West Demographic Surveillance System (KWDSS) and Keneba Electronic Medical Records System (KEMReS) databases.[24] The population comprises socially homogenous, rural subsistence farmers, of whom >95% are Mandinka (self-reported ethnicity); ethnicity was therefore not considered as covariate in our analyses. Sibship was determined by shared maternal ID to account for relatedness within the population, as this society is polygamous and characterized by a complex pedigree structure, for example, the presence of a large proportion of half-sibs (Supplementary Table 1, http://links.lww.com/MD/B610). Children younger than 5 years were not considered in these analyses, as no BP measure was available for this age group. Individuals with active infection (positive malaria rapid test of blood film,

N=2) and those not fasted at blood collection (N=15) were also dropped from the analyses. This research was approved by the joint Gambia Government/MRC Ethics Committee and all participants and/or legal guardians provided written, informed consent.

2.2. Definitions for outcome measures and covariates

All anthropometric measurements were conducted by trained field assistants using equipment calibrated daily. Height was measured without footwear or headwear with the participants standing fully erect against a stadiometer with the measurement to the nearest 0.1 cm. Weight was measured to the nearest 10 g using portable weighing scales (Tanita WB100, Tokyo, Japan) and body composition using a digital bioimpedance analysis scale (Tanita, Tokyo, Japan). Body mass index (BMI) was calculated in those 18 years of age or older as weight in kilograms divided by height in metres squared. Based on BMI, individuals were classified using standard cut-offs as underweight ($<18 \text{kg/m}^2$), normal weight ($18-24.9 \text{kg/m}^2$), overweight ($25-29.9 \text{kg/m}^2$), and obese ($\geq 30 \text{kg/m}^2$). As BMI is strongly age-dependent below the age of 18 years, we deemed internally calibrated weight-for-height z scores (zWT-HT) as best measure of body composition in our population. The zWT-HT and zBMI were calculated as previously described.[25,26]

Hemoglobin was measured by Medonic M-series 3-part hematology analyser (Boule Medical) or HemoCue. Anemia was defined using WHO criteria (Supplementary Table 2, http://links.lww.com/MD/B610).[27]

BP was recorded in triplicate (separated by 5 minutes) with an Omron 705IT machine (Omron, Kyoto, Japan) according to the manufacturer instruction with the participant in a seated position and the participant's arm positioned at heart level. The first measurement was discarded to eliminate error that may occur because of stress or excitement during the first measurement and the average of the second and third BP measurements was used for further analyses. The mean BP measurement, determined cross-sectionally at one time point, was employed to define high BP as primary outcome, rather than hypertension per se, as the latter requires repeat measures at separate time points.

As our rural Gambian population covered a wide spectrum of age, sex, and height, we estimated reference values of 50th, 90th, 95th, and 99th percentiles for SBP and DBP by age and height (at the 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles) for boys and girls aged 5 to <18 years (Supplementary Table 3, http://links.lww.com/MD/B610). High BP in those aged 5 to <18 years was then defined as the average systolic BP (SBP) and/or diastolic BP (DBP) that is ≥95th percentile for sex, age, and age-sex specific height z scores in our own population (see statistical methods below and Supplementary Materials for details, http://links.lww.com/MD/B610). Note that this high BP definition broadly follows the guidelines for definition of hypertension as stipulated by the National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents (hereafter referred to as the 4th Report).[28] For those ≥18 years, high BP was defined as SBP ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg and/or receiving treatment for hypertension in the 3 months before BP measurement and/or being diagnosed as hypertensive in MRC Keneba clinical database.[29] Those who had stated to receive hypertension treatment from elsewhere than the MRC Keneba clinic were excluded (N=24), as we had no means to verify the details of their prescription. Furthermore, as pregnancy affects BP

especially in the second half, we excluded women whose BP was measured during this period (i.e., who gave birth in the time frame of 7 weeks before BP measurement or up to 20 weeks after it [N=134]). Those with missing information on BP were also excluded from the analyses (N=7).

Those at risk of having diabetes (high fasting glucose/diabetes) were identified based on a fasting plasma glucose level of >7 mmol/L measured by Accu Check (Roche Diagnostics) or receiving diabetes medication from the MRC Keneba clinic where the drugs supplied are Glibenclamide and Metformin. None of our participants stated to receive diabetes treatment from elsewhere than the MRC Keneba clinic.

Information on education was available for those aged ≥18 years; a participant was defined to be educated if s/he had attended at least primary school.

2.3. Statistical analyses

First, we plotted the distribution of SBP and DBP for the whole study population (N=6160) by age and sex employing a cubic spline regression (Fig. 1), accounting for relatedness by sibship (i.e., shared mother; see above and Supplementary Table 1, http://links.lww.com/MD/B610). All statistical analyses were stratified by age (5 to <18 years and ≥18 years) because we applied different body composition measures (internal zWT-HT and zBMI, respectively) and different definitions of high BP in these 2 age groups (see above). We computed zBMI and constructed age- and sex-dependent growth curves for BMI for the ≥18-years olds using the generalized additive models for location, scale, and shape (GAMLSS) with Box-Cox Power Exponential (BPCE) distribution.[30,31] The GAMLSS models are widely used for constructing growth percentiles curves.[32–34] As internal zWH-HT and zBMI are both age- and sex-independent and normalized, each was divided into quartiles.

Second, we estimated age- and sex-specific height z scores using GAMLSS with Box-Cox t-distribution where the mean, coefficient of variation, skewness, and kurtosis were modeled as nonparametric smoothing cubic spline functions of age. Next, we computed the 95th percentiles for SBP and DBP by sex for children aged 5 to <18 years using Box-Cox Cole and Green (BCCG) distribution with the mean values of SBP and DBP as function of a smoothing cubic spline of age and height z scores.[35] These 95th percentiles were used to define high BP in 5 to <18 year olds[28] as outlined above. Further details are shown in the Supplementary materials including Supplementary Tables 3 and 4, http://links.lww.com/MD/B610.

We next compared the sex, educational level, and high fasting glucose/diabetes status between those with high BP and those within the normal range of BP using Wald-adjusted test accounting for clustering by sibship. Both zWT-HT and zBMI, which were normally distributed, were compared between the high BP and normal range BP groups using Wald-adjusted test, whereas age, weight, height, BMI, SBP, DBP, and hemoglobin levels, which were skewed, were compared using Somers' D statistics, which is a nonparametric measure of association and allows accounting for relatedness by sibship.[36,37] We continued by estimating the prevalence of high BP stratified by age, sex, and anemia category. Finally, univariable and multivariable Poisson regressions were performed with clustered sandwich estimator accounting for relatedness by sibship. Age, sex, zWT-HT or zBMI, high fasting glucose/diabetes status, and hemoglobin level were investigated as potential risk factors. Explanatory variables associated with high BP at 10% significance level were included in the multivariable analysis. The GAMLSS was performed using the package GAMLSS in R[38] and other analyses done in Stata 13.1.
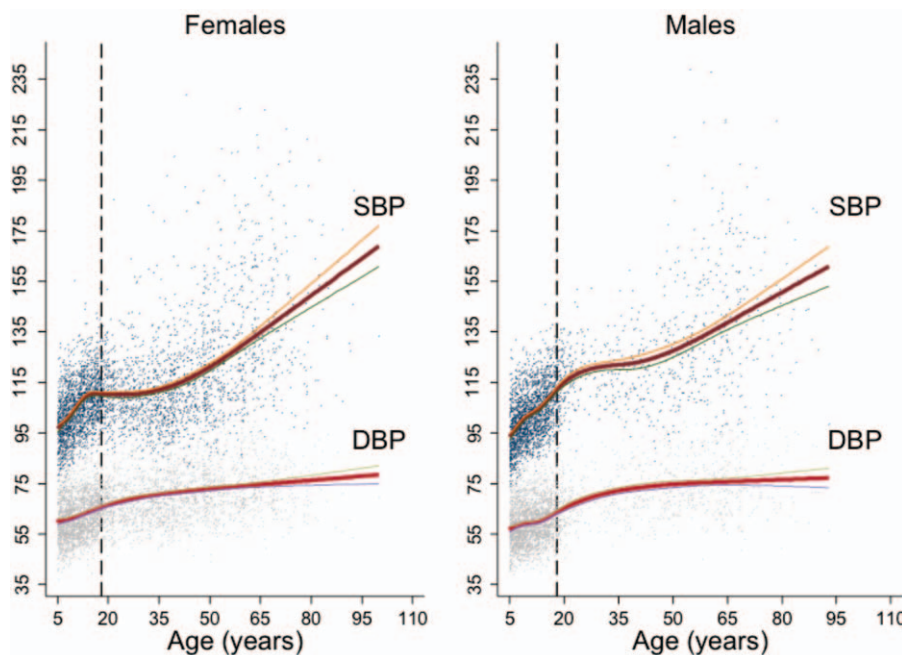
Figure 1. Systolic and diastolic blood pressure (SBP and DBP) in rural Gambian males and females. Cubic spline fit was employed to plot SBP (black dots) and DBP (grey dots) by age and sex for the whole study population (N=6160); orange and green thin lines indicate the 95% upper and lower boundaries and the thick red line represents the mean. The dashed line represents age 18 years, above and below of which we applied different criteria to define high BP as outlined in the materials and methods section. DBP = diastolic BP, SBP = systolic BP.

3. Results

3.1. Study population summary statistics

Summary statistics on the study population by age group and association of high BP with demographic, anthropometric, and clinical characteristics are given in Table 1. Of 6160 study participants, 3637 were aged 5 to <18-years old and 2523 aged 18 years and older. There is a preponderance of women (>70%) in the adult population because of outmigration of males for work purposes in this region. Information on mother's ID was not available for 568 (27.9%) individuals aged 5 to <18 years and 1309 (59.1%) individuals aged ≥18 years; these were treated as singletons in our analyses (Supplementary Table 1, http://links.lww.com/MD/B610).

The distribution of SBP and DBP by age and sex indicated slight differences between males and females, and a steady increase in BP measures across all ages (Fig. 1). We provide here for the first time the estimated population-specific reference values of 50th, 90th, 95th, and 99th percentiles for SBP and DBP by age and height (at the 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles) for boys and girls aged 5 to <18 years in rural Gambia (Supplementary Table 3, http://links.lww.com/MD/B610). The population-specific 95th BP percentile was used as basis for the determination of high BP in our Gambian children and adolescents, broadly following the guidelines for hypertension definition in the 4th Report. Although our high BP and the hypertension categories as stipulated by the 4th Report are not directly comparable, we show for information purposes our population-specific estimates of age, sex, and age- and sex-specific BP alongside the SBP and DBP 95th percentiles from the 4th Report[28] in Supplementary Table 5, http://links.lww.com/MD/B610 and as 3D plots (Supplementary Figure 1, http://links.lww.com/MD/B610). These indicate that our SBP and DBP percentiles by sex, age, and age- and sex-specific height percentile were generally lower in our Gambian population than those in

the 4th Report[28] (representing data from a mixed-ethnicity US population), particularly in boys.

In adults aged 18 years and older, BP increased with age as expected, with higher measures in females compared to males as indicated in Figure 1.

3.2. Analysis of high BP prevalence by covariates

Association analyses of individual covariates (employed as categorical variables) with high BP demonstrated correlations with demographic and most clinical parameters, but not anthropometric characteristics as shown in Table 1.

i) 5 to <18-year olds: In this age group 1730 (47.6%) were females, with similar proportion of females among those with high BP and normal BP (45.7% vs. 47.7%, P = 0.48). Those with high BP were younger than those not affected by high BP (median [range] = 9.5 and 10.6, respectively, P = 0.001). The zWT-HT was also higher in those with high BP (mean [SD] = −0.05 [1.3] vs. −0.28 [1.0], P = 0.004). Both high and normal BP groups had similar hemoglobin levels (median [range] = 12 [5–15.9] vs. 11.9 [5.9–17.0] g/dL, P = 0.11). Three individuals with high fasting glucose/diabetes were observed in the young age group, although none were observed to have high BP.

ii) ≥18-year olds: This age group (N = 2523) comprised more women than men; sex was not associated with high BP. The median age of those with high BP was almost 20 years more than those within the normal BP range (median [range] = 59.5 [18.2–91.1] vs. 38.3 [18–100.1] years, P < 0.0001). BMI was slightly higher in high BP than in the comparative lower BP group (median [range] = 21.6 [13.1–39.2] vs. 20.6 [12.5–41.7] kg/m², respectively, P < 0.0001); likewise, zBMI was higher in those with high BP (mean [SD] = 0.23 [1.1] vs. −0.05 [1.0], P < 0.0001). Only 525 (20.8%) of our adult participants had received some level of education and we observed fewer

Table 1

Summary statistics on rural Gambian study population by age group and association of high blood pressure with demographic, anthropometric, and clinical characteristics.

	5 to <18 y of age			≥18 y of age		
	High BP (n = 300)	Normal range BP (n = 3337)	P	High BP (n = 462)	Normal range BP (n = 2061)	P
Demographic characteristics						
Female, n (%)	137 (45.7)	1593 (47.7)	0.48	342 (74.0)	1,463 (71.0)	0.18
Age in y, median (range)	9.5 (5–17.9)	10.6 (5–17.9)	0.001	59.5 (18.2–91.1)	38.3 (18–100.1)	<0.0001
Educated*, n (%)	n/a	n/a	n/a	22 (4.8)	503 (24.4)	<0.0001
Anthropometric characteristics						
Weight, kg, median (range)	24.6 (11.7–75.8)	26.7 (11.4–89.1)	0.02	56.3 (33–115.2)	54.8 (30.3–111)	0.07
Height in cm, median (range)	130.4 (97–191.5)	135.0 (93.9–187.7)	0.001	160 (140.5–194.3)	162.5 (139.4–194.4)	<0.0001
zWT-HT, mean (SD)	−0.05 (1.34)	−0.28 (1.01)	0.004	n/a	n/a	n/a
BMI, kg/m², median (range)	n/a	n/a	n/a	21.6 (13.1–39.2)	20.5 (12.5–41.7)	<0.0001
zBMI, mean (SD)	n/a	n/a	n/a	0.23 (1.05)	−0.05 (0.98)	<0.0001
Clinical characteristics						
SBP, mmHg, median (range)	118.8 (96–155.5)	101.5 (67.5–131)	<0.0001	139.8 (87.5–239)	113.0 (80.5–218)	<0.0001
DBP, mmHg, median (range)	76.0 (44.5–101.5)	59.0 (37–82)	<0.0001	79.0 (49.5–125.5)	69.0 (44–121.5)	<0.0001
Hemoglobin, g/dL, median (range)	12.0 (5–15.9)	11.9 (5.9–17.0)	0.11	11.9 (7–17.2)	12.1 (5.1–17.3)	0.004
High fasting glucose/diabetes status†, n (%)	0 (0.0)	3 (0.09)	0.08	15 (3.2)	3 (0.1)	0.0002

BMI = body mass index calculated for those ≥18 years, DBP = diastolic blood pressure, high BP = high blood pressure (for definition please see main text and Supplementary Materials including Supplementary Tables 3 and 4, http://links.lww.com/MD/B610), P = P value, SBP = systolic blood pressure, y = years, zBMI = BMI z score calculated in ≥18-y olds only (for details see main text), zWT-HT = weight-for-height z score calculated in <18-y olds only.

* A participant was defined to be educated if s/he attended at least primary school.
† High fasting glucose/diabetes status was defined using a fasting glucose cut-off of >7 mmol/L.

Table 2

Prevalence of high blood pressure in rural Gambians stratified by age, sex, anthropometric trait, and anemia status.

	Prevalence of high BP, % (95% CI)					
	5 to <18 y of age (N=3637)			≥18 y of age (N=2523)		
	Male	**Female**	**All**	**Male**	**Female**	**All**
Overall	8.5 (7.4–9.9)	7.9 (6.7–9.3)	8.2 (7.4–9.2)	16.7 (14.1–19.6)	18.9 (17.2–20.9)	18.3 (16.8–19.9)
Age group						
5–9	10.1 (8.3–12.3)	9.4 (7.6–11.6)	9.8 (8.5–11.3)	n/a	n/a	n/a
10–17	7.0 (5.6–8.8)	6.7 (5.2–8.5)	6.9 (5.8–8.1)	n/a	n/a	n/a
18–29	n/a	n/a	n/a	1.0 (0.02–3.8)	3.6 (2.2–5.7)	2.8 (1.8–4.4)
30–39	n/a	n/a	n/a	3.4 (1.1–10.1)	11.1 (8.4–14.5)	9.8 (7.4–12.7)
40–49	n/a	n/a	n/a	9.6 (5.2–17.0)	15.4 (12.1–19.7)	14.2 (11.2–17.7)
50–59	n/a	n/a	n/a	18.3 (12.6–25.8)	28.3 (23.0–34.1)	25.0 (20.9–29.6)
60–69	n/a	n/a	n/a	35.2 (27.3–44.0)	52.7 (45.5–59.7)	45.7 (40.2–51.3)
70–79	n/a	n/a	n/a	55.3 (41.1–68.8)	52.9 (41.2–64.2)	53.8 (44.7–62.7)
≥80	n/a	n/a	n/a	57.9 (35.6–77.4)	45.8 (27.5–65.4)	51.2 (36.5–65.6)
zWT-HT*						
<−0.68	6.6 (4.8–8.9)	6.3 (4.5–8.6)	6.4 (5.1–8.0)	n/a	n/a	n/a
−0.68–0	7.6 (5.7–9.9)	7.6 (5.6–10.1)	7.6 (6.1–9.3)	n/a	n/a	n/a
0–<0.68	9.4 (7.1–12.4)	8.9 (6.5–12.1)	9.2 (7.5–11.3)	n/a	n/a	n/a
>0.68	14.0 (10.1–19.2)	11.4 (7.7–16.7)	12.8 (10–16.4)	n/a	n/a	n/a
BMI, kg/m²†						
Underweight	n/a	n/a	n/a	16.0 (14.6–21.7)	14.0 (10.6–18.2)	14.8 (12.0–18.1)
Normal	n/a	n/a	n/a	15.1 (12.1–18.6)	17.7 (15.6–20.0)	16.9 (15.2–18.9)
Overweight	n/a	n/a	n/a	32.6 (20.3–47.7)	28.0 (22.7–33.9)	28.6 (23.7–34.1)
Obese	n/a	n/a	n/a	75.0 (23.8–96.7)	34.5 (22.9–48.4)	37.3 (25.7–50.6)
Anemia‡						
Normal	9.5 (7.8–11.5)	8.5 (6.9–10.3)	9.0 (7.8–10.4)	11.3 (8.6–14.9)	17.8 (15.1–20.9)	15.4 (13.3–17.7)
Mild	6.1 (4.3–8.8)	4.3 (2.6–7.2)	5.4 (4.0–7.3)	21.0 (16.1–27.0)	18.3 (15.2–21.9)	19.1 (16.4–22.2)
Moderate or severe	7.0 (4.5–10.7)	7.5 (4.7–11.9)	7.2 (5.3–9.9)	26.8 (15.5–42.3)	17.6 (14.3–21.5)	18.4 (15.1–22.1)

BMI=body mass index calculated for those ≥18 years, CI=confidence interval, y=years, zWT-HT=weight-for-height z score calculated in 5 to <18 y of age only.

* For zWT-HT, we used the z statistics that divide a Gaussian distribution into quartiles (25% are <−0.68, 25% between −0.65 and 0, 25% between 0 and 0.68, and 25% >0.68)

† BMI categories: underweight (<18.5 kg/m²), normal (18.5 kg/m² ≤BMI <25 kg/m²), overweight (25 kg/m² ≤ BMI <30 kg/m²), and obese (BMI ≥30 kg/m²).

‡ Anemia was defined as described in the Supplementary materials and methods, http://links.lww.com/MD/B610.

educated people in the high BP versus the normal BP group (22 [4.8%] vs. 525 [24.4%], $P < 0.0001$). Hemoglobin levels were slightly lower in those with high BP (median [range]=11.9 (7–17.2) g/dL) versus those with normal BP (median [range]= 12.1 [5.1–17.3] g/dL, $P = 0.004$). A total of 18 individuals with high fasting glucose/diabetes were observed, 15 (3.2%) among the high BP and 3 (0.1%) among lower BP groups ($P = 0.0002$).

Estimated prevalence and 95% confidence interval of high BP by age group, sex as well as zWT-HT quartile or BMI category, and anemia category are shown in Table 2. As only 21 individuals with high fasting glucose/diabetes were identified in our population, the estimated effect of this risk factor on high BP is unlikely to be reliable. However, we decided not to exclude these individuals from any further analyses, as this study reports population-specific determinants of high BP.

i) 5 to <18-year olds (Table 2): The prevalence of high BP in this age group was 8.2% (95% confidence interval [CI]: 7.4–9.2) and comparable in females (7.9% [95% CI: 6.7–9.3]) and in males (8.5% [95% CI: 7.4–9.9]). Children aged 5 to 9 years appeared to present more frequently with high BP (prevalence 9.8% [95% CI: 8.5–11.3]) than those aged 10 to 18 years (prevalence 6.9% [95% CI: 5.8–8.1]).

ii) ≥18-years olds (Table 2): In those aged 18 years or above, the prevalence of high BP was 18.3% (95% CI: 16.8–19.9), and slightly higher in females than in males (18.9% [95% CI:

17.2–20.9] and 16.7% [95% CI: 14.1–19.6], respectively). In both males and females, the prevalence of high BP increased with age.

3.3. Univariable and multivariable analyses

All univariable and multivariable models were performed with continuous explanatory variables with exception of sex and high fasting glucose/diabetes status. Education was not considered in the univariable and multivariable analyses, as we observed a strong association between age and education ($P < 0.0001$, Supplementary Table 6, http://links.lww.com/MD/B610).

i) 5 to <18-year olds (Table 3): The univariable analyses demonstrated an increase in risk of high BP with higher zWT-HT ($P < 0.0001$) and surprisingly a slightly reduced risk with increasing age ($P < 0.0001$), but no evidence of association with hemoglobin level ($P = 0.16$). There was also no evidence of difference in the risk of high BP between males and females ($P = 0.48$) in children and adolescents. High fasting glucose/ diabetes was not assessed because there were only 3 individuals affected by this risk factor in this age group. The multivariable analysis therefore included age and zWT-HT but not sex and hemoglobin and gave comparable adjusted prevalence ratios as seen in the univariable analysis.

ii) ≥18-year olds (Table 3): In adults we assessed age, high fasting glucose/diabetes status, zBMI, hemoglobin level, and sex in the univariable analyses, with the former four being associated with high BP. These variables were hence included in the

Table 3

Risk factors of high blood pressure in rural Gambians aged 5 to <18 years and 18 years or above.

	Unadjusted PR (95% CI)	P	Adjusted PR (95% CI)	P
5 to <18 y olds[*]				
Age, y	0.95 (0.92–0.98)	0.001	0.95 (0.92–0.98)	0.002
zWT-HT	1.13 (1.07–1.19)	<0.0001	1.13 (1.07–1.19)	<0.0001
Sex (ref.: male)				
Female	0.93 (0.75–1.15)	0.48	—	—
Hemoglobin, g/dL	1.09 (0.97–1.23)	0.16	—	—
18-y old or above[†]				
Age, y	1.05 (1.04–1.05)	<0.0001	1.05 (1.04–1.05)	<0.0001
High fasting glucose/diabetes status[‡] (ref.: No)				
Yes	4.67 (3.73–5.84)	<0.0001	2.60 (2.02–3.36)	<0.0001
zBMI	1.26 (1.16–1.37)	<0.0001	1.28 (1.16–1.40)	<0.0001
Hemoglobin, g/dL	0.92 (0.87–0.97)	0.002	0.90 (0.85–0.96)	0.001
Sex (ref.: male)				
Female	1.13 (0.94–1.37)	0.19	—	—

CI = confidence interval, P = P value, PR = prevalence ratio, y = years, zBMI = BMI z score, zWT-HT = weight-for-height z score. We stratified the cohort into those <18 y and those ≥18 y of age as different body composition measures were applied in these age groups (internal zWT-HT and zBMI, respectively).

[*] N = 3637.

[†] N = 2523.

[‡] Those with high fasting glucose/diabetes status (N = 21) were categorized based on a fasting glucose cut-off of >7 mmol/L.

multivariable analysis, which showed an increase in risk of high BP with age as expected and about 3-fold higher risk in high fasting glucose/diabetes (however, there were only 21 affected by this risk factor in adults).

4. Discussion

In The Gambia, population-based data from over a decade ago reported prevalence rates for hypertension in >15-year olds of around 24% (based on BP ≥140/90 mmHg), with slightly reduced levels observed in rural groups.[20,22] Given the rise of noncommunicable diseases including cardiovascular disease in sub-Saharan Africa and the increased risks to health in the context of infectious comorbidities in this region,[39] it is essential to assess children and adolescents as target group for the evaluation of risk factors and health intervention. With this in mind we analyzed BP data on rural Gambians from the Kiang West Longitudinal Population Study (KWLPS) cohort[24] in The Gambia, served by the MRC Keneba field station. This included >6000 rural Gambians across all ages above 5 years, for whom BP measurements were collected as part of the Keneba Biobank (http://ing.mrc.ac.uk/home/research-areas/the-keneba-biobank/) and paid particular attention to those younger than 18 years of age. We constructed reference percentiles for BP by sex, age, and height in Gambians aged 5 to <18-year for the first time (Supplementary Table 3, http://links.lww.com/MD/B610), with those with SBP above the 95th percentile for age, sex, and height categorized as "high BP." Our high BP cutoff reference values are overall lower than the US 4th Report norms,[28] particularly in boys. Although our high BP and the 4th Report hypertension groups are not directly comparable for reasons outlined above, we considered BP reference standards represented in this study more applicable to identify individuals with high BP among Gambian children and adolescents. For those aged 18 years and above, we applied the definition of high BP as those with BP >140/90 and/or on hypertensive treatment and/or with recorded hypertension diagnosis in our clinical database. We employed different covariates of body composition (zWT-HT vs. BMI) in the children and adolescents versus adults (≥18 years), as BMI is strongly age-dependent below the age of 18 years (as outlined in

the methods section). To summarize, across all ages our high BP, outcome measure is based on a cross-sectional assessment of BP, and it does reflect a clinical diagnosis of hypertension; however, high BP can be viewed as preclinical indication of hypertension.

Our analyses resulted in some surprising findings. We observed a higher prevalence of high BP of 9.8% in 5 to 9-year olds compared to 6.9% in those aged 10 to <18 years; in all <18-year olds the proportion of high BP was greater among the girls (Table 2). We do not deem this to be owing to measurement error, as we measured BP in triplicate and excluded the first measurement to avoid "white coat" bias and all measurements were taken by trained field assistants in the field (not wearing a white coat), rather than a clinic environment. However, we cannot exclude the possibility that particularly the youngest study participants were more intimidated leading to slightly inflated BP values. Our finding may also be influenced by the age-sex-height distribution in 5 to 9-year olds, wherein growth restriction because of malnutrition and infection in earlier life is more evident than in 10 to 18-year olds, who have had more time for catch-up growth.

Following on from this, our multivariable models revealed associations with substantially increased risk of high BP for females and slightly increased risk in those with higher zWT-HT and decreased risk by age, respectively, in the <18-year olds. We do as of yet not have an explanation for this finding; however, we propose that these findings in children and adolescents warrant further investigation. Our data are in line with our previous study in the same population which collected data on cardiovascular risks in adolescents (N = 1317, aged 14.1 ± 1.5y) as part of a follow-up study on maternal nutritional supplementation.[40] This study showed that 8.5% of boys and 7.9% of girls were hypertensive, defined as SBP above the 95% percentile for height and age in our rural Gambian population. A cross-sectional survey in schoolchildren in Uganda also demonstrated high BP to be associated with female sex and zBMI, as well as age[18] and higher prevalence of hypertension in girls was likewise seen in South Africa and Nigerian children/adolescents with higher body mass and/or living in more urban environments.[15,16,41] The studies in children in Uganda, South Africa, and Nigeria all appear to apply the internationally used US 4th Report[28]

normograms to identify hypertensives in their children and adolescents. However, it is of note that, like in our present study, although BP was measured multiple times, these measurements were not always conducted on different occasions and therefore the designation as hypertensive in these studies is not necessarily in line with the 4th Report[28] or represents a clinical diagnosis of hypertension. Having analyzed for the first time the whole spectrum of ages 5 to <18 years in a large proportion of our Gambian population and applying our own population-specific 95th percentile reference cut-offs to define high BP (following broadly the 4th Report[28] guidelines), we deem such population-specific reference values more appropriate, as age, sex, and height percentiles used to determine BP percentiles differ between populations in LMIC including in sub-Saharan Africa and those observed in US children. This echoes the conclusion made by colleagues investigating pediatric hypertension in Iran.[42]

In the adult age groups (≥18 years), high BP prevalence was shown to rise with age and tends to be more frequently seen in men compared to women, as expected. The multivariable analyses considered age, sex, zBMI, and high fasting glucose/diabetes status, all of which were associated with high BP, although zBMI only marginally and the number of those with high fasting glucose/diabetes were very low. These data are comparable to other studies conducted previously in The Gambia and elsewhere in the region.

There are some limitations to our analyses. Several risk factors including smoking, salt and alcohol intake, education, breast-feeding, prepubertal stage, family history, diabetes, and infection could be considered in the context of high BP/hypertension particularly in adult populations. We had no or limited data available on these as part of this study. Smoking is considered a risk factor for cardiometabolic disease (though not hypertension). The prevalence of smokers in rural Gambia was previously reportedly as 42% in men and 6% in women.[43] However, anecdotally we believe the prevalence of smoking to be lower in the rural Kiang West district and thus to be a less relevant risk factor, particularly in women. Alcohol intake is negligible in our predominantly Muslim population. Salt is added as an ingredient of most dishes; however, how much of this is consumed on average per person is difficult to assess. This would be an interesting area to explore further, particularly in view of salt-sensitive hypertension, which is known to be more prevalent in African ancestry population and is in part owing to genetic factors.[44] We had data on education only in those aged ≥18 years and applied a crude binary measure of with/without education based on attendance at primary school at least for our exploratory analyses. Education was found to be highly associated with age (as expected, Supplementary Table 6, http://links.lww.com/MD/B610) and we thus dropped education from all further analyses. Breastfeeding is considered to have a beneficial effect on lowering of later BP.[45] In The Gambia, exclusive breastfeeding for the first 6 months of age is strongly promoted both by the government and the MRC and practiced routinely; any effect would therefore be assumed to be universal across our population. Pubertal development may affect differences in BP level owing to stage of sexual maturity, for example, age of menarche. Although we did not have data on puberty staging available to include in our analyses, adjustments for age, sex, height, and weight will at least to some degree indirectly account for pubertal development. Family history of high BP/hypertension could not be evaluated, as our electronic clinical records system set up in 2009 is not mature enough for the investigation of health outcomes in family pedigrees. We were

also not able to estimate the true prevalence of diabetes in our population, as we did not have data from an oral glucose tolerance or HbA1c test. However, we employed high fasting glucose (>7 mmol/L) as indicator of risk of diabetes. Finally, other studies have stipulated effects of infection (e.g., helminth or malaria) on BP in children.[18] We did not have any information on infection status for our population, but because data on this cohort were collected as part of the MRC Keneba Biobank, all participants are considered healthy at recruitment. In adults, hemoglobin level was inversely associated with BP (Tables 1 and 3), which could indicate that underlying nonsymptomatic infection may be present. However, this effect was not seen in children and adolescents, and anemia as categorical variable was not associated with high BP.

Our study also has several strengths. Primarily, with >6000 individuals this represents to our knowledge the largest dataset on BP across a healthy rural sub-Saharan population covering all ages above 5 years. We focused our analyses particularly on children and adolescents <18 years of age and constructed population-specific reference percentiles for BP by sex, age, and height for the first time. Furthermore, stored biological samples collected at the same time as the BP measurement are available through the MRC Keneba Biobank. Therefore, there is opportunity to conduct future analyses on blood and urine biomarkers, which may be indicative of underlying factors contributing to the observed high prevalence of high BP in this younger age group, particularly in girls. We are also able to follow-up these individuals longitudinally, as the KWLPS[24] is a live prospective cohort, which allows for an integrated system of research and health care provision for this population. For instance, we are currently conducting an analysis of the role of known and putative functional genetic variants affecting high BP/hypertension based on Illumina HumanExome array data on a subset of ~3000 individuals.

Like in other settings across sub-Saharan Africa, rising rates of hypertension are reported in The Gambia.[3] Stroke and ischemic heart disease are now counted among the 4th and 7th cause of death in the WHO African region.[46] However, data from rural areas and in younger age groups across sub-Saharan Africa remain scarce. Recently, a systematic review and meta-analysis protocol for hypertension prevalence, incidence, and risk factors among children and adolescents in Africa was published.[47] The authors highlight that there is considerable variability in the prevalence estimates for published studies in Southern and Western African pediatric populations ranging from 0% to 22.3%. This we propose is in part because of differences in the definition of hypertension as discussed above, emphasizing the need for more consistent methodological and clinical evaluation of such health outcomes and/or the application of population-specific references as we describe here. As far as we are aware, this is the largest study of its kind evaluating risk factors for high BP in a rural population in West Africa. We observe a prevalence of high BP of 8.2% in these rural children and adolescents, which poses health risks that need to be addressed urgently given that raised BP in childhood can aggravate cardiovascular outcomes in later life. Strategies must be developed particularly in this younger age group to modify behavior that reduces cardiovascular risk factors (e.g., salt intake) and to build capacity for maintenance of long-term follow-up and continued treatment where applicable. Importantly, awareness also needs to be raised in view of early detection, treatment, and control of high BP/hypertension, thereby prompting appropriate policy responses to minimizing disease risks and optimizing related health outcomes.[28]

Acknowledgments

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