Cardiovascular Topics

Prevalence and associated risk factors for elevated blood pressure in young adults in South Africa

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Abstract

Background: Sub-Saharan Africa has been shown to have a high prevalence of hypertension (58% in rural black South Africans) with an accelerated course ending in end-stage renal disease. We sought to determine whether the prevalence of elevated blood pressure (EBP) in early adulthood was associated with any risk factors and/or renal target-organ damage in young adulthood, which could prevent development of these cardiorenal sequelae.

Methods: Data including risk factors for hypertension and markers of kidney damage were collected from young adults (n = 933; age 28 years; 52% female) participating in the Birth to Twenty Plus (BT20) cohort in Soweto, South Africa. Blood pressure was measured on one occasion.

Results: Fifty-four per cent of the study sample had EBP with more men affected (62%) than women (47%) ($p < 0.001$). Body mass index (BMI), hyperuricaemia and albuminuria had significant associations with EBP in men. In women, BMI, hyperuricaemia and a self-reported history of gestational hypertension had significant associations.

Conclusion: Our findings suggest that the pathophysiology of EBP in young adults differs between the genders and highlights a number of modifiable factors in its development.

Keywords: hypertension, young adults, risk factors, target-organ damage

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Chronic non-communicable diseases (NCD) are responsible for 71% of deaths worldwide and four out of five of these deaths occur in low- and middle-income (LMIC) countries. Of these, cardiovascular disease is the most common, with hypertension accounting for 7.1 million deaths annually.

Many LMIC countries face combined burdens of infectious and chronic disease, with the latter starting to predominate. For example, in 2018 the leading cause of death in South Africa was tuberculosis, but when grouping chronic diseases together (most frequently diabetes, cardiac and cerebrovascular disease and hypertension), they were responsible for 51% of deaths. Furthermore, chronic diseases tend to emerge earlier in the life course and are responsible for 85% of premature adult NCD deaths in those from LMIC.[1]

Previously, urban study sites in South Africa have shown that when compared to other population groups, hypertension in black Africans is more severe and associated with greater degrees of target-organ damage (malignant hypertension or kidney injury/kidney failure) for any given level of blood pressure.[2] In rural black South Africans, the prevalence of hypertension has been reported as high as 58%, however, studies assessing consequent target-organ damage in the form of kidney injury remain scarce.[3]

From available data published by the South African Renal Registry (2018), the most common cause of end-stage renal disease in patients on chronic dialysis therapy is hypertension (35%), contradicting high-income countries where the most common cause is diabetes. Similarly, the median age of those receiving chronic dialysis in South Africa was younger (53 years), compared to similar cohorts in the USA, at 63 years.[4]

We recently reported that the prevalence of elevated blood pressure (EBP) in the Birth to Twenty Plus (BT20) cohort in urban Soweto, South Africa, was 36% at age 22 years and that blood pressure (BP) tracked through childhood and adolescence into early adulthood.[5] While our data provide strong evidence of the emergence of EBP early along the life course, we have not investigated whether EBP is associated with target-organ damage, a strong predictor of adverse outcomes. In this study from the BT20 cohort, now aged 28 years, we aimed to determine the prevalence of EBP, characterise associated risk factors and establish whether there was evidence of target-organ damage using surrogate markers for vascular and kidney injury.

Methods

BT20 is a longitudinal birth cohort following singleton infants (n = 3 273) born to mothers in Soweto, Johannesburg, a predominantly black, urban area, in 1990. Details of recruitment and cohort attrition are described elsewhere.[6] For this study, participants who were seen at the 2012 data-collection wave (n = 1 540) were invited to participate at age 28 years. Participants were excluded if they were pregnant at the time of assessment. Participants with missing data relating to kidney function were excluded from the analysis.

Blood pressure was measured using an Omron M6 (HEM-7321-E) automated machine (Kyoto, Japan). This device has been validated according to the European Society of Hypertension International Protocol in a European population.[7] Blood pressure was measured by trained research assistants and inter-observer variability was determined by checking for reproducibility and repeatability between all research assistants prior to commencement of the study.

Participants had to have refrained from smoking or doing any physical exercise for 30 minutes prior to the measurement. They were asked to sit comfortably with legs uncrossed and backs supported for five minutes before readings were taken. Three measurements were taken on the left arm at two-minute intervals using an appropriately sized cuff determined by the mid-upper arm circumference of the participant. The average of the three recordings was recorded for analysis. If there was a difference of > 5 mmHg between any of the three measurements, a fourth measurement was taken and the average of the lowest three measurements was recorded for analysis.

Participants were grouped into one of three categories, as defined by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, the JNC7 report. Normotensive was defined as systolic blood pressure (SBP) < 120 mmHg and diastolic blood pressure (DBP) < 80 mmHg; prehypertensive: SBP ≥ 120 mmHg and <140 mmHg or DBP ≥ 80 mmHg and < 90 mmHg; or hypertensive: SBP ≥ 140 mmHg or DBP ≥ 90 mmHg. This classification is supported by the JNC7 report to better identify those at risk for developing hypertension.[8] Participants in the prehypertensive or hypertensive categories were classified for analysis as having EBP.

Trained research assistants carried out anthropometric measurements. These research assistants underwent assessment prior to the study and the co-efficient of variation was < 2%. Weight was measured on a digital scale to the nearest 0.1 kg and standing height to the nearest 0.1 cm with a wall-mounted stadiometer (Holtain, United Kingdom). Waist circumference was measured with a tape measure at the midpoint between the iliac crest and the lowest palpable rib in the mid-axillary plane to the nearest 0.1 cm. Hip circumference was measured at the most protruding part of the buttocks with the participant standing. The average of three measurements was recorded. Waist:hip ratios and body mass indices (BMI) [weight (kg) divided by height squared (m^2)] were derived from these data.

A standardised questionnaire was administered by trained research assistants. Participants answered questions with regard to past and current risk factors relating to hypertension and kidney disease. These included questions relating to any family history of hypertension, diabetes, hypercholesterolaemia, heart disease and/or renal disease, any history of being diagnosed with any of the above, any history of childhood or adult urinary tract infections, kidney stones or dialysis (acute or chronic) and questions relating to smoking and alcohol habits, over-the-counter and illegal drugs, traditional medicines and use of snuff.

Women were asked about their number of pregnancies and live births, contraceptive use and gestational hypertension. Socio-economic status (SES) was measured using an asset-based household SES measured tool based on a validated standardised questionnaire by the Demographic and Health Survey for Developing Countries (available at http://www.dhsprogram.com/).

Fasting blood samples were obtained in serum separator tubes for measurement of serum creatinine and uric acid levels. Blood tubes were allowed to stand for 30 to 60 minutes before being centrifuged at 3 000 rpm for 10 minutes and serum was decanted and frozen at –80ºC. Serum creatinine level was measured by the Jaffe method that was IDMS-traceable to a standard reference material, using a Cobas 6000/c501 analyser. The laboratory adheres to standard daily internal quality-control procedures, and a strict external quality-control programme through the College of American Physicians with approved certification for urine and serum chemistry for the time period in which testing was performed. Estimated glomerular filtration rate (eGFR) was then calculated using the $CKD\text{-}EPI_{(creatine)}$ 2009 equation not corrected for African-American ethnicity. Uric acid level was measured by enzymatic colorimetric testing on the Roche/Hitachi Cobas c analyser.

Mid-stream urine samples were collected after clear instructions to participants to ensure minimal contamination of specimens. Women had to be at least two days post menses for urine to be collected. Urine dipstick testing was performed by trained research assistants using the Roche Combur® 10 sticks, which were calibrated weekly. Urine dipstick results for haematuria, leukocyturia and proteinuria were recorded as per dipstick result. Any degree of positivity for blood or protein was then analysed as positive. Urine pregnancy tests were performed on all female participants using an antibody-based urine HCG strip test.

Specimens were then stored in ice for a maximum of two hours before being centrifuged at 1 600 rpm for 10 minutes and stored at –80ºC. Urine albumin concentration was measured using a colorimetric method on the Cobas 6000/c501 analyser and urine creatinine by the Jaffe method on the same analyser. The urine albumin:creatinine ratio (uACR) was calculated and used to classify albuminuria as normal (uACR < 3 mg/mmol); microalbuminuria (3–30 mg/mmol); and overt albuminuria (uACR > 30 mg/mmol). Participants with microalbuminuria and overt albuminuria were grouped together due to small numbers in the overt albuminuria group.

Finger-prick testing for HIV using an antibody ELISA-based test kit was performed by nurses or research assistants who had completed a certified course in HIV counselling and testing. All participants signed consent for testing and received pre- and post-test HIV counselling. Participants who had positive test results were referred to their local HIV clinic for confirmatory testing and the initiation of anti-retroviral therapy.

Statistical analysis

All statistical analyses were done using STATA 15.0. For categorical variables and continuous variables with normal

distribution, *t*-tests, chi-squared tests and ANOVAs were done to compare study characteristics by gender and hypertension risk. Mann–Whitney and Kruskall–Wallis tests were done to compare variables that were not normally distributed. Multiple linear regression models were run to assess the associations between SBP and DBP with contemporary growth factors, risk factors and measures of renal function. Participants with missing data related to kidney function such as serum creatinine or uACR were excluded in the analytical sample. Level of significance was set at $p < 0.05$.

Results

Table 1 shows study participant characteristics by gender (n = 933, 48% male) at the 28-year follow-up visit. Overall, 54% of the cohort had EBP with more men affected (62%) than women (47%) ($p < 0.001$). For those with EBP at 22 years, 75% had EBP at the 28-year follow up. When compared to males, young females had significantly higher BMI ($p < 0.001$), higher HIV prevalence ($p < 0.001$), and increased frequencies of dipstick-positive haematuria ($p < 0.001$) and leukocyturia ($p < 0.001$). Of the females who had previously been pregnant, 19% reported a history of gestational hypertension.

Kidney function was well preserved with eGFR above 90 ml/min/1.73 m² in 96% of all participants. Only two participants had an initial eGFR less than 60 ml/min/1.73 m² but both normalised (> 90 ml/min/1.73 m²) with repeat testing after a minimum period of three months. More women (6%) than men (2.5%) had albuminuria (uACR > 3 mg/mmol) ($p = 0.02$)

When we investigated gender-specific risk for EBP, we found that increased weight, increased waist-to-hip ratios, higher BMI, the presence of EBP at age 22 years, and hyperuricaemia were associated with EBP in both genders compared to normotensive males and females (Tables 2, 3). A history of gestational hypertension was associated with EBP among females. eGFR did not differ significantly between males and females or have any significant association with blood pressure. When comparing males with EBP to their normotensive counterparts, there was a significant association with albuminuria [0.9 mg/mmol (0.3–1.5) vs 0.3 mg/mmol (0.2–0.3); ($p < 0.001$), and dipstick-positive haematuria (5.7 vs 0.6%; $p = 0.003$), respectively]. Neither albuminuria nor haematuria was associated with EBP in the female cohort.

Table 1. Sociodemographic and clinical characteristics of young adults (28 years) from the BT20 cohort, stratified by gender

Variables	*Total*	*Male*	*Female*	p-*value*
Sample size, *n* (%)	933	450 (48)	483 (52)	
Age (years)	933	27.9 (0.34)	27.9 (0.98)	0.95
Socio-economic status	933	10 (8–11)	10 (9–11)	
Weight (kg)	931	66.9 (14.3)	71.9 (18.5)	< 0.001
Height (cm)	932	171.6 (6.4)	159.3 (6.1)	< 0.001
Waist:hip ratio	933	0.83 (0.1)	0.78 (0.8)	< 0.001
BMI (kg/m²)	931	22.7 (4.5)	28.3 (7.0)	< 0.001
Average SBP (mmHg)	933	121.3 (12.9)	112.5 (12.6)	< 0.001
Average DBP (mmHg)	933	81.1 (9.6)	79.2 (9.3)	0.003
Blood pressure, *n* (%)				
Elevated blood pressure	507 (54)	281 (62)	226 (47)	< 0.001
Prehypertension	384 (41)	216 (48)	168 (35)	< 0.001
Hypertension	124 (13)	65 (14)	59 (12)	
Women with self-reported gestational hypertension	483		67 (19)	
HIV status, *n* (%)				
HIV negative	612	282 (63)	330 (68)	< 0.001
HIV positive	92	21 (5)	71 (15)	
Refused test	229	147 (33)	82 (17)	
Laboratory investigations				
eGFR (ml/min/m²)	933	119.2 (110.3–124.9)	121.4 (114.0–126.3)	< 0.001
> 90, *n* (%)	896	430 (96)	466 (96)	0.77
60–90, *n* (%)	35	19 (4)	16 (3)	
< 60, *n* (%)	2	1 (0.2)	1 (0.2)	
uACR (mg/mmol)	911	0.2 (0.1–0.3)	0.2 (0.1–0.5)	< 0.001
< 3, *n* (%)	872	436/447 (97.5)	436/464 (94)	0.02
3–30, *n* (%)	33	10 (2.2)	23 (5)	
> 30, *n* (%)	6	1 (0.2)	5 (1)	
Uric acid, *n* (%)	933			
Normal	819	383 (85)	436 (90)	
High	114	67 (15)	47(10)	0.016
Urine dipsticks, *n* (%)				
Haematuria	914	17 (4)	84 (18)	< 0.001
Proteinuria	914	8 (1.8)	9 (1.9)	0.86
Leucocyturia	914	13 (3)	114 (25)	< 0.001

Summary statistics presented as mean (SD), median (IQR) or *n* (%); estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI$_{(creatinine)}$ equation without adjustment for African-American ethnicity and data represent single screen only; urine albumin:creatinine ratio (uACR) data represent single screen only. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 2. Gender-specific associated risk factors for EBP in young male adults (28 years) from the BT20 cohort

Variables	*Total*	*Normal BP*	*Elevated BP*	p-*value*
Sample size, *n* (%)	450	169 (37.6)	281 (62.4)	
Age (years)	450	27.9 (0.3)	27.9 (0.3)	0.802
Weight (kg)	450	63.4 (11.1)	68.9 (15.6)	< 0.001
Height (cm)	450	171.9 (6.3)	171.5 (6.5)	0.457
Waist:hip ratio	450	0.81 (0.05)	0.84 (0.1)	< 0.001
BMI (kg/m²)	450	21.4 (3.5)	23.4 (4.9)	< 0.001
Normotensive age 22 years, *n* (%)	165	117 (70.9)	100 (37.7)	< 0.001
EBP age 22 years, *n* (%)	265	48 (29.1)	165 (62.3)	
HIV status, *n* (%)				
HIV negative	282	108 (63.9)	174 (61.9)	0.476
HIV positive	21	10 (5.9)	11 (3.9)	
Refused test	147	51 (30.2)	96 (34.2)	
Laboratory investigations				
eGFR (ml/min/m²)	450	116.7 (114.8–118.6)	116.2 (114.5–117.8)	0.985
> 90, *n* (%)	430	165 (97.6)	265 (94.3)	0.179
60–90, *n* (%)	19	4 (2.4)	15 (5.3)	
< 60, *n* (%)	1	0 (0)	1 (0.4)	
Urine ACR (mg/mmol)	447	0.3 (0.2–0.3)	0.9 (0.3–1.5)	< 0.001
< 3, *n* (%)	436	167 (99.4)	269 (96.4)	0.041
≥ 3, *n* (%)	11	1 (0.6)	10 (3.6)	
Uric acid (mmol/l)	449	0.3 (0.1)	0.3 (0.1)	0.186
< 0.43 mmol/l, *n* (%)	383	152 (89.9)	231 (82.2)	0.017
≥ 0,43mmol/l, *n* (%)	67	17 (10.1)	50 (17.8)	
Urine dipsticks, *n* (%)				
Haematuria	17	1 (0.6)	16 (5.7)	0.003
Proteinuria	8	1 (0.6)	7 (2.5)	0.134
Leucocyturia	13	4 (2.4)	9 (3.2)	0.426

Summary statistics presented as mean (SD), median (IQR) or *n* (%); estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI$_{(creatinine)}$ equation without adjustment for African-American ethnicity and data represent single screen only; urine albumin:creatinine ratio (uACR) data represent single screen only. BMI, body mass index; EBP, elevated blood pressure.

Table 3. Gender-specific associated risk factors for EBP in young female adults (28 years) from the BT20 cohort

Variables	*Total*	*Normal BP*	*Elevated BP*	p-*value*
Sample size	483	257 (53.2%)	226 (46.8%)	
Age (years)	483	27.8 (0.3)	27.9 (1.4)	0.072
Weight (kg)	483	68.7 (16.4)	75.7 (20.0)	< 0.001
Height (cm)	483	158.9 (6.1)	159.7 (6.1)	0.138
Waist:hip	483	0.78 (0.08)	0.79 (0.09)	< 0.025
BMI (kg/m^2)	483	27.2 (6.3)	29.7 (7.6)	< 0.001
Normotensive age 22 years, *n* (%)	332	206 (85.8)	126 (61.8)	< 0.001
EBP age 22, *n* (%)	112	34 (14.2)	78 (38.2)	
HIV status, *n* (%)	483			
HIV negative	330	169 (65.8)	161 (71.2)	0.106
HIV positive	71	46 (17.9)	25 (11.1)	
Refused test	82	42 (16.3)	40 (17.7)	
Laboratory investigations				
eGFR (ml/min/m^2)	483	118.9 (117.3 – 120.4)	118.2 (116.5 – 120.0)	0.402
> 90, *n* (%)	466	247 (96.1)	219 (96.9)	1.000
60–90, *n* (%)	16	9 (3.5)	7 (3.1)	
< 60, *n* (%)	1	1 (0.4)	0 (0.0)	
Urine ACR (mg/mmol)	464	1.3 (0.4 – 2.1)	1.4 (0.7 – 2.2)	0.761
< 3, *n* (%)	436	238 (92.6)	198 (87.6)	0.259
≥ 3, *n* (%)	28	13 (5.2)	15 (7.0)	
Uric acid (mmol/l)	483	0.26 (0.25 – 0.27)	0.28 (0.27 – 1.29)	< 0.001
< 0.36 mol/l), *n* (%)	436	239 (93.0%)	197 (87.2%)	0.031
≥ 0.36 mmol/l), *n* (%)	47	18 (7.0%)	29 (12.8%)	
Urine dipsticks, *n* (%)				
Haematuria	84	45 (17.9)	39 (18.2)	0.934
Proteinuria	9	3 (1.2)	6 (2.8)	0.313
Leucocyturia	114	66 (26.3)	48 (22.4)	0.334
Risk factors, *n* (%)				
Have children	358	189 (73.5)	169 (74.8)	0.835
Gestational hypertension	67	21 (11.1)	46 (27.2)	< 0.001
Type of contraception, *n* (%)				
Combined oral	47	27 (25.2)	20 (18.4)	0.458
Intrauterine device	23	13 (12.2)	10 (9.2)	
Injectable progesterone	143	66 (61.7)	77 (70.7)	
Sterilisation	3	1 (0.9)	2 (1.8)	

Summary statistics presented as mean (SD), median (IQR) or *n* (%); estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI$_{(creatinine)}$ equation without adjustment for African-American ethnicity and data represent single screen only; urine albumin:creatinine ratio (uACR) data represent single screen only. BMI, body mass index; EBP, elevated blood pressure.

Being female was associated with a 10-mmHg lower SBP than being male and a 3-mmHg lower DBP ($p < 0.001$ and $p = 0.001$). A unit higher change in BMI contributed to a 0.5-mmHg higher SBP and 0.3-mmHg higher DBP. Albuminuria was associated with a 7.8-mmHg higher SBP ($p < 0.001$) and 3.9-mmHg higher DBP ($p = 0.01$). There was no association found between eGFR and BP. Uric acid on its own was associated with both higher SBP and DBP, however the association for SBP was completely attenuated when BMI was added to the model. Being HIV positive was found to be associated with lower SBP and DBP by 2.9 and 2.4 mmHg, respectively (Table 4).

Regression analyses for SBP were analysed separately for males and females (Tables 5, 6). Adult BMI remained significantly associated with SBP in males and females, however each unit increase in BMI was associated with a relatively greater increase in SBP for males (+0.8 mmHg, $p < 0.001$) compared to females (+0.4 mmHg, $p < 0.001$). Similarly, albuminuria was associated with a 9-mmHg higher SBP in males ($p = 0.017$) and 6-mmHg higher SBP in females ($p = 0.013$).

Table 4. Cross-sectional associations with SBP and DBP at age 28 years

	SBP (mmHg)			*DBP (mmHg)*		
Models	Beta	*95% CI*	p-*value*	*Beta*	*95% CI*	p-*value*
Model 1 (931)						
Age (years)	1.5	0.4–2.5	0.01	0.7	–0.1–1.5	0.11
Female (vs male)	–10.0	–12.4 to –7.7	< 0.001	–3.0	–4.7 to –1.1	0.001
BMI	0.5	0.4–0.6	< 0.001	0.3	0.2–0.4	< 0.001
Height (cm)	0.1	–0.0–0.2	0.07	0.03	–0.1–0.1	0.58
Model R^2			0.159			0.038
Model 1 + urine ACR (909)						
Urine ACR (mg/mmol)	0.2	0.1–0.3	0.01	0.1	–0.0–0.1	0.22
Model R^2			0.165			0.040
Model 1 + eGFR (931)						
eGFR (ml/min/ 1.73 m^2)	–0.0	–0.1–0.0	0.51	–0.0	–0.1–0.0	0.50
Model R^2			0.159			0.038
Model 1 + uric acid (930)						
Uric acid (mmol/l)	10.9	–0.4–2.1	0.06	9.6	1.1–18.1	0.03
Model R^2			0.162			0.043
Model 1 + HIV status (931)						
HIV positive (vs negative)	–2.9	–5.7 to –0.2	0.04	–2.4	–4.4 to –0.3	0.03
Refused test	0.8	–1.2–2.7	0.44	0.8	–0.6 2.3	0.27
Model R^2			0.164			0.046

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; ACR, albumin:creatinine ratio.

The effect of the significance of uric acid being eliminated by BMI remained in males but not for females. Each unit increase in uric acid was associated with a 19.7-mmHg higher SBP ($p = 0.03$) in females. The lower BP associated with HIV-positive status remained significant only in females.

Table 5. Cross-sectional associations with SBP at age 28 years in males vs females

	Males (n = *448*)			*Females* (n = *483*)		
Models	*Beta*	*95% CI*	p-*value*	*Beta*	*95% CI*	p-*value*
Model 1						
Age (years)	2.9	–0.5–6.3	0.10	1.3	0.2–2.4	0.02
BMI	0.8	0.6–1.1	< 0.001	0.4	0.2–0.5	< 0.001
Model R^2			0.085			0.043
Model 1 + urine ACR *n* = 445 *n* = 462						
Urine ACR ≥ 3 mg/ mmol	9.0	1.6–16.4	0.017	6.1	1.3–10.8	0.013
(vs < 3 mg/mmol) Haematuria (vs no haematuria)	8.7	2.7–14.6	0.005	0.1	–2.8–3.1	0.92
Model R^2			0.113			0.049
Model 1 + eGFR (931) *n* = 448 *n* = 483						
eGFR (ml/min/ 1.73 m^2)	0.0	–0.1–0.1	0.78	–0.1	–0.1–0.0	0.21
Model R^2			0.089			0.059
Model 1 + uric acid (930) *n* = 447 *n* = 483						
Uric acid (mmol/l)	1.7	–13.6–17.1	0.83	19.7	2.5–36.9	0.03
Model R^2			0.089			0.065
Model 1 + HIV status (931) *n* = 448 *n* = 483						
HIV positive (vs negative)	–2.4	–7.9–3.1	0.39	–3.2	–6.3 to –0.0	0.047
Refused test	0.6	–2.0–3.2	0.63	0.6	–2.4 3.6	0.68
Model R^2			0.092			0.065

BMI, body mass index; eGFR, estimated glomerular filtration rate; ACR, albumin:creatinine ratio.

Table 6. Cross-sectional associations with SBP in females at age 28 years

Models	*Beta*	*95% CI*	p-*value*
Model 1 (n = 483)			
BMI	0.3	0.1–0.4	0.004
Height (cm)	0.2	0.0–0.4	0.04
Uric acid	22.1	4.7–39.5	0.01
Urine ACR ≥ 3 mg/mmol (vs < 3 mg/mmol)	6.3	1.6–11.0	0.008
Model R^2			0.060
Model 1 + contraception use (n = 481)			
Combined oral contraceptive (vs no contraception)	0.0	–3.9–3.9	1.0
Intra-uterine device	–1.5	–6.6–3.7	0.57
Injectables	4.6	2.1–7.2	< 0.001
Sterilisation	–0.6	–14.3–13.2	0.93
Model R^2			0.083
Model 1 + gestational hypertension (n = 358)			
BMI	0.1	–0.1–0.3	0.47
Height (cm)	0.2	0.0–0.4	0.03
Uric acid	20.7	0.8–40.6	0.04
Urine ACR ≥ 3 mg/mmol (vs < 3 mg/mmol)	7.6	2.5–12.7	0.003
Gestational hypertension (vs no gestational hypertension)	9.5	6.2–12.8	< 0.001
Model R^2			0.133

BMI, body mass index; ACR, albumin:creatinine ratio.

Due to the high numbers of females with EBP having given a history of gestational hypertension, female-specific risk factors were analysed separately for SBP (Table 6). Those of significance included a history of gestational hypertension and type of contraceptive use, specifically injectable contraceptives, which were associated with an increase in SBP of +4.6 mmHg compared to those not using contraception. Of the 358 (74%) females with a history of prior pregnancies, those who self-reported a history of gestational hypertension had a 9.5-mmHg higher SBP ($p < 0.001$).

Discussion

In this study of young black Africans living in urban South Africa, we have shown a high prevalence of EBP, particularly in males, and that an overwhelming proportion who had EBP at 22 years continued to have EBP six years later. In addition, EBP in females was associated with a history of gestational hypertension and injectable contraceptive use, while in males EBP was associated with haematuria. Albuminuria, a surrogate marker for vascular and renal target-organ damage was associated with EBP (in particular, SBP) in males and with SBP in females, with profound implications for premature cardiovascular and all-cause mortality while also providing opportunities for lifestyle and therapeutic interventions to mitigate risk.

Our findings suggest that earlier surveillance or screening for hypertension and microalbuminuria in younger population groups could perhaps allow earlier detection of at-risk groups. A review of our contraception policy with a current strong emphasis on the injectable progesterone method as well as follow up of women with gestational hypertension for longer than just six weeks post delivery could also result in at-risk groups being detected prior to long-term hypertensive damage occurring.

The BT20 cohort is the longest running birth cohort in sub-Saharan Africa and there are few studies from Africa with which to compare our findings. The Coronary Artery Risk Development in Young Adults (CARDIA) study in the USA showed similar results with 2 277/4 851 (47%) of the cohort developing EBP, stage 1 or stage 2 hypertension, before the age of 40 years. This group was at higher risk for adverse cardiovascular events in later life compared to their normotensive counterparts.[9]

Factors associated with BP included gender and BMI. Females in our study had lower SBP and DBP, a finding consistent with many other studies and attributable possibly to differences in the developmental programming of BP between men and women, gender-mediated differences in the response to angiotensin II, and differences in sympathetic activation.[10-12]

It is contrary that females had higher BMIs than males in our study yet a higher BMI was associated with higher SBP and DBP. It is noteworthy that the association with BP was stronger for males despite their lower BMIs overall. Prior studies have shown that at age 17 years, BMI was a strong independent predictor for hypertension in older males aged 30 years, and held true across all BMI categories. In contrast for females, only BMI ≥ 30 kg/m^2 or ≥ 95th percentile was associated with elevated risk of hypertension when adjusting for BMI at adulthood.[13]

The pathogenesis of obesity-related hypertension includes insulin- and leptin-mediated sympathetic nervous system stimulation, renin–angiotensin–aldosterone system (RAAS) activation, increased sodium reabsorption by the kidney by neural, hormonal and renovascular mechanisms and endothelial dysfunction with blunting of physiological vasodilation.[14,15] The role of sex hormones, specifically testosterone and oestrogen, and their effects on both weight and BP as well as their effects on the sympathetic nervous system and the RAAS could explain the stronger association with BMI and BP in males.[10,16]

In those with EBP, albuminuria is recognised as a marker for vascular and endothelial dysfunction and predicts increased risk for cardiovascular and all-cause mortality. Albuminuria is also a marker of glomerular damage and can precede a drop in eGFR. Treating EBP and targeting albuminuria with anti-proteinuric pharmacotherapeutics (such as ACE inhibitors) has been proven to reduce cardiovascular risk, with less impact on preserving kidney function. However, most studies elucidating the risk associated with EBP have been conducted in older cohorts from high-income countries, with few studies from sub-Saharan Africa, especially in young adults.[17-20]

In the CARDIA study, increased SBP was associated with a higher uACR in midlife.[19] Similarly, in a recent study from China examining the effect of BP trajectories from childhood to middle age on renal function, participants with higher levels of SBP in early life had higher uACRs in middle age. In addition, rapid increases in SBP from adolescence to middle age predicted the highest uACRs in middle age.[20]

In our study, the association between hyperuricaemia and SBP was attenuated in males when adjusting for BMI, but this association persisted in females. Controversy regarding whether the association between hyperuricaemia and BP is cause or effect (or perhaps both), still persists in the literature.

Hyperuricaemia in rat models, which resulted in hypertension, showed that these rats developed afferent renal arteriolar vasoconstriction, resulting in renal blood flow reduction, similar to findings in essential hypertension.[21,22] This has been postulated to be mediated by endothelial dysfunction and uric acid-induced stimulation of the renin–angiotensin system.[21,22]

Two meta-analyses have shown a consistent association of uric acid elevation and a higher risk of incident hypertension.[23,24] Grayson *et al.* found that this risk appeared to be more pronounced in females and in younger individuals.[23] A 10-year

follow up of over 5 000 individuals, with an average age of 38 ± 7 years, found that higher uric acid levels were associated with a higher incidence of hypertension in females (hazard ratio: 1.180; 95% CI: 1.018–1.369) but not in males.[25]

The reasons for the greater susceptibility in females despite their having lower circulating levels of uric acid are not well understood. The renal handling of uric acid is different in men and women, which seems to be linked to female sex hormones and the regulation of uric acid transporters, specifically ABCG2 and SLC2A9.[26]

Hypertensive disorders of pregnancy (HDP) have been linked in many studies to increased risk for future hypertension.[27-29] Gestational hypertension in our study was self-reported and we were unable to differentiate between the different subtypes of HDP. Studies have shown that women with gestational hypertension or pre-eclampsia are two to three times more likely to develop chronic hypertension than women with normotensive first pregnancies.[27,30,31]

The mechanism behind this is not clearly understood. It is thought that HDP could unmask underlying cardiovascular risk already present due to the 'stress' of pregnancy or that pregnancy could induce endothelial or organ damage, altering the woman's trajectory towards cardiovascular risk-factor development.[27] Regardless of the underlying mechanism, these women represent a large proportion of society who could be monitored for the development of hypertension with appropriate institution of treatment prior to the development of complications.

Studies conducted with synthetic progesterone used for contraception or hormone replacement therapy have shown an elevating effect on BP.[32,33] This is thought to be due to an increase in sodium retention as well as androgenic properties of synthetic progesterone.[34,35] An Ethiopian study of 100 women (50 using injectable progesterone and 50 controls) found no difference in BP between the two groups.[36] Two-thirds of the females who were using some form of contraception were using injectable progesterone in our cohort and this was found to be associated with a 4.6-mmHg higher SBP than those females on no contraception. This is also a modifiable factor that could prevent hypertension in young pre-menopausal women.

There are some limitations to the study. As the study sample was derived from a cohort of participants who were seen at age 22 years and screened for EBP, we could have created a bias towards those with higher BPs at age 22 returning aged 28 years. As BMI showed such a strong association, more information relating to dietary patterns, physical activity, sedentary behaviours and sleep would have been useful.

Conclusion

We found a significant association of higher BP with albuminuria, suggesting that vascular or subclinical renal damage may already be present at a young age. Although we found no association with eGFR, possibly as our cohort was too young for this effect to be noticeable, we have a good baseline to follow this cohort up in future to assess decline in eGFR. Our findings suggest that the underlying pathophysiology of EBP in young adults differs in men and women. They also highlight the negative impact of HDP and injectable contraceptives on the development of EBP in women. These findings are important as this population group has a very high prevalence of hypertension and end-stage kidney disease secondary to hypertension occurring in a relatively younger age group.

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