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ARTICLE

Associations of central and peripheral blood pressure with the renin-angiotensin-aldosterone system in healthy young adults: the African-PREDICT study

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Abstract

This study investigated associations of brachial and central blood pressure (BP) with detailed renin-angiotensin-aldosterone system (RAAS) components in a healthy young population stratified according to ethnicity and sex. We included healthy black men ($n = 285$) and women ($n = 304$) and white men ($n = 278$) and women ($n = 305$) aged 20–30 years old. We derived central systolic BP (cSBP), measured clinic and 24-h systolic and diastolic BP. Aldosterone and equilibrium angiotensin levels were assessed and used for calculating angiotensin-derived markers for plasma renin activity (PRA-S, Angiotensin I + Angiotensin II), angiotensin-converting enzyme (ACE-S, Angiotensin II/Angiotensin I), and two markers for adrenal effects of angiotensin II, the aldosterone-to-renin ratio (ARR-S, Aldosterone/PRA-S) and the aldosterone-to-angiotensin II-ratio (AA2-R, Aldosterone/Angiotensin II). Young black men and women presented with lower RAAS components and higher cSBP compared to their white counterparts (all $p \le 0.001$). In multivariable-adjusted regression analyses, positive associations of cSBP with ARR-S and AA2-R and negative associations with PRA-S and angiotensin II were found for black women (all $p \le 0.001$); this pattern was also observed for 24-h and clinic BP ($p \le 0.045$). A similar trend of RAAS associations was present in black men but only for clinic BP (all $p \le 0.047$). In white men, negative associations between clinic SBP and PRA-S, angiotensin II and aldosterone were detected (all $p \le 0.048$). No associations were observed in white women. Positive associations of central and peripheral BP with the ratio of aldosterone to PRA-S and angiotensin II only in healthy, young black adults suggest that relative aldosterone excess may contribute to early hypertension development in this group.

Keywords Central systolic blood pressure · Renin · Angiotensin II · Aldosterone · Black · African

Introduction

The low activity of the renin-angiotensin-aldosterone system (RAAS) in populations of African ancestry compared to white populations is well established [1–3]. The low renin phenotype is mainly attributable to enhanced sodium retention and potential aldosterone sensitivity, which has been associated with an increase in 24-h systolic blood pressure (SBP) only in black individuals [4, 5]. Clinic and ambulatory BP are inversely associated with renin in both black and white cohorts, and the ratio of aldosterone-to-renin (ARR) modified the relationship between urinary Na^+/K^+ and BP in two different study populations of black ethnicity [6, 7]. In African Americans, ARR has been positively associated with BP in cases of high dietary sodium, suggesting that insufficiently suppressed aldosterone in relation to renin may contribute to BP sensitivity to sodium [8]. Another measure of relative

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aldosterone excess is the aldosterone-to-angiotensin II ratio (AA2-R, Aldosterone/Angiotensin II), which was found to be higher in individuals with hypertension and high aldosterone levels than in individuals with hypertension and low aldosterone levels in a study sample of black South African men [9]. AA2-R was recently shown to be a marker for primary aldosteronism, with suggestions that this ratio may be advantageous over ARR when screening for primary aldosteronism in patients taking angiotensin-converting enzyme (ACE) inhibitors [10, 11]. Using angiotensin II (Ang II), the direct molecular regulator of aldosterone secretion, instead of its upstream surrogate renin as a biomarker for aldosterone-mediated hypertension might show a closer link to BP. However, unlike ARR, the direct relationship of this ratio with BP is not well documented, and information on such associations may allow use of the ratio beyond primary aldosteronism in hypertension.

Previous studies examining the relationship between RAAS and BP while taking ethnicity into consideration have included either middle-aged, elderly, hypertensive individuals or used peripheral BP only [6, 7, 9, 12]. In addition, prior studies investigated associations without stratification for sex, which is known to influence levels of RAAS components [13, 14]. Hence, it is not clear whether both brachial and central BP (suggested to have superiority over other BP components in cardiovascular risk prediction and basis for therapy [15–20]) are associated adversely with a range of RAAS components in healthy young adults. Whether such associations differ based on ethnicity and/or sex also remains to be established. In this study, we investigated the association of central and peripheral BP with RAAS components (Ang II, Ang II-based markers for plasma renin activity (PRA-S, Ang I + Ang II) and ACE activity (ACE-S, Ang II/Ang I), aldosterone, ARR-S, and AA2-R) in young healthy black and white men and women.

Materials and methods

Study design and population

Data were collected from participants enrolled in the African Prospective study on Early Detection and Identification of Cardiovascular disease and Hypertension (African-PREDICT) study. The study included 1202 young participants to be followed over a period of 10 years to identify novel and early markers of cardiovascular risk [21]. The inclusion criteria were black and white men and women aged 20–30 years with screening clinic BP < 140/90 mmHg. Pregnant or lactating women and individuals who were on chronic medication or had been previously diagnosed with a chronic health condition were excluded. The present sub-study used cross-sectional baseline data for 1172 participants with complete data for central and brachial BP as well as components of the RAAS (Fig. 1).

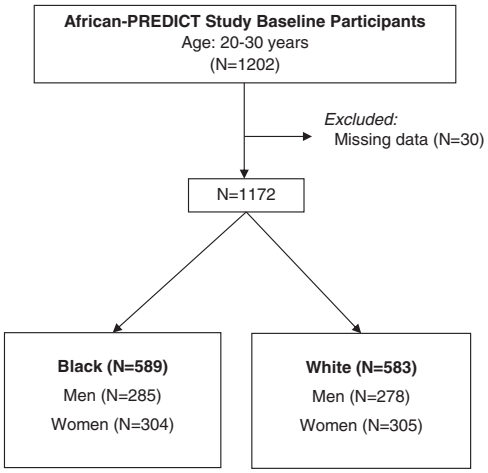

Fig. 1 Study flow chart

All participants provided written informed consent. The African-PREDICT study was approved by the Health Research Ethics Committee of North-West University (NWU-00001-12-A1) and complied with the Declaration of Helsinki criteria for human research. The study is registered on ClinicalTrials.gov (NCT03292094).

Demographic and anthropometric measurements

Data on age, sex, ethnicity, alcohol, and tobacco were obtained using a demographic and health questionnaire. The socioeconomic status (SES) of each participant was obtained from three categories included in the questionnaire and adapted to the South African context [22].

All anthropometric measurements were performed based on the International Standards for Anthropometric Assessment [23] and included weight (kg) (SECA electronic scales, SECA, Birmingham, UK), height (m) (SECA stadiometer, SECA, Birmingham, UK) and waist circumference (Holtain, Crymych, UK). Body mass index (BMI) was calculated using the standard weight (kg)/height (m^2) calculation.

Physical activity measurements

The ActiHeart device (CamNtech Ltd., Cambridgeshire, UK), worn for a maximum of 7 days, was used to quantitatively measure physical activity for the calculation of total energy expenditure.

Cardiovascular measurements

We performed pulse wave analysis using the SphygmoCor XCEL device (SphygmoCor XCEL, AtCor Medical,

Sydney, Australia) [24] with the participant in the supine position. The device uses a built-in generalized transfer function to determine estimated central SBP from the brachial arterial waveform [25]. The measurements were performed in duplicate, and if the two values differed by more than 3 mmHg, a third measurement was performed; the two that were closer to each other were used to calculate an average, which was then used for statistical analysis.

The Dinamap® Procare BP monitor (GE Medical Systems, Milwaukee, USA) with appropriate cuff sizes was used to measure office BP and heart rate, which was taken four times, twice on each arm with the participant seated and in a relaxed state. Prior to the measurement, the participants were requested not to have exercised, smoked, or eaten for 30 min beforehand. The first measurement was taken on the left arm after the participants were in a quiet state for 5 min (seated with the arm supported at heart level). The average of the two left-side measurements was used for statistical analysis.

Ambulatory BP data were collected over 24 h with CardXplore devices (MediTech, Budapest, Hungary), programmed to take recordings every 30 min during the day (06:00–22:00 h) and every hour during the night (22:00–06:00 h). The device was fitted to each participant at approximately the same time every day (late morning) by using an appropriate-sized cuff, as specified by the manufacturer. The mean inflation rate for this study population was calculated as 88% (standard deviation ±12.3).

Biological sampling and biochemical analyses

Participants were asked not to eat or drink anything except water overnight for at least 8 h prior to undertaking the research measurements. Blood samples were collected early in the morning by a qualified nurse and then prepared according to standardized protocols and stored at −80 °C until the time of analysis.

Serum samples were analyzed for creatinine, C-reactive protein (CRP), total and high-density lipoprotein cholesterol (TC, HDL-c), glucose, and gamma-glutamyl transferase (GGT) (Cobas Integra 400plus, Roche, Basel, Switzerland). Equilibrium angiotensin levels were quantified based on a liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) multiplex assay using 350 µL of equilibrated serum samples (Attoquant Diagnostics, Vienna, Austria). Briefly, following a solid-phase-based and internal standard-controlled extraction procedure, LC-MS/MS quantification was performed using highly specific and simultaneous multiple reaction monitoring (MRM) detection of endogenous angiotensin peptides and internal standards [26, 27]. Equilibrium angiotensin levels were further used to calculate combined parameters and ratios as surrogate markers(s) for the activity of circulating RAS enzymes, including ACE-S (Ang II/Ang I) and PRA-S (Ang I + Ang II). Aldosterone was quantified by LC-MS/MS using stable isotope-labeled aldosterone (D4) for internal standardization. ARR-S was calculated based on aldosterone and PRA-S and AA2-R based on Ang II and aldosterone. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology (CKD-EPI) formula [28] without the race factor [29]. Each participant collected a 24-h urine sample on a day that was convenient. The participants were instructed to discard the first urine of the day and collect all urine passed thereafter, including the first urine of the next day (Day 2). The start and finish times of urine collection were recorded. The protocol for 24-h urine collection is in accordance with the Pan American Health Organization/World Health Organization (PAHO/WHO) protocol [30]. The urine samples were aliquoted and placed at −20 °C until analyzed. We excluded participants with urine volume <300 mL per 24 h, a 24-h creatinine excretion of <5 mmol or higher than 30 mmol from statistical analysis [31]. Urinary sodium and potassium were measured by means of ion-selective electrode potentiometry using a Cobas Integra® 400 plus (Roche, Basel, Switzerland) and used to calculate the 24-h urinary sodium:potassium ratio (Na^+/K^+).

Statistical analyses

Data analysis was performed with Statistica v13.3 (TIBCO software, Palo Alto, California, USA). Normality was tested using the Kolmogorov–Smirnov test and visual inspection of histograms. Logarithmic transformation was performed when data were not normally distributed. Continuous data with normal distribution are reported as the mean and standard deviation; variables with a non-Gaussian distribution are shown by the geometric mean with 5th and 95th percentile intervals. Data are presented by stratification according to ethnicity and sex based on interaction terms and the well-known suppressed RAAS in black compared to white populations as well as the influence of sex hormones on some RAAS components [1, 3, 13, 14]. Comparisons were performed between black and white men and women as well as between men and women within the two ethnic groups by using independent *t*-tests for continuous variables and the Chi-square test for categorical variables. Pearson and partial correlations were used to explore associations between BP as the dependent variable and RAAS components as main independent variables as well as potential confounders. Forward stepwise multiple regression analyses were performed to determine independent associations of brachial BP and cSBP with components of the RAAS. Variables considered for entry in the multivariable regression analysis were chosen based on exploratory Pearson and partial correlations. Covariates included in the models

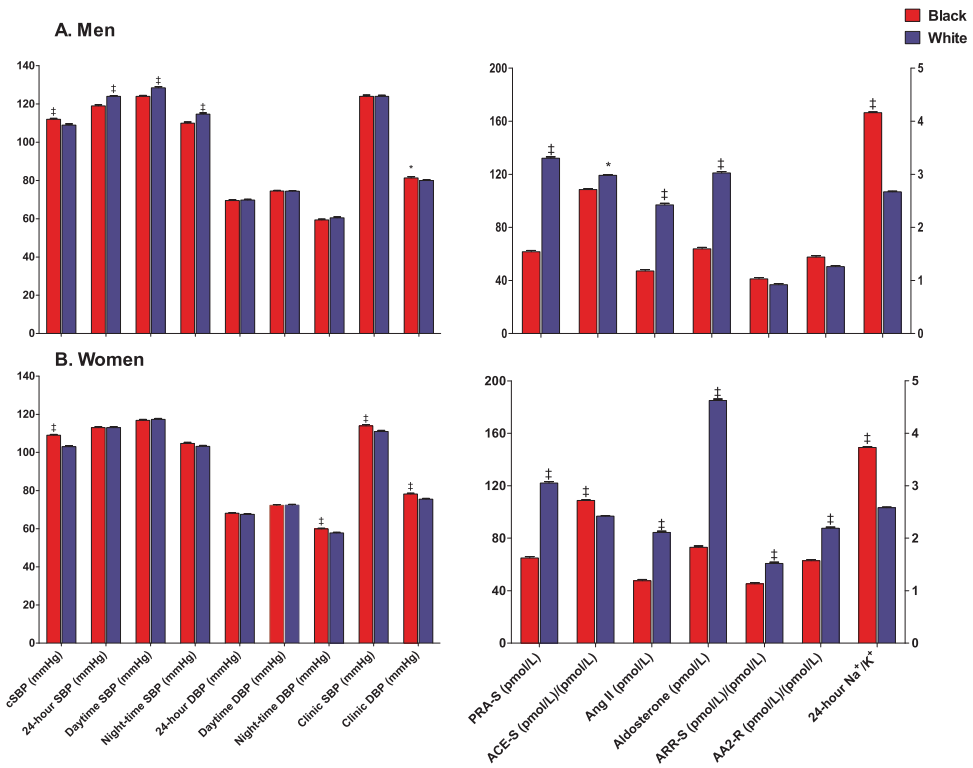

Fig. 2 Sex-specific ethnic comparisons of blood pressure and renin-angiotensin-aldosterone system profiles. RAAS renin-angiotensin-aldosterone system, PRA-S angiotensin-based plasma renin activity, ACE-S angiotensin-based angiotensin-converting enzyme activity, ARR-S aldosterone-to-renin ratio, AA2-R angiotensin-to-aldosterone ratio. $^{\ddagger}p < 0.001$; $^{\dagger}p < 0.01$; $^{*}p < 0.05$

include socioeconomic score, age, total energy expenditure, waist circumference, GGT, self-reported smoking, urinary Na^+/K^+, total cholesterol, glucose, CRP, and eGFR. In addition, heart rate was included as a covariate for models with cSBP as a dependent variable. A p value of 0.05 was considered statistically significant.

Results

Characteristics of the population

Due to the interaction of ethnicity and sex on associations between cSBP and PRA-S, Ang II, and ACE-S (all $p \leq 0.034$), data were stratified according to ethnicity and sex (Supplementary Table 1). Figure 2 depicts the ethnic differences in central and peripheral BP as well as the RAAS. Both black men and women had higher cSBP (both $p \leq 0.001$) and clinic DBP (both $p \leq 0.046$) than their white counterparts (Fig. 2). Black women also had higher clinic SBP than white women ($p < 0.001$); white men had higher 24-h SBP ($p < 0.001$) than black men (Fig. 2). Furthermore, both day- and night-time SBP were higher in white men than in black men (both $p < 0.001$), whereas black women had higher night-time DBP ($p < 0.001$). PRA-S, ACE-S, Ang II and aldosterone were higher in white men than in black men (all $p \leq 0.019$). The ratio of aldosterone to both PRA-S and Ang II was comparable (both $p \geq 0.055$), and Na^+/K^+ was higher in black men than in white men ($p < 0.001$). A similar trend was observed when comparing women, except for ACE-S, which was higher in black women and ARR-S and AA2-R, which were higher in white women (all $p \leq 0.001$) (Fig. 2).

Table 1 represents the sex differences within the black and white groups. Within ethnicity, central and peripheral BP were higher in black and white men compared to women (all $p \leq 0.005$). When comparing RAAS components between men and women, they were similar between black men and women (all $p \geq 0.21$), except for aldosterone, which was higher in black women than men ($p = 0.049$). However, compared to black women, a higher Na^+/K^+ ratio was detected in black men ($p < 0.011$). In contrast, components of the RAAS were higher in white men than in women (all $p \leq 0.021$), except for aldosterone, ARR-S, and AA2-R, which were higher in women than in men (all $p < 0.001$); Na^+/K^+ was similar ($p = 0.42$). Another marked difference between the groups was higher measures of adiposity (waist circumference, weight, and BMI) in black women compared to black men, but white men presented with higher values than white women (all $p \leq 0.002$).

Regression analyses

Based on the aim of the study, we explored whether independent associations exist between central and peripheral

Table 1 Characteristics of the study population

	Black ($n = 589$)			White ($n = 583$)		
	Men	Women	*P*	Men	Women	*P*
N	285	304		278	305	
Demographics						
Age (years)	24.4 ± 3.05	24.6 ± 3.31	0.44	24.8 ± 3.04	24.4 ± 3.07	0.17
Socioeconomic status			**0.049**			0.96
Low *n* (%)	183 (64.2)	165 (54.3)		55 (19.8)	62 (20.3)	
Middle *n* (%)	67 (23.5)	91 (29.9)		86 (30.9)	91 (29.8)	
High *n* (%)	35 (12.3)	48 (15.8)		137 (49.3)	152 (49.8)	
Anthropometric measurements						
Waist circumference (cm)	76.5 ± 9.23	79.1 ± 12.3	**0.005**	88.9 ± 10.8	76.2 ± 11.3	**<0.001**
Weight (kg)	64.3 ± 13.0	68.0 ± 15.9	**0.002**	85.9 ± 16.1	67.7 ± 15.4	**<0.001**
Height (cm)	170 ± 6.66	159 ± 6.06	**<0.001**	179 ± 6.26	167 ± 6.12	**<0.001**
Body mass index (kg/m^2)	22.2 ± 4.06	26.9 ± 6.19	**<0.001**	26.7 ± 4.87	24.4 ± 5.47	**<0.001**
Cardiovascular measurements						
Clinic central SBP (mmHg)	112 ± 9.25	109 ± 8.91	**<0.001**	109 ± 8.69	103 ± 8.75	**<0.001**
Clinic brachial SBP (mmHg)	124 ± 11.7	114 ± 10.3	**<0.001**	124 ± 9.77	111 ± 10.2	**<0.001**
Clinic brachial DBP (mmHg)	81.4 ± 8.75	78.2 ± 7.78	**<0.001**	80.0 ± 7.48	75.5 ± 7.06	**<0.001**
24-h SBP (mmHg)	119 ± 8.27	113 ± 8.40	**<0.001**	124 ± 7.53	113 ± 8.41	**<0.001**
24-h DBP (mmHg)	69.5 ± 6.24	68.1 ± 4.48	**0.005**	69.8 ± 8.94	67.5 ± 5.58	**<0.001**
24-h heart rate (b/min)	68.9 ± 8.59	81.0 ± 8.70	**<0.001**	70.1 ± 9.32	76.7 ± 10.2	**<0.001**
RAAS and kidney function						
PRA-S (pmol/L)	61.6 (10.8; 244)	64.9 (12.8; 271.3)	0.51	132 (40.2; 339)	121.6 (39.4; 323)	0.13
ACE-S (pmol/L)/(pmol/L)	2.71 (1.30; 6.20)	2.72 (1.40; 5.20)	0.98	2.98 (1.50; 6.60)	2.42 (1.20; 4.90)	**<0.001**
Angiotensin II (pmol/L)	47.5 (8.40; 176)	47.14 (10.1; 194)	0.92	98.0 (28.5; 248)	84.4 (28.1; 228)	**0.010**
Aldosterone (pmol/L)	63.8 (13.9; 232)	73.0 (16.0; 281)	**0.049**	121 (28.2; 340)	185 (24.4; 996)	**<0.001**
ARR-S (pmol/L)/(pmol/L)	1.03 (0.23; 4.29)	1.13 (0.31; 5.82)	0.21	0.92 (0.30; 2.61)	1.52 (0.30; 5.73)	**<0.001**
AA2-R (pmol/L)/(pmol/L	1.44 (0.33; 6.38)	1.57 (0.41; 9.26)	0.26	1.26 (0.42; 3.56)	2.19 (0.44; 9.18)	**<0.001**
24-h urinary Na/K ratio	4.16 (2.15; 8.60)	3.73 (1.87; 6.94)	**0.011**	2.67 (1.17; 5.80)	2.58 (1.16; 5.25)	0.42
eGFR (ml/min/1.73 m^2)	118 ± 14.4	118 ± 14.6	0.94	103 ± 16.8	108 ± 15.4	**0.001**
Metabolic variables						
Glucose (mmol/L)	3.50 (2.16; 5.36)	4.08 (2.69; 5.42)	**<0.001**	4.08 (2.49; 5.64)	4.11 (2.66; 5.45)	0.72
Total cholesterol (mmol/L)	3.11 (1.80; 4.95)	3.55 (2.23; 5.20)	**<0.001**	3.74 (2.01; 6.19)	3.91 (2.19; 6.00)	0.13
C-reactive protein (mg/L)	0.56 (0.07; 5.49)	1.78 (0.16; 13.7)	**<0.001**	0.65 (0.07; 5.89)	0.93 (0.08; 10.8)	**0.002**
GGT (U/L))	23.2 (8.30; 70.7)	21.3 (9.00; 59.7)	0.090	18.4 (6.40; 51.2)	12.3 (5.00; 35.0)	**<0.001**
Lifestyle factors						
Smoking *n* (%)	122 (43.0)	28 (9.21)	**<0.001**	77 (27.7)	48 (15.7)	**0.0004**
Alcohol use *n* (%)	176 (62.4)	152 (50.7)	**0.004**	163 (58.8)	162 (53.1)	0.16
TEE (kCal)	2222 (1803; 2843)	2127 (1568; 2978)	**0.006**	2561 (1978; 3309)	2093 (1603; 3041)	**<0.001**

Values are arithmetic mean ± standard deviation; geometric mean (5th and 95th percentile interval) for logarithmically transformed variables

Bold text indicate $p < 0.050$

N number of participants, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *PRA-S* angiotensin-based plasma renin activity (Ang I + Ang II), *ACE-S* angiotensin-based angiotensin-converting enzyme activity (Ang II/Ang I), *ARR-S* aldosterone-to-renin ratio, *AA2-R* aldosterone-to-angiotensin II ratio, *eGFR* estimated glomerular filtration rate, *GGT* gamma-glutamyl transferase, *TEE* total energy expenditure

BP and components of the RAAS (PRA-S, Ang II, ACE-S, aldosterone, ARR-S, AA2-R) based on sex and ethnicity stratification. After single (Supplementary Table 2) and partial (Table 2) and forward stepwise multiple (Table 3) regression analyses, we observed the following associations. In black women, cSBP was positively associated with ARR-S ($\beta = 0.294$; $p < 0.001$) and AA2-R ($\beta = 0.287$; $p < 0.001$) and negatively associated with PRA-S ($\beta = -0.346$; $p < 0.001$) and Ang II ($\beta = -0.342$; $p < 0.001$). The only association with cSBP in black men was for PRA-S ($\beta = -0.181$; $p = 0.047$). None of the associations were present in white men or white women.

Regarding peripheral BP, 24-h SBP was positively associated with AA2-R ($\beta = 0.15$; $p = 0.043$) and negatively associated with PRA-S ($\beta = -0.149$; $p = 0.045$) and Ang II ($\beta = -0.153$; $p = 0.041$) only in black women. The same tendency was observed for 24-h DBP (AA2-R: $\beta = 0.238$; $p = 0.004$, PRA-S: $\beta = -0.277$; $p = 0.001$, Ang II:

Table 2 Partial correlations of central and peripheral blood pressure with components of the RAAS

	Black group ($n = 589$)				White group ($n = 583$)			
	Men ($n = 285$)		Women ($n = 304$)		Men ($n = 278$)		Women ($n = 305$)	
	Central systolic blood pressure, (mmHg)							
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*
PRA-S, (pmol/L)	**−0.147**	**0.014**	**−0.30**	**<0.001**	−0.094	0.122	−0.002	0.968
ACE-S, (pmol/L)/(pmo/L)	−0.035	0.564	0.019	0.739	−0.034	0.576	0.008	0.887
Angiotensin II, (pmol/L)	**−0.133**	**0.027**	**−0.30**	**<0.001**	−0.097	0.112	−0.006	0.127
Aldosterone, (pmol/L)	−0.053	0.381	−0.021	0.721	−0.089	0.143	−0.023	0.688
ARR-S, (pmol/L)/(pmo/L)	0.105	0.082	**0.291**	**<0.001**	−0.014	0.824	−0.027	0.639
AA2-R, (pmol/L)/(pmo/L)	0.111	0.069	**0.285**	**<0.001**	−0.013	0.832	−0.023	0.687
	24-h systolic blood pressure, (mmHg)							
PRA-S, (pmol/L)	−0.069	0.248	−0.106	0.066	−0.012	0.850	0.111	0.055
ACE-S, (pmol/L)/(pmo/L)	−0.071	0.235	−0.090	0.119	0.053	0.383	−0.067	0.248
Angiotensin II, (pmol/L)	−0.006	0.915	−0.105	0.069	−0.015	0.801	0.088	0.127
Aldosterone, (pmol/L)	0.016	0.789	0.058	0.322	0.071	0.248	0.052	0.366
ARR-S, (pmol/L)/(pmo/L)	0.078	0.198	**0.162**	**0.005**	**0.091**	**0.138**	−0.021	0.715
AA2-R, (pmol/L)/(pmo/L)	0.092	0.128	**0.172**	**0.003**	**0.123**	**0.044**	−0.003	0.955
	24-h diastolic blood pressure, (mmHg)							
PRA-S, (pmol/L)	−0.057	0.345	**−0.210**	**<0.001**	0.021	0.735	0.107	0.064
ACE-S, (pmol/L)/(pmo/L)	−0.072	0.222	−0.081	0.159	−0.0003	0.996	**−0.155**	**0.007**
Angiotensin II, (pmol/L)	−0.022	0.717	**−0.204**	**<0.001**	0.017	0.926	0.068	0.236
Aldosterone, (pmol/L)	0.043	0.474	−0.006	0.915	−0.006	0.925	0.065	0.260
ARR-S, (pmol/L)/(pmo/L)	0.095	0.116	**0.212**	**<0.001**	−0.012	0.843	−0.002	0.970
AA2-R, (pmol/L)/(pmo/L)	0.108	0.074	**0.219**	**<0.001**	−0.006	0.926	0.027	0.649
	Clinic systolic blood pressure, (mmHg)							
PRA-S, (pmol/L)	**−0.204**	**0.001**	**−0.262**	**<0.001**	**−0.235**	**<0.001**	−0.056	0.329
ACE-S, (pmol/L)/(pmo/L)	−0.029	0.620	0.009	0.876	0.10	0.103	0.057	0.324
Angiotensin II, (pmol/L)	**−0.170**	**0.005**	**−0.264**	**<0.001**	**−0.230**	**<0.001**	−0.051	0.378
Aldosterone, (pmol/L)	−0.037	0.541	−0.002	0.970	**−0.177**	**0.004**	−0.052	0.365
ARR-S, (pmol/L)/(pmo/L)	**0.189**	**0.002**	**0.269**	**<0.001**	0.18	0.774	−0.021	0.714
AA2-R, (pmol/L)/(pmo/L)	**0.193**	**0.001**	**0.264**	**<0.001**	0.021	0.729	−0.024	0.675
	Clinic diastolic blood pressure, (mmHg)							
PRA-S, (pmol/L)	**−0.183**	**<0.001**	**−0.256**	**<0.001**	**−0.124**	**0.041**	0.03	0.956
ACE-S, (pmol/L)/(pmo/L)	−0.093	0.118	0.058	0.320	0.028	0.644	−0.007	0.903
Angiotensin II, (pmol/L)	**−0.130**	**0.031**	**−0.261**	**<0.001**	**−0.124**	**0.042**	−0.002	0.980
Aldosterone, (pmol/L)	−0.004	0.946	−0.040	0.494	**−0.139**	**0.023**	0.012	0.841
ARR-S, (pmol/L)/(pmo/L)	**0.193**	**0.001**	**0.228**	**<0.001**	−0.041	0.498	0.012	0.836
AA2-R, (pmol/L)/(pmo/L)	**0.208**	**<0.001**	**0.217**	**<0.001**	−0.034	0.574	0.015	0.798

Adjusted for age, waist circumference, and socioeconomic score. Bold indicates $p < 0.05$

RAAS renin-angiotensin-aldosterone system, *PRA-S* angiotensin-based plasma renin activity (Ang I + Ang II), *ACE-S* angiotensin-based angiotensin-converting enzyme activity (Ang II/Ang I), *ARR-S* aldosterone-to-renin ratio, *AA2-R* aldosterone-to-angiotensin II ratio

$\beta = -0.279$; $p = 0.001$), with an additional positive association with ARR-S ($\beta = 0.226$; $p = 0.006$).

For clinic SBP, the association with the RAAS in black women mimicked that observed between cSBP and RAAS (albeit with higher p values), and black women exhibited the same pattern of associations with the RAAS as for clinic and 24-h SBP and DBP as well as cSBP. In black men, negative associations were observed between clinic SBP and PRA-S ($\beta = -0.221$; $p = 0.013$) and Ang II ($\beta = -0.176$; $p = 0.047$) and, for the first time, positive associations between ARR-S ($\beta = 0.194$; $p = 0.032$) and AA2-R ($\beta = 0.205$; $p = 0.024$). The same pattern of associations

Table 3 Independent associations between central and peripheral blood pressure and components of the RAAS

Variables	Black group ($n = 589$)				White group ($n = 583$)			
	Men ($n = 285$)		Women ($n = 304$)		Men ($n = 278$)		Women ($n = 305$)	
	Central systolic blood pressure (mmHg)							
	Adj. R^2	β (95% CI)	Adj. R^2	β (95% CI)	Adj. R^2	β (95% CI)	Adj. R^2	β (95% CI)
PRA-S, (pmol/L)	**0.105**	**−0.181 (−7.935; −0.094)***	**0.201**	**−0.346 (−11.14; −4.150)‡**	**0.178**	−0.105 (−8.283; 1.667)	**0.360**	_
ACE-S, (pmol/L)/(pmo/L)	**0.090**	_	**0.102**	_	**0.178**	_	**0.360**	_
Angiotensin II, (pmol/L)	**0.099**	−0.162 (−7.907; 0.337)	**0.199**	**−0.342 (−11.40; −4.202)‡**	**0.177**	−0.082 (−7.735; 2.559)	**0.360**	_
Aldosterone, (pmol/L)	**0.090**	_	**0.102**	_	**0.178**	_	**0.360**	_
ARR-S, (pmol/L)/(pmo/L)	**0.097**	0.135 (−1.161; 7.659)	**0.177**	**0.294 (3.073; 10.0) ‡**	**0.178**	_	**0.360**	
AA2-R, (pmol/L)/(pmo/L)	**0.098**	0.139 (−1.043; 7.492)	**0.174**	**0.287 (2.876; 9.710) ‡**	**0.178**	_	**0.360**	_
	24-h systolic blood pressure (mmHg)							
PRA-S, (pmol/L)	**0.183**	_	**0.30**	**−0.149 (−6.116; −0.092)***	**0.153**	_	**0.293**	0.084 (−1.523; 6.444)
ACE-S, (pmol/L)/(pmo/L)	**0.183**	_	**0.286**	−0.093 (−10.92; 2.287)	**0.152**	_	**0.293**	_
Angiotensin II, (pmol/L)	**0.183**	_	**0.30**	**−0.153 (−6.394; −0.169)‡**	**0.152**	_	**0.293**	0.070 (−1.932; 6.002)
Aldosterone, (pmol/L)	**0.183**	_	**0.283**	_	**0.152**	_	**0.293**	_
ARR-S, (pmol/L)/(pmo/L)	**0.183**	_	**0.297**	0.138 (−0.099; 5.90)	**0.152**	_	**0.293**	_
AA2-R, (pmol/L)/(pmo/L)	**0.184**	0.090 (−1.726; 5.468)	**0.30**	**0.150 (0.132; 6.045)***	**0.157**	0.104 (−1.381; 6.667)	**0.293**	_
	24-h diastolic blood pressure (mmHg)							
PRA-S, (pmol/L)	**0.172**	_	**0.216**	**−0.277 (−5.877; −1.659)†**	**0.234**	_	**0.145**	_
ACE-S, (pmol/L)/(pmo/L)	**0.172**	_	**0.151**	−0.098 (−7.667; 1.740)	**0.233**	_	**0.148**	−0.095 (−7.332; 1.798)
Angiotensin II, (pmol/L)	**0.172**	_	**0.217**	**−0.279 (−6.083; −1.735)‡**	**0.233**	_	**0.145**	_
Aldosterone, (pmol/L)	**0.172**	_	**0.148**	_	**0.233**	_	**0.145**	_
ARR-S, (pmol/L)/(pmo/L)	**0.173**	0.093 (−1.312; 4.352)	**0.188**	**0.226 (0.928; 5.264)†**	**0.233**	_	**0.145**	_
AA2-R, (pmol/L)/(pmo/L)	**0.175**	0.106 (−1.091; 4.424)	**0.193**	**0.238 (1.071; 5.339)†**	**0.233**	_	**0.145**	_
	Clinic systolic blood pressure (mmHg)							
PRA-S, (pmol/L)	**0.157**	**−0.221 (−10.97; −1.396)***	**0.173**	**−0.262 (−10.65; −2.821)†**	**0.135**	**−0.223 (−13.56; −2.203)***	**0.228**	_
ACE-S, (pmol/L)/(pmo/L)	**0.118**	_	**0.109**	_	**0.101**	_	**0.228**	_
Angiotensin II, (pmol/L)	**0.140**	**−0.176 (−10.28; −0.126)***	**0.174**	**−0.265 (−11.05;−2.872)‡**	**0.134**	**−0.20 (−12.96; −1.260)***	**0.228**	_
Aldosterone, (pmol/L)	**0.118**	_	**0.109**	_	**0.112**	**−0.165 (−9.581; −0.081)***	**0.228**	_
ARR-S, (pmol/L)/(pmo/L)	**0.146**	**0.194 (0.575; 11.29)***	**0.166**	**0.251 (2.49; 10.48)†**	**0.101**	_	**0.228**	_
AA2-R, (pmol/L)/(pmo/L)	**0.150**	**0.205 (0.875; 11.19)***	**0.164**	**0.246 (2.319; 10.19)†**	**0.101**	_	**0.228**	_
	Clinic diastolic blood pressure (mmHg)							
PRA-S, (pmol/L)	**0.137**	**−0.191 (−7.644; −0.358)†**	**0.114**	**−0.264 (−8.20; −2.009)†**	**0.169**	−0.111 (−7.291; 1.284)	**0.150**	_
ACE-S, (pmol/L)/(pmo/L)	**0.130**	−0.098 (−10.89; 3.077)	**0.052**	_	**0.163**	_	**0.150**	_
Angiotensin II, (pmol/L)	**0.128**	_	**0.117**	**−0.271 (−8.58; −2.206)†**	**0.168**	−0.109 (−7.30; 1.359)	**0.150**	_
Aldosterone, (pmol/L)	**0.128**	_	**0.052**	_	**0.171**	−0.116 (−6.128; 0.903)	**0.150**	_
ARR-S, (pmol/L)/(pmo/L)	**0.155**	**0.207 (0.744; 8.709)***	**0.094**	**0.226 (1.183; 7.588)***	**0.163**	_	**0.150**	_
AA2-R, (pmol/L)/(pmo/L)	**0.161**	**0.223 (1.047; 8.754)***	**0.088**	**0.213 (0.914; 7.239)***	**0.163**	_	**0.150**	_

Adjusted R^2 was significant for all models. Forward regression analyses models included age, socioeconomic score, waist circumference, self-reported smoking, gamma-glutamyl transferase, estimated glomerular filtration rate, 24-h sodium:potassium ratio, glucose, c-reactive protein, total cholesterol, total energy expenditure. and hear rate for central systolic blood pressure models

"_" denotes major independent variable did not enter model. Bold indicates $p < 0.05$. $^{‡}p \le 0.001$; $^{†}p < 0.01$; $^{*}p < 0.05$

RAAS renin-angiotensin-aldosterone system, *PRA-S* angiotensin-based plasma renin activity (Angiotensin I + Angiotensin II), *ACE-S* angiotensin-based angiotensin-converting enzyme activity, *ARR-S* aldosterone-to-renin ratio, *AA2-R* aldosterone-to-angiotensin II ratio

was observed for clinic DBP; however, Ang II lost significance and did not enter into the model. In addition, for the first time, negative associations between clinic SBP and PRA-S ($\beta = -0.223$; $p = 0.007$), Ang II ($\beta = -0.20$; $p = 0.019$), and aldosterone ($\beta = -0.165$; $p = 0.048$) were evident in white men. We did not observe any associations between BP and RAAS components in white women.

Discussion

We investigated the association of central and brachial BP with a range of RAAS components in a relatively large sample of young healthy black and white men and women. The main finding was the independent, consistent positive associations of cSBP, 24-h and clinic SBP, 24-h, and clinic DBP with measures of excess aldosterone (ARR-S, AA2-R) and negative associations with PRA-S and Ang II in black women. Positive associations with ARR-S and AA2-R were present for only clinic SBP and DBP in black men, and this trend was not observed in white men or women.

Associations between ARR and brachial and central BP

Our findings are consistent with a study in African Americans consisting of men and women aged 18–45 years, in which ARR was positively associated with clinic SBP and DBP [8]. In our study, both clinic SBP and DBP were positively associated with ARR-S and AA2-R in both black men and women but not in their white counterparts. The study by Huan et al. [8] did not report associations in men and women separately; however, we noted in the current study higher aldosterone levels in women than in men and similar renin and ARR. The higher BP in men than women is also consistent between the two studies. In addition, higher waist circumference and BMI in black women than their male counterparts were also apparent in both studies [8]. In another study, Tomaschitz et al. [32] did not find differences in BMI across sex-specific quartiles of ARR. Regardless, it is known that adipose tissue is associated with higher aldosterone levels, independent of the circulating RAAS [33, 34]. In the present study, adiposity did not affect the independent associations between BP and measures of aldosterone excess. In terms of central BP, it was found in a prospective study that included a white patient cohort that ARR, across a broad range of values, was the second most significant determinant of both clinic and central BP [32]. This is in contrast to our study, which found no associations between ARR-S and any component of BP in the white group. These differences may be explained by the fact that our white population was young (mean age: 24.6 years versus 62.5 years), normotensive at screening, without known cardiovascular disease and not taking chronic medication. Technically, instead of measuring plasma renin concentration as performed by Tomaschitz et al. [32], we determined plasma renin activity using a novel angiotensin-based marker (PRA-S). PRA-S reflects a more physiological measure for RAAS activity, as angiotensinogen, a driver of RAAS activity, is only reflected by methods that depend on sample-intrinsic rates of angiotensin formation, which is not the case for direct renin measurements [26]. In a community-based study that included participants of African ancestry, Scott et al. [7] observed that higher SBP was associated with urinary Na^+/K^+ in a group of participants with ARR above the median of the study population.

Associations between RAAS and cSBP

The current study shows, for the first time, that the impact of relative aldosterone excess on BP is pronounced in black women even at a young age, especially for cSBP. We observed an increase of more than 2 mmHg in cSBP per unit increase in ARR-S and AA2-R, which was also evident (albeit less significant) with 24-h SBP and DBP as well as clinic SBP and DBP. Aldosterone excess in the form of primary aldosteronism has been linked to low-renin hypertension, which is common in black populations [35–37]. Although our associations were independent of urinary Na^+/K^+, it is well known that aldosterone's effects on BP are mainly driven by renal sodium and water retention [35, 36, 38]. Volume expansion is likely to increase ventricular afterload and cSBP, subsequently suppressing the RAAS, as indicated by the strong negative associations of cSBP with renin activity and Ang II in black women (>3 mmHg increase in cSBP per unit decrease in PRA-S and Ang II). Weber et al. [16] recently showed in a prospective multicenter study that cSBP is associated more strongly with left ventricular mass and hypertrophy than with brachial ambulatory pressure in a young population [16]. In our group of young black women, in addition to cSBP, we confirmed the positive association of measures of relative aldosterone excess with peripheral BP, even though the beta coefficients were less than those for cSBP and the p values were less significant. The presence of cSBP associations only in black women may be partly due to the influence of sex-specific hormones, which are known to influence aldosterone and renin levels and subsequently fluid retention during different phases of the menstrual cycle [13]. It was also shown that elevated ARR levels are common in hypertensive women compared to men [14]. Nonetheless, in our study, ARR-S was similar between black men and women; aldosterone was slightly higher in women than in men, but both groups had normal BP. In hypertensive states, blockade of the RAAS with ACE inhibitors and angiotensin receptor blockers is more beneficial for reducing cSBP and

preserving central hemodynamic function compared to other classes of medication [19, 20, 39]. On the other hand, in the black women in this study, both central and brachial BP showed negative associations with Ang II while associating positively with the ratio of aldosterone to renin and Ang II. The lack of association with aldosterone but with ARR-S and AA2-R highlights the role of autonomous aldosterone secretion independent of circulating renin and Ang II, such as in primary aldosteronism often reported in black populations, and the potential presence of aldosterone sensitivity [5, 40]. The negative RAAS feedback mechanism may explain the inverse relationship between BP and RAAS in black men and women as well as in white men, though the physiological reasons for the complete absence of the associations in white women remain to be explored. Of note, this group of white women had the lowest central and peripheral clinic BP profiles and highest levels of aldosterone compared to white men and black women while showing urinary Na^+/K^+ similar to that of white men but lower than that of black women. The higher levels of aldosterone in white women than in black women may be mediated by higher levels of PRA-S and subsequently higher Ang II, a trend also observed when comparing white men with black men. Furthermore, there seems to be a difference in the adrenal cortex's responsiveness to stimuli such as K^+, Ang II, or adrenocorticotropic hormone (ACTH) [41] between white women and black women, which would explain the stronger increase in aldosterone compared to the observation made in black women.

Strengths and limitations

Our study should be interpreted within the context of its limitations and strengths. The study is of cross-sectional design that prevents speculation on causality. The study population was recruited from a specific region and is not representative of all black and/or white populations. The main result remained robust after multiple adjustments; however, we cannot rule out residual confounding factors. The strengths of the study are that it included a relatively large sample size with young, healthy black and white adults with detailed phenotypes, including RAAS and BP profiles. RAAS components were measured with the RAS™ Fingerprint using a highly sensitive LC-MS/MS-based technology, and in addition to ARR-S, we used the novel AA2-Ratio to represent aldosterone excess [26, 27, 42]. We did not assess salt sensitivity; however, we adjusted for 24-h urinary Na^+/K^+, and the findings persisted.

Conclusion and implications

In conclusion, we found independent positive associations of central and peripheral BP with aldosterone excess relative to renin and Ang II in young black women with no known cardiovascular disease, including hypertension. A similar pattern was observed with clinic BP pressure in black men but not in their white counterparts. Our findings suggest that black populations, particularly women, may be more predisposed to aldosterone-mediated low-renin hypertension and the associated organ damage later in life.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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