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RACIAL DIFFERENCES IN SENSITIVITY OF BLOOD PRESSURE TO ALDOSTERONE

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Abstract

Blacks in comparison to whites are at risk for a more serious form of hypertension with high rates of complications. Greater sodium retention is thought to underlie the blood pressure (BP)-determining physiology of blacks, but specific mechanisms have not been identified. In a prospective observational study of BP, 226 black children and 314 white children (mean age 10.6) were enrolled initially. Assessments were repeated in 85 blacks and 136 whites after reaching adulthood (mean age 31). The relationship of BP to the plasma aldosterone concentration (PAC) in the context of the prevailing level of plasma renin activity (PRA) was studied in blacks and whites. In a secondary interventional study, 9-α fludrocortisone was administered for 2 weeks to healthy adult blacks and whites to simulate hyperaldosteronism. BP responses in the two race groups were then compared. Although PRA and PAC were lower in black children, BP was positively associated with PAC, an effect that increased as PRA decreased (p=0.004). Data from black adults yielded similar results. No similar relationship was observed in whites. In the interventional study, 9-α fludrocortisone increased BP in blacks but not in whites. In conclusion, aldosterone sensitivity is a significant determinant of BP in young blacks. Although its role in establishing risk of hypertension is not known, it could be as relevant as the actual level of aldosterone.

Keywords

aldosterone; renin; blood pressure; sodium; race; children

INTRODUCTION

Blacks in comparisons to whites have disproportionately more hypertension[1] and suffer hypertensive complications at higher rates [2, 3]. The etiology of hypertension appears to

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DISCLOSURES
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center on overly efficient sodium reabsorption by the kidney. The renin-angiotensin system, for example, is more likely to be suppressed in blacks than in whites consistent with greater volume expansion from sodium accumulation and water retention[4, 5]. In addition, the blood pressure (BP) in blacks in contrast to the BP in whites is more likely to increase in response to sodium intake (there is greater 'salt sensitivity')[6, 7]. Whether blacks have a unique renal physiology that puts them at risk for a more aggressive form of hypertension is unclear. A more complete understanding of how BP is regulated in blacks could revise current approaches for treatment should hypertension develop.

A higher production rate of aldosterone, the principal sodium-retaining hormone, is becoming increasingly appreciated as a contributor to the pathophysiology of hypertension. Primary hyperaldosteronism, for example, accounts for ~10% of cases of essential hypertension [8] and ~20% of cases of resistant hypertension [9]. In the Framingham Offspring Study, normotensive individuals with levels of plasma aldosterone in the upper quartile of the normal range compared to those in the lower quartile when studied four years later had significantly higher BPs and were more likely to be hypertensive[10]. In blacks, BP has been shown in several studies to be positively related to the level of plasma aldosterone[11-15]. In some instances, BP [14, 15], presence or absence of hypertension[11-13] and/or left ventricular mass [12, 15] were positively associated with the aldosterone-renin ratio. Despite evidence that aldosterone has the potential to affect BP, blacks often achieve a higher BP without a proportionate increase in the aldosterone level.

More than twenty years ago, we initiated a cohort study of BP regulation where enrollees were children, blacks and whites, from Indianapolis, IN [16]. We found that the black children had lower plasma aldosterone levels and urinary aldosterone excretion rates than the white children; there was little if any race difference in BP. Other investigative groups have also found lower aldosterone production in blacks [15, 17, 18]. The presumptive explanation was a suppressed renin-angiotensin axis from greater sodium retention in blacks. On a background of more positive sodium balance and lower aldosterone production rates, the role of aldosterone in determining BP could be diminished in blacks. Alternatively, pre-existing sodium retention might enhance an effect of aldosterone on BP – just as blacks are more salt-sensitive, they may also be more sensitive to aldosterone.

The present study sought to determine the extent of aldosterone's influence on BP in blacks in comparison to whites. We undertook a new assessment of the Indianapolis cohort data collected in childhood as well as an assessment of data collected recently with subjects now adults. On novel analyses, BP in blacks was found to increase as the plasma aldosterone concentration (PAC) increased and the level of plasma renin activity (PRA) decreased, a relationship that was largely absent in whites. The results from observational data led us to perform a second study, an intervention where blacks and whites were treated with the synthetic mineralocorticoid 9-α fludrocortisone to simulate modest hyperaldosteronism. The BP responses in the two race groups were then compared.

METHODS

Observational Cohort Study

Subjects and Study Design—Data for the main analysis were collected from a prospective observational cohort study that was started in 1986. The characteristics of the study participants and the data collection process were described in detail previously.[16, 19] Briefly, however, healthy black children and white children between 5 and 17 years of age were recruited from schools in Indianapolis selected to provide a range of socioeconomic levels. Renal or cardiac disease, hypertension, diabetes mellitus, and use of medications that could affect BP excluded subjects from participation. Subjects were seen twice a year. BP was measured in the right arm while in the seated position after resting for approximately five minutes. Three BP readings were taken two minutes apart. The average of the last two readings was used as the final BP measurement. Height and weight were also measured. Blood samples were drawn in most subjects only once and between 0800 and 1000 hr after sitting for 15 min. Urine samples were collected overnight.

In 2008, we invited those who had participated as children to return for further evaluations as adults. The data collection protocol and procedures followed for the adults remained unchanged from the child study with the exception that blood sampling was carried out at each visit. To eliminate the possible influences of antihypertensive medication on BP and biochemical measurements, the current analysis excluded 32 visits from 14 individuals (7 blacks and 7 whites) who were receiving antihypertensive medications. The study protocol was approved by the Institutional Review Board of Indiana University. Consent was obtained from all adult participants and from parents of children under 18; assent was obtained from children as appropriate.

Fludrocortisone Interventional Study

In a secondary study, we tested the hypothesis that administration of a synthetic mineralocorticoid similar to aldosterone, 9-α fludrocortisone, would raise BP more in blacks than in whites. In addition, parameters reflective of the state of sodium balance including level of PRA, PAC and B-type natriuretic peptide (BNP)[20] were measured at baseline and after two weeks of treatment. Healthy subjects were recruited from local medical center facilities. The study was approved by the Indiana University and the Department of Veterans Affairs Institutional Review Board. Each subject gave informed consent.

Measurements made at baseline and after two weeks of treatment with 9-α fludrocortisone were used in the analysis. Subjects were also seen at one week as part of an overall assessment. Ambulatory BP monitoring (ABPM) was carried out at baseline and after the two weeks of treatment (Spacelab 90207, Redmond, WA). BP was automatically measured every 30 minutes during the day and every 60 minutes overnight (2200 to 0800 hr) for 24 hr. After the first set of measurements, subjects were given 9-α fludrocortisone (0.2 mg as tablets each morning, which was approximately twice the replacement dose of aldosterone) for two weeks. Compliance was determined from pill counts at 1 and 2 weeks; no difference between groups was observed.

Assay Procedures (see online Supplement)

Statistical Analysis—Demographic and clinical characteristics of the study participants were summarized by selfreported black and white categories. Continuous variables were compared by t test and categorical variables by chi-squared tests. To assess the accuracy of the self-identified race information, we performed a principle component analysis [21]. Specifically, we compared the self-reported race identified in the collected samples to seven ethnic groups in HAPMAP phase 3 data. Analysis (shown in Supplemental Figure S1) revealed close genetic resemblance between self-identified blacks in our cohort and individuals of African ancestry in Southwest United States, and between self-identified whites and Utah residents of Northern and Western European ancestry.

For the childhood data, we converted all BP values into age, sex, and height adjusted percentile values.[22] We then used varying-coefficient regression models to examine the influences of aldosterone on BP percentile at different renin levels. Unlike traditional linear regression analysis, varying-coefficient regression characterizes the effect of aldosterone on BP as a smooth function of renin.[23] In this analysis, regression analysis was performed using systolic BP percentile as the response variable and the regression coefficient of aldosterone was modeled as a function of renin. Separate analyses were performed for blacks and whites. Estimated aldosterone effects on BP were displayed graphically with corresponding 95% confidence intervals. We analyzed the adult data similarly using systolic BP values instead of percentiles as the response variable. The same analytical approach was used to examine the effects of urinary aldosterone excretion rate (per mg. of urinary creatinine) on systolic BP percentile in children and systolic BP in adults at different levels of PRA.

In the interventional study, we determined changes in clinic BP, ABPM (day time, night time and 24 hours) and body weight, as well as changes in plasma levels of BNP, renin activity and aldosterone. The responses of the aldosterone-renin ratio were also calculated over the two weeks. The magnitudes of the within-subject changes were examined using a paired t-test; changes between the race groups were compared using analysis of variance adjusted for the effects of age, BMI, and sex. The analysis was implemented by using in R software (R Core Team (2013). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/). Throughout the analysis, p values less than 0.05 were considered statistically significant.

RESULTS

Subjects

Characteristics of the children at the initial enrollment and of the adults when re-enrolled are presented in Table 1. Characteristics of the subjects in the interventional study are also presented. The levels of PRA and the PAC in children (obtained at a visit that was subsequent to the enrollment visit) and in adults were significantly lower in blacks regardless of the age group (Figure 1); in black children, the PAC/PRA ratio was significantly lower. Mean values for plasma measurements and for urinary aldosterone and electrolyte excretion rates are available in Supplemental Table S1.

Aldosterone sensitivity

Using varying-coefficient regression analysis, we estimated the effect of PAC on systolic BP in blacks and whites in children as well as in adults. The effects of aldosterone on systolic BP percentiles are depicted in Figure 2 as smooth functions of PRA. The plots showed two distinctly dissimilar patterns of influences of PAC on systolic BP at the various levels of PRA in the two race groups. In whites, the estimated PAC-BP association consisted of a barely discernable increase as PRA increased, the confidence interval overlapped with the zero effect and thus this was not statistically significant. In blacks, the estimated BP effect of aldosterone was highly significant (p=0.004) and became stronger as the level of PRA declined. For example, in children with PRA of 1.0 ng/ml/h, there was on average a 2% increase in the systolic BP percentile for each ng/dl increase in PAC. Importantly, the PAC effect on systolic BP in the adults showed similar patterns: the BP responded strongly to aldosterone in the blacks, especially in those with lower PRA. A similar pattern was once again not evident in the whites. The relation of urinary aldosterone excretion to BP at different PRA levels was also examined. Analysis showed a similar race difference (see Supplemental Figure S2).

9-α Fludrocortisone

The BP responses to 9-α fludrocortisone administered over 2 weeks were clearly different in blacks and whites (Figure 3). Whereas in whites BP did not change, in blacks systolic BP increased by 5-6 mmHg (p=0.034 for clinic BP, p<0.001 for daytime ABPM, p=0.006 for nighttime ABPM, and p=0.001 for ABPM over 24 hours). Weight increased in blacks (p=0.028) and not in whites (p=0.11). Similarly, levels of BNT increased only in blacks (p=0.012). PRA decreased in blacks (p=0.002) and in whites (p<0.001). Although PAC decreased significantly in both race groups (p=0.010 for blacks and p<0.001 for whites) the magnitude of the decrease was significantly greater for whites (p=0.014). The aldosterone-renin ratio increased in response to 9-α fludrocortisone in whites (p=0.036) and showed a marginally significant decrease in blacks (p=0.09). In blacks only, the serum potassium concentration decreased by 0.2 mmol/L with treatment (p=0.0008).

DISCUSSION

In the current study, we assessed the role of aldosterone in regulating BP in young blacks and whites. We employed an analytical approach that took into account the prevailing state of sodium retention as reflected in the level of PRA. In the blacks, BP showed a significant association with PAC. This effect of aldosterone on BP or aldosterone sensitivity intensified as PRA decreased. The findings were evident in both children and adults. A similar effect pattern was not observed in whites. In a separate study, the 24 hour ambulatory BP response of young blacks and whites to administrated 9-α fludrocortisone were determined, an intervention that in effect directly tested for aldosterone sensitivity. BP increased significantly in the blacks but not in the whites. The results corroborated the finding in the association study. Sensitivity of BP to the circulating level of aldosterone may be an integral component of the BP-determining physiology in young blacks.

A mechanism for why young blacks have a heightened sensitivity to aldosterone may reside with a pre-existing state of increased sodium retention. This was implied by the lower level of PRA that inversely correlated with aldosterone's positive influence on BP, pointing to an expansion of fluid volume. In blacks, less additional sodium uptake by aldosterone would be required to reach a threshold where BP might increase. The response by blacks to treatment with 9-α fludrocortisone was also consistent with having greater baseline sodium stores. In contrast to whites, blacks experienced significant weight gain and an increase in their level of BNP, a marker of volume and which would be expected to increase as extracellular fluid volume expanded[20]. It was as if the capacity for taking on any additional sodium had already been fully realized in the blacks and achieving sodium balance would rely more on a natriuresis from an increase in BP [24, 25] . The whites on the other hand seemed to adjust to additional sodium or an increase in volume without resorting to an increase in BP. Indeed, the whites showed a significant decrease in levels of PRA and PAC whereas the blacks did not, suggesting that whites have a greater capacity for accommodating additional sodium. Urinary excretion rates of sodium and potassium were not measured in the interventional study. Although a potential shortcoming, race differences in what was consumed would likely have affected findings at baseline more than response to 9-α fludrocortisone and it was these results that were most noteworthy.

Aldosterone sensitivity was delineated in the blacks using analyses that simultaneously took into account the dual influences of plasma aldosterone and PRA on BP. If we had relied only on the aldosterone-renin ratio, which is used commonly as a clinical tool to assist in diagnosing primary hyperaldosteronism [8], it could have led to our having missed recognizing aldosterone sensitivity in the blacks. Various combinations of the levels of aldosterone and renin activity can give identical values for the aldosterone-renin ratio while at the same time quite different propensities for affecting BP. The black children in our study, for example, had significantly lower aldosterone-renin ratios than the white children yet ultimately we found that aldosterone was a principal determinant of the BP.

The present study was not intended to lend itself to suggesting a better treatment for hypertensive blacks. However, in an earlier randomized, placebo-controlled study limited to blacks with poorly controlled low-renin hypertension, adding in small doses of spironolactone (a mineralocorticoid receptor antagonist) and/or amiloride (an inhibitor of the epithelial sodium channel, a principal target of aldosterone) lowered the average BP into the normal range [26]. In a comparison between race groups of the antihypertensive properties of the mineralocorticoid receptor antagonist, eplerenone, blacks and whites were found to respond equally [27]. In the same study, however, the blacks showed a significantly better BP-lowering response to eplerenone than to the angiotensin receptor blocker, losartan, whereas in the whites eplerenone as an antihypertensive was not superior to losartan.

The propensity to retain sodium and develop hypertension is very much age-dependent [7]. As people become older, aldosterone sensitivity may also become more common and may occur regardless of race but earlier and probably more often in blacks. Non-pressor effects of aldosterone [28] might also be enhanced when sensitivity to aldosterone is increased. The present findings also raise the question of what constitutes a normal aldosterone level in blacks and at what level is it too high, especially for the level of PRA and thus amendable to

a treatment that mitigates aldosterone's actions. Answers to these questions could impact greatly on management of hypertension.

Our findings suggest that the serious nature of the hypertension in blacks is related to mechanisms specific for this population group. Genetic backgrounds selected for the survival advantages offered by highly developed renal sodium conservation mechanisms were likely contributors. We did not study hypertension per se but instead the normal physiology, although in so doing, we avoided the confounders that can accompany inclusion of hypertensives such as effects of antihypertensive medications.

PERSPECTIVE

Until now, aldosterone production has been the focus of studies for how aldosterone influences BP. We can now add aldosterone sensitivity to the equation for a more complete picture of aldosterone's sodium-retaining properties that affect risk for hypertension. The mechanisms that confer aldosterone sensitivity, which would seem to include increases in sodium retention, will be challenging to delineate. Treatment approaches that antagonize aldosterone's actions or target mechanisms that instill sensitivity to aldosterone could have enormous relevance to the prevention of stroke, end stage renal disease and heart disease in blacks.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Novelty and Significance

What Is New?

- Sensitivity of blood pressure to aldosterone is described for the first time.
- It was present in black children and in black young adults but not in whites of comparable age.
- Although blacks may have on average lower plasma aldosterone levels than whites, the level of aldosterone may nonetheless still impact on BP because of aldosterone sensitivity.

What Is Relevant?

- Although we did not study hypertension per se, the findings strongly imply a fundamental role of aldosterone in the development of hypertension in many blacks. A normal plasma aldosterone level in a black patient with hypertension may not rule out participation by aldosterone in the pathophysiology.

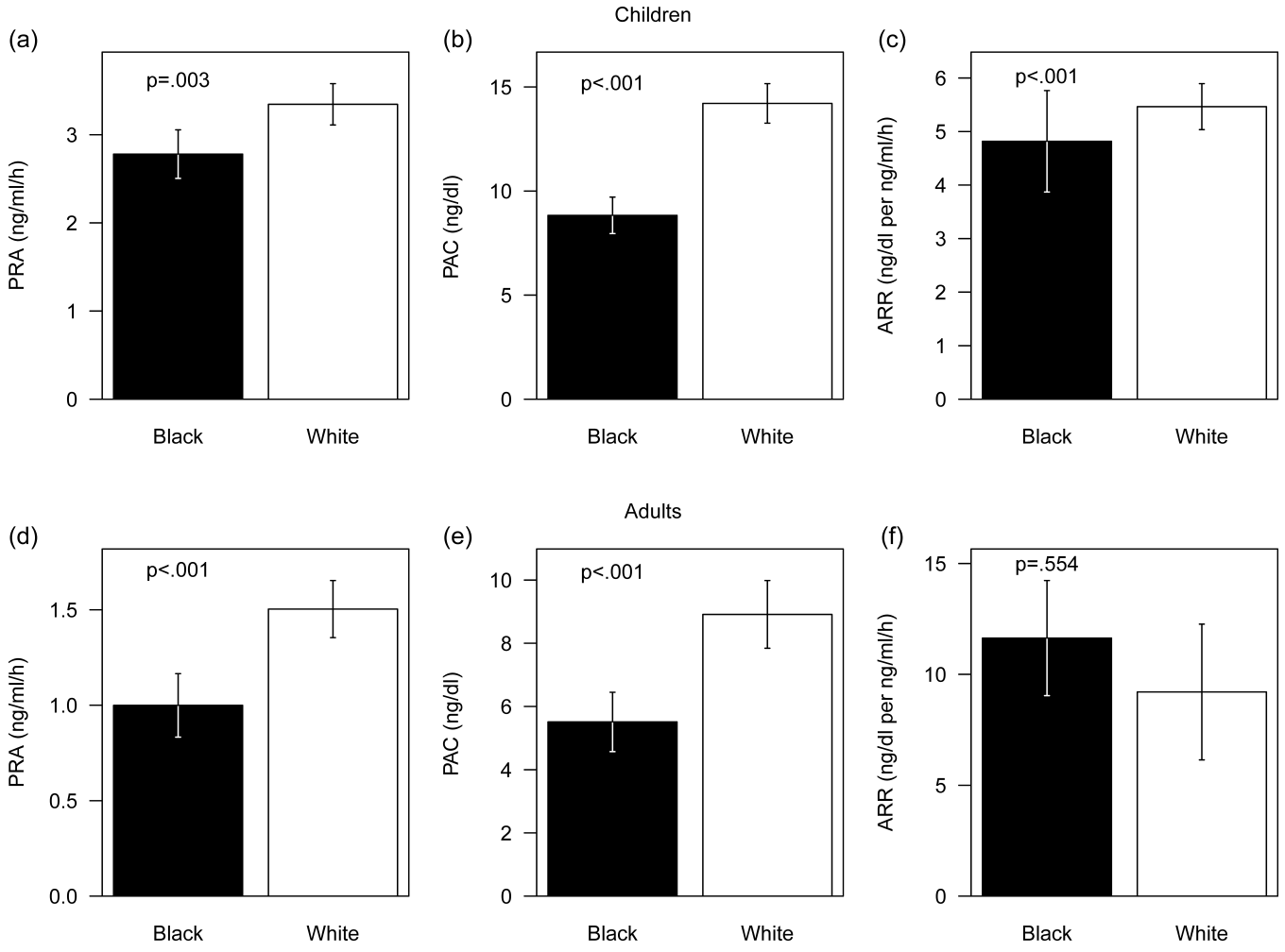

Figure 1.

The mean levels of plasma renin activity (PRA), plasma aldosterone concentration (PAC), and the aldosterone-renin ratio (ARR) with corresponding 95% confidence intervals in blacks and in whites, in children and in adults.

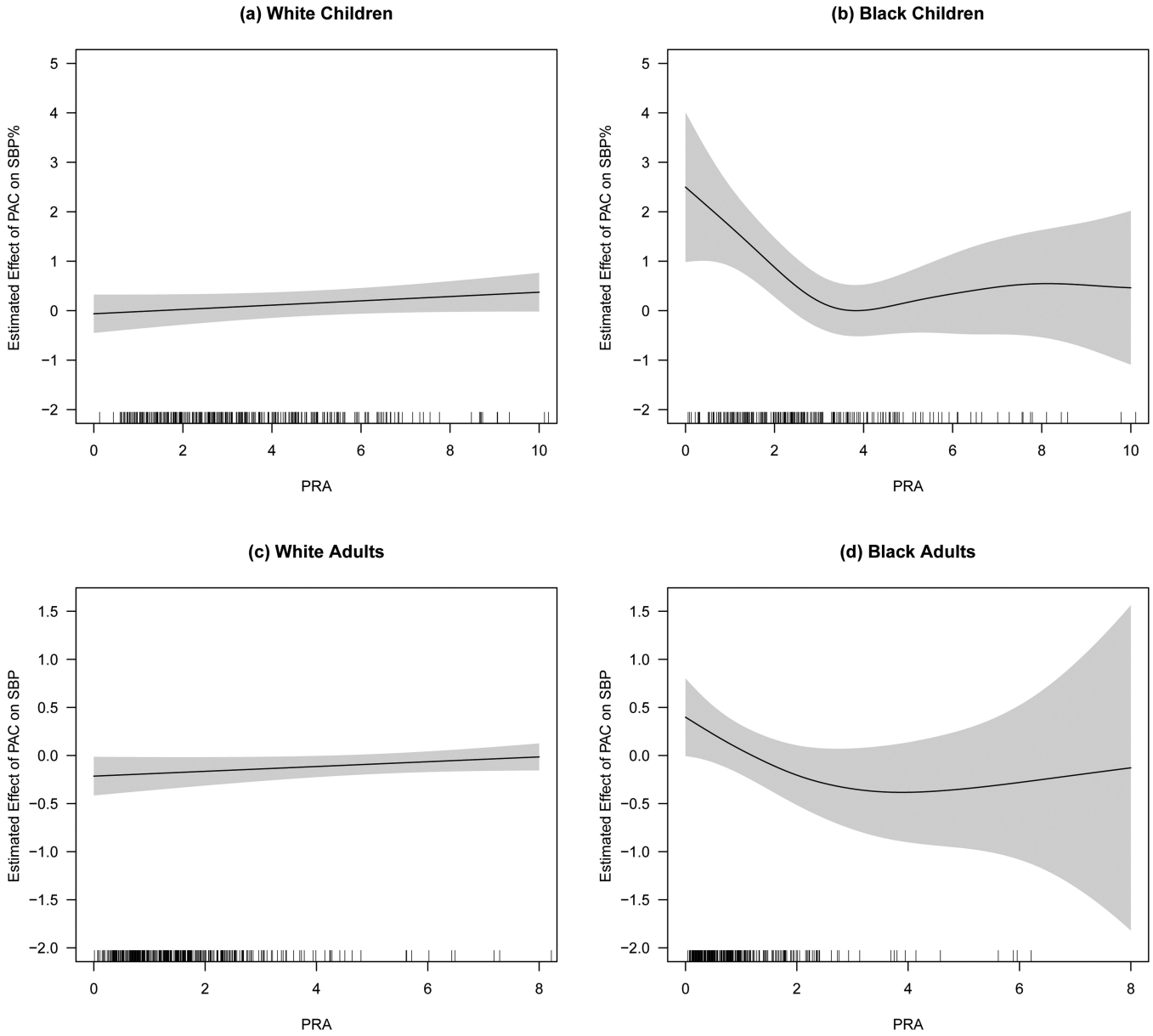

Figure 2.

Estimated aldosterone effects on systolic BP (SBP) and systolic BP percentiles (SBP%) in blacks and in whites. For children, the effect is expressed as the average increase in SBP% associated with 1 ng/dL increase in PAC. For adults, the effect is expressed as the average increase in SBP associated with 1 ng/dL increase in PAC at a given level of PRA. (a) Estimated effect of PAC on SBP% at different levels of PRA in white children, (b) in black children, (c) estimated effect of PAC on SBP as a function of PRA in white adults and (d) in black adults. The analyses were adjusted for age, sex, and BMI.

In black children, PAC was significantly associated with SBP%, especially when PRA was low. In white children, no significant association was detected (Panels (a) and (b)). Similar associations were found in adults [Panels (c) and (d)].

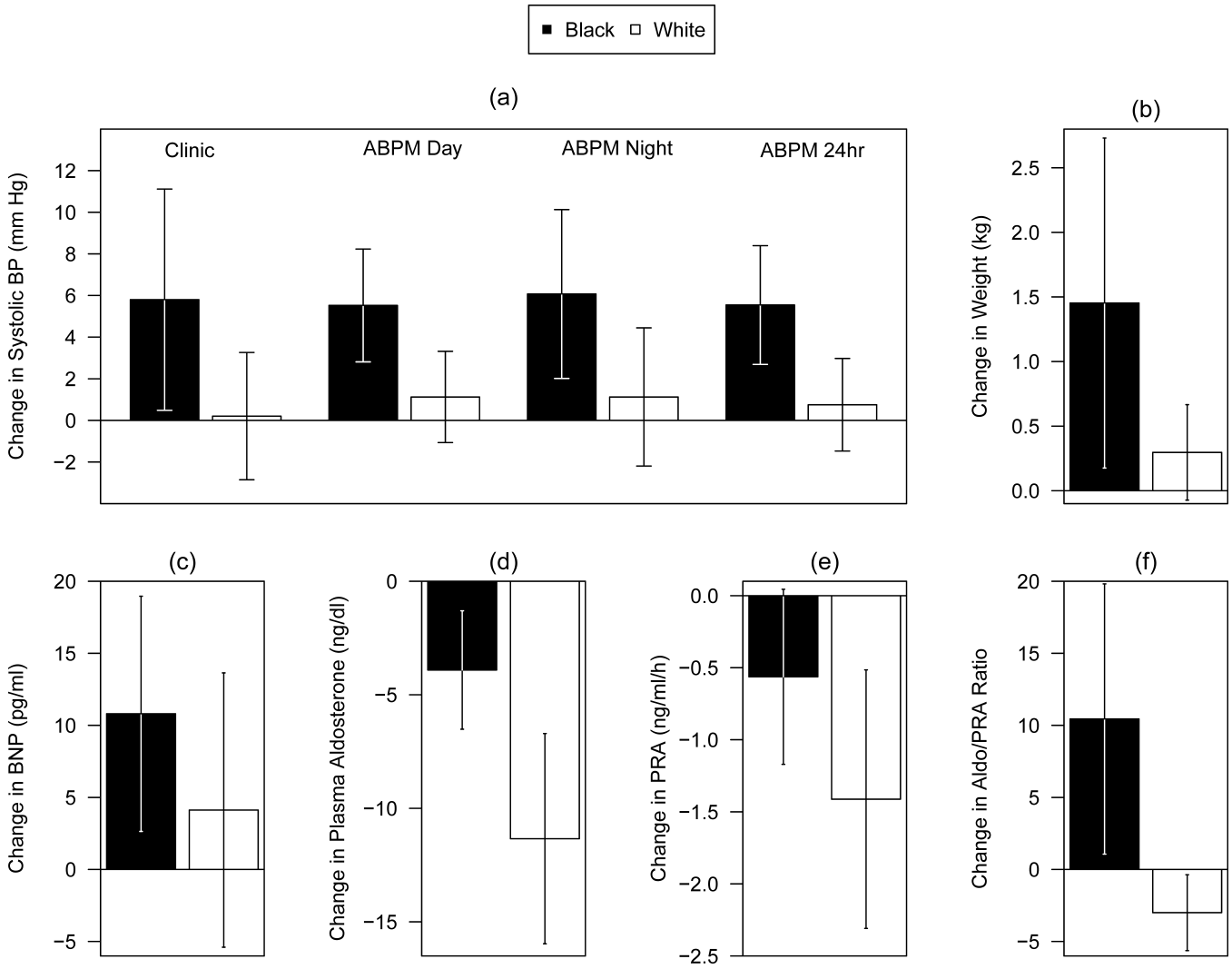

Figure 3.

Changes from baseline in response to two weeks of treatment with 9-α fludrocortisone for systolic BP measured manually ('clinic') and with ambulatory BP monitoring (ABPM), weight, level of B-type natriuretic peptide (BNP), level of PRA, PAC, and PAC/PRA (values depicted with corresponding 95% confidence intervals).

Systolic BP increased in blacks measured in clinic (p=0.034) and with ABPM (p<0.001 during daytime, p=0.006 overnight, and p<0.001 over 24 hr). In blacks, there were significant increases in weight (p=0.028) and BNP (p=0.012). PRA decreased significantly in blacks (p =0.002) and whites (p<0.001); PAC decreased in blacks (p=0.010) and whites (p<0.001). PAC/PRA increased in whites (p=0.036) and decreased marginally in blacks (p=0.09).

Table 1

Characteristics of subjects.

Variable	Full sample	Black	White	P value
Characteristics of the children at time of enrollment.				
N	540	226	314	
Male, n (%)	273 (51%)	105 (46%)	168 (54%)	0.107
Age (yrs) (range: 5 -17)	10.6 (3.0)	11.5 (2.9)	10.0 (2.9)	<0.001
Systolic BP (mm Hg)	101 (12)	103 (11)	100 (12)	<0.001
Systolic BP%	42 (26)	43 (27)	41 (26)	0.448
Diastolic BP (mm Hg)	62 (10)	63 (10)	61 (11)	0.027
Diastolic BP%	52 (26)	52 (25)	51 (26)	0.712
BMI%	63 (28)	70 (28)	58 (28)	<0.001
Characteristics of the adults at time of re-enrollment.				
N	221	85	136	
Male, n (%)	106 (48%)	39 (46%)	67 (49%)	0.626
Age (yr) (range 20 -39)	30.8 (4.2)	29.4 (4.0)	31.6 (4.1)	<0.001
Systolic BP (mm Hg)	116 (11)	116 (11)	116 (11)	0.713
Diastolic BP (mm Hg)	74 (10)	74 (11)	74 (10)	0.975
BMI (kg/m^2)	29 (8)	31 (8)	28 (8)	0.002
Characteristics of subjects in the intervention study.				
N	38	20	18	
Male, n (%)	15 (39%)	9 (45%)	6 (33%)	0.463
Age (yr) (range 19 -36)	27.0 (4.9)	27.9 (4.8)	26.1 (5.0)	0.455
Systolic BP (mm Hg)	112 (10)	110 (8)	115 (12)	0.022
Diastolic BP (mm Hg)	68 (8)	68 (8)	69 (8)	0.524
BMI (kg/m^2)	27 (6)	28 (5)	25 (6)	0.167