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THE PROSPECTIVE RELATIONSHIP BETWEEN PREHYPERTENSION, RACE, AND WHOLE BRAIN WHITE MATTER MICROSTRUCTURE

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Abstract

Compared to whites, blacks develop hypertension earlier in life, progress from prehypertension to hypertension at an accelerated rate, and exhibit greater hypertension mediated organ damage (e.g., kidney disease, stroke). In this paper we tested whether the longitudinal associations between elevated systolic blood pressure and disruption of brain white matter structural integrity differs as a function of race. A community sample of 100 middle-aged adults with prehypertension underwent diffusion imaging to quantify indirect metrics of white matter structural integrity, including fractional anisotropy. Blood pressure and diffusion imaging measurements were collected at baseline and at a two-year follow-up. Regression analyses showed that higher systolic blood pressure at baseline was associated with a decrease in fractional anisotropy over two years in blacks only ($\beta = -0.51$ [95% C.I. = −0.85, −0.16], $t = -2.93$, $p = .004$, $\Delta R^2 = .09$). These findings suggest that blacks are more susceptible to the impact of systolic prehypertension on white matter structural integrity.

Keywords

Blood Pressure; Magnetic Resonance Imaging; Race and Ethnicity

Hypertension has a range of deleterious effects on the brain.(1, 2) Central to the impact of hypertension on the brain is altered structure and function of the cerebral blood vessels.(3) Cerebrovascular pathology linked to hypertension causes hypoperfusion and eventual cavitation of brain tissue.(4, 5) White matter is particularly susceptible to hypoperfusion because of the high vulnerability of oligodendrocytes to anoxia resulting from ischemia.(6)

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Thus, white matter damage has become a hallmark brain abnormality associated with hypertension.

Fixed, essential hypertension has been consistently associated with punctate white matter lesions, as indicated by atypical bright spots on magnetic resonance images (MRI), known as white matter hyperintensities (WMH).(7) WMH are commonly reported late in the lifespan and indicate overt, macrostructural lesions in white matter tissue that are reportedly absent in people with prehypertension.(8) A different characteristic of white matter has been useful in studies of normal and preclinical blood pressure (BP) levels. Subtle, microstructural differences in white matter integrity that precede the macrostructural WMH lesions have been investigated early in the lifespan using a neuroimaging technique termed diffusion imaging.(9) Diffusion imaging studies suggest a gradient between BP levels (normotensive to hypertensive) and white matter abnormalities (microstructural to macrostructural integrity).(10, 11)

Diffusion imaging estimates the direction in which hydrogen molecules flow within white matter tissue.(12) Based on the premise that white matter is composed of bundles of myelinated axons, healthy white matter tissue shows a robust pattern of diffusion parallel to the axonal membrane, known as anisotropy.(13) Our primary measure of white matter microstructural integrity was fractional anisotropy (FA), which reflects the degree to which hydrogen molecules diffuse in one dominant direction. Reduced FA has been reported in a number diseases associated with white matter damage (e.g., multiple sclerosis and leukoaraiosis).(14) Lower FA values can result from reduced diffusion parallel to a white matter tract (axial diffusivity), or from increased diffusion perpendicular to a white matter tract (radial diffusivity).(12) Animal studies have validated increased radial diffusivity as an indirect marker of demyelination, whereas decreased axial diffusivity was indicative of axonal changes.(13)

Blacks may be particularly vulnerable to the impact of prehypertension on white matter microstructure. Relative to whites, blacks develop hypertension earlier in life,(15) progress from prehypertension to hypertension at an accelerated rate,(16) and exhibit greater hypertension mediated organ damage (e.g., kidney disease, left ventricular hypertrophy).(17) Moreover, compared to elderly whites, elderly blacks exhibit a greater volume of white matter lesions, as well as a stronger association between white matter lesions and vascular disease history.(18) Despite these racial differences, evidence of the effects prehypertension on the brain is based primarily on studies of whites. Evidence that blacks with prehypertension are more likely to exhibit changes in white matter structure over time would support race based risk-stratification and more aggressive hypertension prevention regimens for blacks.

In this study we used diffusion imaging to test two hypotheses: 1) elevated BP within the prehypertensive range predicts a greater 2-year decrease in the integrity of white matter microstructure, and 2) compared to whites, blacks exhibit greater decreases in white matter microstructure associated with baseline BP levels. Primary analyses focused on systolic BP averaged across multiple occasions at the start of the study because of extensive evidence that systolic BP is a strong predictor of all-cause mortality and hypertension mediated organ

damage.(19) Secondary analyses examined: a) whether alternative BP measures were similarly predictive of change in FA, and b) whether the relationship between BP and change in FA was driven primarily by axial or radial diffusivity.

Method

Relevant data from this study are available from the corresponding author upon reasonable request. Subjects were recruited over the 4 year period between July 2010 and July 2014 using community advertisements and databases of individuals interested in participation in research, e.g., those participating in the Adult Health and Behavior Study.(20) This study was conducted once. Subjects were screened via telephone with the goal of enrolling healthy middle-aged adults in a longitudinal study on the impact of possible increases in BP over 2 years. Inclusion criteria were age (35 to 65 years) based on previous research that showed neuropsychological deficits in early hypertension within the same age range. Additional inclusion criteria were pre-hypertensive levels of BP (either systolic BP<140 and >120 mmHg or diastolic BP <90 and >80 mmHg and not taking any cardiovascular medications. (21) Exclusion criteria included: a) general medical conditions: pregnancy, ischemic coronary artery disease (prior positive stress test, myocardial infarction or revascularization), cancer, chronic liver disease, chronic kidney disease, or type 1 diabetes; b) neuropsychiatric conditions: stroke, multiple sclerosis, serious head injury, epilepsy, brain tumor or major mental illness (e.g., bipolar disorder and schizophrenia); and c) use of prescription medications for hypertension or psychotropic drugs. Additional exclusions included: current heavy alcohol consumption (≥ 21 standard drinks per week, non-fluency in English (speaking/reading English every day for <10 years), nightshift workers, and MRI scanning incompatibility due to claustrophobia, metal in body, or body habitus. The local Institutional Review Board approved the study and all participants gave informed consent.

The data for this study was originally collected to test the hypothesis that structural and functional brain anomalies relate to blood pressure in the normotensive through prehypertensive range as they do in normotensive/hypertensive comparisons. A diffusion tensor imaging scan was performed for the purpose of obtaining an ancillary indicant of brain structure. Of the 154 participants recruited for this study, 6 did not complete an MRI due to claustrophobia or discomfort in the MRI scanner, 23 did not undergo the DTI scan due to time constraints, 20 had acquisition problems during the diffusion imaging scan (i.e., clipping), and 2 had diffusion images corrupted by movement artifact (based on visual inspection). Three subjects who reported an Asian ethnicity were excluded because of our interest in black and white comparisons. The resulting sample of 100 adults had complete blood pressure data and valid diffusion imaging scans at both time points. Participants with and without diffusion imaging data were not significantly different in any of the demographics listed in Table 1.

Blood Pressure and Adiposity Measurement

Blood pressure values were determined based on the average of four measurements collected across two separate days. Participants were asked to abstain from eating, smoking, drinking caffeinated beverages, and heavy physical activity for at least 30 minutes prior. Participants

were seated with back supported and feet flat on floor for at least 5 minutes. Cuff size was selected based upon arm circumference. At each of the two recording sessions, systolic and diastolic (5th phase) BP was determined twice separated by two minutes using a 2–3 mm Hg/sec deflation rate. All measurements were obtained using the auscultatory method by staff specifically trained in BP measurement using published guidelines.(22) Pulse pressure was calculated as: (average systolic - average diastolic), while mean arterial pressure was calculated as: (2/3 * average diastolic BP + 1/3 * average systolic BP).

Height and weight were measured with subjects' shoes removed. Height and weight were measured digitally using a SECA electronic model #242 Digital output (Hamburg, Germany) and a DETECTO model 758C Digital scale (Webb City, MO), respectively. Body mass index was calculated as: 703* [weight (lb) / (height (in) ^{2}].

DTI Acquisition and Preprocessing

Neuroimaging data was collected on a 3T Trio TIM whole-body MRI scanner (Siemens, Erlangen, Germany), equipped with a 12-channel phased-array head coil. Subjects were positioned in the head coil with an axial series oriented to the plane connecting the anterior and posterior commissures (AC-PC line). The DTI sequence was based on the diffusion weighted echo-planar imaging (EPI) that acquired 40 slices (3 mm, no gap) at a 128×128 resolution (EPI factor 128, voxel size 2×2×3 mm^3). The parameters: TR/TE =5300/88 msec, b=1000 mm^2/s; 12 gradient directions repeated four times and averaged to increase accuracy; scan time = 5 min (GRAPPA acceleration factor = 2).

Raw diffusion images were converted from DICOM to NIFTI format using MRICRON. Eddy current correction was completed using FSL's diffusion toolbox. Non-brain tissue was removed from the diffusion images using FSL's brain extraction tool. (23) Finally, a tensor model was fitted at each voxel to the corrected data using DTIFIT, resulting in whole brain maps of FA, as well as the 1st, 2nd, and 3rd eigenvalue. Following preprocessing, diffusion data was aligned to the FMRIB58_FA template using the nonlinear registration tool FNIRT within the tract based spatial statistics (TBSS) pipeline.(24) Preprocessed diffusion images collected at time 1 and time 2 were merged into a single 4D image file and a mean "skeleton" was created for each diffusion parameter (FA, L1, L2, & L3), with the mean FA skeleton thresholded at 0.2. Average FA, L1, L2, & L3 values were computed using the fslstats command for the entire white matter skeleton. L1, L2, and L3 were used to compute axial (L1) and radial diffusivity ((L2 + L3) / 2).

Data Analysis

All analyses were conducted using two-tailed tests in SPSS 25 and the PROCESS macro v2.16.3 was used to probe interactions.(25) Bootstrapping was performed (10 000 samples) to calculate 95% confidence intervals (C.I.) for all parameter estimates and heteroscedasticity-consistent estimates of standard errors were used. For descriptive purposes, the relationship between self-reported race and a number of potential confounding variables measured at baseline were estimated using correlation coefficients. Independent-sample t-tests were conducted to compare blacks and whites on BP and diffusion imaging

metrics. Pairwise t-tests were conducted separately for whites and blacks as initial descriptive tests of change in BP and white matter integrity from baseline to follow-up.

Longitudinal change in whole brain white matter microstructural integrity in relation to systolic BP was analyzed using a conditional change score model, applied via multiple regression.(26) First, % change scores for white matter integrity variables were computed [((follow-up - baseline) / baseline) * 100]. All variables were converted to Z-scores prior to analyses to standardize regression coefficients. R^2 was used as the effect size for all regression analyses. A decrease in white matter integrity was indicated by a negative change score. The resulting change scores were regressed onto the baseline white matter integrity values (to account for regression to the mean) and systolic BP at baseline.

The standardized regression coefficient for systolic BP was used to test the hypothesis that higher BP levels at baseline predicted greater decreases in white matter integrity. The regression coefficient for the interaction between race and systolic BP was used to test the hypothesis that compared to whites, blacks would exhibit greater changes in white matter integrity associated with systolic BP at baseline (i.e., reject the null if C.I. does not include zero). Simple slopes were calculated separately for whites and blacks

Interactions were also probed further using the Johnson-Neyman technique to calculate the regions of significance.(27, 28) We computed the standardized slope and the 95% C.I.s for the relationship between race and percent change in white matter integrity as a function of systolic BP. This analysis complements the simple effects analysis described above in that it defines the value of systolic BP (e.g., ≥ 130 mmHg) at which racial differences in percent change in white matter integrity emerge. Similar regression models were used to test the secondary hypotheses.

Results

Participant Characteristics

Table 1 shows participant characteristics at baseline stratified by self-reported race. While some of these characteristics are reportedly associated with white matter integrity (e.g., smoking, education), adjustment for these covariates did not change the pattern of findings reported below, and slightly increased the magnitude of primary effects. Unadjusted and adjusted results are reported for primary analyses.

Blacks and whites had similar average systolic BP at baseline and at follow-up (see Figure 1a). Change in systolic BP was also similar between blacks and whites (see Fig 1b). Compared to whites, blacks showed substantially lower average levels of FA at both baseline and at follow-up (see Figure 1c). This was accounted for in all models by including baseline FA as a covariate. There was also greater change in FA in blacks compared to whites (see Figure 1d).

Relationship between baseline systolic BP, race, and % change in FA

Table 2 shows the bootstrapped parameter estimates from the multiple regression model of the prospective relationship between baseline systolic BP, race, and % change in FA. In

contrast to our first hypothesis, there was no significant main effect for systolic BP, suggesting that elevated systolic BP within the prehypertensive range did not predict % change in FA. In support of our second hypothesis, the interaction between race and systolic BP was significant and showed that the relationship between baseline systolic BP and % change in FA varied as a function of race. Estimation of the simple slopes separately for blacks and whites showed that systolic BP at baseline predicted % change in FA for blacks ($\beta = -0.51$ [95% C.I. = −0.85, −0.16], $t = -2.93$, $p = .004$, $\Delta R^2 = .09$) but not whites ($\beta = 0.00$ [95% C.I. = −0.55, 0.25], $t = 0.01$, $p = .985$, $\Delta R^2 = .00$; see Figure 2). The pattern of findings was the same before and after adjustment for potential confounding variables.

Figure 2 shows that the slopes for blacks and whites cross at a systolic BP of 115 mmHg. To determine the level of systolic BP at which racial differences in % change in FA emerged, the Johnson-Neyman technique was used. The standardized simple slope of the relationship between race and % change in FA was significant at all values above a systolic BP of 122 mmHg, which constituted roughly 61% of the sample. Thus, exacerbated decline in FA was primarily characteristic of blacks with BP of 122 mmHg or greater.

Relationship between alternate measures of baseline BP, change in FA, and race

In addition to systolic BP, secondary analyses were conducted using alternative BP metrics (see Supplement Table 1, 2, and 3 for detailed regression analyses). Results from the adjusted models are summarized below. The main effect of pulse pressure ($\beta = -0.02$ [95% C.I. = [−0.27, 0.23], $t = -0.16$, $p = 0.88$, $\Delta R^2 = .00$) and the interaction with race ($\beta = -0.47$ [95% C.I. = [−0.84, −0.09], $t = -2.46$, $p = 0.02$, $\Delta R^2 = .06$) were similar to those reported for systolic BP. In contrast, diastolic BP ($\beta = 0.00$ [95% C.I. = [−0.22, 0.22], $t = -0.01$, $p = 0.99$, $\Delta R^2 = .00$) and mean arterial pressure ($\beta = 0$ [95% C.I. = [−0.24, 0.23], $t = -0.03$, $p = 0.98$, $\Delta R^2 = .00$) did not predict percent change in FA, nor was there evidence of racial differences for diastolic BP ($\beta = 0.09$ [95% C.I. = [−0.39, 0.57], $t = 0.38$, $p = 0.71$, $\Delta R^2 = .00$) or mean arterial pressure ($\beta = -0.2$ [95% C.I. = [−0.72, 0.32], $t = -0.76$, $p = 0.45$, $\Delta R^2 = .00$).

Relationship between systolic BP and Change in Radial and Axial Diffusivity

In our last set of secondary analyses, we examined whether the racial differences in the relationship between baseline systolic BP and % change in FA reported above were driven by changes in radial or axial diffusivity (see Supplemental Tables 4 and 5 for detailed regression analyses). Simple slopes from the adjusted models are summarized below. There was a trend for systolic BP at baseline predicting % change in radial diffusivity for blacks ($\beta = 0.36$ [95% C.I. = [−0.05, 0.79], $t = 1.71$, $p = 0.08$, $\Delta R^2 = 0.03$) but not whites ($\beta = 0.06$ [95% C.I. = [−0.16, 0.28], $t = 0.53$, $p = 0.59$, $\Delta R^2 = 0.00$). The magnitude of the regression coefficient for blacks was roughly 67% of the size found with % change in fractional anisotropy. Conversely, systolic BP at baseline did not predict % change in axial diffusivity for blacks ($\beta = 0.11$ [95% C.I. = [−0.12, 0.35], $t = 0.94$, $p = 0.34$, $\Delta R^2 = 0.01$) or whites ($\beta = -0.15$ [95% C.I. = [−0.66, 0.35], $t = -0.60$, $p = 0.54$, $\Delta R^2 = 0.00$)

Discussion

Our results show that blacks with baseline systolic BP of 122 mmHg or higher show a decline in white matter integrity, as indexed by FA, at a rate of 1% per year. Blacks showed an exacerbated decline in FA related to baseline systolic BP even after taking into account baseline racial differences in white matter integrity and other characteristics (e.g., smoking, sodium). Conversely, blacks and whites with baseline systolic BP ≤ 120 mmHg show little to no change in FA.

Results with FA were primarily driven by increases in radial diffusivity. Changes in radial but not axial diffusivity suggest that blacks with elevated baseline systolic BP (i.e. ≥130 mmHg) are likely to exhibit early stages of demyelination. The same pattern of findings has been reported in rodent and human models of hypoxic-ischemic insult.(29, 30) For example, following ligation of the carotid artery, rats with non-cystic white matter injury and reduced myelination exhibited decreased fractional anisotropy, increased radial diffusivity, and no change in axial diffusivity.(30) These findings are also consistent with models of BP related white matter damage in vascular cognitive impairment, which suggest that high BP damages cerebral blood vessels, initiates vascular repair, and results in gliosis, inflammation, and demyelination.(31, 32)

While a negative relationship between systolic BP and white matter integrity was detected in blacks, the relationship was nil in whites. This finding is in contrast to cross-sectional and longitudinal diffusion imaging studies which have shown relationships between white matter integrity and BP in whites.(33–35) However, the majority of longitudinal studies to date have examined high levels of systolic BP (≥ 140 mmHg) as a predictor of reduced white matter integrity across much longer time intervals (≥ 10 years) than the 2-year duration in our study. Findings from an investigation of the third generation of the Framingham Heart Study showed a relationship between FA and systolic BP in the prehypertensive range, though this study was cross-sectional and failed to report any descriptive statistics about the racial composition of the cohort analyzed.(11) Overall, this suggests that, at least in whites, even a systolic BP of 130 mmHg may not result in a demonstrable change in white matter integrity over two years.

Thus, the next step is to determine why the same levels of systolic BP predict a decline in white matter integrity in blacks but not whites. One possibility is that other chronic risk factors make blacks more sensitive to elevated systolic BP (≈ 130 mmHg) over a short duration (e.g., 2 years). One potential factor is racial differences in the cerebral vasculature that perfuse white matter tissue. For example, a recent postmortem study of cerebral arteries in white matter tissue showed that compared to whites, blacks exhibited greater mean arteriolar wall thickness, resulting in an increased risk for cerebral small vessel disease.(36) Of particular interest is a study showing that independent of age and BP, the renal arteriole lumen in black children was 23% smaller compared to white children.(37) Overall, these findings suggest blacks are at an increased risk for vascular disease, which might explain our finding that the same BP values are more damaging over relatively brief periods for blacks compared to whites.

Among the strengths of this study were the longitudinal design, statistical control of individual differences in white matter integrity at baseline, and examination of relatively young, individuals with prehypertension. Despite these strengths, the study would be improved by having a larger number of blacks, manipulation of BP, higher resolution diffusion imaging and vascular imaging, and 24-hour blood pressure monitoring. Though, concern about the sample size is somewhat attenuated by the size of our reported effects, bootstrap method for parameter estimates, and the fact that our findings are consistent with our *a priori* hypotheses and the extant literature on racial differences in hypertension mediated organ damage. Nonetheless, a confirmatory study should be conducted on a larger cohort. Future research might address these issues by examining the degree to which BP reduction causes the decline in white matter integrity in a large cohort of blacks with systolic BP ≥ 130 mmHg. It may be that reducing systolic BP to 120 mmHg or less is enough to attenuate or even abolish the decline. Moreover, a higher resolution diffusion imaging protocol would be useful to confirm whether BP reduction attenuates both the decline in whole brain FA and the increase in radial diffusivity. Finally, recruiting subjects with a complete blood pressure and vascular injury history would make it possible to account for a potential greater exposure to cerebrovascular challenge in blacks compared to whites.

Perhaps the most important lesson to be learned from this study is that, at least in middle-aged blacks, elevated systolic BP predicts a decrease in white matter integrity in as little as two years. If true, these findings provide evidence supporting future investigations of early preventions efforts in prehypertensive blacks to control BP and other vascular risk factors with the aim of protecting the brain.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Summary Table

What is known about topic

- Hypertension during midlife is associated with white matter lesions late in life
- Compared to whites, blacks exhibit greater hypertension mediated organ damage

What this study adds

- Racial differences in the prospective relationship between white matter integrity and blood pressure (BP) during midlife is described for the first time.
- High prehypertensive systolic BP predicted decline in white matter integrity for blacks but not whites.

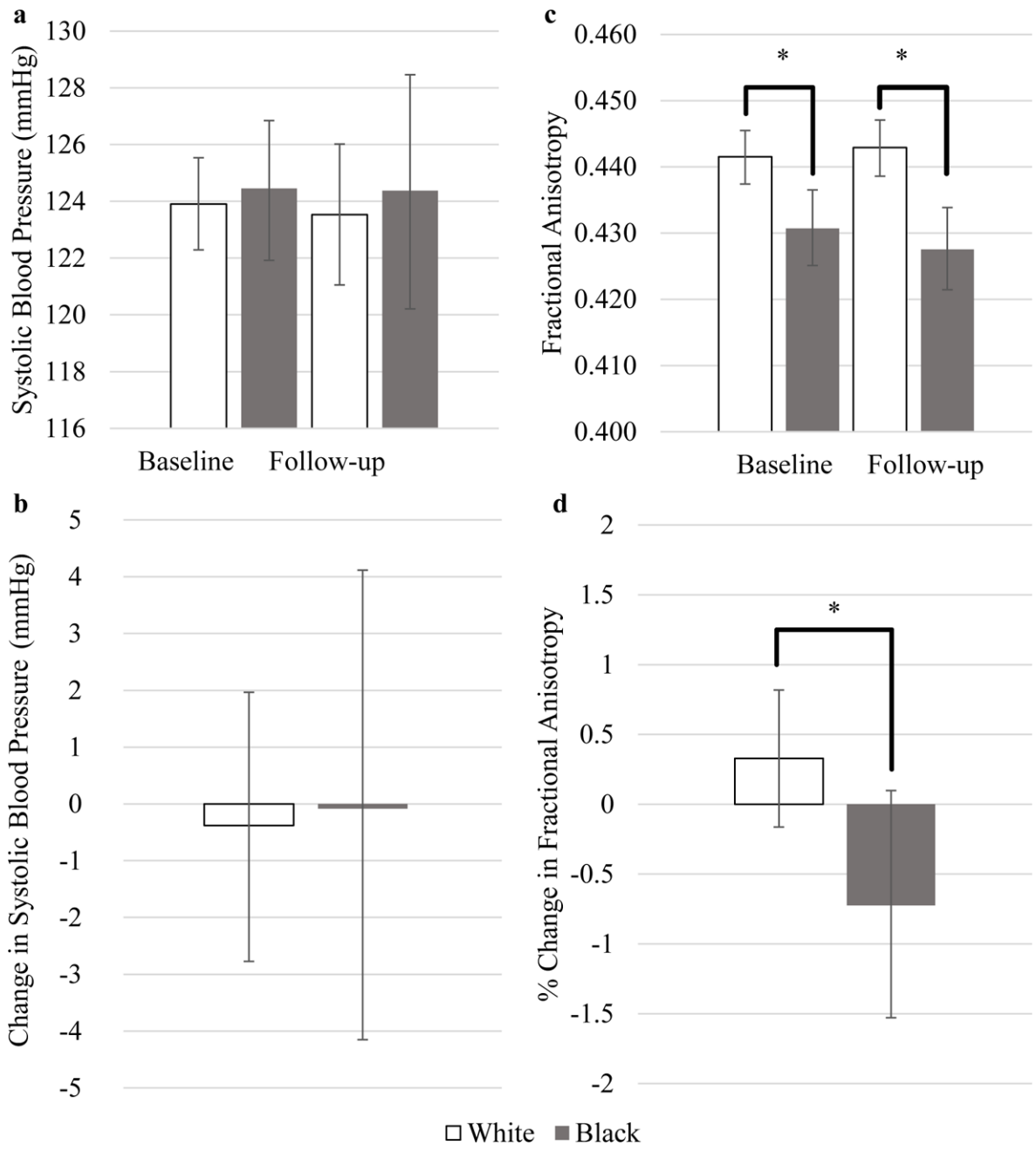

Figure 1.

Means and 95% confidence intervals for baseline, follow-up, and change in systolic blood pressure and fractional anisotropy. Note: * Indicates a significant difference between blacks and whites and that the 95% confidence intervals of the difference did not include zero.

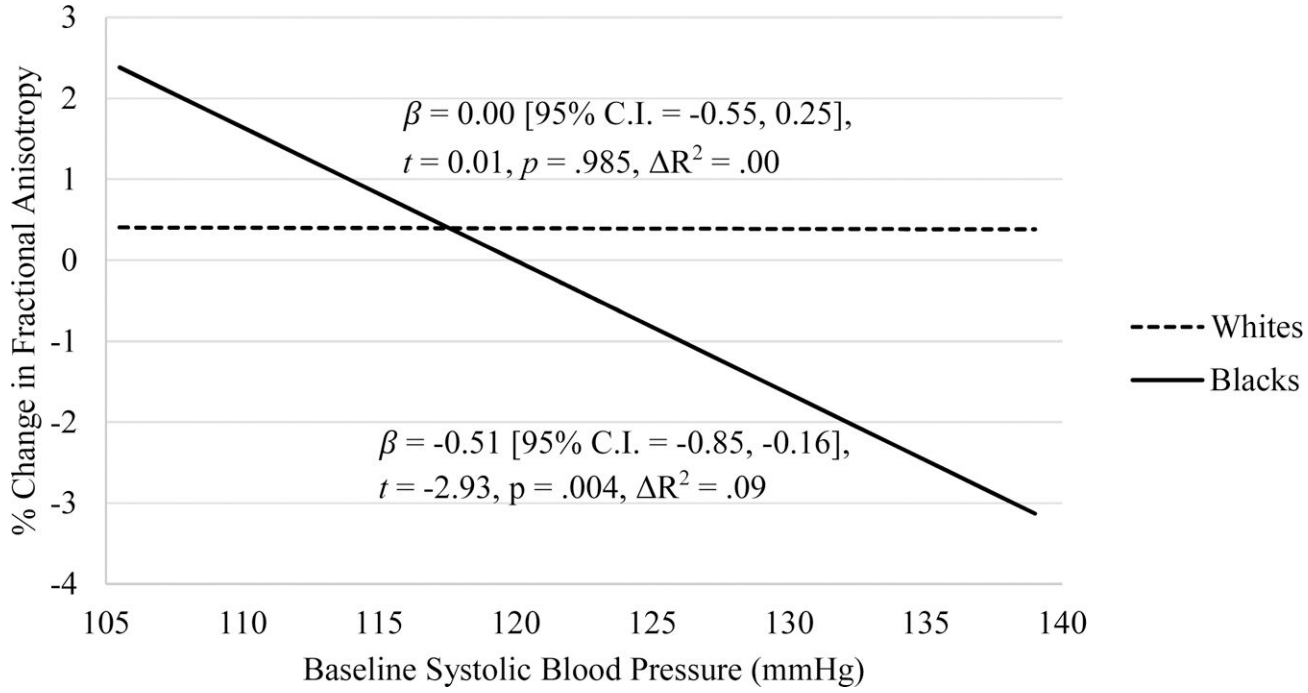

Figure 2.

Simple slopes for the relationship between baseline systolic blood pressure and % change in fractional anisotropy over two years plotted separately for blacks and whites. C.I. = Confidence Interval.

Table 1.

Participant descriptive statistics at baseline stratified by race

	Blacks (n = 36)	Whites (n = 64)	Group Differences
	Mean (SD)	Mean (SD)	Correlation (95% C.I.)
Age (years)	51 (7)	47 (6)	−0.22 * (−0.41, −0.04)
Education (years)	16 (2)	14 (2)	−0.46 * (−0.61, −0.3)
Sex (% male)	41%	47%	−0.06 (−0.26, 0.13)
Body Mass Index (kg/m2)	30 (6)	30 (6)	−0.02 (−0.22, 0.17)
Drank Alcohol in past year (%)	81%	64%	−0.19 (−0.39, 0.01)
Current Smoker (%)	13%	53%	0.43 * (0.24, 0.62)
Urinary sodium, mmol/creatinine (g)	89 (54)	139 (61)	0.08 (−0.12, 0.28)
Urinary potassium, mmol/creatinine (g)	30 (21)	37 (19)	−0.25 * (−0.39, −0.12)

Note: Correlation coefficients with group are point-biserial correlations for continuous variables, phi coefficients for binary variables. SD = Standard Deviation; C.I. = Confidence Interval.

* Indicates a significant correlation and that the 95% confidence interval did not include zero.

Table 2.

Regression models of the relationship between baseline systolic BP, race, and change in FA

Unadjusted Model					
	β	95% C.I.	SE	*t*	*p*
constant	0.21	[−0.02, 0.43]	0.11	1.80	0.07
Baseline FA	−0.18	[−0.34, −0.03]	0.08	−2.34	0.02
Race	−0.55	[−0.96, −0.15]	0.2	−2.71	0.01
Baseline Systolic BP	−0.08	[−0.31, 0.15]	0.12	−0.71	0.48
Systolic BP x Race	−0.45	[−0.88, −0.02]	0.22	−2.07	0.04
Adjusted Model	β	95% C.I.	SE	*t*	*p*
constant	−0.33	[−2.97, 2.30]	1.32	−0.25	0.8
Baseline FA	−0.28	[−0.50, −0.06]	0.11	−2.5	0.01
Race	−0.46	[−1.02, 0.10]	0.28	−1.64	0.1
Baseline Systolic BP	0.00	[−0.25, 0.26]	0.13	0.02	0.99
Systolic BP × Race	−0.51	[−0.94, −0.08]	0.22	−2.38	0.02

Note: The unadjusted model accounted for 20.2% of the variance in % change in FA; the interaction between systolic BP and race accounted for 4.8%. The adjusted model accounted for 34.3% of the variance in % change in FA; the interaction between systolic BP and race accounted for 5.6%. The adjusted model included age, education, sex, body mass index, current smoker (yes/no), current drinker (yes/no), urinary sodium and urinary potassium (mmol/creatinine g) as covariates.