Abstract:
Objectives: Our goal was to assess the relative roles of education and genetic ancestry in predicting blood pressure (BP) within African Americans, and to explore the association between education and BP across racial groups.

Methods: We used t-tests and linear regressions to examine the associations of genetic ancestry, estimated from a genome-wide set of autosomal markers, and education with BP variation among African American participants in the Familial Blood Pressure Program (FBPP). We also performed linear regressions in self-identified African Americans and Whites to explore the association of education with BP across racial groups in FBPP.

Results: Education, but not genetic ancestry, significantly predicted BP variation in the African American subsample (β=-0.51 mmHg/year additional education, p=0.001). Although education was inversely associated with BP in the total population, within-group analyses showed that education remained a significant predictor of BP only in the African American subsample. A significant interaction (β=3.20, p=0.006) was found between education and self-identified race in predicting BP.

Conclusions: Our findings suggest that racial disparities in blood pressure may be better explained by differences in education than by genetic ancestry. Future studies of genetic ancestry and disease should be careful to include measures of the social environment.
with a focus on social factors and socioeconomic position in relation to health.

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**Response to Reviewers:**  
The response to reviewers has been uploaded as a separate file.
April 5, 2011

Dear AJPH Editors:

We would like to submit the manuscript “Education, genetic ancestry, and blood pressure in African Americans and Whites,” to be considered for publication in the American Journal of Public Health. We believe our study is novel and of immediate interest to researchers in public health, as it has important implications for the scientific debate and the public understanding of “race,” and the origins of racial inequalities in health.

While many researchers suggest that health inequalities are rooted in underlying genetic differences between populations, others argue that important social factors explain these disparities, but very few incorporate both types of measures to test these competing hypotheses. In this study, we integrate genetic ancestry data with epidemiologic data from a large and geographically widespread US dataset to test the roles of education and genetic ancestry in contributing to racial inequalities in blood pressure.

Our previous work, based on ethnographic research in Puerto Rico, has shown that social classification better predicts blood pressure than does individual genetic ancestry in Southeastern Puerto Rico.1,2 This new study builds upon our prior work to demonstrate how, in a large US sample, a measure as simple and easily measured as education level can capture an aspect of the social environment that explains blood pressure variation better than genetic ancestry in a large scale population study. We also find that higher education is associated with a greater health benefit for African Americans than Whites in this sample, suggesting that improved access to education among African Americans may reduce racial inequalities in blood pressure.

The data are original and are not under review for publication elsewhere. The authors have complied with the principles of ethics code. Informed consent was obtained from all participants in the original data collection stages, and the research protocol was approved by the University of Florida Institutional Review Board.

Thank you for considering our manuscript for publication.

Sincerely,

Amy L. Non, Clarence Gravlee, and Connie Mulligan

We thank the reviewers for their detailed comments and suggestions for our paper. We have provided a point-by-point response to each reviewer comment below.

Response to Reviewers’ comments:

Reviewer #1: The few comments I have are minor and are as follow:

1. Page 2, line 4: The abbreviation (acronym) for blood pressure that is shown here should be placed in the last paragraph of page 1, where it is shown for the first time in the introduction.
   We moved the abbreviation up to the first time it is used in the introduction.

2. Page 2, first sentence of "Participants": The explanation of the FBPP acronym is already stated in page 1, so there is no need to repeat it here.
   We deleted the acronym.

3. Page 2, "Participants": Since the FBPP has data on more than two races/ethnicities, why only African American and White individuals were included in the current study?
   We chose to examine only African Americans and White individuals because our focus was on the long-studied Black-White health disparity in blood pressure. We added a phrase to explain this in this section.

4. Page 6, last sentence: In table 2, the p-value for education is not lower than 0.001 as reported in the results' section. It is 0.001. Which is correct, the text or the table?
   We have corrected the p-values so they match and both show the correct value.

5. Where p-values are presented as 0.000, in the text and tables, the actual number should be supplied, or at least indicate that it is below 0.001.
   We have changed the p-values to <0.001 where they were listed as 0.000.

Reviewer #3: The etiology of hypertension is unclear so far, thus it is very important to explore pathogenic factors related to hypertension occurrence. This study assessed the relative roles of education and genetic ancestry in predicting blood pressure within African Americans and explored the association between education and BP across racial groups. It provides fundamental evidence that racial disparities in blood pressure may be better explained by differences in education than by genetic ancestry. But just like the author mentioned that hypertension is a complex disease involving in multiple environmental and genetic causes, salty diet is very important risk factor for hypertension. I could not find, in this study, any information about salty diet and hypertension. It is insufficient to discuss roles of environmental factors and genetic ancestry in predicting blood pressure without regard to diet habit especially salty diet. So, the following questions need to be considered.

1. The major environmental and genetic factors related to hypertension should be introduced in introduction and then to raise the research significance of this study.
We added a brief example of a few of the best-studied environmental and genetic factors in the introduction.

2. Salty diet should be considered as a covariate or confounder in the results.
   Dietary intake data were not available in the FBPP dataset.

3. The discussion should be adjusted and extended accordingly.
   Though we were unable to include behavioral factors like sodium intake in our analyses, because those data were not available in the FBPP dataset, we have added a sentence to address the importance of these factors to the limitations section of the discussion: “Finally, we recognize that other risk factors, such as dietary sodium intake, are also associated with BP, though the magnitude of these effects remains unclear (Dumler et al. 2009, Taylor et al. 2011). The FBPP dataset does not have this data, and thus it remains for future studies to determine whether the addition of other behavioral variables alters the associations we observe.”

Reviewer #4: Due to the relatively few papers in AJPH on genetics/ancestry as predictors and limited practitioner exposure to techniques in genetic estimation ancestry, this topic would expand our readers’ knowledge base. However, this also means the section of the paper about these methods should be better explained.
   We have added a brief background explanation of how genetic ancestry is estimated in the Estimation of ancestry section of the methods.

The definitions and distinction of racial groups, self-identified race, genetic ancestry and African Americans need to be clarified even in the abstract of the paper.
   We have added the term ‘self-identified’ to the methods section of the abstract when we first introduce the racial groups, and we added the phrase ‘estimated from a genome-wide set of autosomal markers’ when we describe genetic ancestry in the methods of the abstract.
   In the abstract the actual extent of the interaction and prediction should be stated, not just labeled significant.
   We have added the Beta value and P values for the effect of education in the African American sample, and for the interaction between race and education in the total dataset.
   The idea that racial disparities in blood pressure may be better explained by differences in education than genetic ancestry is not surprising. Authors may want to look at the paper by Boykin et al. (at end) which looked at hypertension and education.
   We have added a reference to the Boykin et al. paper in the discussion of the paper, in the section on education and racial disparities in BP.

In the 5 years from the previous analysis of the dataset by Tang published in 2006 which found no significant association between African genetic ancestry and blood pressure, has anything changed about the type of analysis available since the last study?
   Methods for estimating ancestry from genome-wide data have evolved, but we are limited to the analyses that can be done on the type of data available in the FBPP dataset.
   Was any ancestry assessment done of the self-reported whites to see whether there was any African ancestry in the admix?
We did not assess ancestry in the White population because previous studies have shown very limited magnitude and variation of African ancestry among White Americans (Shriver et al. 2003).

Areas of the methods and analysis sections seem repetitive without becoming clearer with the additional coverage. For example, an interaction term was constructed to test for interactions between education and ancestry, but not reported on except to imply that it was not used in the final models since they only talk about the age and gender interaction term being included.

We have more explicitly stated in the methods that the interaction between education and ancestry was not significant and not included in final models.

In the following section they speak of cross product interactions between education and self-identified race. For the results on Modeling ancestry, education and BP, it seems that African ancestry was not a continuous variable based on percentage of ancestry - but it is not clear how or if they studied the relationship between percentage of African ancestry and BP.

African ancestry was used as a continuous variable based on percentage of African ancestry, and we analyzed its relationship with BP in a linear regression model. To clarify this, we have added the term “continuous” in the first sentence of the methods section entitled Estimation of Ancestry.

Then they proceed to talk about gender, self-identified race, and education all having unique effects on BP which is not clearly demonstrated by the results.

We describe how gender, race, and education have unique effects in the final paragraph on page 8, and as shown by Figure 1 and Supp Table 3. Presentation of p values in text is a bit unclear. For example, doubtful that P=0.000 rather it is likely that P<0.001 or some other number. Apply the AJPH standard for presenting P values.

We have corrected the P-value notation.

Article refers to Supp Table 1 - no supplemental tables were attached to the article for review.

We thought we had properly submitted the supplemental tables to the journal, and apologize if the reviewer was unable to view them.

Table legends are repetitive for significance levels. We have removed the level of significance from all legends.

In the discussion, it should have been put into context of other studies of BP and education whether the 0.51 mmHg decrease in BP associated per year of education is typical.

We have added this sentence to the discussion, “This result is in line with a prior study which reports a similar two mmHg difference in SBP between those with a high school diploma or less and college graduates (Govil et al. 2009).

The larger issue of whether this is a clinically meaningful difference to be considered in prevention efforts should also have been discussed.

We have added this sentence to our discussion: “Thus, with just four years of additional education, our model predicts a population-level decrease of 2mmHg SBP,
which is estimated to result in a considerable reduction in mortality due to BP-related diseases, e.g. 17% decrease in hypertension (Whelton 2002, Stamler et al. 1991, Cook et al. 1995).

The statement that "it is clear that education is strongly associated with BP?" is forceful in terms of what is considered to be a strong association. We have softened this statement.

Explanation of the differences between educational association in AAF BP and White BP re-introduce but do not respond to the minority poverty hypothesis. Our results support the minority poverty hypothesis, as stated in the discussion: “Our results support the minority poverty hypothesis, as the worst blood pressures were predicted for people who face the double burden of being less educated and identifying as African American (Figure 1). The direction of the significant interaction between race and education in the two-level education model suggests that African Americans derive greater health benefit from higher education than do Whites.”

It seems the authors conclude that identifying as African American is predictive of worse BP, but that self-identified race is not equal to African genetic ancestry as estimated in their dataset which was limited by a non-fully representative range of markers and populations.

Though our ancestry data were not fully-representative of the parental populations, they represent the type of data typically used by most researchers who test associations between ancestry and health. Furthermore, we believe the ancestry data is measured in more detail than the sociocultural measures, yet still did not show an association, while the education variable did, suggesting a larger impact for sociocultural factors.


Reviewer #5: This is an interesting, well performed and well written manuscript, describing the effect of genetic ancestry and education on blood pressure in African Americans and Whites. This is a restrospective study of the database collected in a previous large study; the Familial Blood Pressure Program (FBPP) conducted in the USA. The study is well designed, the statistics are elaborate and appropriate and the text is well written. The discussion is concise, adequate and clear. There are suggestions of minor changes that include:

Abstract
1. Objectives: please state your goals, not what you already did.
We have reworded this section appropriately.

Materials and Methods

1. Participants: Paragraph 1, line 9: "subjects included ..... have" should be "had".
   Thanks for catching our mistake, we have changed this.
2. A short paragraph clarifying exclusion criteria should be included.
   The inclusion criteria for each analysis are explained in the second paragraph of the participants section of the methods. To make this more clear, we have added the phrase “inclusion criteria.”
3. The authors should include a brief explanation of the FBPP, outlining how data (especially measurement of blood pressure) was collected in the original study.
   We have added a short description of the purpose of the FBPP under the Participants section of the Methods. “The FBPP study was established in 1995 by the National Heart, Lung, and Blood Institute (NHLBI), for the purpose of studying hypertension and/or cardiovascular outcomes in multiple ethnic groups. This dataset was compiled from 13 different field centers, using standardized clinical and genotyping protocols, as described in detail by the FBPP Investigators.18,
   We have also added a sentence to the description of the blood pressure measurements in the methods, under the section Blood Pressure and Covariates, “The BP measures were averaged from multiple (usually) three measurements taken in a single clinic visit using a Dinamap, or if unavailable, Omron instrument.”

Reviewer #6: The manuscript titled "Education, genetic ancestry, and blood pressure in African Americans and Whites" is an interesting work in the pursuit to find association of factors affecting Blood Pressure in ethnically diverse groups. Single most frequent parameter, education, versus genetic ancestry has been taken into consideration. In my opinion, the educational status is also linked with socioeconomic background. It would have been given more weightage to the paper if this parameter was also included in the model. Nonetheless, an interesting work.
   The FBPP dataset does not have any additional data on socioeconomic background, which is why we use education to represent socioeconomic background. We recognize that this is not an ideal measure in the limitations section, but we also noted that education alone is predictive of BP.

References


Introduction

In recent decades, researchers have struggled to determine the causes of racial disparities in health. Many biomedical researchers speculate that underlying genetic differences between races may contribute to these disparities. With the increasing availability of high-throughput genotyping platforms, a wealth of genomic data is now available to help address this issue. One consequence is that more researchers are estimating genetic ancestry to capture a presumed genetic basis of racial disparities in health.\(^1\)\(^-\)\(^3\) However, any associations found between genetic ancestry and disease could alternatively be explained by unmeasured environmental factors that are also associated with African genetic ancestry, and contribute to health disparities, such as socioeconomic status (SES), neighborhood environment, and psychosocial factors like perceived stress or discrimination.\(^4\)\(^-\)\(^7\) Therefore, in order to avoid unwarranted inferences about the magnitude of genetic influences on health disparities, it is critical for any analysis of ancestry and disease to include appropriate social-environmental variables.

Social-environmental factors may be especially important when studying a complex disease like hypertension. Complex diseases, by definition, involve multiple environmental and genetic causes, as well as interactions within and between the two. Many studies have identified important social-environmental influences on racial inequalities in hypertension, such as socioeconomic status, psychosocial stressors, and neighborhood environment,\(^8\)\(^-\)\(^13\) while other studies have begun to identify relevant genetic variants, such as those in the rennin-angiotensin-aldosterone axis and the adrenergic system.\(^14\)\(^-\)\(^17\) Few studies, however, have examined genetic and environmental factors simultaneously. The limited scope of this research to date has slowed progress toward explaining racial inequalities in hypertension and other complex diseases.
To address the relevance of both genetic and environmental factors in racial inequalities in hypertension, we tested associations between genetic ancestry, education, and blood pressure (BP) among Whites and African Americans in the Family Blood Pressure Program (FBPP) study. A previous analysis of this dataset by Tang et al. found no evidence of a statistically significant association between African genetic ancestry and blood pressure.\(^2\) They concluded nonetheless that the results were “suggestive of genetic differences between Africans and non-Africans that influence blood pressure, but such effects are likely to be modest compared to environmental ones.” No environmental variables were included in their study, however. Here we re-examine the FBPP dataset to test how the addition of education affects the association between ancestry and BP in African Americans. We also explored the association between education and blood pressure across racial groups. We hypothesized that education would show a greater association with BP than would African ancestry among African Americans, and that the association between education and BP may vary by racial and gender groups.

Materials and Methods

**Participants**

We use data from the large, publicly available multi-center FBPP study of 11,357 self-identified White, African American, Mexican American, and Asian individuals. The FBPP study was established in 1995 by the National Heart, Lung, and Blood Institute (NHLBI), for the purpose of studying hypertension and/or cardiovascular outcomes in multiple ethnic groups. These data were compiled from 13 different field centers, using standardized clinical and genotyping protocols, as described in detail by the FBPP
Investigators.\textsuperscript{18} As this study is focused on Black-White disparities in BP, only African American and White individuals were included in the current study. African American individuals came from field sites in Birmingham, Alabama, Forsyth County, North Carolina, Jackson, Mississippi, and Maywood, Illinois. The White individuals came from field sites in Tecumseh, Missouri, Rochester, Minnesota, Forsyth County, North Carolina, Minneapolis, Minnesota, Framingham, Massachusetts, and Salt Lake City, Utah. The subjects included in this study had a mean age of 45.29 years, (range: 13 to 80), and 55.9% of participants were female. IRB approval was obtained from the University of Florida to analyze the FBPP dataset.

We conducted two main sets of analyses. The first set was designed to address within-group hypotheses about relationships of genetic ancestry, education, and blood pressure in African Americans. We constructed two datasets from the full FBPP database for within-group analyses with the following inclusion criteria: 1) a sample of unrelated African American individuals with relevant phenotype data and >80% complete genotypes (n=1077) for t-tests of ancestry and hypertensive status and 2) a sample of African Americans including all individuals with ancestry measures (n=1463) for regression analyses, including both related and unrelated individuals, as relatedness could be accounted for in the modeling of the various BP measures. Next, we conducted a series of analyses to test between-group hypotheses of education and blood pressure, using two additional datasets: 1) all unrelated African Americans and Whites with BP measures and education data (n=1604 African Americans and n=1283 Whites) for t-tests of education and continuous BP measures, and 2) all African Americans and Whites with BP measures and education data, including related and unrelated individuals, but
excluding those who were taking hypertensive medication (n=2034 African Americans, n=1656 Whites). As the FBPP dataset was comprised of large pedigrees, and some tests required only unrelated individuals, a single individual was chosen from each pedigree to create the unrelated datasets in the manner described by Tang et al.¹⁹

**Blood Pressure and Covariates**

We used three measures of blood pressure: systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP), along with a categorical variable of hypertensive status. The BP measures were averaged from (usually) three measurements taken in a single clinic visit using a Dinamap, or if unavailable, Omron instrument. Hypertensive status was classified as hypertensive or normotensive by FBPP investigators based on consideration of clinical blood pressure measurements and antihypertensive medication status, though precise ascertainment criteria varied among FBPP networks.¹⁸ Additional covariates included in regression models were age (in years), gender, self-identified race (as chosen from census categories), field site from where individuals were recruited, and education level.

**Education Data**

Education was coded in three different ways: 1) as a continuous variable, ranging from no school to ≥1 year of graduate school; 2) as a 5-category variable of <High school (HS) degree, HS degree, some vocational-technical school (vo-tech), some college, and some graduate school; and 3) as a 2-category variable of ≤HS degree, and >HS degree. Individuals in categories of “no school” and 1st Grade were excluded from all analyses as there were too few for statistical comparison (n=3).
Estimation of Ancestry

Our methods for estimating the continuous variable of genetic ancestry of the African Americans closely follow those of Tang et al.\textsuperscript{2, 19} to facilitate comparison across studies. In brief, we used a Bayesian estimation technique within the program Structure 2.2\textsuperscript{20} to assign a probability of African genetic ancestry to each individual, based on genotype frequencies among a set of genome-wide markers measured in both the study population and in the putative parental populations. As African-Americans are an admixed population of European and African ancestry, we used a set of randomly selected unrelated self-identified Whites from across all FBPP networks (n=1300) to represent the parental European population, and all unrelated sub-Saharan Africans from the World Diversity Panel (n=119) to represent the parental African population. A matching set of 294 autosomal microsatellite markers were used for the ancestry estimation because they were common between the available datasets on the two parental populations and the FBPP samples. The average values of African ancestry among hypertensives (HT: 80.68\%) and normotensives (NT: 79.1\%) differ from those reported by Tang et al. (HT: 86.4\% vs NT: 85.1\%), due to differences in study participants available in the online public database versus the internally pooled databases of Tang et al.\textsuperscript{2}

Statistical Analyses

Analyses of genetic ancestry and BP.

T-tests were used to test for significant differences in African genetic ancestry between HTs and NTs among the unrelated African Americans within each field site and
across all sites. Multiple linear regression models were used to test for associations between African genetic ancestry and each response variable of blood pressure (SBP, DBP, MAP) in all untreated African American participants, including related individuals. Each model adjusted for age, body mass index (BMI), gender, and field site. Two interaction terms were constructed to test for interactions between age and gender, which was significant in previous studies\(^2\), and between education and ancestry. Only the interaction between age and gender was included in final models of SBP, where it was a significant predictor (but not in the models of DBP or MAP, where it was not significant). The interaction between education and ancestry was not found to be significant.

**Analyses of education and BP**

T-tests and ANOVAs were used to compare mean differences in SBP, DBP, and MAP between the two and five education categories in the total sample of unrelated African Americans and Whites, and also separately within each racial group. Regression models were also used to test for associations between education and each BP variable (SBP, DBP, MAP) in the total set of combined and related African American and White samples. The models were adjusted for age, gender, BMI, self-identified race, field site, and cross product interactions between education and self-identified race and between age and gender. Other cross-product interaction terms were constructed to test for all two-way and a three way interaction between gender, self-identified race, and education. To demonstrate direction and magnitude of interactions, mean SBP measures were estimated for each racial and gender groups using LSMEANS in SAS (Figure 1).
Sensitivity analyses

Two different modeling techniques were tested to adjust for relatedness in the regression analyses. The presented data were modeled with generalized estimating equations (GEE) using PROC GENMOD and an exchangeable working correlation matrix to account for correlated observations within families.\textsuperscript{21} The second method used a random effects model in SOLAR, which uses pedigree information to calculate residual heritability, a random effect included in the modeling of the BP outcome. Both methods produced similar results; only the regression estimates based on GEE are presented. Note that under the GEE modeling, measures from related individuals are correlated with each other, and thus standard $R^2$ values cannot be estimated. Quasilikelihood under Independence Model Criterion (QIC) values are reported in each table as a measure of goodness of fit of the model, which is analogous to AIC in likelihood-based methods. QICu adds a penalty to Q based on the number of parameters, and the smaller QIC is preferred.

Regression diagnostics were examined with plots of residuals against predictors in each model. As some plots of residuals were imperfectly centered, and because residual kurtosis was high in all the SOLAR models, BP outcomes were also tested following a log-transformation. The transformed models showed the same substantive results; the non-log-transformed results are reported in all tables for ease of interpretation. Finally, regression diagnostics for multicollinearity were tested and found to be satisfactory across all models (maximum variance inflation factor= 1.09). All presented analyses were conducted in SAS version 9.2.
Results

*Genetic Ancestry and BP among African Americans*

Average levels of African ancestry did not differ significantly between HT or NT individuals in the total African American sample ($P=0.103$), or at each individual field site (all $P>0.200$) (Table 1). These results are comparable to Tang et al.$^2$

*Modeling ancestry, education, and BP*

In the African American sample, none of the regression models found African ancestry to be a significant predictor of BP, either as a main effect or in an interaction with education. Model A shows the association of African ancestry with SBP was not significant, after adjusting for age, gender, BMI, and field center (Table 2). In Model B, education was added as a continuous variable and found to be a significant predictor of SBP ($P=0.001$). Specifically, the coefficient for education suggests that each increasing year of education is associated with a 0.51 mmHg decrease in SBP. An interaction term between education and ancestry was not found to be significant (data not shown). Similar results were found with measures of DBP and MAP (Supp Tables 1 and 2), e.g. African ancestry was not significantly associated with either BP measure, but education showed a significant negative association with MAP ($P=0.011$, Supp Table 1).

In regression analyses where education was divided into two categories, education $\leq$ HS degree predicted a significant increase in SBP by 3.77±1.38 mmHg ($P=0.006$) relative to those with greater than a HS degree, while African ancestry had no statistically significant effect on SBP ($b =6.29\pm 4.57$, $P=0.168$), and the interaction term between ancestry and education was not significant. Substantive results did not change when
education was coded as five categories (Supp text). We also note that across all models, gender has a strong and statistically significant association with BP, such that men are predicted to have 18.95 mmHg higher SBP, 4.16 mmHg higher DBP, and 8.72 mmHg higher MAP, as compared to women (all $P<0.001$).

**Education and BP in African American and Whites**

We next explored the role of education in predicting BP disparities between African Americans and Whites. Educational achievement was not evenly distributed across racial groups in this sample; 28.4% of the African American sample had less than a HS degree versus only 6.5% of the White sample. In the total combined sample, SBP and MAP, but not DBP, were significantly higher among people with $\leq$HS degree relative to those with $>HS$ degree ($\delta$ SBP=$4.9$ mmHg, $P\leq0.001$, $\delta$ MAP=$1.87$ mmHg, $P\leq0.001$, $\delta$ DBP=$0.35$ mmHg, $P=0.423$). However, the role of education differed within each racial group. In the African American sample, SBP and MAP were higher among those with $\leq$HS degree, but no significant differences by education were found in the White sample (Table 3). DBP did not differ significantly by education within either group (data not shown). Similar results were found with ANOVA analyses when education was divided into five categories (Supp text).

We next tested for associations of education and self-identified race with BP using linear regressions in the combined African American-White sample (Figure 1 and Supp Table 3). The interaction term between education and race was significant for SBP, DBP, and MAP (Supp Table 3). The difference in BP between $\leq$ and $>$ HS degree was greater for African Americans (e.g. $b$-SBP =$4.68\pm0.83$ mmHg, $P\leq0.001$) than for Whites ($b$-SBP
=1.48 ±0.83 mmHg, \( P=0.077 \)); similar results were seen with DBP and MAP. In these analyses, gender again showed the strongest association with BP such that men were predicted to have 18.13 mmHg higher SBP, 3.09 mmHg higher DBP, and 8.08 mmHg higher MAP than women (all \( P \leq 0.001 \)), adjusting for other variables in the model.

Given the magnitude of gender estimates across all analyses, we also tested for interactions between race and gender, gender and education, and a three-way interaction between race, gender, and education. None of these interactions were significant. When comparing estimates of SBP from models stratified by gender, African American men were predicted to have the highest average SBP, followed by White men, African American women, and White women across the levels of education (Figure 1). The decline in SBP with increasing education was sharper in African American men and women than in White men or women (Figure 1). This pattern was similar when the same model was tested with five categories of education (see Supp text). In sum, these analyses suggest that gender, self-identified race, and education all have unique effects on BP, and should be considered simultaneously in order to understand the complete effects of education on health disparities.

Discussion

*Genetic Ancestry, Education, and BP in African Americans*

The availability of data on genetic ancestry and education in the FBPP dataset allowed for a comparison of genetic versus environmental hypotheses for excess hypertension among African Americans. Consistent with previous analyses,\(^2\) we found that genetic ancestry was not associated with BP. However, we did identify a significant association between education and BP that had not previously been found in this dataset.
Even after adjusting for ancestry and all other covariates, each year of education was associated with a 0.51 mmHg decrease in blood pressure. This result is in line with a prior study which reports a similar two mmHg difference in SBP between those with a high school diploma or less and college graduates. Thus, with just four years of additional education, our predicted decrease of 2mmHg SBP is estimated, on a population level, to result in a considerable reduction in mortality due to BP-related diseases, e.g. 17% decrease in hypertension.

These results are consistent with general findings in the literature that education is associated with risk of complex diseases and mortality. Braveman et al. specifically highlight three interrelated pathways through which education likely confers health benefits: 1) increased health knowledge and health behaviors, 2) improved employment opportunities (e.g. better working conditions, healthcare, and income), and 3) a positive influence on psychosocial factors (e.g. increased sense of control, subjective social status, and social support). Education may also serve as a marker for personality traits that are associated with better health. Regardless of the direct mechanism, it is clear that education is significantly associated with BP, while African genetic ancestry is not.

These findings shed new light on recent studies that claim a genetic basis to disease, often based solely on genetic ancestry measures—or sometimes without any genetic data at all. We have demonstrated that even a single crude measure of the social environment, like education, can better explain variation in BP than can genetic ancestry. Our result is consistent with recent studies that show genetic ancestry to be a poor predictor of BP, while other measures of the social environment better explain variation in BP.
Education and Racial Disparities in BP

Across all our analyses, we find that the association between education and BP is stronger in African Americans than in Whites, suggesting that educational inequalities may contribute, in part, to racial disparities in BP. The differential association between BP and education across racial groups contributes to the long-standing debate over the relationships between SES, race, and health disparities. Though race and SES are clearly important predictors of health, controversy remains over the direction of the interaction between SES and race, which often differs according to ethnic group, geographic location, or disease phenotype under study. One hypothesis, termed “minority poverty,” posits that the largest gap in health between African American and White Americans is at the lower end of the SES spectrum, and this gap diminishes as health improves for African Americans at higher SES levels. This hypothesis is based on the compounded disadvantages faced by African American people living in poverty and experiencing discrimination, which exaggerate the differences in health at lower levels of SES. An alternative hypothesis of ‘diminishing returns’ suggests that a greater gap in health is found at the higher end of the SES spectrum. This gap is explained by the idea that African Americans do not benefit as much as Whites from higher SES, or higher education in particular, perhaps due to fewer income benefits of higher education or the stress resulting from greater awareness of social injustices and discrimination at higher levels of SES.

Our results support the minority poverty hypothesis, as the worst blood pressures were predicted for people who face the double burden of being less educated and identifying as African American (Figure 1). The direction of the significant interaction
between race and education in the two-level education model suggests that African Americans derive greater health benefit from higher education than do Whites. The direction of the interaction was the same in the five-level model, though the interaction was not significant, likely due to reduced power when education was divided into five categories. Nevertheless, it is clear that increasing education is associated with reduced BP in the African American sample more than in the White sample, suggesting that increasing African Americans’ access to educational resources may help diminish the racial disparity in BP.

Limitations and Strengths

There are several limitations to our study that are worth noting. First, genetic ancestry was estimated from only 294 loci and a widespread set of parental populations from throughout Africa that may not best represent the West African ancestry of African Americans. A larger set of markers and alternative reference populations could potentially alter the relationship between ancestry and BP. Second, in our analyses, education served as the only available measure of the social environment. Education is only one aspect of SES among many other important factors including wealth and residential neighborhood environment. However, the significance of a simple measure of education level in these analyses suggests that when multiple measures of the socioeconomic environment are not readily available, simple proxies for SES, like education, can still be useful for capturing an aspect of the social environment that is feasible to assess in genetic studies. Other, more comprehensive measures of the sociocultural environment—such as residential segregation, psychosocial stress and
everyday discrimination—may help to account more fully for excess BP among African Americans. Finally, we recognize that other risk factors, such as dietary sodium intake, are also associated with BP, though the magnitude of these effects remains unclear. The FBPP dataset does not have these data, and thus it remains for future studies to determine whether the addition of other variables alters the associations we observe.

Conclusions and Future Directions

We find that education, but not genetic ancestry, is associated with BP among African Americans in the US. Furthermore, education is significantly associated with BP in African Americans, but not in Whites, suggesting that improved access to education in African American communities may help to reduce racial inequalities in health. An important next step is to explore the mechanisms by which higher education is associated with reduced hypertension, and in particular, why the association is stronger among African Americans than among Whites. One hypothesis is that BP-related stressors, such as poverty, racial discrimination, and perhaps social isolation, are higher in African American than in White communities in the US, and that higher education may reduce these stressors by enhancing social networks or by increasing material wealth. Further studies are also needed to determine whether education is causally related to BP, or if it only serves as a marker for other aspects of the social environment. Our results also imply that future genetic research on racial disparities in health must explicitly measure social-environmental variables to test competing explanations for racial inequalities in health.
References

Table/Figure Legends

Table 1 Mean levels of African genetic ancestry in unrelated African American individuals by hypertensive status.
*P value for t-tests of difference in levels of genetic ancestry between NT and HT at each individual site and at all sites combined. None are significant at alpha=0.05. δ = Mean difference in genetic ancestry between Normotensive and Hypertensive groups.

Table 2 Linear regression models for SBP in African Americans (N=1463).
Note: b=unstandardized regression coefficient, SE=standard error. ‡Education is treated as a continuous variable. *Indicates statistical significance.

Table 3 Comparison of SBP, DBP, and MAP in African American and White individuals across low and high education using t-tests.
*Indicates statistical significance. † Satterthwaite method used as variances were not equal. δ = Mean difference in BP between racial groups.

Figure 1 Interaction plots of self-identified race and education.
Interaction plots of education*self-identified race, with education divided into ≤HS degree, or >HS degree (panel A), and separated by gender (Panel B). SBP measures are adjusted for covariates of age, gender, age*gender, and BMI. AA=African American.

Supp Table 1 Linear regressions for DBP in African Americans (n=1463).
Note b=unstandardized regression coefficient, SE=standard error. ‡Education is treated as a continuous variable. *Indicates statistical significance.

Supp Table 2. Linear regressions for MAP in African Americans (N=1463).
Note b=unstandardized regression coefficient, SE=standard error. ‡Education is treated as a continuous variable. *Indicates statistical significance.

Supp Table 3 Multiple linear regression coefficients for BP measures in African Americans (N=2034) and Whites (N=1656).
Note b=unstandardized regression coefficient, SE=standard error. *Indicates statistical significance. The interaction between education and race in this model is displayed in Figure 1.
Table 1. Mean levels of African genetic ancestry in unrelated African American individuals by hypertensive status.

<table>
<thead>
<tr>
<th></th>
<th>Normotensive</th>
<th>Hypertensive</th>
<th>$\delta$</th>
<th>$P^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean (SD)</td>
<td>N</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Maywood</td>
<td>135</td>
<td>0.799 (0.10)</td>
<td>60</td>
<td>0.807 (0.11)</td>
</tr>
<tr>
<td>Jackson</td>
<td>21</td>
<td>0.786 (0.12)</td>
<td>262</td>
<td>0.793 (0.12)</td>
</tr>
<tr>
<td>Forsyth</td>
<td>42</td>
<td>0.761 (0.13)</td>
<td>150</td>
<td>0.785 (0.11)</td>
</tr>
<tr>
<td>Birmingham</td>
<td>28</td>
<td>0.804 (0.09)</td>
<td>379</td>
<td>0.821 (0.09)</td>
</tr>
<tr>
<td>Total African Americans</td>
<td>226</td>
<td>0.792 (0.11)</td>
<td>851</td>
<td>0.805 (0.11)</td>
</tr>
</tbody>
</table>
Table 2. Linear regression models for SBP in African Americans (N=1463)

<table>
<thead>
<tr>
<th></th>
<th>Model A</th>
<th>Model B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>b (SE)</td>
<td>P</td>
</tr>
<tr>
<td>Intercept</td>
<td>70.81 (4.74)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Age</td>
<td>0.70 (0.06)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male versus Female</td>
<td>18.06 (3.05)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>age*gender</td>
<td>-0.26 (0.08)</td>
<td>0.001*</td>
</tr>
<tr>
<td>BMI</td>
<td>0.61 (0.07)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Field Site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jackson vs. Maywood</td>
<td>-8.04 (1.63)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Forsyth vs. Maywood</td>
<td>-4.11 (1.81)</td>
<td>0.023*</td>
</tr>
<tr>
<td>Birmingham vs.</td>
<td>0.27 (1.29)</td>
<td>0.836</td>
</tr>
<tr>
<td>Maywood</td>
<td></td>
<td></td>
</tr>
<tr>
<td>African ancestry</td>
<td>7.33 (4.74)</td>
<td>0.110</td>
</tr>
<tr>
<td>Education‡</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>QICu</td>
<td>1472.0</td>
<td></td>
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</table>
Table 3. Comparison of SBP, DBP, and MAP in African American and White individuals across low and high education using t-tests.

<table>
<thead>
<tr>
<th></th>
<th>African Americans</th>
<th></th>
<th>Whites</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;=HS degree</td>
<td>&gt;HS degree</td>
<td>Diff</td>
<td>t value (p-value)</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>960</td>
<td>644</td>
<td>5.190</td>
</tr>
<tr>
<td>Mean SBP (SD)</td>
<td>(95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>136.2 (23.08)</td>
<td>(134.8,137.7)</td>
<td>131.0 (20.17)</td>
<td>(129.5, 132.6)</td>
</tr>
<tr>
<td>Mean DBP (SD)</td>
<td>(95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>75.42 (12.26)</td>
<td>(74.64,76.19)</td>
<td>74.98 (11.24)</td>
<td>(74.11, 75.85)</td>
</tr>
<tr>
<td>Mean MAP (SD)</td>
<td>(95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>95.69 (14.45)</td>
<td>(94.78,96.60)</td>
<td>93.67 (12.75)</td>
<td>(92.68, 94.66)</td>
</tr>
</tbody>
</table>
Figure 1 Interaction plots of self-identified race and education.