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Genetic and Environmental Risks for High Blood Pressure Among African American Mothers and Daughters

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Abstract

Objective—To determine the relationship between genetic and environmental lifestyle factors (physical activity and sodium) on blood pressure (BP) among African-American women.

Method—In this cross-sectional study involving 108 African-American mothers and daughters from a Midwestern area, investigators obtained BP measurements, information on minutes of physical activity, amount of sodium intake, and buccal swab saliva samples.

Results—Of the 4 single nucleotide polymorphisms (SNPs) on the sodium bicarbonate cotransporter gene (*SLC4A5*), rs8179526 had a statistically significant interaction with cytosine/thymine (C/T) genotype by sodium status on systolic BP (SBP; $p = .0077$). For gene × physical activity interaction, 2 significant interactions (cytosine/adenine [C/A] genotype by physical activity and adenine/adenine [A/A] genotype by physical activity, $p = .0107$ and $p = .0171$, respectively) on SBP and 1 on diastolic BP (DBP; A/A genotype by physical activity, $p = .0233$) were found on rs1017783. Two significant guanine/adenine [G/A] genotype by physical activity interactions were found on rs6731545 for SBP and DBP ($p = .0160$ and $p = .0492$, respectively).

Discussion—A gene × environmental interaction with rs8179526 has a protective effect on SBP in African-American women with high sodium intake. Participants with C/T genotype of rs8179526 who consumed greater than 2,300 mg of sodium had lower SBP than those who consumed less than recommended. Women with thymine/thymine (T/T) genotype of rs8179526 who consumed greater than 2,300 mg had lower SBP than those who consumed less. Awareness of both the protective and deleterious properties of rs8179526 in African-American women may one day assist in determining appropriate treatment plans.

Keywords

high BP; gene-environment; African-American women

Cardiovascular (CV) changes that lead to high blood pressure (HBP) have become commonplace in American society, often beginning in childhood. The national trend of obesity has been suggested as a leading cause of HBP (American Heart Association [AHA], 2003; Din-Dzietham, Liu, Bielo, & Shamsa, 2007; Litwin et al., 2007). The percentage of children

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with body mass indices (BMIs) surpassing the 95th percentile, indicating obesity, has risen steadily over the last 20 years (aCenters for Disease Control and Prevention [CDC], 2007a). Statistically, African American women and girls are more overweight and obese than those of other ethnic groups. From 2003 to 2004, statistical trends among 6–11 years olds indicated that 14% of White and 17% of African American boys and 13.1% of White and 22.8% of African American girls were obese. The adolescent years produced an increase in the percentage of obese children in each group, excluding White girls. For ages 12–19 years, 14.6% of White boys and 12.7% of White girls were obese, while 18.7% of African American boys and 23.6% of African American girls were obese. The trends among adult African American women were even more alarming, with 78% of African American women overweight and 50.8% obese. Clearly, though obesity is a concern for everyone, African American females are disproportionately at risk.

The increase in the number of overweight and obese children has been associated with the number of children being diagnosed with essential hypertension (Din-Dzietham et al., 2007). Between 1988 and 2002, the percentage of children with prehypertension rose from 7.7% to 10%, with the percentage of children with hypertension increasing from 2.7% to 3.7%. These percentage increases translate into approximately 410,150 additional children diagnosed with pre or essential hypertension across the nation. These statistics signify an important public health concern as hypertensive children usually become hypertensive adults who often develop CV disease along with additional comorbidities at younger ages.

Studies have shown linkages among obesity, insulin resistance, metabolic syndrome, and CV changes that lead to HBP (Barlow & the Expert Committee, 2007; Berenson, Srinivasan, Chen, Li, & Patel, 2006; Din-Dzietham et al., 2007; Litwin et al., 2007). Maternal obesity has been recognized as a contributing factor in developing obesity in childhood (Strauss & Knight, 1999), and metabolic syndrome among parents is associated with a higher incidence of metabolic syndrome in children, especially within the African American population (Meis, Schuster, Gaillard, & Osei, 2006). Findings from the CDC National Health and Nutrition Examination Survey (2007b) maintained that African American women have the highest rate of obesity in the 20–39 age groups. Unlike for Mexican American and White women, this prevalence continues to rise throughout African American women's lifetime to reach a staggering 61% by the time they reach age 60.

The American Heart Association (AHA, 2007; Rosamond et al., 2007) has reported that CV disease is the primary cause of death among African Americans, with nearly 5 out of 10 African Americans developing CV disease. African American women have the highest prevalence of HBP of all demographic groups (AHA, 2007; Nesbitt & Victor, 2004). African Americans also experience a high percentage of HBP-related morbidity at an earlier age (Sile et al., 2007). In 2004, 40.9% of the 31,608 women who died from HBP-related diseases were African American; in contrast, 14.5% were White women (AHA). HBP-related diseases include stroke, heart attack, and other cardiovascular compromise.

The purpose of the study described below was to examine the risk factors for development of HBP, or hypertension, in African American women. A secondary purpose was to determine the extent to which genetic precursors for hypertension affect the gene-environment interaction for development of HBP early in life. We hypothesized that both genetics and environmental lifestyle behaviors can contribute to the development of hypertension. The research questions address the following: (a) What is the relationship between genetic polymorphisms and blood pressure (BP) readings in African American mothers and daughters? and (b) What is the interaction effect between genetic polymorphisms and environmental lifestyle behaviors (dietary sodium intake and minutes of physical activity) on BP among African American mothers and daughters?

Review of the Literature

Genetics and Physiology of HBP

Research regarding the roles of specific polymorphisms in HBP has been inconclusive (Lohmueller et al., 2006). However, studies conducted in molecular genetics have successfully identified chromosome 2, particularly 40 to 140 cM from the tip of the p region, as significantly influencing hypertension among African Americans (Cooper et al., 2002; Province et al., 2003; Rao et al., 2003). However, there were no significant findings regarding chromosome 2 and other ethnic groups' predisposition for hypertension. Genetic studies on hypertension susceptibility genes were conducted among samples of sibling pairs and parent-offspring pairs (Barkley et al., 2004; Stassen, Hoffman, & Scharfetter, 2003). Both sibling-sibling and parent-offspring dyads had BP readings that were significantly associated with the presence of the hypertension susceptibility allele in the family 4, sodium bicarbonate cotransporter member 5 gene, *SLC4A5*, which is found on chromosome 2.

Hunt et al. (2006) found a significant linkage between *SLC4A5* and BP-related phenotypes, confirming the linkages between BP and chromosome 2 discovered by the National Heart, Lung, and Blood Institute Family Blood Pressure Program (Province et al., 2003). *SLC4A5* encodes a protein that transports sodium and bicarbonate across cell membranes while regulating cellular pH. The gene is thought to contain several single nucleotide polymorphisms (SNPs) linked to elevated BP. However, the SNPs involved have not been consistently associated with elevated BP (Hunt et al., 2006). The four SNPs investigated within the context of this study are the exact SNPs found to be most consistently associated with HBP in previous studies among African Americans.

Obesity can lead to a cluster of symptoms, termed metabolic syndrome, that are risk factors for CV disease (AHA, 2005). In adults, these criteria consist of elevated triglycerides, BP, and fasting glucose; reduced high-density lipoprotein cholesterol (HDLC); and a larger waist circumference. The AHA maintains that individuals who meet at least three of the criteria are considered to have metabolic syndrome. Researchers involved in the Bogalusa Heart Study (Chen, Srinivasan, Li, Xu, & Berenson, 2007) modified these criteria to be applicable to children, using homeostasis model assessment of insulin resistance, mean arterial pressure, BMI, and triglyceride:HDLC ratio as the components. Following children into adulthood, Chen et al. (2007) found that obesity is a better determinate of metabolic syndrome than is insulin resistance. This finding is significant because 50% of obese children meet the criteria for a diagnosis of metabolic syndrome and are likely to become adults with metabolic syndrome and the associated morbidities. The prevalence of metabolic syndrome is 57% greater among African American women than among African American men (Ford, Giles, & Dietz, 2002).

Adipose tissue has been recognized to produce increased levels of circulating acute-phase proteins (proteins that increase or decrease based on inflammation) and adipokines (signaling proteins) in obese individuals that lead to low-grade inflammation, which is linked to insulin resistance and metabolic syndrome (Trayhurn & Wood, 2004). Adipokines associated with inflammation include tumor necrotizing factor α, interleukin 1β, interleukin-6, interleukin-8, interleukin-10, transforming growth factor β, and nerve factor, while the associated acute-phase proteins include plasminogen activator inhibitor-1, haptoglobin, and serum amyloid A. Adipose tissue surrounding vessels acts in two ways: first, the inflammation process results in macrophages and T-cells migrating from the adipose tissue into the vessels, damaging them; second, adipokines affect endothelial function by modulating nitric oxide and superoxide release, resulting in HBP and insulin resistance (Guzik, Mangalat, & Korbut, 2006).

Reasonable attention has been directed toward genes involved in the renin-angiotensin system (RAS) due to its influence on fluid and electrolyte balance (Zhu et al., 2003). Angiotensinogen

interacts with renin, producing angiotensin I, the prehormone of angiotensin II, which promotes sodium retention and increases vascular resistance. Research from the Bogalusa Heart Study found that African American children excrete less sodium and potassium than White children (Berenson et al., 2006). Furthermore, activation of the RAS has been observed in adipose tissue, further implicating obesity as a risk factor for HBP (Segura & Ruilope, 2007).

African American children, especially males, are noted to have higher BP even when not obese. Several genotypes have been associated with HBP. A study of White and African American children examining the T235 allele of the angiotensinogen gene found that angiotensinogen levels were higher and the T235 allele was more common in African American children (Bloem, Manatunga, Tewksbury, & Pratt, 1995). Four genes involved in renal salt absorption (*CLCNKA, CLCNKB, BSND, NEDD4L*) have shown high Fst scores, indicating differences in phenotypes between populations (Sile et al., 2007). All of the genes except *BSND* differed in HBP expression by 50% between African Americans and Whites. Some researchers (Baker et al., 2007) have demonstrated that the C-532T polymorphism of the angiotensinogen gene has a significant effect on arterial stiffness without necessarily resulting in higher BP, while another group (Sethi, Nordestgaard, & Tybjaerg-Hansen, 2003) concluded in their meta-analysis that the same polymorphism is indicative of hypertension risks, although their study participants were all White. Another gene associated with electrolyte balance is the *G protein-coupled receptor kinase 4* (*GRK4*) gene, which is thought to inhibit the dopamine receptor D1 from excreting sodium appropriately (Lohmueller et al., 2006). The researchers found that African Americans had shorter haplotype blocks than Whites.

Rame et al. (2007) found a statistically significant correlation between the minor corin I555 allele and systolic BP (SBP) in African Americans, leading to left ventricular hypertrophy. Sherva et al. (2007) pointed to two candidate genes, *GPR-25* and *SMOC-1*, that might contribute to arterial stiffness and resultant hypertension. The *G-protein-coupled receptor* (*GPR-25*) gene is involved in binding hormones, neurotransmitters, and signaling processes that regulate BP. The secreted modular *calcium binding protein* (*SMOC-1*) gene is believed to be involved in vascular remodeling. Sheva et al. concluded that arterial stiffness is 20% heritable in African Americans. The *endothelin-1* gene, a vasoconstrictor peptide encoder, is also associated with HBP. The −37/in2C allele of this gene may protect from hypertension progression in African American males, while the −1370G allele may lead to left ventricular hypertrophy if the carrier is under chronic stress (Dong, Wang, Zhu, Treiber, & Snieder, 2004). The researchers suggested a gene-environment interaction for the −1370G allele and African American youth who live in stressful lower socioeconomic environments.

Environmental and Lifestyle Risks for HBP

Although researchers have hypothesized several genetic associations for hypertension, environment remains a central and related factor. Because of continued disparities in society, African American children are more likely than other children to live in lower socioeconomic-status (SES) environments (Yancey & Kumanyika, 2007). The U.S. Census Bureau (DeNavas-Walt, Proctor, & Smith, 2007) estimated that in 2006, 33% of African American children lived below the poverty threshold of US$20,614 per year income for a family of four. Lower SES communities lead to lower activity levels for children and increased intake of nutritionally poor, calorie-dense foods, resulting in overweight and obese children. Poverty's role as a risk factor for obesity is apparent when one considers the violence in lower SES communities that prevents children from playing outside, the lack of funding for school physical education programs, and the lack of stores providing reasonably priced, nutritious food (Yancey & Kumanyik, 2007).

Higher BP is present in African American children even when obesity is not an issue. Sodium and potassium renal clearance have been reported throughout the literature as possible reasons

for hypertension in African American youth (Berenson et al., 2006; Bloem et al., 1995; Dong et al., 2004; Sile et al., 2007). The U.S. Department of Agriculture (USDA, 2005) has reported that children in general and African Americans specifically consume far greater than the maximum recommended 2,300 mg per day of sodium and less than the recommended 3,000 to 4,700 mg (depending on age) of potassium. A direct correlation has been reported between the intake of sodium and the rise in BP, while potassium has been reported to counter sodium's effect, consequently lowering BP.

The literature suggested a number of possible interactions between environment and genotype and their effect on BP. Although genetic predisposition may be difficult to alter, modifying one's environment may be more feasible and could modulate phenotypic expression of genetic disorders. Understanding which SNPs are responsive to which environmental influences could help guide health care providers' decision-making process for treatment, management, and prevention of disease.

Method

Participants

This study was cross-sectional in design and included 108 African American participants from the Detroit metropolitan area. Recruitment strategies commenced after approval from the Institutional Review Boards (IRB) of the University of Michigan and Wayne State University.

For the parent study, "Hypertension and Heredity: Hypertension Genetic Polymorphisms in Three Generations of African American Women," the investigator and research assistants recruited African American women who lived in a large Midwestern urban area. Multiple recruitment procedures were used: (a) flyers posted in neighborhood areas including local stores, markets, and community centers, (b) advertisements and announcements at local churches, (c) advertisements and announcements at historically Black sororities, and (d) use of participant resource pools at the University of Michigan and Wayne State University (Taylor, 2009). To meet the inclusion criteria, participants were required to self-identify as African American and have a living family of at least three generations to constitute the triad of grandmother-mother-granddaughter. Participants also had to be able to read and write English. For those with a diagnosis of hypertension, BP had to average 140/90 or higher (Stage 1 or 2 hypertension) without medication. Individuals who reported taking antihypertensive medications were included in the study. More detailed information on inclusion and exclusion criteria can be found in Wu, Prosser, & Taylor (2009).

Research assistants were trained by the principal investigator regarding all data collection methods, home visitation, and coordinating visits. After women agreed to participate in the study, the research assistants obtained informed consent during the home visits that served as the sites for data collection. Study participants were compensated with US$20.00 gift certificates for each time they participated in data collection.

The parent study required participants to take part in a 1-year follow-up study that measured changes in lifestyle behaviors after a genetic counseling intervention (Taylor & Wu, 2009). The current study included 54 mother-daughter dyads (N = 108) who completed the 1-year follow-up. Findings of a power analysis indicated that a multiple regression with five variables requires 84–91 participants to generate a power of .80 at an α level of .05 with a moderate effect size (Cohen, 1992).

Measures

Demographic survey—Participants completed a demographic survey that collected information regarding age, gender, educational level, household income, employment status,

and extensive family history of hypertension (age at diagnosis, medications, and other treatments).

Physical activity—The recommendation for physical activity for people diagnosed with hypertension is 30 minutes each day (Chobanian et al., 2003). As a measure of physical activity, participants were asked two questions: (a) Had they taken part in a minimum of 30 minutes of moderate or greater physical activity on any day in the past 7 days? and (b) For how many minutes had they participated in moderate or greater physical activity over the past 7 days? More details on use of the physical activity measure can be founding in Taylor, Washington, Artinian, and Lichtenberg (2008). The self-reported minutes of moderate or greater physical activity were used for analyses in the current study.

Sodium intake—Sodium intake (i.e., mg of sodium per day) was determined using self-reported data from 24-hr food recalls. Data were translated into nutrient intakes using the Food Processor computer software (ESHA Research, Salem, OR). Multiple-day food recall is considered valid because it represents a person's usual or habitual intake accurately (Block, 1982). Participants were contacted on 2 randomly selected weekdays and 1 weekend day to ask them to recall what they had eaten within the last 24 hr. Each recall took approximately 10 minutes to complete. Food models and measuring cups and spoons were used as memory aids to assist participants in reporting accurate serving sizes.

BP, height, and weight—BP was measured using a digital BP monitor with a size-appropriate upper arm cuff (model # A&D UA 767PC). BP measurements reported represent an average of three seated BP readings. Procedures for participant preparation for BP measurement were in accordance with JNC-7 recommendations (Chobanian et al., 2003).

Height was measured by a portable stadiometer (Model 214 Road Rod, Seca Corporation, Hanover, MD). Weight was measured by an electronic scale (BWB/807 Tanita, Tokyo, Japan). BMI is a relationship between weight and height that is associated with body fat and health risk. The formula for calculating BMI is weight in pounds divided by the height in inches squared. The result is multiplied by 703 to provide the BMI. BMI from 25 to 29 is considered overweight, with BMI equal to or greater than 30 indicative of obesity (CDC, 2008).

Buccal swab and genotyping—Buccal swab saliva samples were collected at baseline from all participants by rubbing the swab on the inside of the cheek. DNA was isolated using the PureGene DNA Isolation Kit from Gentra Systems (Minneapolis, MN). Genotyping, based on polymerase chain reaction (PCR) amplification techniques, was conducted at the University of Michigan Molecular and Behavioral Sciences Laboratory using the TaqMan assay and ABI Prism Sequence Detection System (Applied Biosystems, Foster City, CA). Quality control measures for genotyping assays included robotic liquid handling, separate pre- and post-PCR areas, standard protocols, and quality control analyses, including 5% duplicates, positive and negative controls, computerized sample tracking, and data validity checks (Taylor, Sun, Chu, Mosley, & Kardia, 2008).

Data Analysis

SAS 9.1 (SAS Institute, NC) was used to analyze Hardy-Weinberg equilibrium test, *t* test, linear mixed models with interactions of gene × sodium and gene × physical activity, and interaction plots. Separate *t* tests were used to test the mean differences of age, BMI, and BP between two groups (physical activity status 30 min/day or greater = 0, less than 30 min/day = 1; sodium status less than 2300 mg/day = 0, 2300 mg/day or greater = 1). As mothers and daughters were both included in these analyses, linear mixed model analysis was used to control for correlation among observations on the same family. Unadjusted linear mixed models were

used to test the effect of four SNPs on SBP and diastolic BP (DBP). Also, linear mixed models were used to test the gene × environmental interactions on BP after adjusted for age, BMI, and taking antihypertensive medication. Demographic variables in the study included age (continuous), BMI (continuous), physical activity status (0 or 1, as described above), sodium status (0 or 1, as described above), and antihypertensive medication (categorical: yes = 1, no = 2). For women aged ≥21 years, hypertension was defined as SBP ≥ 140 mmHg or DBP ≥ 90 mmHg or taking antihypertensive medication. For women aged <21 years, hypertension was defined based on BP percentile rankings in the "Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents" (National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents, 2004). All decisions on the statistical significance of the findings were based on a criterion α level of .05. No deviation from Hardy-Weinberg equilibrium was found in this population.

Results

Description of the Sample

The descriptive statistics for the 108 African American mothers and daughters who participated in this study are presented in Table 1. The mean BMI was the same for mothers and daughters at 32 ± 7 kg/m^2, which meets the definition of obesity according to the CDC (CDC, 2008). Mothers had higher SBP and DBP compared to daughters, with more than half of the mothers being hypertensive as compared to only 37% of the daughters.

Association of Sodium Intake, Physical Activity Status, and BP—Table 2 presents mean differences of age, BMI, and BP using dichotomized sodium intake status and physical activity status as independent variables. Mothers who were consuming less than 2,300 mg/day sodium were significantly older than those who were consuming more than 2,300 mg/day sodium. No significant mean differences in BMI, SBP, or DBP were found for either sodium intake or physical activity.

Association of Four SNPs on SLC4A5 and BP

Tables 3 and 4 present the linear mixed model analysis of four SNPs of the *SLC4A5* gene on predicting BPs on the unadjusted data. The SNPs rs8179526, rs10177833, rs6731545, and rs6726450 were tested in the study. SNP rs10177833 was found to be statistically significantly related to SBP in a positive direction (Table 3). For SNP rs10177833, women with cytosine/adenine (C/A) or adenine/adenine (A/A) genotype had higher SBP (p = .030 and p = .046, respectively) compared to women with a cytosine/cytosine (C/C) genotype. No statistically significant associations were found between any of these four SNPs and DBP.

Interactions of Gene × Sodium Status and Gene × Physical Activity on BP

To further investigate gene × sodium status interaction and gene × physical activity interaction on BP, linear mixed model analyses with adjustments for age, BMI, and the taking of antihypertensive medication were used. rs8179526 had a statistically significant interaction of C/T genotype by sodium status on SBP (p = .007; Table 5). Furthermore, two statistically significant interactions of gene × physical activity on SBP (C/A genotype by physical activity and A/A genotype by physical activity; p = .010 and p = .017, respectively) and one on DBP were found on rs1017783 (A/A genotype by physical activity, p = .023; Table 6). Two statistically significant G/A genotype by physical activity interactions were found on rs6731545 for SBP and DBP (p = .016 and p = .049, respectively). No significant gene × physical activity interaction was found concerning rs8179526 or rs6726450 (Table 6). These interactions indicate that the slopes differ significantly across the three genotype groups for sodium intake status and physical activity on SBP (Figures 1 to 5).

Discussion

As hypothesized, findings of the present study suggest some associations between genetic polymorphisms and environmental lifestyle variables on BP in African American mothers and daughters. Hunt et al. (2006) have proposed that certain SNPs on *SLC4A5*, while inconsistent in phenotypes, may compensate for abnormal $NaHCO_3$ transporting by modifying other ion transporters. Furthermore, they questioned if it is these SNPs alone or in linkage disequilibrium with other SNPs that result in changes to Na and HCO_3 transport. Hunt et al. found a significant relationship between *SLC4A5* and BP in 96 Utah pedigrees, which is consistent with findings of the current study, in which SNP rs10177833 genotypes C/A and A/A on *SLC4A5* have statistically significant associations with SBP ($p = .030$ and $p = .046$, respectively).

Although no significant main effects were found for sodium intake on BP, both SBP and DBP were slightly higher for the total sample of participants who consumed less than 2,300 mg/day of sodium than for people who consumed 2,300 mg/day or more (135 mmHg vs. 129 mmHg for SBP, and 83 mmHg vs. 80 mmHg for DBP, respectively, Table 2). Similarly, Ajani, Dunbar, Ford, Mokdad, and Mensah (2005) reported that participants with hypertension revealed a lower intake of dietary sodium than those with normal BP. This result may be due to the large variability of using a single 24-hr recall of dietary data. The true rate of sodium consumption may have been underestimated for this study population. Further, women who were diagnosed with hypertension may have received suggestions from physicians to reduce their consumption of sodium.

In the current study, surprisingly, participants with C/T genotype of rs8179526 who consumed the recommended 2,300 mg per day of sodium or more had lower SBP than those who consumed less than 2,300 mg per day. This finding is inconsistent with reports by the AHA (2005) and Douglas et al. (2003) that indicated that increases in dietary sodium are related to increases in SBP. Other studies have shown that high amounts of dietary sodium are a risk factor for hypertension among African Americans due to increased salt sensitivity in this population (Flack, 2003). Flack et al (2002) also indicated that women tend to be more salt sensitive than men. Given the findings of the present study and their inconsistency with previous studies, genetic counseling and rs8179526 genetic and urinary sodium sensitivity testing may be beneficial when treating and managing hypertension in African American women (Taylor & Wu, 2009).

Women with the T/T genotype of rs8179526 who consumed more the recommended 2,300 mg of sodium or more per day had higher SBP readings than those who consumed less than 2,300 mg per day. Genotype T/T on rs8179526 thus resulted in a risk effect on SBP when participants reported higher than recommended intakes of sodium. These results indicate that there is a gene × environmental interaction with sodium intake on BP. However, these differences of BP may also be due to other environmental factors, such as physical activity, socioeconomic status, and social support (Table 5, Figure 1). No significant gene × sodium interaction was found on DBP for any of the four SNPs tested.

An additional finding is that exercising a minimum of 30 minutes per day was associated with lower SBP and DBP readings, though the differences were not statistically significant (Table 2). These findings are consistent with previous studies and the recommendations of JNC-7 (Chobanian et al., 2003). Two statistically significant interactions of gene × physical activity on SBP were found on rs1017783l. Participants with C/A and A/A genotypes of rs1017783l showed increased SBP among those reporting less than 30minutes of physical activity per day while those with a C/C genotype and less than 30 minutes of physical activity per day reported had decreased SBP (Table 6, Figure 2). This pattern also was found with DBP on rs10177831. Participants with the A/A genotype of rs10177831 who reported less than 30 minutes of

physical activity per day had statistically significantly increased DBP, while those with a C/C genotype had decreased DBP (Table 6, Figure 3). For rs6731545, two statistically significant interactions of gene × physical activity on both SBP and DBP were found. Participants with the G/A genotype reporting less than 30 minutes of physical activity per day had increased SBP and DBP, while no significant interactions were found with BP and physical activity for those with the G/G genotype (Table 6; Figures 4 and 5).

Several limitations of this study need to be considered. This study was restricted to African American women residing in a large urban metropolitan area. The results may, thus, not be generalizable to other ethnic groups or to those living in suburban or rural areas. Also, a single 24-hr food recall was used for sodium intake data. The reliability and validity of this method increases with the number of days of food recall and objective measures (e.g., urinary sodium). A 24-hr recall of dietary intake may result in a larger variability as a result of underestimation (e.g., could not eat too much because of illness) or overestimation (e.g., had eaten at a buffet before this interview) of sodium consumption in this population.

The approach for this study was based on the premise that susceptibility alleles for common diseases were not under strong negative selection, and common variants contributed to common disease traits (i.e., the common disease–common variant hypothesis; Reich & Lander, 2001). However, the allelic spectrum for genes associated with complex quantitative traits, such as HBP, has not been fully delineated. It is possible that multiple rare polymorphisms in the biological and positional candidate genes that were not included in this study could influence HBP. Despite these limitations, the approach employed in the current study with an adequate sample size illustrates the use of SNPs in candidate genes to construct a more complete picture of the genetic architecture of complex traits such as HBP.

Clinically, the roles of rs8179526 and rs10177833 in African American mothers and daughters can be confusing. When patients with known risk factors such as high sodium intake are assessed, genotype can provide clues as to the appropriate treatment options for lowering BP. Clinicians should be aware of the gene-environment effects of rs8179526 and sodium intake when assessing and treating African American women and girls for HBP. These findings add to the body of evidence suggesting a role for rs8179526 and rs10177833 in HBP among African American females.

Nurses need to educate their African American female patients about the possibility of having an increased risk for developing HBP based on their individual genotypes. Modifying dietary sodium intake and physical activity routines can lower BP, but interventions should be based on the individual profile of the patient (i.e., genotype). If gene-environment screening occurs earlier in life, appropriate interventions can be implemented to reduce morbidity and mortality related to HBP. The next step in studying gene-environment interactions on HBP among African American parents and children could use a similar research design but incorporate a genome-wide association approach.

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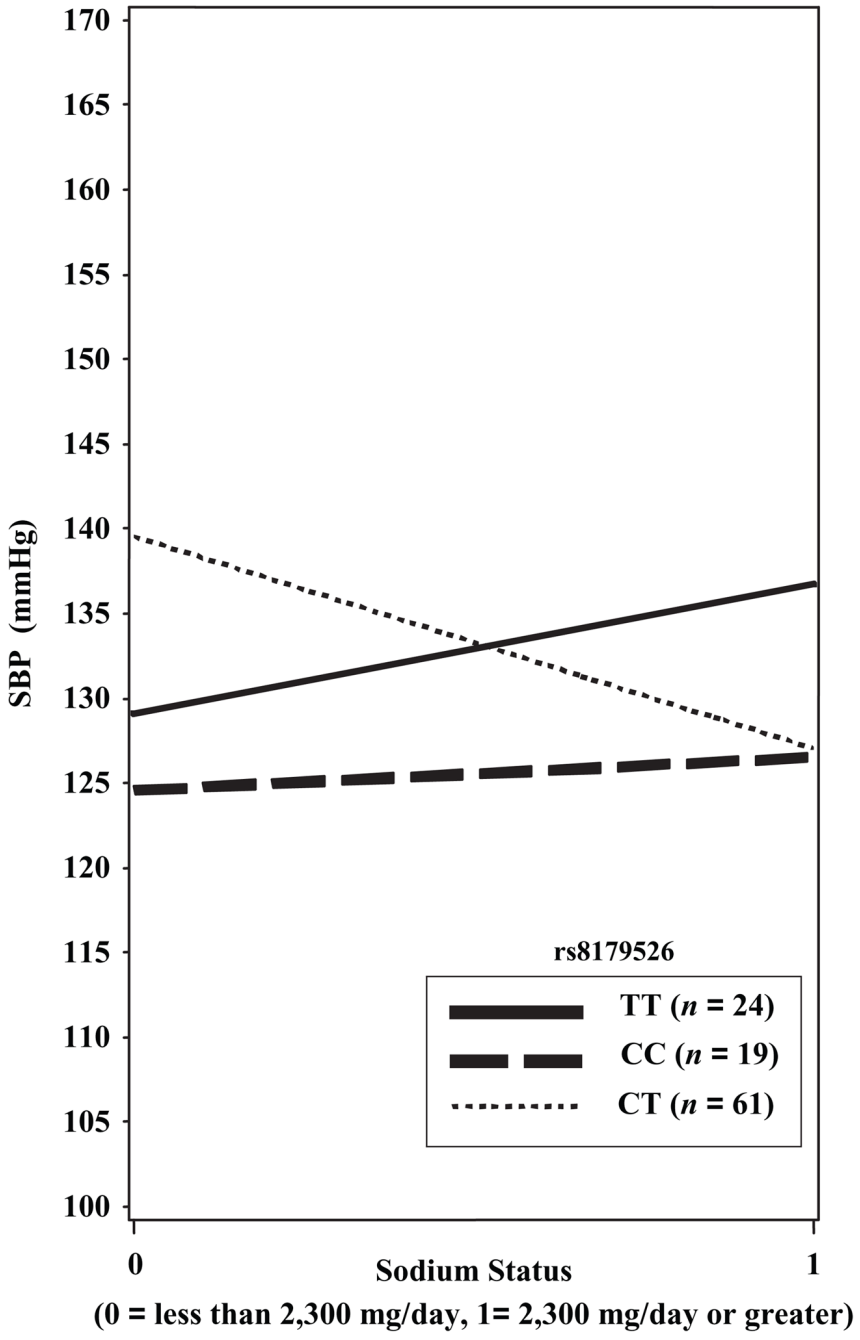

Figure 1.
Interaction of rs8179526 × sodium status on systolic blood pressure (SBP). C = cytosine; T = thymine.

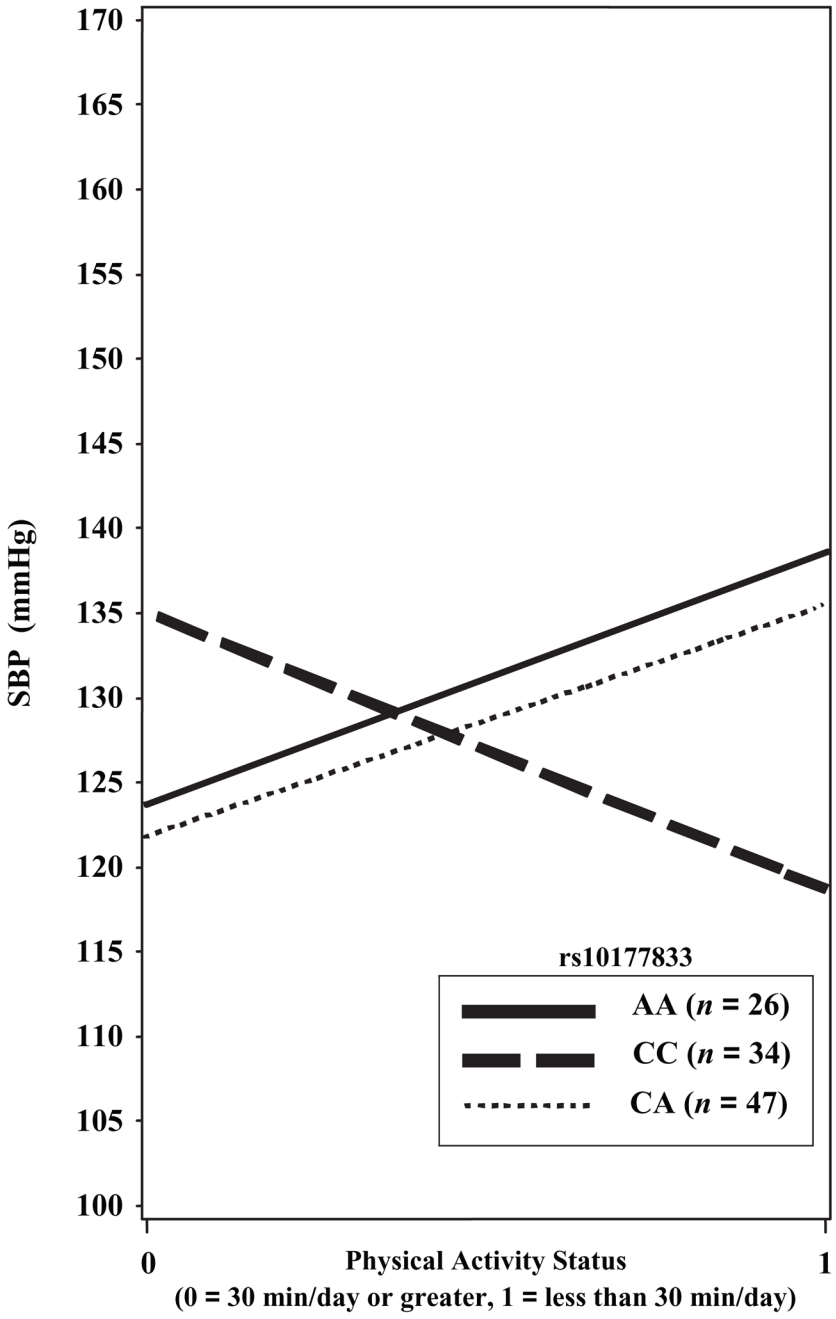

Figure 2.
Interaction of rs10177833 × physical activity status on systolic blood pressure (SBP). A = adenine; C = cytosine.

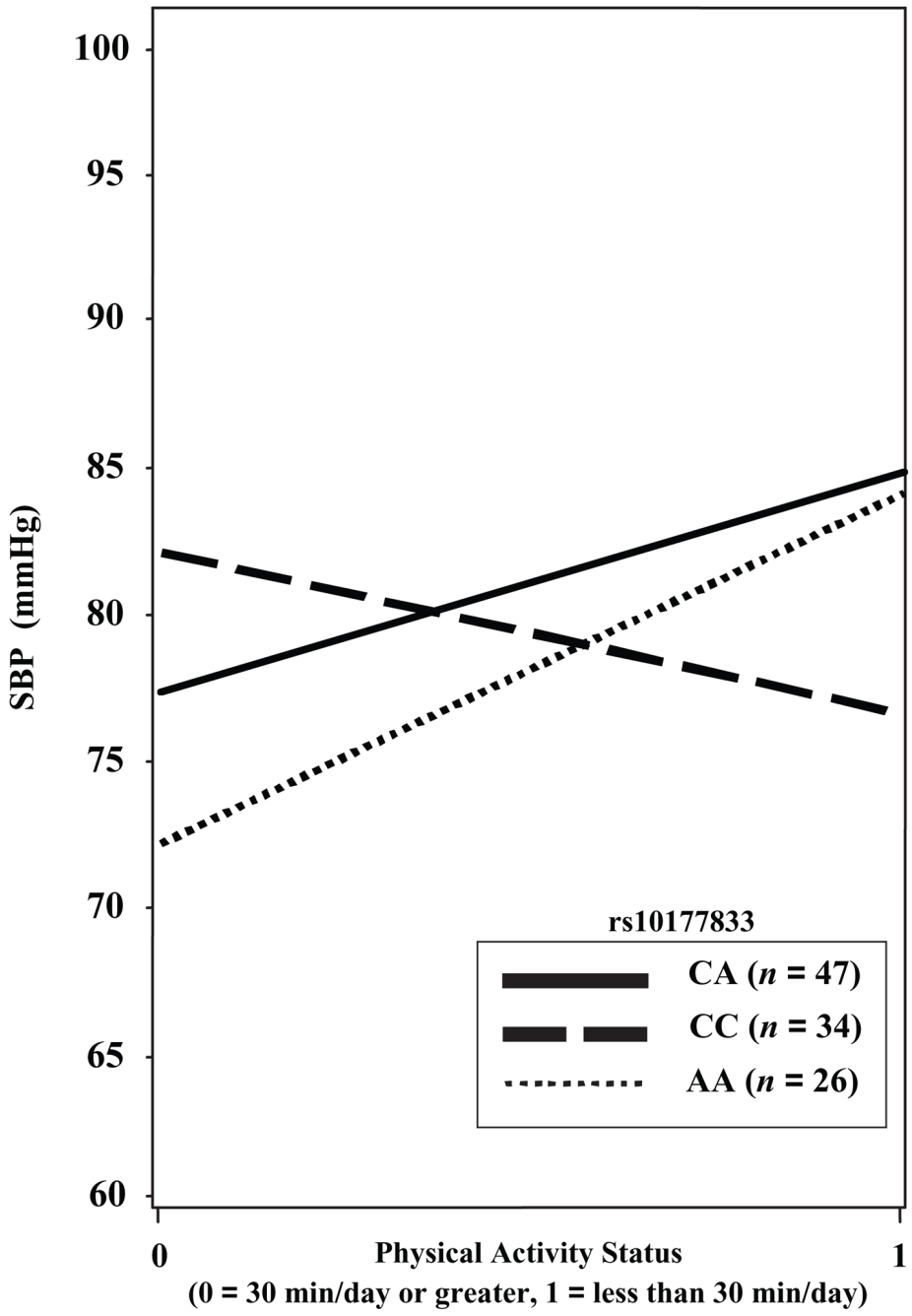

Figure 3.
Interaction of rs10177833 × physical activity on diastolic blood pressure (DBP). A = adenine; C = cytosine.

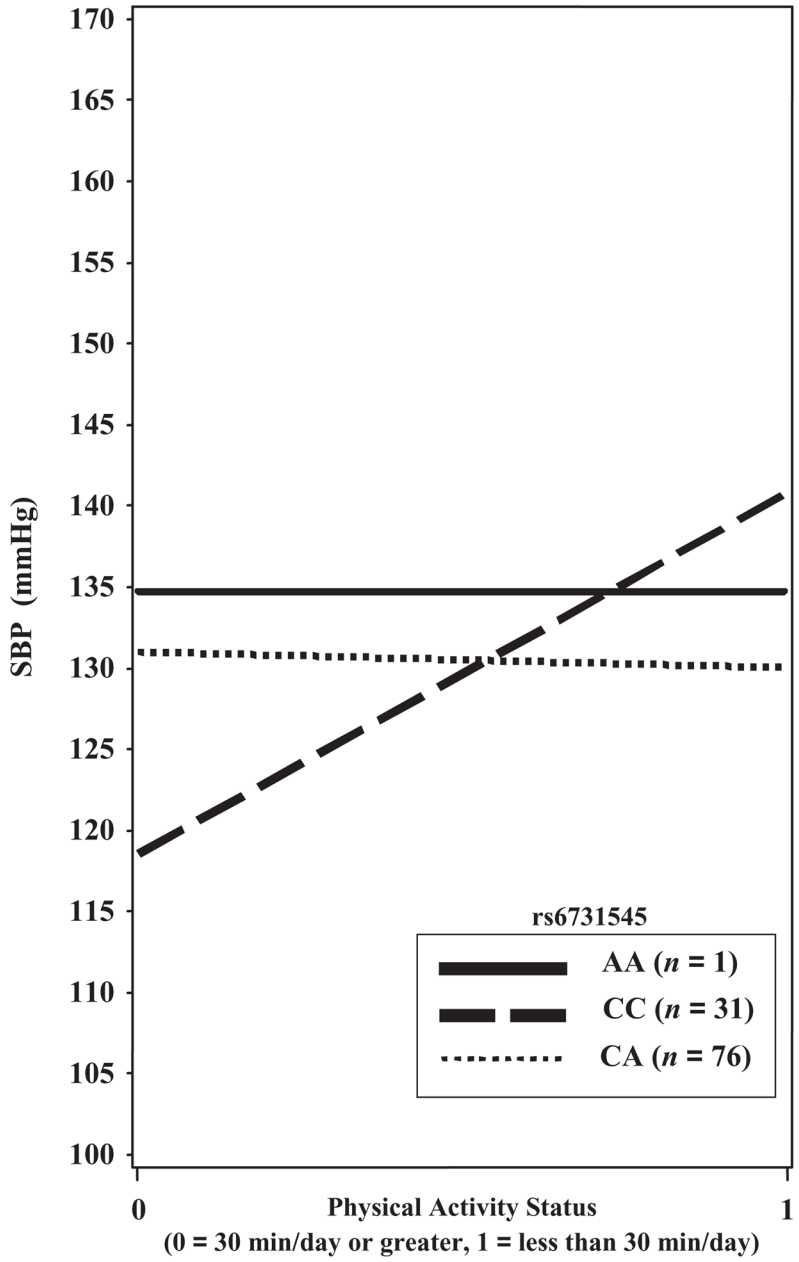

Figure 4.
Interaction of rs6731545 × physical activity on systolic blood pressure (SBP). A = adenine; G = guanine.

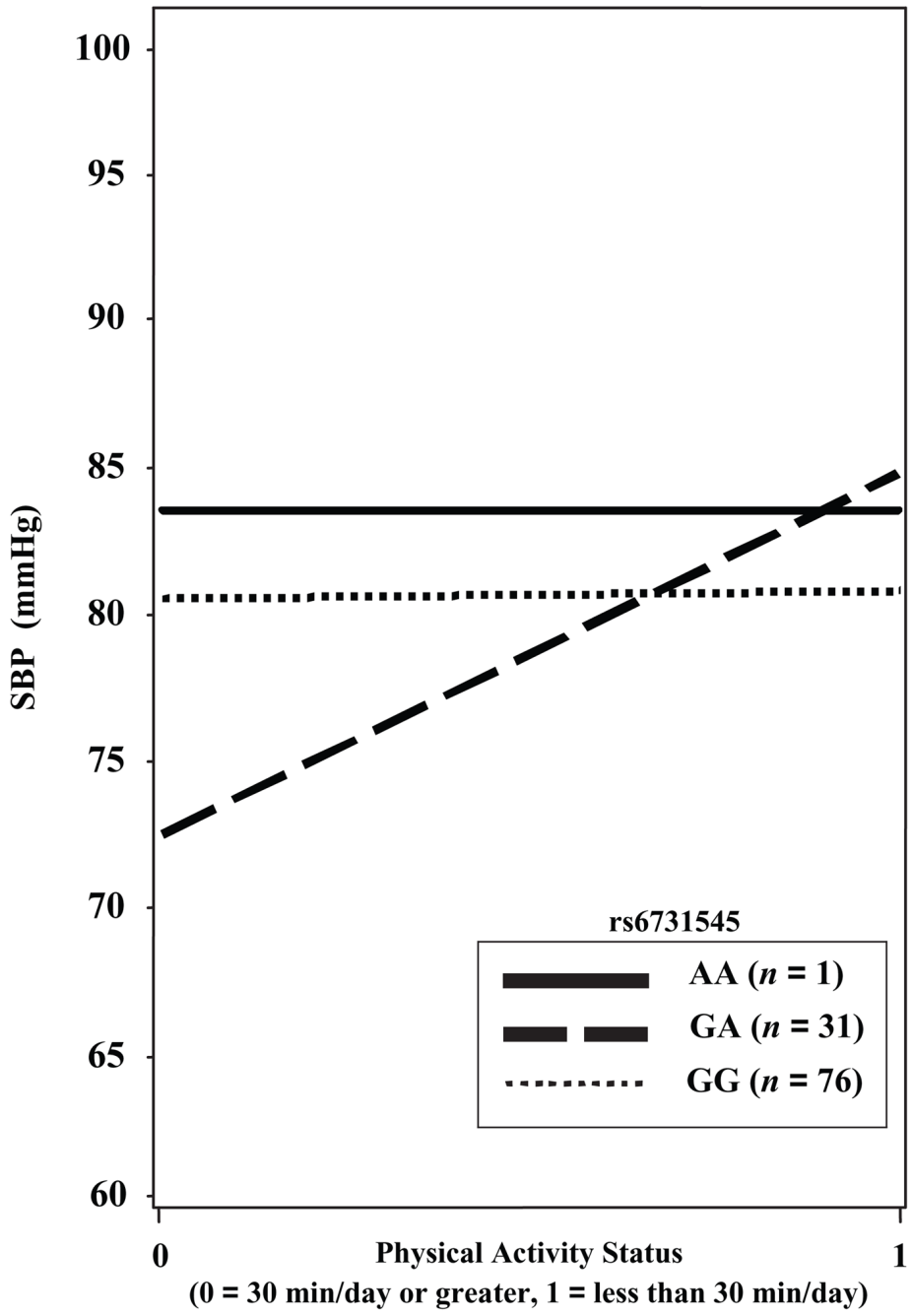

Figure 5.
Interaction of rs6731545 × physical activity on diastolic blood pressure (DBP). A = adenine; G = guanine.

Table 1

Demographic Characteristics Among Participating African American Mothers and Girls

	Mothers (*n* = 54)	Daughters (*n* = 54)	Total (*n* = 108)
Demographic Characteristics		**Mean ± SD**	
Age (years)	59 ± 13	35 ± 14	47 ± 18
BMI (kg/m^2)	32 ± 7	32 ± 7	32 ± 7
Systolic BP (mmHg)	138 ± 25	124 ± 14	131 ± 21
Diastolic BP (mmHg)	82 ± 15	79 ± 10	81 ± 13
	n (%)		
Blood pressure			
Normal	17 (31)	34 (63)	51 (47)
Hypertension[a]	37 (69)	20 (37)	57 (53)
Taking antihypertensive medication	28 (52)	8 (15)	36 (33)

NOTE: BMI = body mass index.

[a]For age ≥ = 21, hypertension was defined as systolic blood pressure (SBP) ≥ 140 mmHg or DBP ≥ 90 mmHg or taking antihypertensive medication. For age <21, hypertension was defined based on BP percentile rankings in *The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents* (National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents, 2004).

Table 2

Demographic Statistics Among Participating African American Mothers and Daughters Stratified by Sodium Intake and Physical Activity Status

	Sodium Intake Status			Physical Activity Status		
	≥2,300 mg/day (*n* = 76)	<2,300 mg/day (*n* = 32)		<30 min/day (*n* = 84)	≥30 min/day (*n* = 24)	
	Mean ± *SD*	Mean ± *SD*	*p*-Value	Mean ± *SD*	Mean ± *SD*	*p*-Value
Age (years)						
Mothers	55.82 ± 13.96	64.19 ± 11.10	.0244*	60.18 ± 14.04	53.56 ± 8.60	.180
Daughters	33.84 ± 13.12	40.09 ± 15.49	.1796	34.79 ± 11.69	35.93 ± 18.43	.787
Total	43.38 ± 17.31	55.91 ± 17.09	.0008*	48.39 ± 18.15	42.54 ± 17.56	.163
BMI (kg/m^2)						
Mothers	31.83 ± 7.22	31.36 ± 6.29	.8069	31.28 ± 6.55	33.48 ± 8.20	.383
Daughters	32.79 ± 7.66	28.59 ± 3.69	.0846	33.09 ± 7.48	28.94 ± 5.63	.575
Total	32.38 ± 7.44	30.41 ± 5.63	.1827	32.12 ± 7.01	30.64 ± 6.91	.362
SBP (mmHg)						
Mothers	135.96 ± 23.08	142.17 ± 26.78	.3690	139.82 ± 26.13	131.15 ± 12.63	.337
Daughters	124.29 ± 15.08	122.15 ± 10.92	.6608	124.97 ± 14.95	120.96 ± 12.30	.358
Total	129.36 ± 19.71	135.29 ± 24.38	.1867	132.93 ± 22.80	124.78 ± 13.16	.097
DBP (mmHg)						
Mothers	81.51 ± 13.29	83.95 ± 18.56	.5747	82.77 ± 16.67	80.89 ± 12.63	.741
Daughters	78.21 ± 15.08	80.42 ± 8.79	.5369	80.33 ± 9.95	74.31 ± 10.94	.057
Total	79.64 ± 12.04	82.74 ± 15.81	.2696	81.64 ± 13.93	76.78 ± 9.96	.113

NOTES: BMI = body mass index; DBP = diastolic blood pressure; SBP = systolic blood pressure; SD = standard deviation.

* $p < .05$.

Table 3

Unadjusted Linear Mixed Model Analysis for Each Solute Carrier Family 4, Sodium Bicarbonate Cotransporter, Member 5 (SLC45A) Single Nucleotide Polymorphism (SNP) on Predicting Systolic Blood Pressure

	SNP			*n*			β		SE		*p*-Value		
SNP Name	**ii**	**ij**	**jj**	**ii**	**ij**	**jj**	**ij**	**jj**	**ij**	**jj**	**ij**	**jj**	**Model**
rs8179526	TT	CT	CC	24	61	19	−2.80	−7.60	5.10	6.49	.587	.251	.507
rs10177833	CC	CA	AA	34	47	26	10.84	11.33	4.60	5.28	.030*	.046*	.056
rs6731545	GG	GA	AA	76	31	1	2.82	5.05	4.50	21.52	.551	.821	.810
rs6726450	GG	GA	AA	64	37	6	−8.64	−5.86	4.29	8.83	.062	.517	.160

NOTES: A = adenine; C = cytosine; G = Guanine; T = thymine; i = allele 1 of SNP; j = allele 2 of SNP; SE = standard error.

*p-Value < .05.

Table 4

Unadjusted Linear Mixed Model Analysis for Each Solute Carrier Family 4, Sodium Bicarbonate Cotransporter, Member 5 (SLC45A) Single Nucleotide Polymorphism (SNP) on Predicting Diastolic Blood Pressure

	SNP			*n*			β		SE		*p*-Value		
SNP Name	**ii**	**ij**	**jj**	**ii**	**ij**	**jj**	**ij**	**jj**	**ij**	**jj**	**ij**	**jj**	**Model**
rs8179526	TT	CT	CC	24	61	19	−2.59	−5.54	3.18	4.00	.422	.177	.394
rs10177833	CC	CA	AA	34	47	26	5.98	2.88	2.89	3.31	.054	.396	.146
rs6731545	GG	GA	AA	76	31	1	−0.40	2.57	2.72	13.33	.888	.852	.970
rs6726450	GG	GA	AA	64	37	6	0.36	−4.25	2.66	5.38	.894	.441	.710

NOTES: A = adenine; C = cytosine; G = guanine; T = thymine; i = allele 1 of SNP; j = allele 2 of SNP; SE = standard error.

Table 5

Linear Mixed Model Analysis with Interactions of Gene × Sodium Status on Predicting Systolic and Diastolic Blood Pressure (SBP and DBP)[a]

SNPs	Sodium Status β (SE)	SNPij β (SE)	SNPjj β (SE)	SNPij × Sodium β (SE)	SNPjj × Sodium β (SE)	SNPij × Sodium *p*-Value	SNPjj × Sodium *p*-Value
Outcome: SBP							
rs8179526	17.00 (8.25)	15.44 (7.74)	−0.10 (11.32)	−27.42 (9.80)	−7.40 (13.31)	.007*	.581
rs10177833	0.79 (6.82)	16.37 (7.25)	11.51 (12.16)	−6.34 (9.03)	−1.90 (13.69)	.486	.890
rs6731545	−1.28 (5.13)	2.14 (7.75)	−7.11 (20.23)	2.33 (9.29)	NA	.802	NA
rs6726450	0.26 (5.85)	−1.53 (7.33)	−6.16 (14.70)	−7.92 (8.73)	4.43 (17.70)	.369	.803
Outcome: DBP							
rs8179526	2.58 (5.55)	1.71 (5.25)	−3.06 (7.62)	−7.64 (6.68)	−2.86 (9.00)	.259	.752
rs10177833	−4.51 (4.57)	2.43 (4.80)	7.81 (7.90)	5.16 (6.07)	−4.95 (8.98)	.399	.584
rs6731545	−4.22 (3.33)	−4.26 (5.00)	3.25 (13.16)	5.85 (6.01)	NA	.335	NA
rs6726450	0.063 (3.83)	4.61 (4.67)	−0.02 (9.66)	−6.21 (5.70)	−7.05 (11.79)	.281	.552

NOTES: i = allele 1 of SNP; j = allele 2 of SNP; SE = standard error; SNP = single nucleotide polymorphism.

[a]Reference genotype = SNPii. These models were adjusted for age, BMI, and the taking of antihypertensive medication.

*p-Value < .05.

Table 6

Linear Mixed Model Analysis with Interactions of Gene × Physical Activity on Predicting Systolic and Diastolic Blood Pressure (SBP and DBP)[a]

SNPs	Physical Activity β (SE)	SNPij β (SE)	SNPjj β (SE)	SNPij × Physical Activity β (SE)	SNPjj × Physical Activity β (SE)	SNPij × Physical Activity *p*-Value	Snpjj × Physical Activity *P*-Value
Outcome: SBP							
rs8179526	−1.34 (20.38)	−7.36 (20.73)	−9.47 (21.66)	6.67 (21.35)	8.38 (22.59)	.756	.712
rs10177833	−15.04 (7.97)	−10.20 (9.21)	−11.11 (9.66)	27.22 (10.22)	27.58 (11.13)	.010*	.017*
rs6731545	−3.68 (5.77)	−12.08 (7.83)	−6.89 (19.34)	23.28 (9.31)	NA	.016*	NA
rs6726450	10.52 (5.66)	1.51 (9.27)	14.79 (11.92)	−10.74 (10.24)	−31.49 (16.61)	.300	.064
Outcome: DBP							
rs8179526	−11.04 (13.23)	−16.27 (13.60)	−19.83 (14.05)	14.13 (13.98)	17.22 (14.63)	.317	.245
rs10177833	−6.61 (5.24)	−4.55 (6.09)	−10.74 (6.39)	12.03 (6.76)	17.41 (7.41)	.082	.023*
rs6731545	−1.10 (3.73)	−8.08 (5.03)	0.88 (12.81)	12.21 (6.05)	NA	.049*	.770
rs6726450	4.12 (3.81)	1.33 (6.38)	1.64 (7.70)	−1.02 (7.03)	−10.40 (10.69)	.885	.335

NOTES: i = allele 1 of SNP; j = allele 2 of SNP; SE = standard error; SNP = single nucleotide polymorphism.

[a]Reference genotype = SNPii. These models were adjusted for age, BMI, and the taking of antihypertensive medication.

*p-Value < .05.