**Social and Biological Predictors of Blood Pressure in Hypertensives**

**by**

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**A dissertation submitted in partial fulfillment**
**of the requirements for the degree of**
**Doctor of Philosophy**
**(Epidemiological Science)**
**in The University of Michigan**
**2009**

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To my wife and best friend Colleen, and our wonderful children.

**Acknowledgements**

First and foremost, I would like to thank my wife and best friend Colleen for her undying support and patience along the way. The process of completing this dissertation often felt like a Sisyphean task and I am certain that without Colleen's constant support and encouragement the huge rock would have bowled me over completely on its way back down. I would also like to thank my parents Michael and Mary Greene, my two brothers Matthew and Christopher, my grandparents Richard and Elaine Greene and Bill and Jean Hale, my in-laws John and Kathleen O'Neil, and my great lifelong friend Charlie Stanley for believing in me.

I would like to graciously thank my committee members Sharon Kardia, Ana Diez Roux, Allison Aiello, and Jeffrey Morenoff for their guidance and support in this journey. I would particularly like to acknowledge and thank Sharon Kardia for her mentorship and support over the past few years. It has been a wonderful learning experience to work in the Kardia Research Group and I feel very fortunate to have had the opportunity to develop as scientist alongside all of the great people in this lab.

I am grateful for the pioneers of skateboarding for creating something that I have been able to use for creative expression and cathartic release for nearly all of my life.

## Table of Contents

## List of Tables

## List of Figures

**Abstract**

Hypertension affects 1 in 4 adults in the United States and is a major contributor to cardiovascular morbidity and mortality. Blood pressure control is observed in slightly less than two-thirds of those on antihypertensive pharmacologic treatment, and racial/ethnic disparities persist with significantly lower blood pressure control rates observed among minority populations. Hypertension is a multifactorial disease, involving both genetic and environmental pathogenic mechanisms. This dissertation used the Genetic Epidemiology Network of Arteriopathy (GENOA) study to examine (1) cross-sectional associations of individual characteristics (demographic, medical history, physiological, and lifestyle) with blood pressure outcomes, (2) cross-sectional associations of neighborhood socioeconomic environment with blood pressure outcomes, (3) familial aggregation of blood pressure outcomes, and (4) cross-sectional associations of gene-drug interactions with systolic blood pressure (SBP). The first study found that blood pressure control rates were suboptimal among treated hypertensives, and blood pressure control rates were lower among African Americans, compared to non-Hispanic whites. Increasing age and the presence of co-morbidities were associated with decreased odds of blood pressure control. Individual education was significantly associated with blood pressure control in African Americans, but not non-Hispanic whites, even after control for other individual level factors. The second study found that neighborhood socioeconomic environment was associated with increased odds of

combination antihypertensive pharmacological therapy, but not blood pressure control, among African Americans. The third study found evidence of moderate familial aggregation of quantitative blood pressure measures and blood pressure control in both African Americans and non-Hispanic whites. Among African subjects, sib-sib correlations of quantitative blood pressure values and familial aggregation of blood pressure control were detected among sibpairs in which both siblings resided in poor neighborhoods. The fourth study found that single nucleotide polymorphisms in the *SELE* and *VCAM1* genes had significant main effects, as well as gene-drug interaction effects, on SBP in both African Americans and non-Hispanic whites. Findings from these studies illustrate the multifactorial nature of hypertension and the importance of understanding how multiple factors across multiple levels influence variation in blood pressure levels. This dissertation research took important, novel steps in building connections between the physiological, lifestyle, socio-demographic, familial, genetic and antihypertensive therapy factors that influence blood pressure control in hypertensives from the general clinical population.

# Chapter 1

# Introduction

## BACKGROUND

Hypertension, defined by a systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg (1), affects more than 65 million adults in the United States (US) and is the most common disease for which adults seek medical attention (2, 3). Uncontrolled hypertension is an established risk factor for cardiovascular, cerebrovascular, and renal disease morbidity and mortality (4). Despite the recognized health and economic burdens of hypertension, the prevalence of hypertension is increasing (5) and success in achieving and maintaining target blood pressure levels necessary to reduce cardiovascular risk has been limited. Data from the National Health and Nutrition Examination Survey (NHANES) from 1999-2002 indicate that the age- and sex- adjusted prevalence of hypertension across racial groups (non-Hispanic white, non-Hispanic black, and Mexican American) is approximately 28.6%. Of those with hypertension, 63.4% were aware of their condition, 45.3% were receiving antihypertensive medication, and 29.3% had their blood pressure under control (<140/90 mm Hg) (6). Although national awareness, treatment, and control of hypertension have all increased in recent years (7), rates remain suboptimal and improvements in these measures are necessary to meet national health objectives (8) and to minimize the public health impact of hypertension and related morbidity and mortality.

**Race and Ethnicity Differences**

Hypertension prevalence, awareness, treatment, and control are distributed unevenly across racial/ethnic groups in the US (5, 6, 9). According to recent NHANES data, hypertension prevalence is statistically significantly higher in non-Hispanic blacks (40.5%), compared to comparable rates in non-Hispanic whites (27.4%) and Mexican Americans (25.1%) (6). Other studies (10, 11) have detected similar trends and have noted even higher hypertension prevalence rates for blacks in the range of 48-60%. The racial/ethnic disparity in hypertension prevalence is a highly publicized public health issue that may contribute to higher levels of hypertension awareness and treatment among blacks compared to whites. Findings from a recent NHANES analysis indicate that blacks have higher percentages of hypertension awareness and treatment (70.3% and 55.4%, respectively), compared to lower awareness and treatment rates among whites (62.9% and 48.6%, respectively), although these differences were not statistically significant (6). The percentages of treated individuals that had their condition under control were comparable between blacks and whites based on this national sample (6). In contrast, other studies (10-12) have found that among those on antihypertensive treatment, blacks were less likely than whites to have their condition under control.

Based on recent national data, the prevalence of hypertension among Mexican Americans was lower, yet comparable, to rates among non-Hispanic whites and substantially lower than rates among non-Hispanic blacks. Despite having the lowest prevalence rates, Mexican Americans were the least likely to be aware of their condition (49.8%), to be undergoing treatment (34.9%), and to have their condition under control (17.3%), when compared nationally to whites and blacks, and these differences were

statistically significant (6). In a separate analysis, Hispanics (including Hispanic subgroups other than Mexican Americans) were less likely to be taking antihypertensive medications, compared to whites and blacks (13), which may stem from low awareness among the Hispanic population (14) and may subsequently contribute to lower control rates among this group.

**Age and Sex Effects**

In addition to the racial/ethnic trends described above, other demographic factors influence the distribution of hypertension prevalence, awareness, treatment, and control. Results from NHANES (6) indicate that across racial/ethnic groups, hypertension prevalence statistically significantly increased with increasing age and was higher in women compared to men, although the sex difference was not statistically significant. The respective proportions of hypertensive individuals that were aware of their hypertension, were currently being treated, and had their blood pressure controlled all generally increased with age. One notable exception to this general trend is a decrease in the percentage of individuals who had their blood pressure controlled among the oldest age category relative to previous younger age group. Hypertension awareness, treatment, and control rates were all higher in women compared to men. Recent research has also suggested that the age trajectories of adult hypertension prevalence follow steeper gradients for blacks (compared to whites) and women (compared to men), with black women having the highest rates of hypertension and the steepest age-gradient by the age of 40 (15).

**Hypertension as a Co-Morbidity**

Elevated blood pressure levels are associated with an increased risk for cardiovascular disease (CVD), independent of other risk factors. Despite this consistent relationship, previous research (16) has demonstrated that the presence of additional CVD risk factors compounds the risk from hypertension alone. In addition to contributing to an increased overall risk of developing CVD, the presence of other risk factors may also concurrently contribute to elevations in blood pressure levels, thereby hindering the ability to achieve target blood pressure control. The presence of other CVD risk factors and/or resulting co-morbidities may also influence the probabilities of hypertension awareness, and control. For instance, individuals that have been diagnosed with high cholesterol levels or diabetes may be more likely than their comparatively healthy counterparts to seek more frequent medical care and may be more likely to be aware of their hypertension status, by virtue of increased exposure to blood pressure measurements that are part of routine care. The presence of co-morbidities may also impact the probabilities of hypertension treatment and subsequent control. As discussed briefly below, African-American individuals typically respond favorably to diuretic therapy compared to other forms of treatment. If, for example, a hypertensive African-American individual also has an established dyslipidemia profile of some type, treatment with certain diuretic regimens may be contraindicated (17), which could reduce both the probabilities of treatment (assuming prescription practices were influenced by knowledge of indications and contraindications) and control (if a drug that might normally prove efficacious were not administered as a result of directed prescribing). Although these examples are hypothetical, they help to illustrate the importance of considering the influences of other CVD risk factors on blood pressure levels and hypertension

awareness, treatment, and control. It is also intuitive, yet important to note that concurrent management of blood pressure and other CVD risk factors is essential in reducing overall CVD risk (1).

**Anthropometric Factors**

Obesity has become an epidemic problem in the US. The strong positive association between body weight and hypertension is well documented, with both overweight and obesity related to increases in blood pressure levels. Findings from recent NHANES data suggest that body mass index (BMI) is associated with hypertension prevalence after controlling for age, sex, and race/ethnicity and has contributed to more than half of the hypertension prevalence increase from 1998 – 2000 (5). Recent research has suggested that a higher intensity of treatment may be required to control blood pressure in obese individuals (18) and a lack of blood pressure control with both increasing BMI (4) and waist circumference (19) has been documented. Decreases in BMI have been shown to reduce hypertension risk (20) and blood pressure levels (21), suggesting that lifestyle modifications leading to weight reductions are important in preventing hypertension and controlling blood pressure levels in hypertensive adults.

**Lifestyle Factors**

The adoption of healthy behaviors is essential in reducing and maintaining appropriate blood pressure levels, preventing hypertension incidence, improving antihypertensive drug efficacy, and reducing cardiovascular disease (CVD) risk (1). Lifestyle modifications should be used as initial therapy to control blood pressure and should be standard in all hypertensive patients (17). The current recommended lifestyles with proven efficacy for preventing hypertension include: maintaining normal body

weight; adopting a diet that is low in sodium and saturated fats, and rich in fruits, vegetables, and potassium; engaging in regular aerobic physical activity; and limiting alcohol consumption (22). Although cigarette smoking has not been established as an independent risk factor for hypertension, it does increase risk for both coronary heart disease and stroke. As such, smoking cessation is suggested for overall CVD risk reduction (1).

Results from a recent clinical trial on lifestyle interventions has suggested that combining two or more of the recommended behaviors may be even more effective at reducing and maintaining blood pressure levels (23). Accordingly, combining a diet rich in fruits and vegetables (and hence potassium) with low dietary sodium intake has been shown to decrease SBP by at least 5 mmHg (24), a reduction that is comparable to the reductions obtained with an effective antihypertensive agent (17).

Antihypertensive medications are among the most frequently used medications in the United States. One of the challenges in achieving broad blood pressure control is the difficulty in predicting how effective a particular antihypertensive regimen will be for a particular patient. Without a priori knowledge of how individuals will respond to a medication, a "trial-and-error" approach is typically employed to find the ideal drug for a given patient (25). Furthermore, it is recognized that hypertension is a multifactorial disease and that combinations of antihypertensive agents, acting through different mechanisms at different sites, are often prescribed (17), with most patients requiring two or more drugs to achieve target blood pressure (26). This illustrates the importance of incorporating lifestyle modifications into treatment plans and public health efforts, versus

a predominant reliance on the prescription of antihypertensive medications, as a means of controlling blood pressure levels among hypertensive individuals.

**Genetic Factors**

A positive family history of hypertension is another known risk factor for developing hypertension. In addition to the demographic and environmental factors discussed above, genetic factors play a role in inter-individual blood pressure variation (CITE GWAS STUDIES HERE), and the notion that hypertension results from complex interactions between genetic and environmental factors has become widely accepted. Single-gene disorders, including glucocorticoid-remediable aldosteronism, apparent mineralocorticoid excess and Liddle's syndrome, are known to cause hypertension. However, these disorders are rare and are only likely to explain a small proportion of the total genetic variation in blood pressure (27). Several linkage studies of hypertension have concluded that there is no single gene for hypertension (28-33). It is more likely that hypertension is a polygenic disorder in which the additive and interactive effects of polymorphisms at numerous gene loci contribute to inter-individual blood pressure variation and differential risk of developing hypertension. Variations in candidate genes, such as those encoding components of the renin-angiotensin-aldosterone-system (RAAS) (e.g. – angiotensinogen and angiotensin converting enzyme), may predispose individuals to hypertension by altering various blood pressure regulation pathways (34). Furthermore, genetic variation in the RAAS genes may contribute to differences in hypertension control between blacks and whites. It has been suggested that hypertension among blacks is characterized by sodium dependence and low plasma renin and responds better to treatment with diuretics and calcium channel blockers. Conversely,

hypertension among whites is characterized by high plasma renin and exaggerated sodium elimination, and responds better to ACE inhibitors, angiotensin blockers, and beta-blockade (35). Investigating genetic variations in the RAAS and other pathways may offer insights into the etiology of hypertension and the reasons for disparities in blood pressure levels and hypertension control across various groups.

Genome wide association studies (GWAS) analyze whole-genome information to identify genetic associations with observable traits and/or the presence of disease conditions. Many GWAS on blood pressure are ongoing (36-39) and have identified a number of genomic regions that influence blood pressure levels. Replication of findings across these and other GWAS may identify genomic regions involved in the pathogenesis of hypertension and/or blood pressure regulation.

Although difficult to dissect and interpret, the potential for numerous gene*environment interactions should not be ignored. In a discussion regarding genes, environment and cardiovascular risk, Sing et al. (40) have described the incidence of common chronic diseases such as CVD and hypertension as a consequence of a population's distribution of susceptibility genetic factors interacting with the numerous, population–specific, environmental factors over time. Under this paradigm, these researchers pose the following fundamental question:

> "…which variations, in which genes, and in which populations are useful for understanding disease and predicting which individuals will develop disease in which strata of environmental histories? (40)"

Investigation of variations within genes and appropriately measured interactions with other genes and various environmental factors may offer insights into the etiology hypertension and possible explanations for blood pressure control for certain individuals within particular environmental contexts.

**Socioeconomic Status and Education**

A comprehensive review of the literature indicates that there is a general inverse relationship between various SES measures (income, education, and occupation) and hypertension (41). A recent trend analysis of NHANES data has found that, despite the overall decrease in the prevalence of hypertension, reductions in income- and education-related disparities in hypertension have not followed suit. Across all race/ethnicity groups, the age- and sex-adjusted prevalence of high blood pressure was consistently higher for individuals in lower income and education categories for each of the four-year periods investigated (1971-1974; 1976-1980; 1988-1994; and 1999-2002) (42). A separate analysis of the NHANES data has confirmed that CVD risk factors, including hypertension, cluster according to SES status (43).

Individual measures of SES, such as income and education level attained, are also likely to influence hypertension awareness, treatment, and control. For example, individuals in higher SES categories may be more likely to have access to quality health care and more likely to seek routine medical care. If this were the case, such individuals may also be more likely to be aware of their conditions, as

> "…awareness of hypertension presumes sufficient contact with a health care professional to permit an accurate diagnosis and communication of the finding to the effected party (44)".

SES status may also impact the probability that a hypertensive individual is currently being treated and has his or her condition under control. For example, the cost of expensive antihypertensive medications, such as calcium channel blockers, may reduce the probability that a hypertensive individual in a low SES category is currently being

treated. Furthermore, financial strain has been linked with non-adherence with medication (45), which may in turn reduce the probability of blood pressure control.

Both low SES and lack of education are also associated with unhealthy behaviors, such as cigarette smoking (42). Poor health behaviors are likely associated with less overall concern over health, and reduced likelihoods of adopting healthy lifestyles, seeking routine medical care, and adhering to recommended treatment regimens. Further investigation of how individual measures of SES may contribute to the distributions of hypertension awareness, treatment, and control is important in determining why the recent reductions in hypertension prevalence are not uniformly seen in all segments of society.

**Familial Factors**

In addition to sharing similar genetic profiles, individuals within the same family share a number of environmental factors throughout the life course, such as physical environment, dietary habits, health beliefs and practices, and socioeconomic status. These familial genetic and environmental factors may condition a common blood pressure level. If evident, such between-family variation in blood pressure levels would suggest that genetic and environmental (or interactions between the two) contextual effects could operate in ways that might influence individual blood pressure levels and/or the probability of hypertension control. Furthermore, evidence for familial clustering of blood pressure levels and hypertension outcomes suggests that strategies for preventing and controlling hypertension that are focused at the family level may prove to be effective.

**Neighborhood Factors**

Much of the CVD epidemiology research has focused on the contribution of individual-level risk factors (46). Recently, there has been a resurgence of interest in examining the health consequences of living in particular areas or neighborhoods (47). The broad hypothesis surrounding neighborhood effects on health is that the contextual features of neighborhoods may be related to health outcomes, independently of individual-level characteristics (47, 48). Many studies examining the potential role of neighborhood effects have used readily available, census-defined areas as proxies for neighborhoods and aggregate socioeconomic measures as proxies for specific features of neighborhoods (49). A recent summary of the empirical research focusing on neighborhood effects has indicated that living in low SES neighborhoods is associated with increased coronary heart disease, cardiovascular mortality, and related CVD risk factors (including blood pressure), even after accounting for individual-level socioeconomic characteristics (46). A recent study (50), investigating the extent to which neighborhood effects influence disparities in blood pressure levels and hypertension outcomes, has suggested that contextual features of neighborhoods may play a role in explaining social disparities in elevated blood pressure, and in hypertension prevalence and awareness, but not in hypertension treatment, or control. To the authors' knowledge, this was the only study to examine the potential neighborhood effects on continuous measures of blood pressure and dichotomous measures of hypertension prevalence, awareness, treatment, and control. As such, additional investigation of the potential role of neighborhood contextual effects on these blood pressure/hypertension outcomes in other study samples is warranted. Further investigations will contribute to this evolving

area of research and may offer additional insights into the etiology of hypertension and the contexts that shape the distribution of hypertension/CVD risk factors.

**Multilevel Analysis**

There is an inherent organizational structure that extends from biological systems within individuals to higher order groupings of individuals, such as families and neighborhoods, to even higher order classifications of such groupings, such as counties and states. Within this natural organizational structure, a multitude of nesting structures are possible. For example, one possible 2-level nesting structure is individuals nested within families, and this nesting structure could be extended to a 3-level structure of individuals nested within families that are in turn nested within neighborhoods. In order to capture the relevant impact of these different data structures on a given outcome, multilevel analysis is a useful approach. Multilevel analysis permits simultaneous examination of the effects of individual- and group-level characteristics on individual-level outcomes, controls for correlations within groups, and allows for examination of both inter-individual (within-group) and inter-group (between-group) variation (51).

The degree to which group-level contexts exert "independent" effects on individual-level health outcomes may have important implications for public health efforts. If group-level characteristics influence hypertension risk, apart from individual-level characteristics, interventions that are directed towards the relevant group (e.g. families or neighborhoods) may prove beneficial in reducing blood pressure levels and increasing the levels of hypertension awareness, treatment, and control. Accounting for group-level features may also be important in providing the context that determines the distribution of hypertension risk factors.

## DISSERTATION RESEARCH OBJECTIVES

The goal of this dissertation was to investigate social and biological factors that influence interindividual variation in quantitative blood pressure measures and the relative odds of hypertension treatment and control. The first paper (Chapter 2) examined the associations of individual characteristics (demographic, medical history, physiological, and lifestyle) with quantitative SBP and DBP measures, blood pressure treatment with a combination antihypertensive medication regimen, and blood pressure control among aware and treated hypertensives. Analyses for this paper were conducted in an exclusively African American cohort and separately in an exclusively non-Hispanic white cohort. This stratification permitted racial/ethnic comparisons of the associations detected within each cohort. The second paper (Chapter 3) examined how neighborhood-level socioeconomic variables, after controlling for individual-level risk factors, influenced quantitative blood pressure measures, blood pressure combination therapy, and blood pressure control among African Americans. The third paper (Chapter 4), investigated sibling correlation structures of quantitative blood pressure measures and the degree to which blood pressure control aggregated within families. Additionally, the African American sib-sib correlation structures indexed by sib-sib concordance of neighborhood-level socioeconomic indicators were also investigated to determine if sibs living in similar (or dissimilar) types of neighborhoods demonstrated similar blood pressure outcomes. Finally, the fourth paper (Chapter 5) examined effects of polymorphisms in inflammation genes (*SELE* and *VCAM1*) stratified by antihypertensive medication classes, in order to assess the potential influence of gene-drug interactions on SBP. As in the first paper, stratification by racial/ethnic group

permitted the investigation of the influence of gene-drug interactions on SBP in racially/ethnically homogeneous samples.

## STUDY POPULATION

### The Genetic Epidemiology Network of Arteriopathy (GENOA)

In 1995, the National Heart, Lung and Blood Institute (NHLBI) established The Family Blood Pressure Program (FBPP) to assess the genetic influence on inter-individual blood pressure variation and the occurrence of hypertension. One of the four networks established by the NHLBI to meet this objective is the Genetic Epidemiology Network of Arteriopathy (GENOA). Subject recruitment for GENOA was population based and took place in three geographic locations: Jackson, Mississippi; Starr County, Texas; and Rochester, Minnesota. The Rochester field center recruited non-Hispanic whites (N=1578), the Jackson field center recruited African-Americans (N=1854), and the Starr County field center recruited Mexican-Americans (N=1804) (52).

In Rochester and Jackson, recruitment was restricted to sibships containing a minimum of two individuals diagnosed with essential hypertension before the age of 60. Hypertensive probands in Rochester, MN and Jackson, MS were identified through the Rochester Epidemiology Project/Mayo Clinic diagnostic index (53) and the Atherosclerosis Risk in Communities (ARIC) study (54), respectively. Due to the high prevalence of diabetes among Mexican-Americans, the Starr County recruitment was restricted to Mexican-American sibships containing at least two individuals diagnosed with type-2 diabetes mellitus. Mexican American participants less than 60 years of age were identified from participants in the Starr County Health Studies (55). In each cohort, all available siblings, including normotensive individuals, of the index sibling pairs were

invited to participate in interviews, physical examinations, and phlebotomy. Exclusion criteria for participation included secondary hypertension, alcoholism or drug abuse, pregnancy, insulin-dependent diabetes mellitus, or active malignancy. Approximately 67% of the GENOA sample was hypertensive. The initial phase of the GENOA study took place from September 1996 through June 2000 (52). The analyses in this dissertation will focus on the African American and non-Hispanic white GENOA subjects, and will primarily focus on two general classes of reduced analytic samples: (1) all hypertensive subjects, regardless of hypertension awareness, treatment, or control status (African American, N=1329; non-Hispanic white, N=1129); and (2) hypertensive subjects that are aware of their hypertension diagnosis and are currently taking prescribed antihypertensive medication(s) to control their blood pressure (African American, N=1123; non-Hispanic white, N=970).

**PUBLIC HEALTH SIGNIFICANCE**

Uncontrolled blood pressure affects 1 in 4 adults in the US (2), accounts for nearly $1 billion annually in direct medical expenditures (56) and is a major contributor to cardiovascular morbidity and mortality (5). Blood pressure control is observed in only 64% of hypertensives on antihypertensive pharmacologic treatment. Racial/ethnic disparities persist with minority populations (particularly non-Hispanic blacks) demonstrating poorer treated blood pressure control compared to non-Hispanic whites (7). Identifying potential predictors of inadequate blood pressure control is crucial for determining key areas that public health and clinical efforts should concentrate on in order to reduce disparities, as well as the health and economic burdens related to hypertension. Few studies focused on blood pressure have investigated the influence of

characteristics defined across a broad framework of health determinants. This dissertation research took an important, novel step of attempting to build connections between the social, behavioral, physiological, genetic and antihypertensive therapy factors that influence variations in blood pressure levels and hypertension outcomes within and across racial/ethnic groups.

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# Chapter 2

## Control of Hypertension in the Genetic Epidemiology Network of Arteriopathy (GENOA) Study

### INTRODUCTION

Hypertension affects more than 65 million adults in the United States (US) and is the most common disease for which adults seek medical attention (1, 2). Uncontrolled hypertension is an established risk factor for cardiovascular, cerebrovascular, and renal disease morbidity and mortality (3). Despite the recognized health and economic burdens of hypertension, the prevalence of hypertension has increased in recent years (4) and success in achieving and maintaining target blood pressure levels necessary to reduce cardiovascular risk has been limited. Recent age-adjusted data from the National Health and Nutrition Examination Survey (NHANES) indicate that among all individuals with hypertension, 54% were receiving antihypertensive medication and only 33% have their blood pressure under control. The importance of adequate antihypertensive therapy is clear, as blood pressure control rates among treated individuals are markedly better at nearly 64% (4). Although national rates of treatment and control of hypertension have increased in recent years (4), rates remain suboptimal and improvements in these measures are necessary to meet national health objectives (5) and to minimize the public health impact of hypertension and related morbidity and mortality.

One of the key goals of the Healthy People 2010 objective is to eliminate health disparities (5). African Americans in the US have consistently higher prevalence of

hypertension in nationally representative samples (4) and about 30% of mortality among African Americans is attributable to hypertension (6). The racial/ethnic disparity in hypertension prevalence is a highly publicized public health issue that may contribute to higher levels of hypertension awareness and treatment among blacks compared to whites. Despite this, national data (4) and results from other studies (7-9) indicate that among those on antihypertensive treatment, blacks are less likely than whites to have their condition under control.

Many studies have illustrated the trends of hypertension prevalence, awareness, treatment, and control among the general US population (1, 4, 10, 11). Fewer studies have examined the influence of specific determinants on blood pressure control among clinical populations of treated hypertensive individuals. The objective of this study was to examine the associations between various demographic, lifestyle, biological, and personal medical history factors and blood pressure control in a bi-ethnically diverse sample of hypertensive subjects, with the intentions of offering insights into the potential determinants of blood pressure control within racial/ethnic groups and identifying factors that may contribute to the observed disparities in blood pressure control.

## METHODS

### Study Population

In 1995, the National Heart, Lung and Blood Institute (NHLBI) established The Family Blood Pressure Program (FBPP) to assess the genetic influence on inter-individual blood pressure variation, hypertension, and hypertensive target organ damage. One of the four networks established by the NHLBI to meet this objective is the Genetic Epidemiology Network of Arteriopathy (GENOA). GENOA field centers in Jackson,

MS, Starr County, TX, and Rochester, MN recruited hypertensive African American, Hispanic, and non-Hispanic white sibships, respectively, for linkage and family-based association studies. Subject were diagnosed with hypertension if they had a previous clinical diagnosis of hypertension by a physician with current antihypertensive treatment or an average systolic blood pressure (SBP) >=140 mmHg and/or an average diastolic blood pressure (DBP) >=90 mmHg.

In Rochester, MN and Jackson, MS, recruitment was restricted to sibships that contained a minimum of two individuals diagnosed with essential hypertension before the age of 60. Once this criterion was met, the entire sibship was invited to participate in the study. As the prevalence of diabetes among Mexican-Americans is high, the Starr County recruitment was restricted to Mexican-American sibships containing at least two individuals diagnosed with type-2 diabetes (12). Data was collected through personal interviews, and physical and laboratory examinations. The initial phase of the GENOA study took place from September 1995 through June 2001 (13).

The study presented here focuses on 2458 hypertensive subjects from the Rochester, MN and Jackson, MS cohorts. Although a majority of the subjects in both cohorts have been diagnosed as hypertensive, approximately 25% of the sibship members invited to participate were identified as normotensive during the baseline examination and have been excluded from this analysis. Other exclusion criteria included secondary hypertension, alcoholism or drug abuse, pregnancy, insulin-dependent diabetes, or active malignancy. Of the 1579 non-Hispanic white subjects enrolled in the study, 1129 (72%) subjects from 548 sibships were identified as having essential hypertension. Of the 1854

African American subjects enrolled in the study, 1329 (72%) subjects from 637 sibships were identified as having essential hypertension.

**Covariates**

Height was measured by stadiometer, weight by electronic balance, and body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Diabetes was defined as having a fasting glucose level ≥ 126 mg/dL or currently being treated with insulin or oral agents. Blood was drawn by venipuncture after an overnight fast. Serum cholesterol, triglycerides, and high-density lipoprotein (HDL) cholesterol were measured by standard enzymatic methods. Subjects were categorized as having a positive high-risk lipid profile if one or more of the following criteria were met: high-density lipoprotein (HDL) cholesterol <35 mg/dL; triglycerides >200 mg/dL; total cholesterol >240 mg/dL; or total cholesterol to HDL ratio >6. Although calculation of low-density lipoprotein (LDL) cholesterol by the Friedewald formula (14) has been commonly used in epidemiologic studies and validated (15), calculated LDL values are invalid for subjects with very high (>400 mg/dL) triglyceride levels, as the ratio of LDL to triglycerides is not constant as triglyceride levels increase. A number of subjects from each racial/ethnic group (30 (2%) African Americans, 53 (5%) non-Hispanic whites) with triglyceride values that exceeded the validated cutpoint of 400 mg/dL were excluded from the respective samples when calculating LDL values. Given these modest reductions in sample size for both racial/ethnic groups, LDL was investigated as an independent risk factor for the outcomes of interest, but was not included as criteria for the dichotomization of high-risk lipid profiles. Trained interviewers asked subjects standard questions on numerous factors, including

sociodemographic, lifestyle, behavioral and cardiovascular health history. Age in years was assessed on the baseline examination date. Education was defined as the total number of years of education completed and was also categorized as < 12 years; ≥ 12 years, < 16 years; and ≥ 16 years (reference group). Marital status was based on self-reports and was defined as "married" for subjects currently married and "single" otherwise. Physical activity was based on the number of miles each subject jogged and/or walked per week. Current smoking status and alcohol consumption (sometimes versus never) were based on self-reports. Presence of coronary heart disease (CHD) was based on self reported positive history of heart attack, myocardial infarction, coronary bypass surgery, coronary angioplasty, coronary balloon dilation, and/or coronary stent. History of cerebrovascular disease was based on self-reported positive history of stroke and/or carotid artery surgery. Where applicable, the duration of hypertension for each subject was based on the difference between the baseline examination date and the date of hypertension diagnosis.

**Measurement of Blood Pressure Outcomes**

**Blood Pressure Readings**

Blood pressure measurements were made with random zero sphygmomanometers and cuffs appropriate for arm size. Three readings were taken in the right arm after the subject rested in the sitting position for at least five minutes according to the Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7, 2003) guidelines (16). The SBP and DBP values were determined by the first and fifth phase Korotkoff sounds, respectively, and the last two blood pressure readings were averaged for the analyses. The diagnosis of

hypertension was established based on blood pressure levels measured at the study visit (≥140/90 mmHg), or a prior diagnosis of hypertension and current treatment with antihypertensive medications.

**Antihypertensive Medications**

Based on lists of all antihypertensive medications available in the US each prescription antihypertensive drug recorded at the study visit was assigned a code number corresponding to the first 6 digits of the Medi-Span Generic Product Identifier. This number, which identifies pharmacologically equivalent drug products, was used to categorize agents with similar mechanisms of antihypertensive action. The number of subjects classified for each antihypertensive medication group is summarized in Table 2.4.

**Blood Pressure Awareness, Treatment and Control**

Subjects were considered to be "aware" of their hypertension status if they were (a) defined as hypertensive, and (b) answered yes to the question, "Have you ever been told by a physician that you have high blood pressure or hypertension?" Conditional upon being hypertensive and aware of their hypertension status, subjects were considered to be "treated" if they answered yes to the questions, "Has medication ever been prescribed by a physician to lower your blood pressure?" and "During the last month, have you used any medication that was prescribed or recommended by a physician?" Official guidelines propose that patients with a SBP ≥ 140 mmHg or DBP ≥ 90 mmHg be considered as hypertensive (16, 17). Accordingly, in this study controlled blood pressure was defined as SBP < 140 mmHg and DBP < 90 mmHg for a treated subject with hypertension. If either one, or both, of the two requirements were not met, a hypertensive

subject's blood pressure was defined as uncontrolled. In 1997, the sixth report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood pressure (JNC-VI) put forth the recommendation that the threshold for control should be lowered to 130/85 mmHg for diabetic patients (18). This more stringent definition of blood pressure control among diabetics was used to derive general blood pressure control rates for diabetics within each racial/ethnic group, in order to reflect the clinical recommendations that were in place during the study time period.

**Statistical Analysis**

Means and standard deviations (SD) for continuous variables, and frequencies and percentages for categorical variables, were used to summarize the study sample characteristics. Continuously distributed variables were examined graphically by histogram plots and analytically by subjective observations of associated skewness values to ensure approximation to the normal distribution. Variable comparisons between male and female genders were assessed within racial/ethnic groups, and pooled sex variable comparisons were assessed between racial/ethnic groups. Continuous variables were compared using standard t-tests, and categorical variables were compared using the $\chi^2$ statistic. To account for familial correlations in the data, linear mixed effects models, using maximum likelihood estimation methods, were used to assess linear associations between quantitative SBP and DBP values and baseline participant variables.

Generalized linear mixed models, using penalized quasi-likelihood estimation methods, were used to assess associations where the probabilities of blood pressure treatment and blood pressure control were the designated outcomes of interest, and odds ratios (OR) and 95 % confidence intervals (CIs) were calculated for each variable.

Adjusted regression models including age and sex plus the baseline variable of interest were assessed to account for potential confounding by age and/or sex. An alpha-level of 0.05 was used to determine statistical significance for all models. Regression analyses were stratified by race/ethnicity, as they were carried out separately in the Rochester, MN (distinctly non-Hispanic White) and Jackson, MS (distinctly African American) cohorts. Since hypertension awareness and treatment were high in both racial/ethnic groups, the focus of all regression analyses was on reduced hypertensive samples containing subjects that were both aware of their hypertension diagnoses and taking antihypertensive medications to reduce blood pressure (African American n = 1123, non-Hispanic white n = 970). The objective of investigating these reduced analytic samples was to provide insights into the potential reasons for (a) the observed lack of blood pressure control, even among treated hypertensives, and (b) blood pressure control disparities along racial/ethnic lines. Analyses were performed using the R statistical language (19).

**Cross-Validation**

The predictive ability of the variables of interest on quantitative blood pressure outcomes was assessed using cross-validation methods (20) and results are displayed in Appendices 2.1 and 2.2. Cross-validation significantly reduces false positive results by eliminating associations that lack predictive ability in independent test samples. Four-fold cross-validation was performed by dividing the full sample into four equally sized groups. Three of the four groups were combined into a training dataset, and the modeling strategy outlined above was carried out to estimate model coefficients. These coefficients were then applied to the fourth group, the testing dataset, to predict the value of the outcome variable of each subject in the independent test sample. This process was

repeated for each of the 4 testing sets. Predicted values for all subjects in the test set were then subtracted from their observed values, yielding the total residual variability (SSE), $\sum_{i=1}^{n}(y_i - \hat{y}_i)^2$. The total variability in the outcome (SST) – the difference between each subject's observed value and the mean value for the outcome – was then calculated, $\sum_{i=1}^{n}(\bar{y} - y_i)^2$. In order to estimate the proportion of variation in the outcome predicted in the independent test samples, the cross-validated $R^2$ (CV $R^2$) was calculated as follows: $CV\ R^2 = \frac{SST - SSE}{SST}$. This cross-validation method provides a more accurate measure of the predictive ability of the regression models and will be negative when the model's predictive ability is poor. Because random variations in the sampling of the four mutually exclusive test groups can potentially impact the estimates of CV $R^2$, this procedure was repeated 10 times and the CV $R^2$ values were averaged (21). Covariate associations were considered cross-validated if the average percent variation predicted in independent test samples was greater than 0.5%.

**RESULTS**

A total of 2458 subjects from the Rochester, MN and Jackson, MS phase I cohorts of the GENOA study were identified as being hypertensive. The sample characteristics by racial/ethnic group are shown in Table 2.1. Among all hypertensive subjects, SBP values were significantly higher among African Americans compared to non-Hispanic whites. While DBP values did not differ by racial/ethnic group, overall blood pressure control (<140/90) was significantly lower among African Americans (44%) compared to non-Hispanic whites (52%). The majority of both racial/ethnic groups were female.

African Americans were significantly older, had higher BMI, were diagnosed earlier with hypertension, were more likely to have diabetes, smoked more frequently, reported less physical activity, and completed fewer years of education compared to non-Hispanic whites. Non-Hispanic whites had significantly poorer lipid profiles (higher total cholesterol and triglycerides, and lower high-density lipoprotein (HDL) cholesterol), reported higher positive history of CHD, and consumed alcoholic beverages more frequently compared to African Americans.

The distributions of hypertension awareness, treatment and control by sample characteristics are presented in Table 2.2 for African Americans and Table 2.3 for non-Hispanic whites. As awareness of previously diagnosed hypertension in two or more siblings was a criterion for participation in the GENOA study, the overall proportion of hypertension awareness was high and largely consistent by baseline characteristics in both racial/ethnic groups. Similarly, a high proportion of subjects that were aware of their hypertension diagnosis were currently taking antihypertensive medications in both racial/ethnic groups. While hypertension awareness was greater among African Americans, treatment (conditional on awareness) and blood pressure control (conditional on awareness and treatment) were lower compared to non-Hispanic Whites. Blood pressure control is poorer among all (including untreated) hypertensive subjects in both racial/ethnic groups, which clearly illustrates the benefits of antihypertensive medication therapy. Despite this parallel, a disparity still exists, with all African American hypertensive subjects having poorer blood pressure control, compared to their non-Hispanic white counterparts (Figure 2.1).

Among the 1329 African American, hypertensive subjects, 1294 (97.4%) were aware of their hypertension diagnoses, 1123 (86.8%) of those that were aware were currently taking antihypertensive medications, and 590 (52.5%) of those that were both aware and taking antihypertensive medications had their blood pressure controlled. blood pressure control was achieved in less than half (44%) of African Americans, regardless of awareness or treatment status. While awareness was high and did not differ greatly by baseline characteristics, subjects that were older, overweight or obese, diabetic, and had high-risk lipid profiles were significantly more likely to be aware of their hypertension diagnoses. Treatment varied quite a bit by baseline characteristics. Subjects that were female, had greater BMI values, and had co-morbidities present, including diabetes, history of CHD, and history of CBVD, were significantly more likely to be taking antihypertensive medications compared to counterparts without co-morbidities. Subjects that did not smoke cigarettes or consume alcohol were also significantly more likely to be receiving treatment. Blood pressure control among subjects that were both aware and treated was largely consistent by baseline characteristics, but older subjects were significantly less likely to have their blood pressure controlled to 140/90 mmHg. Subjects with diabetes were much less likely to have their blood pressure controlled compared to their non-diabetic counterparts and had the lowest blood pressure control across all age, sex, co-morbidity, lifestyle, and education groups.

Among all 1129 non-Hispanic white, hypertensive subjects, 1025 (90.8%) were aware of their hypertension diagnoses, 970 (94.6%) of those that were aware were currently taking antihypertensive medications, and 587 (60.5%) of those that were both

aware and taking antihypertensive medications had their blood pressure controlled. Blood pressure control was achieved in just over half (52%) of non-Hispanic whites, regardless of awareness or treatment status. Awareness and treatment were generally high across age, sex, co-morbidity, lifestyle, and education groups, but older subjects were significantly more likely to be aware of their hypertension diagnoses, and women were significantly more likely to be aware and taking antihypertensive medications compared to men. A marginally significant trend for awareness was detected among the education groups, with more educated subjects more likely to be aware of their hypertension diagnoses. A marginally significant trend for treatment was detected among the BMI groups, with overweight and obese subjects less likely to be taking antihypertensive medications. Among subjects that were both aware and treated, subjects that were older (particularly those ≥ 60 years of age), reported positive histories of CHD, and were less educated were significantly less likely to achieve blood pressure control rates. Women and subjects without diabetes had marginally better blood pressure control compared to men and those with diabetes, respectively.

**Systolic and Diastolic Blood Pressure**

The least squares linear regression results for the covariates of interest regressed on SBP are shown in Appendix 2.1. As expected, age, independent of sex, was a highly statistically significant and cross-validated predictor of SBP in both racial/ethnic groups, with estimated averages of 4.5% and 8.1% variation in SBP predicted in African Americans and non-Hispanic whites respectively. Among African Americans, diabetes and years of education completed were also statistically significant and cross-validated predictors of SBP, after adjusting for age and sex. Diabetics had SBP values that were on

average 5.5 mmHg higher than their non-diabetic counterparts and diabetes predicted an average of 1.1% variation in SBP. For every year increase in education, SBP decreased by 0.5 mmHg and education predicted an average of 0.6% variation in SBP. Increases in total cholesterol and having hypertension for longer than 5 years both led to increases in SBP, however these associations only reached marginal significance. Among non-Hispanic whites, BMI was the only other covariate that demonstrated a statistically significant and cross-validated association with SBP, after controlling for age and sex. Per unit increase in BMI, SBP increased 0.19 mmHg and just over 0.5% variation in SBP was predicted by BMI. Increased triglyceride levels were statistically significantly associated with increased SBP, however the association did not cross-validate. Diabetic non-Hispanic white subjects also had higher SBP values compared to their non-diabetic counterparts, however this association only reached marginal significance.

The least squares linear regression results for the covariates of interest regressed on DBP are shown in Appendix 2.2. Age, female sex, total cholesterol and LDL cholesterol all demonstrated statistically significant and cross-validated associations with DBP, in both racial/ethnic groups. As with SBP, age, independent of sex, was the strongest predictor of DBP, with estimated averages of 6.9% and 8.4% variation in SBP predicted in African Americans and non-Hispanic whites respectively. Contrary to increases in SBP with increasing age however, increases in age led to modest reductions in DBP levels in both racial/ethnic groups. Since each of the analytic samples was comprised largely of older individuals, this relationship accurately reflects the slight decrease of DBP values commonly observed after 50 years of age (Figure 2.2., from Burt et al. (10)). While no age-adjusted sex differences in SBP were noted in either

racial/ethnic group, females had statistically significantly lower DBP values compared to males in both groups. The predictive ability of female sex on DBP was greater among non-Hispanic whites, compared to African Americans, as the estimated averages of variation predicted were 4.5% and 1.2% respectively. Increases in total cholesterol and LDL cholesterol led to statistically significant increases in DBP and approximately 1% of the variation in DBP was predicted by each of these cholesterol types in both racial/ethnic groups. Although a strong statistically significant association between diabetes and SBP was detected among African Americans, no such relationship was found for DBP. Conversely, diabetic non-Hispanic whites had statistically significantly lower DBP values on average, compared to their non-diabetic counterparts, although this association failed to cross-validate. A marginal association between the number of years of education completed and DBP was detected among African Americans, with a one-year increase in education associated with a 0.20 reduction in DBP.

**Blood Pressure Treatment**

Table 2.4 lists the use of antihypertensive drug classes verified at baseline among the aware and treated hypertensive GENOA subjects by race/ethnicity. Diuretics were the most commonly used antihypertensive drug, regardless of race/ethnicity. This is an expected result as diuretics are the most commonly prescribed drug as a first line defense against hypertension. Among the main antihypertensive drug classes, the use of diuretics and calcium channel blockers was statistically significantly higher among African Americans, whereas the use of β-blockers and renin-angiotensin-aldosterone-system (RAAS) inhibitors was statistically significantly higher among non-Hispanic whites. This trend may reflect prescription patterns motivated by conventional wisdom that

African Americans tend to have lower renin activity compared to non-Hispanic whites and likely respond better to calcium channel blockers and diuretics, and less effectively to RAAS inhibitors and β-blockers (22). The use of 'other' drugs, including α-blockers, vasodilators, and sympatholytics, was statistically significantly higher among African Americans. While the majority of treated hypertensive GENOA subjects in both racial/ethnic groups were taking some type of antihypertensive drug as monotherapy regimens, the percentage was significantly higher in non-Hispanic whites compared to African Americans. The use of antihypertensive drugs in combination was higher in African Americans compared to non-Hispanic whites, particularly among those taking three or more antihypertensive drugs. This potentially reflects a general clinical attempt to treat African Americans more aggressively, given the consistently lower blood pressure control rates among African Americans on a national level (4).

Overall, the percentage of antihypertensive treatment, conditional on being aware of hypertension status, was high in both racial/ethnic groups (87%, African Americans and 95%, non-Hispanic whites), and this low variability limited the ability to identify significant predictors of the antihypertensive treatment outcome.. There was, however, substantial variability among aware and treated subjects with respect to those that were taking antihypertensive drugs in monotherapy or combination form. Table 2.5 lists the results of age- and sex-adjusted generalized linear mixed models examining potential significant predictors of taking antihypertensive drugs in combination versus monotherapy form.

Many of the predictors investigated were statistically significantly associated with the odds of taking antihypertensive drugs in combination form, relative to monotherapy

form, and the results were largely consistent across the racial/ethnic groups. Increasing age and BMI were associated with slight increased odds of combination therapy in both African Americans and non-Hispanic whites. Each of the co-morbidities investigated, including Type 2 diabetes, history of CHD and history of CBVD, was associated with greatly increased odds of combination therapy (African American, OR=1.71, $p<0.001$, OR=3.62, $p<0.001$, OR=2.05, $p=0.008$; non-Hispanic white, OR=2.16, $p<0.001$, OR=1.58, $p=0.041$, OR=2.37, $p=0.020$), respectively). These associations reflect not only the difficulty in managing blood pressure and the common need for multiple drugs in the presence of co-morbidities, but also that hypertensive patients with other conditions may have greater likelihoods of being both treated by health professionals and subsequently prescribed combination regimens. In line with this, the duration of hypertension was also statistically significantly associated with increased odds of combination therapy, as expected, in both African Americans (OR=2.19, $p<0.001$) and non-Hispanic whites (OR=2.31, $p<0.001$). Among non-Hispanic whites only, the odds of taking antihypertensive medications in combination form were higher among subjects with high-risk lipid profiles (OR=1.33, $p=0.033$) compared to those with moderate to low risk lipid profiles, and the odds of taking antihypertensive medications in combination form were lower among subjects that consumed alcohol (OR=0.72, $p=0.025$) compared to those that did not consume alcohol.

**Blood Pressure Control**

Table 2.6 lists the results of age- and sex-adjusted generalized linear mixed models examining the influence of various predictors on blood pressure control (< 140/90 mmHg) among treated hypertensive subjects, conditional upon being aware of their

hypertension diagnosis. As expected, control was lower with increasing age, independent of sex, among African Americans (OR=0.97, p<0.001) and non-Hispanic whites (OR=0.95, p<0.001). The duration of hypertension was also statistically significantly associated with decreased odds of blood pressure control, even after adjustment for age and sex, in both racial/ethnic groups. African Americans that were diagnosed with hypertension for more than 5 years (prior to baseline) were less likely (OR=0.62, p =0.012) to have their blood pressure controlled compared to those with shorter durations of hypertension. Similarly, non-Hispanic whites that had hypertension for more than 5 years were less likely (OR=0.70, p=0.031) compared to non-Hispanic whites that were diagnosed with hypertension ≤ 5 years prior to baseline.

Among non-Hispanic white subjects, the odds of blood pressure control were higher among current smokers (OR=1.58, p=0.039) compared to never and former smokers. Although this relationship seems counterintuitive given the common risks associated with smoking, evidence does not support the role of smoking as a risk factor for hypertension as numerous studies (23-27) have demonstrated that, despite acute increases in blood pressure stemming from smoking, current smokers had lower blood pressure compared to former and never smokers. The increased likelihood for controlled blood pressure detected among non-Hispanic white, current smokers may reflect the possibility that smokers are more likely to seek healthcare due to other complications related to smoking and an increase in healthcare visits may lead to appropriately guided blood pressure management. This notion is supported by a recent study (28) that found current smoking was associated with higher healthcare utilization compared to former or never smokers.

Among treated African American subjects, the odds of blood pressure control were lower among those with type 2 diabetes (OR=0.62, p<0.001) compared to non-diabetics. Among diabetic GENOA subjects, blood pressure control at the conventional <140/90 mmHg level was observed in 44% and 53% among African American and non-Hispanic whites subjects, respectively. blood pressure control rates to the more stringent <130/85 mmHg, as recommended for subjects with type 2 diabetes in JNC-VI (18), were poorer still, with control observed in 31% of the African American subjects and 28% of the non-Hispanic white subjects, reflecting the need for improvements in managing blood pressure in patients with type 2 diabetes.

The odds of blood pressure control increased with increasing years of education completed among African Americans (OR=1.04, p=0.048), after controlling for age and sex differences. This relationship was maintained (OR=1.04, p=0.044) after additional control for BMI, diabetes, history of CHD, history of CBVD, current smoking, and alcohol consumption. Consistent with trends from recent national data (4), investigation of the pooled GENOA sample of African American and non-Hispanic white aware and treated hypertensive subjects (n=2093) indicated that African American race/ethnicity was statistically significantly associated with poorer blood pressure control compared to non-Hispanic white race/ethnicity, after adjustment for multiple covariates. Table 2.7 lists the odds of blood pressure control associated with African American race/ethnicity. An unadjusted model indicated that the odds of blood pressure control were lower among African Americans (OR=0.69, p<0.001) compared to non-Hispanic whites. This association between African American race/ethnicity and blood pressure control was attenuated, but remained statistically significant, after adjustment for age, sex, BMI, and

co-morbidities including type 2 diabetes, history of CHD, and history of CBVD (OR=0.81, p=0.046). The association of African American race/ethnicity was attenuated further and lost statistical significance with the additional adjustment for years of education completed (OR=0.84, p=0.100), providing additional supporting evidence that factors indexed by SES may influence blood pressure control and contribute to observed disparities in blood pressure control rates between racial/ethnic groups.

**DISCUSSION**

In recent years, national data suggest modest improvements in hypertension awareness, treatment, and control among the general hypertensive population, although hypertension prevalence has not declined and control remains suboptimal, particularly for minority populations (4). Awareness and treatment rates among the hypertensive GENOA subjects were high, regardless of race/ethnicity, and substantially exceeded rates reported from national studies during the similar time period (4), although this reflects a selection bias since essential hypertension was a study inclusion criteria. The GENOA control rates observed among treated hypertensives compared favorably with national rates for both African Americans and non-Hispanic whites (4). Higher than nationally observed rates for both treatment and treated control among the GENOA African American subjects residing in the Jackson, MS area also compared favorably with rates recently observed among African Americans in the Jackson Heart Study (JHS) (29). As Wyatt et al. (29) point out, African Americans residing in the Jackson, MS area have benefited from participation in the Atherosclerosis Risk in Communities (ARIC) study (30) and increased exposure to health education through community outreach efforts of the JHS, and it is likely that such benefits have contributed to higher control rates. As the

ARIC study population was utilized to identify African American hypertensive probands for the GENOA study, similar community resources have also benefited the African American subjects in the GENOA study and may have influenced comparably higher blood pressure control rates. Despite the relative improvement in blood pressure control among African Americans within this particular community, rates remain suboptimal and are significantly lower compared to rates observed in this study among GENOA non-Hispanic white subjects, as well as those reported for non-Hispanic whites in other population and community based samples (4, 7-9, 11, 29, 31, 32).

Epidemiologic studies have provided evidence that age is a key determinant of blood pressure (33). Among the GENOA subjects, strong positive associations between increasing age and both SBP and DBP were observed. The cross-validation of these associations in this study provides further evidence of the predictive ability of age on quantitative blood pressure values. While awareness and treatment among the elderly GENOA subjects in both racial/ethnic groups were comparable to middle aged and younger subjects, the percentages of elderly subjects with controlled treated hypertension were lower in both groups. A number of hemodynamic, metabolic, and nutritional factors certainly contribute to progressive increases in blood pressure values (34) and, subsequently, the difficulty in blood pressure control and simultaneous increased cardiovascular risk among the elderly. Among these factors, hemodynamic alterations over the life-course, manifesting as increased vascular resistance earlier in life and shifting towards a predominance of large artery stiffness later in life (35), contribute to the commonly observed increasing SBP and decreasing DBP later in life. This shift towards isolated systolic hypertension commonly occurs in the sixth decade of life (10),

is associated with increased cardiovascular risk among the elderly (36, 37) and often requires treatment intensification which is often accompanied by tolerability, affordability (29), compliance and other associated issues that in turn influence blood pressure control. Among the treated hypertensives with uncontrolled blood pressure in this study sample, the majority of subjects in each racial/ethnic group (African American, 58%; non-Hispanic white, 67%) had isolated systolic hypertension (SBP≥140/DBP<90 mmHg), reflecting the influence of age on blood pressure, particularly systolic, control.

National blood pressure control rates among treated elderly individuals have steadily improved to approximately 50% over recent years (4), providing further support to trials (38-40) that have demonstrated the ability to achieve blood pressure control among elderly populations. Control rates among the elderly GENOA subjects compared favorably, possibly reflecting a general recognition of the importance of managing blood pressure, particularly SBP, among the elderly in order to reduce overall cardiovascular risk, as well as a shift away from clinical inertia among older individuals. Although this recent trend is encouraging, treatment efforts that couple drug therapy with lifestyle interventions should be increased among the elderly, as treated control rates among individuals ≥ 60 years of age remain sub-optimal and lower than younger age groups. Particular attention to the African American elderly population is warranted, as racial/ethnic disparities in uncontrolled treated hypertension among the elderly still remain and data indicates that African American women ≥ 60 years of age have the poorest blood pressure control rates among those treated for their condition (4). Although sex differences among GENOA subjects within racial/ethnic group did not significantly influence blood pressure control, the vast majority of the African American subjects were

female and this may well have contributed to lower blood pressure control among African Americans compared to non-Hispanic whites, given the difficulty of blood pressure control among African American women. Furthermore, studies have shown that, compared to non-Hispanic whites, African Americans (particularly females) have steeper age-gradients for hypertension prevalence (41, 42), suggesting that the influences of the aging process and life-course exposures may differentially impact blood pressure control among the African American population.

Type 2 diabetes and hypertension are intimately connected and poor blood pressure control among diabetic individuals with co-morbid hypertension has been consistently noted (4, 43-45). The coexistence of diabetes and hypertension is associated with dramatically increased risk of CHD, stroke, renal disease, and mortality (16). Mechanisms contributing to both additive and multiplicative effects of hypertension and diabetes on cardiovascular risk have been proposed (46). Within this GENOA sample, the prevalence of diabetes was statistically significantly higher in African Americans compared to non-Hispanic whites, in line with trends from national data (47-50). This higher percentage of diabetes may be a contributing factor to the more aggressive drug treatment (i.e.- the higher use of combination antihypertensive therapies) observed among African Americans, compared to non-Hispanic whites, in this study.

Recent studies have indicated that African Americans with diabetes may be 3 times less likely to have controlled blood pressure compared to hypertensive African Americans without type 2 diabetes, even after accounting for age and treatment intensity differences, and that the use of 3 or more antihypertensive drugs may be required to adequately achieve and maintain blood pressure control among diabetics (51),

particularly to the more stringent control level of <130/85 mmHg recommended for diabetics in JNC-VI (52). Despite this information, only 24% of the treated African American GENOA subjects with co-existent hypertension and diabetes were treated with 3 or more antihypertensive drugs, while 37% were solely prescribed monotherapy antihypertensive regimens. Although this discrepancy with treatment recommendations among diabetic subjects may point to an area for improvement in blood pressure management among this subgroup, the types of drugs prescribed were found to be relatively consistent with national guidelines (16), with 60% taking a diuretic and 35% taking a calcium channel blocker, alone or in combination, and 20 % were taking both in combination.

Low-dose thiazide diuretics and calcium channel blockers are both effective first-line agents in African Americans (53). Thiazide-type diuretics are also beneficial in hypertensive patients with diabetes, even though these agents pose a small risk for worsening hyperglycemia, and calcium channel blockers, particularly in combination, may also be effective at lowering blood pressure and reducing diabetic related cardiovascular events (16). Studies have shown the benefits of angiotensin-converting enzyme (ACE) inhibitors among diabetic patients (54). These drugs are common first-line agents in this group of patients (53), but ACE inhibitors are potentially less effective in African Americans due to low-renin and salt sensitive profiles (22, 55).

Among the treated African American GENOA subjects with diabetes, 48% were taking RAAS inhibitors, a general class that includes ACE inhibitors and angiotensin receptor blockers, in some form. This potentially reflects a tendency to treat diabetic patients with agents acting on the RAAS system, despite the perceived lack of efficacy of

these agents among African Americans compared to non-Hispanic whites. JNC-VI guidelines highlighted the ability to overcome lack of antihypertensive efficacy by RAAS blockade in African Americans and low-renin populations by increasing RAAS agent dosage and/or adding agents that activate the RAAS system, such as diuretics and calcium channel blockers, in combination (18, 56). Accordingly, 66% of the African American GENOA subjects with diabetes that were taking a RAAS inhibitor were also taking a diuretic and/or a calcium channel blocker. While this may be an encouraging sign that many clinicians are adhering to treatment guidelines, particularly in high-risk hypertensive patients, 22% of the African American GENOA subjects with diabetes that were taking a RAAS inhibitor were taking then in monotherapy form. Paying greater attention to treatment guidelines and key factors that contribute to drug effectiveness in individuals within specific subgroups of the population may be an important step towards achieving blood pressure reduction goals. However, data from a recent study suggests that prescribing patterns are not a major contributor to ethnic differences in blood pressure control (57) and other factors are certain to play contributing roles in both the lack of blood pressure control in the general population, as well as the disparities in blood pressure control that have been consistently noted between African Americans and other (particularly non-Hispanic white) racial/ethnic groups. Nonetheless, the need for adequate drug therapy, coupled with lifestyle interventions, including diet modifications and increased physical activity, is crucial among all hypertensive subjects generally, and among African Americans in particular.

The inverse relationship between SES, for which education has been a common proxy, and cardiovascular disease has been described (58) and many health disparities

between racial/ethnic groups appear to be partially explained by SES differences (59). Inverse, albeit weak, associations between SES and blood pressure have also generally been detected (60). African Americans in the GENOA study had significantly lower levels of education compared to the non-Hispanic whites. Increasing levels of education among the African American subjects were related to increased probabilities of blood pressure control, even after controlling for other cardiovascular risk factors. This effect did not appear to be present among the non-Hispanic white subjects, indicating that targeting areas of intervention indexed by SES may be effective at improving the probability of blood pressure control among African Americans, and reducing disparities in blood pressure control and cardiovascular sequelae. The effects of SES on blood pressure are likely mediated via a range of influences including dietary practices, physical activity levels, and psychosocial stressors. Access to quality health care and proper drug compliance are also likely influenced by SES differences, and numerous studies have related each of these factors to uncontrolled blood pressure (29, 61-63). Promoting the adoption of healthy lifestyles (64) and ensuring access to quality comprehensive health care are essential for blood pressure management and should constitute constructive components of a national initiative to reduce ethnic disparities in blood pressure control and cardiovascular risk (65).

Several limitations and strengths of this study warrant brief discussion. This study utilized cross-sectional data from the first phase of the GENOA study and, as such, the ability to make inferences about causality is limited. The GENOA subjects in this study were aware and treated hypertensives and the results may not be generalizable to the general hypertensive population, or moreover, the general population. Further, as the

African American and non-Hispanic white cohorts of this study were recruited from distinct metropolitan areas (Jackson, MS and Rochester, MN, respectively) the findings may not be generalizable to African Americans or non-Hispanic whites from other regions in the US. Still, many of the findings in this study reflect those derived from US representative samples (1, 4, 11). Although it is standard for many studies investigating hypertension, cross-sectional blood pressure measurements may have lead to misclassification of hypertension and/or blood pressure control status for some subjects. The standard blood pressure control definition (<140/90 mmHg) that was used in this study may have overestimated the clinical blood pressure control rate, as those with co-morbid conditions should clinically be identified as having their blood pressure controlled under a more stringent definition (<130/85 mmHg) (18). Results on the odds of age and sex adjusted blood pressure control using this more stringent definition where applicable did not significantly alter from results using the standard control definition (<140/90 mmHg) in either racial/ethnic group. Given the cross-sectional nature of this study, pre-treatment blood pressure values were not available, precluding the prospective assessment of treatment effects and efficacy of particular regimens. The study did, however, examine the influence of taking combination therapies, relative to monotherapy treatment, on the odds of blood pressure control and found no statistically significant associations in either racial/ethnic group. The definition of 'treatment' in this study only included pharmacological treatment(s) and did not incorporate other interventions such as diet and exercise. Despite this, this study's assessment of treatment based on Medi-Span coding of pharmacological agents used at baseline is more robust than other studies using treatment based on self-reports.

This bi-racially diverse study sample uniquely provided information on both African American and non-Hispanic racial/ethnic groups and allowed for crude comparisons that offered potential insights into the myriad reasons for observed health disparities in hypertension and blood pressure outcomes. It should be noted that the racial/ethnic differences in hypertension and blood pressure control outcomes noted from the comparisons that were made in this study are only valid for demonstrating variability in subgroups of the population and that etiologic inferences based on 'race' as a risk factor in observational studies are hazardous and inherently flawed (66). Despite these caveats, the results from this study lend additional support to other studies (3, 4, 8, 9, 29, 67) indicating that, while general improvements have been made, public health efforts need to remain focused on reducing the observed racial/ethnic disparities in blood pressure control among treated hypertensives. Efforts aiming to achieving goal SBP levels should be a general focus in all hypertensive patients, particularly those that are older, have co-morbid conditions, and/or are in lower SES groups, regardless of race/ethnicity. Although still disparate compared to non-Hispanic whites, blood pressure control rates among the treated African Americans in this study and similar rates recently reported for African Americans in the JHS (29) were better than the comparable rates reported for African Americans nationally (4). This suggests that focused interventions may have been effective at increasing blood pressure control among African Americans in this southern region of the US, and that, as Wyatt et al. (29) conclude, continued efforts using ethnic specific approaches could prove equally effective for African Americans from other regions and help narrow the current gap in blood pressure control and related cardiovascular events.

**Table 2.1. Characteristics of the hypertensive GENOA study subjects by race/ethnicity**

| | African American n = 1329 | non-Hispanic white n = 1129 |
|---|---|---|
| Age (years) | 60.0 (9.4)‡ | 57.6 (10.0) |
| Height (cm) | 168.3 (8.7) | 168.6 (9.3) |
| Weight (kg) | 89.7 (18.8) | 88.7 (20.0) |
| BMI (kg/m$^2$) | 31.8 (6.8)* | 31.2 (6.5) |
| Total cholesterol (mg/dL) | 206.2 (47.4)† | 211.3 (38.8) |
| HDL cholesterol (mg/dL) | 55.4 (17.9)‡ | 51.0 (16.2) |
| LDL[a] cholesterol (mg/dL) | 121.8 (42.7) | 120.7 (33.9) |
| Triglycerides (mg/dL) | 150.8 (83.1)‡ | 202.5 (106.4) |
| Age hypertension diagnosis (years) | 43.6 (10.2)‡ | 45.2 (11.5) |
| Education (years completed) | 11.7 (3.6)‡ | 13.1 (2.4) |
| Jog/walk (miles/month) | 2.8 (6.2)‡ | 6.5 (9.0) |
| Female (%) | 71‡ | 55 |
| Type 2 diabetes (%) | 26‡ | 12 |
| History of CHD (%) | 7* | 10 |
| History of CBVD (%) | 5* | 4 |
| Current smoker (%) | 18‡ | 12 |
| Alcohol consumption (%) | 31‡ | 70 |
| Married (%) | 50‡ | 80 |
| SBP (mmHg) | 142.5 (22.6)‡ | 137.9 (16.6) |
| DBP (mmHg) | 79.8 (12.9) | 80.0 (9.7) |
| Blood pressure controlled[b] (%) | 44‡ | 52 |

Quantitative variables are presented as mean (SD); categorical variables as percentages. [a] LDL values calculated by the Friedewald formula. Friedewald calculation is only valid for subjects with triglyceride levels ≤ 400 mg/dL. 30 African American and 53 non-Hispanic white subjects had triglyceride values that exceeded this validated cutpoint and, as such, LDL values were calculated for 1299 African American subjects and 1076 non-Hispanic white subjects. Blood pressure control defined as systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg. p-values for contrasts between racial/ethnic groups: *<0.05; †<0.01; ‡<0.001. BMI = body mass index; HDL = high-density lipoprotein; LDL = low-density lipoprotein; CHD = coronary heart disease; CVBD = cerebrovascular disease; SBP = systolic blood pressure; DBP = diastolic blood pressure.

**Table 2.2. Hypertension awareness, treatment, and control by baseline characteristics among African Americans**

| Category | % Sample | N | Awareness[a], n (%) | Treatment[b], n (%) | Control[c], n (%) |
|---|---|---|---|---|---|
| Overall | | 1329 | 1294 (97.4) | 1123 (86.8) | 590 (52.5) |
| Age, years | | | ‡ | | † |
| 20 - 39 | 2 | 34 | 32 (94.1) | 30 (93.8) | 18 (60.0) |
| 40 - 59 | 48 | 636 | 605 (95.1) | 525 (86.8) | 304 (57.9) |
| >=60 | 50 | 659 | 657 (99.7) | 568 (86.4) | 268 (47.2) |
| Sex | | | | ‡ | |
| Female | 71 | 942 | 917 (97.3) | 816 (89.0) | 421 (51.6) |
| Male | 29 | 387 | 377 (97.4) | 307 (81.4) | 169 (55.0) |
| BMI, kg/m2 | | | † | ‡ | |
| < 25 | 13 | 174 | 163 (93.7) | 129 (79.1) | 60 (46.5) |
| 25 to 29 | 32 | 425 | 416 (97.9) | 354 (85.1) | 190 (53.7) |
| >= 30 | 55 | 730 | 715 (97.9) | 640 (89.5) | 340 (53.1) |
| High-risk lipid profile[d] | | | ** | | |
| No | 64 | 855 | 826 (96.6) | 714 (86.4) | 378 (52.9) |
| Yes | 36 | 473 | 467 (98.7) | 408 (87.4) | 212 (52.0) |
| Type 2 diabetes | | | | ** | ‡ |
| Absent | 74 | 983 | 951 (96.7) | 811 (85.3) | 454 (56.0) |
| Present | 26 | 346 | 343 (99.1) | 312 (91.0) | 136 (43.6) |
| History of CHD | | | | † | |
| Absent | 93 | 1233 | 1198 (97.2) | 1031 (86.1) | 541 (52.5) |
| Present | 7 | 96 | 96 (100) | 92 (95.8) | 49 (53.3) |
| History of CBVD | | | | † | |
| Absent | 95 | 1257 | 1222 (97.2) | 1053 (86.2) | 556 (52.8) |
| Present | 5 | 72 | 72 (100) | 70 (97.2) | 34 (48.6) |
| Current smoker | | | | ** | |

| | | | | | |
|---|---|---|---|---|---|
| No | 82 | 1086 | 1061 (97.7) | 933 (87.9) | 489 (52.4) |
| Yes | 18 | 243 | 233 (95.9) | 190 (81.5) | 101 (53.2) |
| Alcohol consumption | | | | † | |
| No | 69 | 913 | 888 (97.3) | 789 (88.9) | 413 (52.3) |
| Yes | 31 | 416 | 406 (97.6) | 334 (82.3) | 177 (53.0) |
| Education | | | | | ** |
| >= 16 years | 17 | 226 | 220 (97.3) | 190 (86.4) | 114 (60.0) |
| >= 12 years, <16 years | 42 | 560 | 538 (96.1) | 477 (88.7) | 257 (53.9) |
| < 12 years | 41 | 543 | 536 (98.7) | 456 (85.1) | 219 (48.0) |
| Marital status | | | | | |
| Married | 50 | 666 | 648 (97.3) | 564 (87.0) | 295 (52.3) |
| Single | 50 | 663 | 646 (97.4) | 559 (86.5) | 295 (52.8) |

[a] Awareness of hypertension diagnosis among all subjects identified as hypertensive. [b] Hypertension treatment with antihypertensive medications among those aware of their hypertension diagnosis. [c] Control of blood pressure to 140/90 mmHg among those that are both aware and treated. [d] High-risk lipid profile defined as positive for one or more of the following: high-density lipoprotein (HDL) cholesterol <35 mg/dL; triglycerides >200 mg/dL; total cholesterol >240 mg/dL; total cholesterol to HDL ratio >6. p-value contrasts between baseline characteristic groups: *<0.10; **<0.05; †<0.01; ‡<0.001. BMI = body mass index; CHD = coronary heart disease; CVBD = cerebrovascular disease.

**Table 2.3. Hypertension awareness, treatment, and control by baseline characteristics among non-Hispanic whites**

| Category | % Sample | N | Awareness[a], n (%) | Treatment[b], n (%) | Control[c], n (%) |
|---|---|---|---|---|---|
| Overall | | 1129 | 1025 (90.8) | 970 (94.6) | 587 (60.5) |
| Age, years | | | † | | ‡ |
| 20 - 39 | 4 | 50 | 39 (78.0) | 35 (89.7) | 29 (82.9) |
| 40 - 59 | 54 | 604 | 550 (91.1) | 520 (94.5) | 352 (67.7) |
| >=60 | 42 | 475 | 436 (91.8) | 415 (95.2) | 206 (49.6) |
| Sex | | | ** | ** | |
| Female | 55 | 622 | 576 (92.6) | 554 (96.2) | 346 (62.5) |
| Male | 45 | 507 | 449 (88.6) | 416 (92.7) | 241 (57.9) |
| BMI, kg/m2 | | | | * | |
| < 25 | 15 | 165 | 151 (91.5) | 148 (98.0) | 92 (62.2) |
| 25 to 29 | 34 | 388 | 346 (89.2) | 329 (95.1) | 189 (57.4) |
| >= 30 | 51 | 575 | 527 (91.7) | 492 (93.4) | 305 (62.0) |
| High-risk lipid profile[d] | | | | | |
| No | 47 | 531 | 484 (91.1) | 456 (94.2) | 282 (61.8) |
| Yes | 53 | 598 | 541 (90.5) | 514 (95.0) | 305 (59.3) |
| Type 2 diabetes | | | | | * |
| Absent | 88 | 990 | 897 (90.6) | 847 (94.4) | 522 (61.6) |
| Present | 12 | 139 | 128 (90.8) | 123 (96.1) | 65 (52.8) |
| History of CHD | | | | | † |
| Absent | 90 | 1017 | 919 (90.4) | 868 (94.5) | 539 (62.1) |
| Present | 10 | 112 | 106 (94.6) | 102 (96.2) | 48 (47.1) |
| History of CBVD | | | | | |
| Absent | 96 | 1088 | 985 (90.5) | 932 (94.6) | 564 (60.5) |
| Present | 4 | 41 | 40 (97.6) | 38 (95.0) | 23 (60.5) |
| Current smoker | | | | | * |
| No | 88 | 993 | 906 (91.2) | 856 (94.5) | 508 (59.3) |

| | | | | | |
|---|---|---|---|---|---|
| Yes | 12 | 136 | 119 (87.5) | 114 (95.8) | 79 (69.3) |
| Alcohol consumption | | | | | |
| No | 30 | 334 | 306 (91.6) | 292 (95.4) | 169 (57.9) |
| Yes | 70 | 795 | 719 (90.4) | 678 (94.3) | 418 (61.7) |
| Education | | | * | | ** |
| >= 16 years | 17 | 191 | 181 (94.8) | 172 (95.0) | 116 (67.4) |
| >= 12 years, <16 years | 74 | 840 | 759 (90.4) | 718 (94.6) | 432 (60.2) |
| < 12 years | 9 | 98 | 85 (86.7) | 80 (94.1) | 39 (48.8) |
| Marital status | | | | | |
| Married | 80 | 899 | 822 (91.4) | 775 (94.3) | 470 (60.6) |
| Single | 20 | 230 | 203 (88.3) | 195 (96.1) | 117 (60.0) |

[a] Awareness of hypertension diagnosis among all subjects identified as hypertensive. [b] Hypertension treatment with antihypertensive medications among those aware of their hypertension diagnosis. [c] Control of blood pressure to 140/90 mmHg among those that are both aware and treated. [d] High-risk lipid profile defined as positive for one or more of the following: high-density lipoprotein (HDL) cholesterol <35 mg/dL; triglycerides >200 mg/dL; total cholesterol >240 mg/dL; total cholesterol to HDL ratio >6. p-value contrasts between baseline *<0.10; **<0.05; †<0.01; ‡<0.001. BMI = body mass index; CHD = coronary heart disease; CVBD = cerebrovascular

**Table 2.4. Use of antihypertensive drug class by race/ethnicity***

| | African American n=1123 | non-Hispanic white n=970 |
|---|---|---|
| Diuretic | 57%‡ (14%) | 48% (13%) |
| B-blocker | 17% (4%) | 40%‡ (16%‡) |
| Calcium channel blocker | 36%‡ (13%‡) | 21% (6%) |
| RAAS Inhibitor | 35% (9%) | 41%‡ (16%‡) |
| Other** | 23%‡ (7%‡) | 6% (2%) |
| Mono-therapy | 47% | 53%* |
| 2 of the above drugs in combination | 39% | 38% |
| 3 or more of the above drugs in combination | 14%‡ | 9% |

*Top portion of table data represent percentages of aware and treated hypertensive subjects taking each respective antihypertensive drug class as part of any regimen. Percentages using each class in mono-therapy form shown in parentheses; **Other antihypertensive class includes alpha-blockers, vasodilators, sympatholytics, and study drugs. RAAS = renin angiotensin aldosterone system. p-value contrasts between racial/ethnic groups; $p<0.05$*; $p<0.01$†; $p<0.001$‡.

**Table 2.5. Multivariable[a] predictors of combination antihypertensive treatment by race/ethnicity**

| | Relative Odds of Combination Therapy[b] in Treated Hypertensives, OR (95% CI) | |
|---|---|---|
| Category | African American (n=1123) | non-Hispanic white (n=970) |
| Age, years | 1.02**(1.01-1.03) | 1.04**(1.03-1.05) |
| Sex | | |
| Male[+] | | |
| Female | 1.12 (0.86-1.46) | 1.01 (0.78-1.31) |
| BMI, kg/m$^2$ | 1.06**(1.04-1.08) | 1.03**(1.01-1.05) |
| High-risk lipid profile[c] | | |
| No[+] | | |
| Yes | 0.95 (0.74-1.21) | 1.33**(1.02-1.72) |
| Type 2 diabetes | | |
| Absent[+] | | |
| Present | 1.71**(1.30-2.23) | 2.16**(1.44-3.23) |
| History CHD | | |
| Absent[+] | | |
| Present | 3.62**(2.15-6.10) | 1.58**(1.02-2.45) |
| History of CVBD | | |
| Absent[+] | | |
| Present | 2.05**(1.21-3.47) | 2.37**(1.15-4.90) |
| Current smoker | | |
| No[+] | | |
| Yes | 0.86 (0.63-1.19) | 1.13 (0.76-1.69) |
| Alcohol consumption | | |
| No[+] | | |
| Yes | 0.85 (0.65-1.11) | 0.72**(0.54-0.96) |
| Jog/Walk, miles/week. | 0.99 (0.97-1.01) | 1.01 (1.00-1.03) |
| Education, years | 1.02 (0.99-1.06) | 1.05 (0.99-1.11) |

| | | |
|---|---|---|
| Education | | |
| 16+ years[+] | | |
| 12 - 15 years | 0.94 (0.67-1.32) | 0.90 (0.64-1.28) |
| <12 years | 0.88 (0.62-1.25) | 0.82 (0.46-1.45) |
| Hypertension duration | | |
| ≤ 5 years[+] | | |
| > 5 years | 2.19**(1.52-3.17) | 2.31**(1.69-3.15) |
| Married | | |
| No[+] | | |
| Yes | 1.01 (0.79-1.30) | 0.62**(0.45-0.87) |

[a]All associations age and sex adjusted. Age associations adjusted for sex. Sex associations adjusted for age. All models account for sibling correlations through fitting of generalized linear mixed models. [b]Relative odds of taking 2 or more antihypertensive drugs vs. taking an antihypertensive drug as a monotherapy. [c]High-risk lipid profile defined as positive for one or more of the following: high-density lipoprotein (HDL) cholesterol <35 mg/dL; triglycerides >200 mg/dL; total cholesterol >240 mg/dL; total cholesterol to HDL ratio >6. [+]Referent; OR = odds ratio; CI = confidence interval; BMI = body mass index; CHD = coronary heart disease; CVBD = cerebrovascular disease. **P<0.05; *P<0.10.

**Table 2.6. Multivariable[a] predictors of blood pressure control by race/ethnicity**

| | Relative Odds of Blood Pressure Control[b] in Treated Hypertensives, OR (95% CI) | |
|---|---|---|
| Category | African American (n=1123) | non-Hispanic white (n=970) |
| Age, years | 0.97**(0.95-0.98) | 0.95**(0.94-0.97) |
| Sex | | |
| Male+ | | |
| Female | 0.82(0.63-1.08) | 1.23 (0.94-1.61) |
| BMI, kg/m$^2$ | 1.00 (0.98-1.02) | 0.99 (0.97-1.02) |
| High-risk lipid profile[c] | | |
| No+ | | |
| Yes | 0.99 (0.77-1.27) | 0.90(0.69-1.18) |
| Type 2 diabetes | | |
| Absent+ | | |
| Present | 0.62**(0.47-0.82) | 0.76 (0.51-1.13) |
| History CHD | | |
| Absent+ | | |
| Present | 1.03 (0.66-1.61) | 0.71 (0.46-1.11) |
| History of CVBD | | |
| Absent+ | | |
| Present | 0.83 (0.50-1.36) | 1.26 (0.63-2.51) |
| Current smoker | | |
| No+ | | |
| Yes | 0.93 (0.67-1.29) | 1.58**(1.03-2.43) |
| Alcohol consumption | | |
| No+ | | |
| Yes | 0.90 (0.68-1.18) | 1.13 (0.84-1.52) |

| | | |
|---|---|---|
| Jog/Walk, miles/week. | 1.00 (0.98-1.02) | 1.00 (0.98-1.01) |
| Education, years | 1.04**(1.00-1.08) | 1.01 (0.95-1.07) |
| Education | | |
| 16+ years[+] | | |
| 12 - 15 years | 0.73*(0.51-1.04) | 0.83 (0.57-1.21) |
| <12 years | 0.72*(0.49-1.04) | 0.77 (0.42-1.40) |
| Hypertension duration | | |
| ≤ 5 years[+] | | |
| > 5 years | 0.62**(0.42-0.90) | 0.70**(0.51-0.97) |
| Number of antihypertensive medications | | |
| Monotherapy[+] | | |
| 2 medications | 0.98 (0.75-1.27) | 1.22 (0.92-1.63) |
| 3 or more medications | 1.03 (0.73-1.46) | 0.81 (0.50-1.31) |
| Married | | |
| No[+] | | |
| Yes | 0.89 (0.69-1.15) | 1.08 (0.77-1.52) |

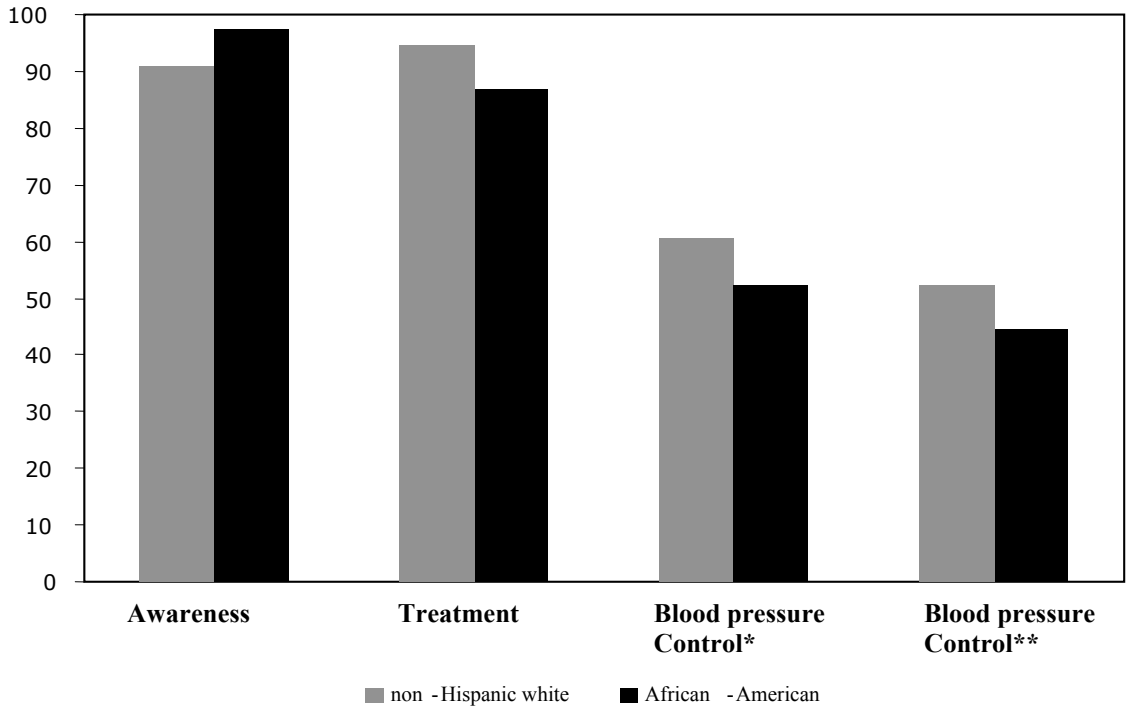
[a]All associations age and sex adjusted. Age associations adjusted for sex. Sex associations adjusted for age. All models account for sibling correlations through fitting of generalized linear mixed models. [b]Relative odds of having blood pressure controlled to <140/90 mmHg. [c]High-risk lipid profile defined as positive for one or more of the following: high-density lipoprotein (HDL) cholesterol <35 mg/dL; triglycerides >200 mg/dL; total cholesterol >240 mg/dL; total cholesterol to HDL ratio >6. [+]Referent; OR= odds ratio; CI = confidence interval; BMI = body mass index; CHD = coronary heart disease; CVBD = cerebrovascular disease. p-value **P<0.05; *P<0.10

**Table 2.7. Blood pressure control[a] by race/ethnicity among GENOA subjects with treated hypertension (n=2093)**

| | Unadjusted OR (95% CI) | Model 1 OR (95% CI) | Model 2 OR (95% CI) | Model 3 OR (95% CI) |
|---|---|---|---|---|
| non-Hispanic white | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) |
| African American | 0.69 (0.57-0.84) | 0.77 (0.63-0.93) | 0.81 (0.66-0.99) | 0.84 (0.68-1.03) |

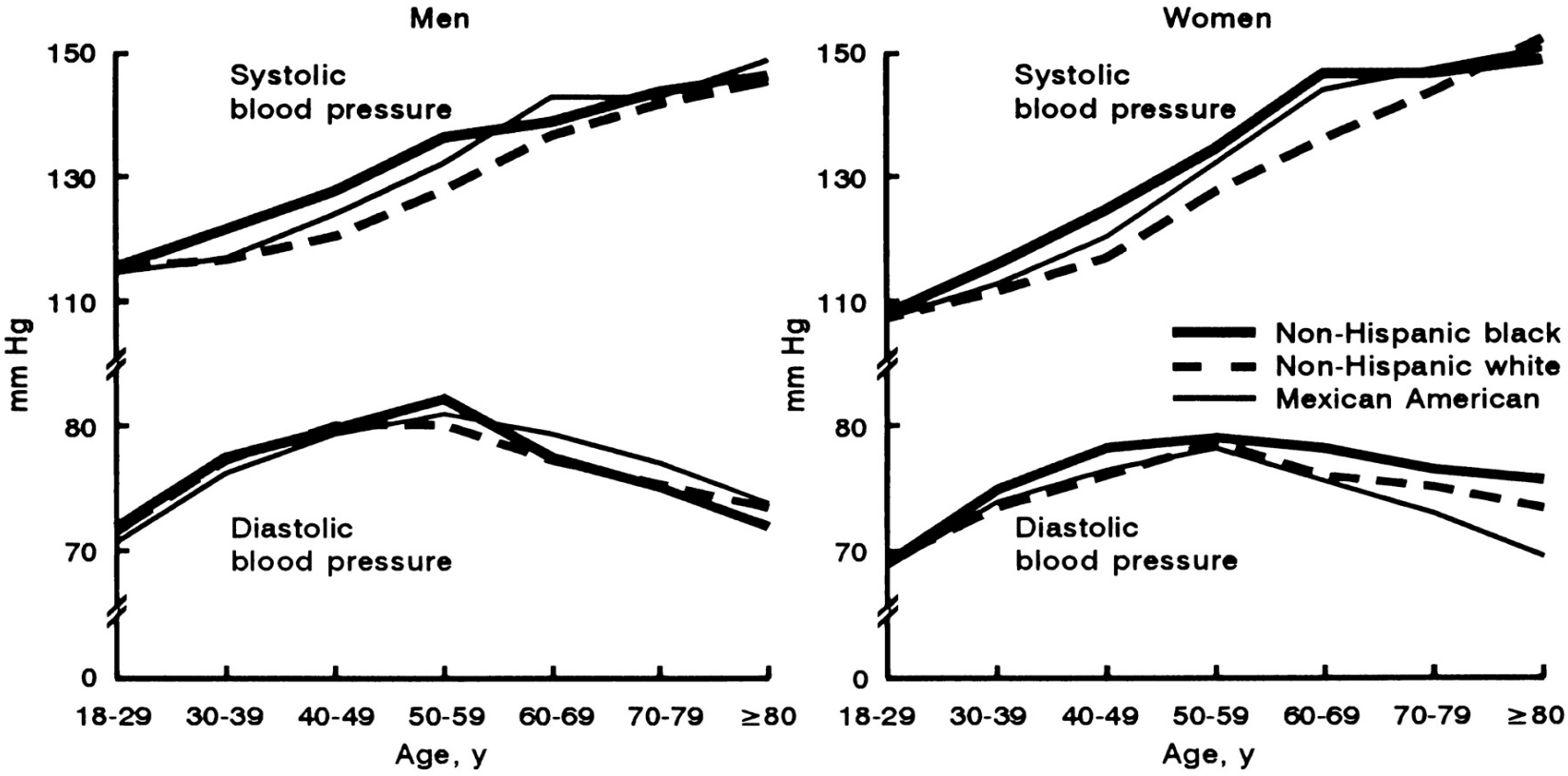
[a] Blood pressure controlled to <140/90 mmHg. OR = odds ratio; CI = confidence interval; ref = referent group.
Model 1 includes age and sex.
Model 2 includes Model 1 and BMI, type 2 diabetes, history of coronary heart disease, and history of cerebrovascular disease.
Model 3 includes Model 2 and number of years of education completed.
All models account for sibling correlations through fitting of generalized linear mixed models.

**Figure 2.1. Hypertension status in the GENOA study**




*Blood pressure control among subjects that were aware of their hypertension diagnosis and currently taking antihypertensive medication(s); ** Blood pressure control among all hypertensive subjects, regardless of awareness and/or treatment status.

**Figure 2.2. Mean systolic and diastolic blood pressures by age and race/ethnicity for men and women, US population 18 years of age and older***




*From Burt, V. L. et al. Hypertension 1995; 25:305-313.

**Appendix 2.1 Multivariable[a] predictors of systolic blood pressure in GENOA study**

| **African American** | | | | | |
|---|---|---|---|---|---|
| Covariate | N | Coef. | 95% CI | p-value | Cross-validated $R^2$ |
| Age (years) | 1123 | 0.510 | (0.367, 0.652) | **0.0000** | **0.0446** |
| Female sex | 1123 | 2.403 | (-0.511, 5.317) | 0.1066 | 0.0017 |
| BMI ($kg/m^2$) | 1123 | 0.074 | (-0.12, 0.268) | 0.4531 | -0.0007 |
| Total cholesterol (mg/dL) | 1122 | 0.024 | (-0.003, 0.052) | 0.0821 | 0.0023 |
| HDL (mg/dL) | 1122 | 0.064 | (-0.011, 0.138) | 0.0959 | 0.0017 |
| LDL (mg/dL) | 1097 | 0.020 | (-0.011, 0.051) | 0.2064 | 0.0010 |
| Triglycerides (mg/dL) | 1122 | 0.005 | (-0.011, 0.020) | 0.5629 | -0.0004 |
| LOG triglycerides (mg/dL) | 1122 | 1.982 | (-5.009, 8.973) | 0.5787 | -0.0004 |
| Type 2 diabetes | 1123 | 5.459 | (2.577, 8.342) | **0.0002** | **0.0112** |
| History of CHD | 1123 | -1.287 | (-6.012, 3.438) | 0.5936 | -0.0001 |
| History of CBVD | 1123 | 2.982 | (-2.333, 8.297) | 0.2720 | 0.0004 |
| Current smoker | 1123 | 1.389 | (-2.070, 4.849) | 0.4315 | 0.0000 |
| Alcohol consumption | 1123 | 0.534 | (-2.313, 3.381) | 0.7132 | -0.0005 |
| Jog/walk (miles/week) | 1123 | -0.067 | (-0.283, 0.149) | 0.5431 | -0.0008 |
| Education (years) | 1123 | -0.522 | (-0.895, -0.149) | **0.0063** | **0.0062** |
| Parental history of hypertension | 1123 | 2.335 | (-0.677, 5.347) | 0.1292 | 0.0020 |
| Married | 1123 | 1.318 | (-1.269, 3.904) | 0.3185 | 0.0004 |
| Hypertension duration ≥ 5 years | 1114 | 3.186 | (-0.477-6.849) | 0.0888 | 0.0016 |
| **non-Hispanic white** | | | | | |
| Covariate | N | Coef. | 95% CI | p-value | Cross-validated $R^2$ |
| Age (years) | 970 | 0.486 | (0.379, 0.592) | **0.0000** | **0.0806** |
| Female sex | 970 | 0.043 | (-1.951, 2.036) | 0.9667 | -0.0008 |
| BMI ($kg/m^2$) | 969 | 0.187 | (0.034, 0.340) | **0.0170** | **0.0052** |
| Total cholesterol (mg/dL) | 970 | 0.015 | (-0.011, 0.041) | 0.2565 | 0.0012 |
| HDL (mg/dL) | 970 | -0.008 | (-0.069, 0.054) | 0.8087 | -0.0005 |

| | | | | | |
|---|---|---|---|---|---|
| LDL (mg/dL) | 924 | 0.007 | (-0.024, 0.038) | 0.6418 | -0.0002 |
| Triglycerides (mg/dL) | 970 | 0.011 | (0.001, 0.021) | **0.0274** | 0.0049 |
| LOG triglycerides (mg/dL) | 970 | 5.698 | (0.524, 10.872) | **0.0314** | 0.0048 |
| Type 2 diabetes | 970 | 2.793 | (-0.173, 5.758) | 0.0656 | 0.0031 |
| History of CHD | 970 | 2.192 | (-1.021, 5.405) | 0.1818 | 0.0007 |
| History of CBVD | 970 | -0.650 | (-5.733, 4.433) | 0.8021 | -0.0010 |
| Current smoker | 970 | -1.607 | (-4.666, 1.452) | 0.3038 | -0.0006 |
| Alcohol consumption | 970 | -1.428 | (-3.594, 0.738) | 0.1970 | 0.0013 |
| Jog/walk (miles/week) | 970 | 0.031 | (-0.079, 0.140) | 0.5828 | -0.0004 |
| Education (years) | 970 | -0.057 | (-0.487, 0.374) | 0.7966 | -0.0005 |
| Parental history of hypertension | 904 | 2.333 | (-0.968, 5.635) | 0.1668 | 0.0020 |
| Married | 970 | -0.389 | (-2.849, 2.071) | 0.7568 | -0.0005 |
| Hypertension duration ≥ 5 years | 970 | 2.325 | (0.165, 4.485) | **0.0354** | 0.0032 |

[a]All associations are age and sex adjusted. Age associations adjusted for sex. Sex associations adjusted for age. Boldface indicates p-value <0.05 and Cross-validated $R^2$ >0.005 respectively. BMI = body mass index; HDL = high-density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol; CHD = coronary heart disease; CBVD = cerebrovascular disease.

**Appendix 2.2 Multivariable[a] predictors of diastolic blood pressure in GENOA study**

| **African American** | | | | | |
|---|---|---|---|---|---|
| Covariate | N | Coef. | 95% CI | p-value | Cross-validated $R^2$ |
| Age (years) | 1123 | -0.346 | (-0.424, -0.268) | **0.0000** | **0.0688** |
| Female sex | 1123 | -2.970 | (-4.542, -1.397) | **0.0002** | **0.0119** |
| BMI ($kg/m^2$) | 1123 | -0.095 | (-0.200, 0.010) | 0.0773 | 0.0034 |
| Total cholesterol (mg/dL) | 1122 | 0.026 | (0.012, 0.041) | **0.0005** | **0.0094** |
| HDL (mg/dL) | 1122 | 0.028 | (-0.012, 0.069) | 0.1685 | 0.0010 |
| LDL (mg/dL) | 1097 | 0.029 | (0.012, 0.046) | **0.0008** | **0.0093** |
| Triglycerides (mg/dL) | 1122 | -0.001 | (-0.009, 0.008) | 0.8577 | -0.0003 |
| LOG triglycerides (mg/dL) | 1122 | -0.195 | (-3.972, 3.581) | 0.9193 | -0.0006 |
| Type 2 diabetes | 1123 | -0.897 | (-2.461, 0.668) | 0.2618 | 0.0004 |
| History of CHD | 1123 | -2.268 | (-4.812, 0.276) | 0.0812 | 0.0031 |
| History of CBVD | 1123 | 0.186 | (-2.672, 3.043) | 0.8986 | -0.0006 |
| Current smoker | 1123 | 0.025 | (-1.841, 1.891) | 0.9790 | -0.0005 |
| Alcohol consumption | 1123 | 1.164 | (-0.373, 2.701) | 0.1383 | 0.0012 |
| Jog/walk (miles/week) | 1123 | 0.050 | (-0.066, 0.167) | 0.3959 | 0.0004 |
| Education (years) | 1123 | -0.198 | (-0.402, 0.006) | 0.0576 | 0.0017 |
| Parental history of hypertension | 1123 | 1.346 | (-0.293, 2.948) | 0.1081 | 0.0021 |
| Married | 1123 | 0.691 | (-0.702, 2.085) | 0.3313 | 0.0010 |
| Hypertension duration ≥ 5 years | 1114 | 1.770 | (-0.203, 3.744) | 0.0793 | 0.0023 |
| **non-Hispanic white** | | | | | |
| Covariate | N | Coef. | 95% CI | p-value | Cross-validated $R^2$ |
| Age (years) | 970 | -0.284 | (-0.344, -0.224) | **0.0000** | **0.0844** |
| Female sex | 970 | -3.831 | (-4.942, -2.721) | **0.0000** | **0.0446** |
| BMI ($kg/m^2$) | 969 | -0.017 | (-0.103, 0.069) | 0.6928 | -0.0001 |
| Total cholesterol (mg/dL) | 970 | 0.030 | (0.015, 0.044) | **0.0001** | **0.0182** |
| HDL (mg/dL) | 970 | -0.002 | (-0.037, 0.032) | 0.8890 | -0.0010 |

| | | | | | |
|---|---|---|---|---|---|
| LDL (mg/dL) | 924 | 0.033 | (0.016, 0.050) | **0.0002** | **0.0150** |
| Triglycerides (mg/dL) | 970 | 0.005 | (0.000, 0.011) | 0.0562 | 0.0034 |
| LOG triglycerides (mg/dL) | 970 | 3.201 | (0.306, 6.095) | **0.0307** | 0.0037 |
| Type 2 diabetes | 970 | -1.993 | (-3.643, -0.343) | **0.0184** | **0.0058** |
| History of CHD | 970 | -1.145 | (-2.934, 0.643) | 0.2100 | 0.0010 |
| History of CBVD | 970 | -1.950 | (-4.778, 0.878) | 0.1771 | 0.0009 |
| Current smoker | 970 | -0.561 | (-2.265, 1.143) | 0.5191 | -0.0006 |
| Alcohol consumption | 970 | -0.055 | (-1.265, 1.155) | 0.9288 | -0.0009 |
| Jog/walk (miles/week) | 970 | 0.044 | (-0.017, 0.105) | 0.1556 | 0.0006 |
| Education (years) | 970 | 0.013 | (-0.229, 0.255) | 0.9171 | -0.0006 |
| Parental history of hypertension | 904 | 1.641 | (-0.226, 3.508) | 0.0856 | 0.0019 |
| Married | 970 | -0.049 | (-1.419, 1.321) | 0.9439 | -0.0009 |
| Hypertension duration ≥ 5 years | 970 | 1.169 | (-0.037, 2.374) | 0.0581 | 0.0024 |

[a]All associations are age and sex adjusted. Age associations adjusted for sex. Sex associations adjusted for age. Boldface indicates p-value <0.05 and Cross-validated $R^2$ >0.005 respectively. BMI = body mass index; HDL = high-density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol; CHD = coronary heart disease; CBVD = cerebrovascular disease.

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# Chapter 3

## Investigating the Influence of Neighborhood Socioeconomic Status on the Treatment and Control of Hypertension in African Americans in the Genetic Epidemiology Network of Arteriopathy (GENOA) Study

## INTRODUCTION

Individual socioeconomic status (SES), commonly quantified by education, income and occupation, is a key determinant of health status and has shown consistent, generally inverse, relationships with cardiovascular disease (CVD), CVD mortality, and CVD risk factors, including hypertension (1). Consistent with this, findings discussed in Chapter 2 of this dissertation suggested that increasing individual education was significantly associated with decreases in quantitative systolic blood pressure (SBP) levels and increases in the relative odds of blood pressure control (<140/90 mmHg) among African Americans. In addition to individual SES, interest in the effects of contextual attributes of neighborhoods and other area-based measures, independent of individual-level attributes, on health outcomes has grown in recent years (2). Numerous studies have identified significant associations between neighborhood socioeconomic environment and coronary heart disease incidence (3-7), stroke risk (8), and blood pressure outcomes (9-13). Many of these and other studies have documented that area characteristics may provide additional information about social inequalities in health that are not fully captured by individual level data.

A majority of the neighborhood effects studies of hypertension outcomes have

focused on quantitative blood pressure measures, hypertension prevalence, and/or hypertension incidence. One previous study examined the influence of neighborhood socioeconomic environment in Chicago neighborhoods on quantitative blood pressure values, hypertension prevalence, as well as awareness, treatment, and control of hypertension, and concluded that residential contexts may play a role in accounting for racial/ethnic and socioeconomic disparities in hypertension prevalence and awareness, but not in the treatment or control of hypertension (12). The central aim of this chapter was to further examine the potential influence of neighborhood socioeconomic environment on quantitative blood pressure measures, as well as the treatment and control of hypertension. I hypothesized that, even after adjustment for other individual-level factors, subjects residing in socioeconomically disadvantaged neighborhoods would have higher quantitative blood pressure measures, would be less likely to be treated with multiple antihypertensive medications, and would be less likely to have their blood pressure controlled to clinical recommendations (<140/90 mmHg) (14), compared to subjects residing in more socioeconomically advantaged neighborhoods.

## METHODS

### Study Population

In 1995, the National Heart, Lung and Blood Institute (NHLBI) established The Family Blood Pressure Program (FBPP) to assess the genetic influence on inter-individual blood pressure variation, hypertension, and hypertensive target organ damage. One of the four networks established by the NHLBI to meet this objective is the Genetic Epidemiology Network of Arteriopathy (GENOA). GENOA field centers in Jackson, MS, Starr County, TX, and Rochester, MN recruited hypertensive African American,

Hispanic, and non-Hispanic white sibships, respectively, for linkage and family-based association studies. Subject were diagnosed with hypertension if they had a previous clinical diagnosis of hypertension by a physician with current antihypertensive treatment or an average SBP >=140 mmHg and/or an average diastolic blood pressure (DBP) >=90 mmHg.

In Rochester, MN and Jackson, MS, recruitment was restricted to sibships that contained a minimum of two individuals diagnosed with essential hypertension before the age of 60. Once this criterion was met, the entire sibship was invited to participate in the study. As the prevalence of diabetes among Mexican-Americans is high, the Starr County recruitment was restricted to Mexican-American sibships containing at least two individuals diagnosed with type-2 diabetes (15). Data was collected through personal interviews, and physical and laboratory examinations. The initial phase of the GENOA study took place from September 1995 through June 2001 (16).

The study presented here focuses on the hypertensive subjects from the Jackson, MS cohort that were both aware of their hypertension status and taking antihypertensive medication(s) to lower blood pressure. Although a majority of the subjects in this cohort were diagnosed as hypertensive, a number of the sibship members invited to participate were identified as normotensive during the baseline examination and have been excluded from this analysis. Other exclusion criteria included secondary hypertension, alcoholism or drug abuse, pregnancy, insulin-dependent diabetes, or active malignancy. Of the 1854 African American subjects enrolled in the study, 1123 (61%) subjects were identified as having essential hypertension and were taking antihypertensive medication(s), conditional upon being aware of their hypertension status. Of these subjects, 1049 (93%)

had valid addresses that were successfully geocoded to the census tract level. An additional 101 of these subjects were excluded from the analyses for residing outside of the tri-county Jackson, MS area (i.e. - Hinds, Madison, or Rankin counties) (n=37), or residing in a census tract within the tri-county Jackson, MS area that was represented by fewer than 5 study subjects (n=64). The final analytic sample for this study contained 948 aware and treated, hypertensive, African American subjects from 48 census tracts within the tri-county Jackson, MS geographic area.

**Covariates**

Trained interviewers asked subjects standard questions on numerous factors, including sociodemographic, lifestyle, behavioral, and cardiovascular health history. Age in years was assessed on the baseline examination date. Education was defined as the total number of years of education completed. Height was measured by stadiometer, weight by electronic balance, and body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Diabetes was defined as having a fasting glucose level $\geq$ 126 mg/dL or currently being treated with insulin or oral agents.

**Blood Pressure Readings**

Blood pressure measurements were made with random zero sphygmomanometers and cuffs appropriate for arm size. Three readings were taken in the right arm after the subject rested in the sitting position for at least five minutes according to the Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7, 2003) guidelines (14). The SBP and DBP values were determined by the first and fifth phase Korotkoff sounds, respectively, and the last two blood pressure readings were averaged for the analyses. The diagnosis of

hypertension was established based on blood pressure levels measured at the study visit (≥140/90 mmHg), or a prior diagnosis of hypertension and current treatment with antihypertensive medications.

**Antihypertensive Medications**

Based on lists of all antihypertensive medications available in the US each prescription antihypertensive drug recorded at the study visit was assigned a code number corresponding to the first 6 digits of the Medi-Span Generic Product Identifier. This number, which identifies pharmacologically equivalent drug products, was used to categorize agents with similar mechanisms of antihypertensive action.

**Blood Pressure Awareness, Treatment and Control**

Subjects were considered to be "aware" of their hypertension status if they were (a) defined as hypertensive, and (b) answered yes to the question, "Have you ever been told by a physician that you have high blood pressure or hypertension?" Conditional upon being hypertensive and aware of their hypertension status, subjects were considered to be "treated" if they answered yes to the questions, "Has medication ever been prescribed by a physician to lower your blood pressure?" and "During the last month, have you used any medication that was prescribed or recommended by a physician?" The number of prescribed antihypertensive medications was tallied for each subject. Subjects taking only one prescribed antihypertensive medication were defined as being treated with a monotherapy regimen, while those taking two or more prescribed antihypertensive medications were defined as being treated with a combination therapy regimen. Official guidelines propose that patients with a SBP ≥ 140 mmHg or DBP ≥ 90 mmHg be considered as hypertensive (14, 17). Accordingly, in this study controlled

blood pressure was defined as SBP < 140 mmHg and DBP < 90 mmHg for a treated subject with hypertension. If either one, or both, of the two requirements were not met, a hypertensive subject's blood pressure was defined as uncontrolled.

**Addresses and Geocoding**

Home addresses were assessed and recorded at baseline examination of the GENOA study. Available, valid addresses were geocoded to the census tract level based on US Census 2000 tract definitions, using the Federal Financial Institutions Examination Council (FFIEC) Geocoding System (18).

**US Census Data**

Census tracts are subdivisions of a county. They generally have between 2,500 and 8,000 residents, and, when first delineated, are designed to be homogeneous with respect to population characteristics, economic status, and living conditions. Summary File 3 was used to gather neighborhood socioeconomic indicator variables. Summary File 1 was used to assess total race tallies by tract and subsequently generate a tract-level percent African American variable that served as a racial composition proxy.

**Neighborhood Socioeconomic Indicators and Neighborhood Summary Score**

US census tracts were used as neighborhood proxies and data from the US Census 2000 was used to obtain measures of the socioeconomic characteristics of each subject's neighborhood (i.e.- census tract) of residence. Previous factor analyses of census derived socioeconomic indicators have highlighted the following six variables that reflect dimensions of income/wealth, education, and occupation: annual median household income; median value of occupied housing units; percentage of households receiving interest, dividends, or net rental income; percentage of adults who completed high school;

percentage of adults who completed college; and percentage of employed adults in executive, managerial, or professional occupations (3). Based on previous methods (3), these six indicator variables were combined to construct neighborhood summary scores (NSS). Briefly, for each census-derived indicator variable, a mean and standard deviation (SD) was calculated across the 48 census tracts represented in the study. Z scores for each census tract were estimated for each of the census-derived variables by subtracting the overall mean (across all 48 census tracts) from each respective census tract and dividing by the SD. The z scores for each of the six census-derived variables were then summed to construct the NSS. The NSS for the 48 census tracts represented in the analytical sample ranged from -8.6 to 14.6 (see Table 3.2), with increasing NSS representing increasing neighborhood-level socioeconomic advantage. Investigation of the distribution of these census-derived indicator variables in this study revealed skewed distributions for annual median household income and median value of occupied housing units. As such, these variables were log transformed to approximate normal distributions, prior to constructing the NSS. The constructed NSS was used as the primary indicator of neighborhood-level socioeconomic status in this study. Additionally, log transformed median annual household income, percentage of poverty, and percentage of African American residential composition were also separately investigated to determine the potential influence of neighborhood context on quantitative blood pressure levels, blood pressure treatment, and blood pressure control. Percentage of poverty was analyzed based on a constructed "poor neighborhood" variable, where a neighborhood was defined as poor if the percentage of poverty was greater than 25%, and more socioeconomically

advantaged otherwise. Individual-level education was used as a measure of individual socioeconomic position.

**Statistical Analysis**

There is an inherent organizational structure that extends from biological components that comprise individuals to higher order groupings of individuals, such as families and neighborhoods, to even higher order classifications of such groupings, such as counties and states. Within this natural organizational structure, a multitude of nesting structures arises. In order to retain such data structures, multilevel analysis is a useful approach, as all available data is not collapsed to the individual-level or aggregated to the group-level. In addition to retaining the multilevel structure of data, multilevel analysis permits simultaneous examination of the effects of individual- and group-level characteristics on individual-level outcomes, controls for correlations within groups by modeling intercepts (as well as coefficients) as random, and allows for examination of both inter-individual (within-group) and inter-group (between-group) variation [46].

The analytic study sample had a natural hierarchical structure, with 948 subjects nested within 48 neighborhoods (defined as US Census 2000 tracts). Given this data structure, multilevel models with a random intercept for each neighborhood were fit to examine the associations of neighborhood socioeconomic characteristics with continuous blood pressure measures, before and after adjustment for individual-level variables. A series of model types were fit: models with a neighborhood-level variable only (i.e.- unadjusted for individual-level variables); and models with both individual-level variables (including age, gender, BMI, type 2 diabetes, and education) and neighborhood-level variables.

The first (individual) level of the model type including individual and neighborhood variables took the following form:

$$Y_{ij} = \beta_{0j} + \beta_{1j}age_{ij} + \beta_{2j}gender_{ij} + \beta_{3j}BMI_{ij} + \beta_{4j}diabetes_{ij} + \beta_{5j}education_{ij} + \varepsilon_{ij}, \quad (1)$$

where $Y_{ij}$ represents the predicted quantitative blood pressure outcome for the $i^{th}$ individual in the $j^{th}$ neighborhood; $\beta_{0j}$ is the intercept specific to the $j^{th}$ neighborhood; $\beta_{1j,}$ $\beta_{2j,}$ $\beta_{3j,}$ $\beta_{4j}$ , and $\beta_{5j}$ are the individual level, fixed effects of age, gender, BMI, diabetes, and education, respectively, that are specific to the $j^{th}$ neighborhood; and $\varepsilon_{ij}$ represents the individual level error for the $i^{th}$ individual in the $j^{th}$ neighborhood. Individual-level errors are assumed to be independent and normally distributed ($\varepsilon_{ij} \sim N(0,\sigma^2)$).

In the second (neighborhood) level, the coefficients listed in model equation (1) were modeled as a function of neighborhoods as follows:

$$\beta_{0j} = \gamma_{00} + \gamma_{01}NSS_j + U_{oj}$$

$$\beta_{1j} = \gamma_{10}$$

$$\beta_{2j} = \gamma_{20}$$

$$\beta_{3j} = \gamma_{30}$$

$$\beta_{4j} = \gamma_{40}$$

$$\beta_{5j} = \gamma_{50}, \quad (2)$$

where $\gamma_{00}$ represents the common intercept across neighborhoods; $\gamma_{01}$ is the fixed effect of the $j^{th}$ neighborhood socioeconomic summary score; $\gamma_{10}$, $\gamma_{20}$, $\gamma_{30,}$ $\gamma_{40,}$ $\gamma_{50}$ are the common

slopes of age, gender, BMI, diabetes, and education, respectively, across neighborhoods; and $U_{oj}$ is a macro error, assumed to be independent and normally distributed ($U_{oj} \sim N(0,\tau_{00})$), that measures the unique deviation of each neighborhood intercept from the common intercept ($\gamma_{00}$). Applying substitution to combine model equations (1) and (2) yields the full multilevel model form:

$$Y_{ij} = \gamma_{00} + \gamma_{01}NSS_j + \gamma_{10}agej + \gamma_{20}gender_{ij} + \gamma_{30}BMI_{ij} + \gamma_{40}diabetes_{ij} + \gamma_{50}education_{ij} + U_{0j} + \varepsilon_{ij}.$$

A similar modeling strategy was employed to investigate the dichotomous hypertension outcomes (blood pressure combination treatment and blood pressure control). Given the non-normal distribution of errors when considering dichotomous outcomes, logistic multilevel models were used to assess the odds of these hypertension outcomes. Models were fitted in R (19) using the "lme" function for quantitative outcomes (SBP and DBP) and the "glmm" function for dichotomous outcomes (blood pressure combination treatment and blood pressure control).

**RESULTS**

Select characteristics of the study sample are presented in Table 3.1. The mean age of the subjects was 61 years of age. Females comprised 73% of the subjects, while diabetics comprised 28%. The subjects were generally obese (mean BMI = 32), and on average completed less than 11.5 years of education.

The median number of subjects per census tract was 11 (range, 5 – 92). The distributions of the selected, US Census derived, neighborhood socioeconomic indicators, as well as the constructed NSS, are presented in Table 3.2. The range of the NSS across

the 48 census tracts included in the present study was -8.6 to 14.6. Compared to men, women had slightly lower mean NSS (p=0.035). Individual education level demonstrated a highly significant, graded positive association with NSS, with subjects who had completed 16 or more years of education having NSS that were on average 4.05 points higher compared to those who had completed less than 12 years of education. Compared to subjects that were between 20 and 39 years of age, subjects that were between 40 and 59 had higher NSS, while subjects that were 60 or older had lower NSS, although neither of these differences reached statistical significance. NSS did not differ by obesity or diabetes status. The median percentage of individuals per census tract living in poverty was 30% (interquartile range, 21-37). The median percentage of African American residents per census tract was 97% (interquartile range, 92-98), indicating that the racial composition across the 48 census tracts investigated was notably homogeneous.

**Neighborhood Socioeconomic Summary Score**

Table 3.3 presents the associations between NSS and SBP, before and after adjustment for individual-level variables. Modeled continuously and unadjusted for individual level variables (Model 1), a one unit increase NSS was statistically significantly associated with a –0.40 mmHg decrease in SBP (p=0.012). Upon additional adjustment for age, sex, BMI, and diabetes (Model 2), the association between NSS and SBP was attenuated and lost statistical significance. Further adjustment for individual education (Model 3) attenuated the association even further and the association remained non-significant. In a separate model, unadjusted for individual variables, that divided the NSS into quintiles, a graded increase in SBP was noted from the highest to lowest quintile. Only the difference between the highest and lowest NSS quintiles reached

statistical significance, with subjects with NSS in the lowest quintile having SBP values 6.85 mmHg higher than those with NSS in the highest quintile (p=0.007). Upon additional adjustment for individual age, sex, BMI, and diabetes, the difference in SBP values between subjects in the highest and lowest NSS quintiles was attenuated (3.95 mmHg higher in subjects in the lowest quintile), yet remained marginally significant (p=0.10). This difference was attenuated even further with additional adjustment for individual education attainment, and resulted in no significant differences in SBP values for any of the NSS quintiles, relative to the highest quintile. No statistically significant associations between NSS and DBP were detected before (Model 1, Table 3.4) or after (Models 2 and 3, Table 3.4) adjustment for individual-level variables.

Table 3.5 presents the association of NSS with taking antihypertensive medications in combination therapy form (versus taking an antihypertensive medication as part of a monotherapy regimen). After adjustment for age, sex, BMI, and diabetes (Model 2), NSS was statistically significantly associated with increased odds of taking 2 or more antihypertensive medications that were prescribed to lower blood pressure (OR=1.03, p=0.044). The magnitude and direction of this association remained upon additional adjustment for individual education (Model 3), however the association was only marginally statistically significant (OR=1.03, p=0.084). No statistically significant associations were detected between NSS and blood pressure control, before (Model 1, Table 3.6) or after (Models 2 and 3, Table 3.6) adjustment for individual-level variables.

**Median Household Income, Poor Neighborhood of Residence, and Neighborhood Racial Composition**

Appendices 3.1-3.4 list the associations between (log) median household income and SBP, DBP, combination antihypertensive therapy, and blood pressure control, respectively. Of note, increasing (log) median household income at the neighborhood level was statistically significantly associated with decreasing SBP, unadjusted (Model 1, Appendix 3.1) for individual-level variables (p=0.006). Additional adjustment for individual-level variables (Models 2 and 3, Appendix 3.1) resulted in no statistically significant association of census tract level (log) median household income with SBP. Log-transformed median household income at the neighborhood level was also statistically significantly associated with increased odds of taking 2 or more prescribed antihypertensive medications to lower blood pressure, even after adjustment for age, sex, BMI, and diabetes (Model 2, Appendix 3.3), and additional adjustment for individual education (Model 3, Appendix 3.3).

62% of the study subjects were residing in a neighborhood that was defined as "poor" (i.e.- a neighborhood with greater than 25 % poverty). Table 3.7 presents the distributions of the types of antihypertensive medications prescribed by neighborhood of residence poverty status. Appendices 3.5-3.8 list the associations between poor neighborhood of residence and SBP, DBP, combination antihypertensive therapy, and blood pressure control, respectively. Poor neighborhood of residence was statistically significantly associated with increased SBP values (4.5 mmHg higher than those residing in more socioeconomically advantaged neighborhoods), before adjustment for individual-level variables (Model 1, Appendix 3.5) (p=0.005). This association was attenuated, yet remained marginally statistically significant (p=0.071) upon adjustment for age, sex, BMI, and diabetes (Model 2, Appendix 3.5), and attenuated further and fell out of

statistical significance (p=0.113) with the additional adjustment for individual education (Model 3, Appendix 3.5). Although the distributions of the types of antihypertensive medications prescribed did not differ significantly by neighborhood poverty (Table 3.7), residing in a poor neighborhood was statistically significantly associated with a decreased odds of being treated with 2 or more prescribed antihypertensive medications to lower blood pressure, after adjustment for age, sex, BMI, and diabetes (Model 2, Appendix 3.7) (OR=0.71, p=0.019). This association remained, even after additional adjustment for individual education (Model 3, Appendix 3.7) (OR=0.72, p = 0.03). No statistically significant associations with quantitative DBP values or blood pressure control were detected in any models using either (log) median household income (Appendices 3.2 and 3.4, respectively) or poor neighborhood of residence (Appendices 3.6 and 3.8, respectively) as the neighborhood-level independent variable.

Models, unadjusted and adjusted for individual-level variables, were fit for all outcomes (SBP, DBP, combination therapy, and blood pressure control) using % African American residents per neighborhood as the neighborhood-level independent variable. This racial composition variable was investigated to explore the potential mechanisms, for example racial segregation, that may influence hypertension outcomes. No statistically significant associations were detected between % African American residents per neighborhood and any of the hypertension outcomes, before or after adjustment for individual-level variables (results not shown). Although racial composition may exert important contextual effects on hypertension outcomes through a variety of mechanisms, the high degree of racial homogeneity (97% African American) across the neighborhoods

investigated in this study limited the ability to thoroughly investigate such potential effects.

**DISCUSSION**

The main aim of this study was to determine the extent to which neighborhood socioeconomic environment influenced blood pressure levels, as well as the probabilities of more aggressive antihypertensive pharmacological treatment and blood pressure control, after controlling for other influential individual-level factors. Neighborhood socioeconomic context did not appear to be an important determinant of quantitative DBP levels or blood pressure control, before or after adjustment for potential confounding factors at the individual-level. In analyses unadjusted for individual-level factors, lower NSS were associated with higher SBP levels. However, this association was attenuated and lost statistical significance after adjustment for age, sex, co-morbid conditions, and education, suggesting that the potential influence of neighborhood socioeconomic context (as quantified by NSS) was confounded by individual-level factors. Residing in neighborhoods marked by a high degree of poverty was associated with higher SBP levels, even after adjustment for individual age, sex and co-morbid conditions. However, this association was also attenuated and lost statistical significance after adjusting for individual education. While the contextual factors of neighborhood socioeconomic environments may indeed influence SBP levels, findings from this study seem to indicate that neighborhood compositional factors, including individual-level SES, may play more important roles in shaping the distribution of SBP among African American hypertensive individuals.

The key significant finding in this study suggests that residing in a socioeconomically disadvantaged neighborhood may reduce the likelihood of being treated for hypertension more aggressively with multiple medications. This finding was consistent regardless of the neighborhood-level variable used to capture neighborhood socioeconomic environments, and associations detected withstood individual-level adjustments, including individual SES. Although this study did not investigate specific mechanisms that may help to explain this finding, several mechanisms (including health and social resource quality/availability, and logistics) are plausible and may warrant further investigation.

Availability of and access to quality health resources is often more limited for minority populations and individuals of lower SES (20-24). Racial/ethnic and socioeconomic differences in prescription practices have been noted (25, 26), and treatment for hypertension has been shown to be less aggressive among African Americans (27). The presence of quality clinics and pharmacies plays an obvious critical role in the delivery of adequate healthcare services and certain clinical services are less accessible in socioeconomically disadvantaged areas (28). The importance of pharmacists and pharmacy services in effectively helping patients with essential hypertension manage their blood pressure has been recognized for decades (29). Socioeconomically disadvantaged areas may be less likely to have quality clinical and pharmacy services available, which could directly and negatively impact both the treatment and control of hypertension. The lack of availability for certain medications in pharmacies located in poorer areas has been noted (30-32), which may restrict acquiring certain medications, even if they were prescribed. Quality of care may be poorer in

socioeconomically disadvantaged, poor-resource areas (33, 34). Proximity to wealthier areas with adequate health resources has been linked with insulin resistance (35), providing further evidence that the general lack of adequate health resources in poorer, underserved areas is a barrier to the delivery of health services and directly impacts health outcomes.

Strong social networks and support can positively influence a variety of health outcomes. A recent study has shown that low SES is related to poor social networks and support (36), and the quality and quantity of such social resources are likely more limited in areas marked by socioeconomic disadvantage. Numerous studies have shown that these social resources are important for hypertension treatment, treatment adherence, and control, particularly among African American populations (37-42). Neighborhood social participation has also been linked to adherence with antihypertensive medications (43), and use of hormone replacement therapy among women (44). In addition to many positive influences, including the promotion of positive health-related group norms, social networking and support provides an excellent platform for education and the exchange of information through group interaction. As a result of missed opportunities to access and/or utilize social resources, hypertensive individuals living in socioeconomically disadvantaged areas may be less likely to receive the pertinent information (e.g. – the fact that multiple antihypertensive medications are often required to achieve and maintain target blood pressure), which could influence the likelihood of being treated with combination therapy regimens.

In addition to a variety of patient, medication, and disease specific factors, basic logistic issues have been reported as barriers to antihypertensive treatment (40). A key

reported logistic issue is difficulty in reaching appointments at clinics and/or pharmacies. Effective blood pressure management commonly calls for antihypertensive medication adjustment and/or intensification, which require repeated provider contact through frequent clinical visits. Low neighborhood SES may be associated with factors (such as inadequate public transportation) that restrict access to health (and social) care resources, which may negatively impact health outcomes.

This study had several limitations that warrant discussion. This study was based on cross-sectional data and residential histories of the subjects were unavailable. As such, temporality, and hence causality, is difficult to establish, as a subject's exposure to certain risk factors (e.g. - neighborhood of residence) at the time of enrollment may not equal exposure status when the disease process began and cumulative exposures may be more relevant. The study findings pertain to hypertensive African American subjects from the tri-county Jackson, MS area and may not be generalizable to other racial/ethnic groups or African Americans in other geographic locations. Baseline address information was not available for the non-Hispanic white GENOA subjects from Rochester, MN or the Mexican American subjects from Starr County, TX, which precluded the examination of neighborhood socioeconomic environment in other racial/ethnic groups from other US geographic locations.

Census tracts were used as proxies for neighborhoods in this study. Census tracts have been commonly employed as an area measure in health research and previous studies indicate that differences between census tracts and smaller area measures (block-groups) are likely small (45). Still, defining neighborhoods in this way has limitations, as the boundaries used to define them may not correspond with what people define/perceive

as their neighborhoods, and a proxy used to define the relevant area may, "grossly underspecify neighborhood contexts" (46). Furthermore, census tracts may not be the most appropriate spatial scale relevant to hypertension (13). Neighborhood SES was relatively homogeneous across the census tracts investigated, which may have limited the ability to detect neighborhood contextual associations.

Data sparseness within certain census tracts may have biased the estimates of neighborhood socioeconomic indicators. Unbalanced data and/or small group size (<2 individuals per group) can lead to over-estimation of group-level random effects and standard errors of these effects, and this decrease in precision can result in decreased power to detect between-group variance. Monte-Carlo simulation work has suggested that 5 observations per group are sufficient for robust estimation of group-level effects (47). Accordingly, this study focused exclusively on subjects residing in neighborhoods with 5 or more subjects and a number of subjects were excluded for residing in neighborhoods with fewer than 5 subjects. Subjects residing in neighborhoods outside of the tri-county Jackson, MS area were also excluded in order to create an analytic sample that was more homogeneous geographically. If the neighborhood socioeconomic indicators related to the excluded subjects systematically differed from those of the subjects included in the study, neighborhood socioeconomic estimates may have been biased.

The need to "identify the specific characteristics of residential environments that are deleterious to health" (48) has been recognized for decades. This study used individual census-derived socioeconomic indicators, as well as constructed NSS, to capture the socioeconomic contexts of the neighborhoods investigated. While such

measures have been used in "area-effects" research (3, 4, 49, 50), they may be poor proxies for the specific neighborhood mechanisms that are potentially relevant to health outcomes (51). This study was limited in this regard, due to the absence of data on specific neighborhood features (e.g. - healthy food availability, built environment, access to quality health care, social cohesion, and stress) that may have more direct influences on the hypertension outcomes examined.

It should also be noted that the detected associations between the neighborhood socioeconomic context and SBP and combination treatment could simply reflect unmeasured individual-level socioeconomic characteristics rather than a contextual effect of the neighborhood (46, 52). The potential for this possibility existed in this study, particularly since individual education was the only measure of individual-level SES investigated, as data on other individual-level measures of SES, such as income and health insurance, was not available. Despite this, education is less prone to reverse causation and has commonly been used as an indicator of individual SES. Given the potential for misspecification of models at one or more of the levels in the proposed analyses, effect estimates at each level should be interpreted with caution, as misspecification at one level can also impact estimates at another level. The degree of familial correlation in the study sample overall, and within given neighborhoods, had the potential to influence the associations (or lack thereof) detected in this study. Despite this, it was unlikely that neighborhood contextual effect estimates were seriously impacted by familial correlations, as the degree of within-neighborhood relatedness was small across the neighborhoods investigated (Appendix 3.9). Furthermore, the inclusion of macro errors in the multilevel regression models theoretically allowed for correlations

within neighborhoods. Still, the individual- and neighborhood-level estimates may have been impacted by unspecified familial factors. Independent of neighborhood context, the familial aggregation of quantitative blood pressure levels and blood pressure control is examined and discussed further in Chapter 4.

The extent to which individuals from different neighborhoods are "exchangeable" and the inability to draw correct causal inferences about neighborhood effects in the absence of the exchangeability assumption has been discussed (46, 53). It has been noted that individuals 'select' into certain neighborhoods for a variety of reasons and such selection may lead to systematic differences in the compositional factors of individuals across neighborhoods. If all relevant compositional factors are not controlled for, obtaining accurate estimates of "independent" neighborhood effects may be difficult (53). Furthermore, if there is little overlap between individual-level characteristics across neighborhoods, adjustment for these variables may bias the estimate of the neighborhood effect, as a result of extrapolation (46). Without more complete data on individual-level SES characteristics, the extent to which this characteristic truly overlaps across neighborhoods was difficult to estimate in this study.

The degree to which neighborhood-level contexts exert "independent" effects on individual-level health outcomes may have important implications for public health efforts. If neighborhood-level characteristics influence hypertension outcomes, apart from individual-level characteristics, interventions that are community focused and directed towards neighborhoods may prove beneficial in reducing blood pressure levels and increasing the levels of hypertension awareness, treatment, and control. Accounting for group-level features may also be important in providing the context that determines the distribution of hypertension risk factors. This study contributed to the "area effects"

research and detected the novel finding that neighborhood socioeconomic environment may influence hypertension treatment and treatment intensity. Future research investigating specific characteristics of neighborhood socioeconomic environments, such as accessibility and proximity to clinics and pharmacies, may highlight areas that need to be addressed in order to improve adequate treatment and control among minority and underserved hypertensive populations.

**Table 3.1. Selected sample characteristics of the treated hypertensive African American GENOA study subjects included in the analyses (n=948)**

| | Mean (SD) |
|---|---|
| Age (years) | 60.7 (9.0) |
| Height (cm) | 168.0 (8.6) |
| Weight (kg) | 89.9 (18.5) |
| BMI ($kg/m^2$) | 31.9 (6.7) |
| Education (years completed) | 11.5 (3.6) |
| SBP (mmHg) | 139.8 (22.9) |
| DBP (mmHg) | 78.0 (12.5) |
| Female (%) | 73 |
| Type 2 diabetes (%) | 28 |
| Blood pressure controlled[a] (%) | 53 |
| Taking 2 or more antihypertensive medications (%) | 53 |
| Residence within poor neighborhood[b] | 62 |

Quantitative variables are presented as mean (SD); categorical variables as percentages. [a]Blood pressure control defined as systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg. [b]Poor neighborhood based on percentage of census tract poverty, where a neighborhood was defined as "poor" if the percentage of poverty was greater than 25%, and "more advantaged" otherwise. BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure.

**Table 3.2. Descriptive statistics of US Census 2000 socioeconomic indicator variables and neighborhood socioeconomic summary scores across 48 census tracts within the tri-county Jackson, MS geographic region**

| Variable | Min | Median | Max | Interquartile range |
|---|---|---|---|---|
| Annual household income in 1999 (US dollars) | 10510 | 25480 | 66350 | 18960, 30730 |
| Value of occupied housing units (US dollars) | 29400 | 47200 | 133200 | 38500, 57300 |
| % of households receiving interest, dividend or net rental income | 1 | 11 | 49 | 9, 18 |
| % of adults who completed high school | 45 | 67 | 95 | 62, 77 |
| % of adults who completed college | 5 | 17 | 49 | 11, 19 |
| % of adults in managerial or professional occupations | 8 | 22 | 63 | 18, 26 |
| % poverty in 1999** | 3 | 30 | 54 | 21, 37 |
| % African American | 7 | 97 | 99 | 92, 98 |
| Neighborhood socioeconomic summary score* | -8.6 | -1.3 | 14.6 | -4.3, 0.7 |

* Neighborhood socioeconomic summary score derived from summation of calculated z-scores from the following indicators: Annual household income in 1999 (US dollars); Value of occupied housing units (US dollars); % of households receiving interest, dividend or net rental income; % of adults who completed high school; % of adults who completed college; % of adults in managerial or professional occupations. ** % poverty to income ratio (PIR) < 1.0.

**Table 3.3. Association of neighborhood socioeconomic score with systolic blood pressure in the African American GENOA subjects included in multilevel linear model analyses (n=948)**

| | Model 1 | Model 2 | Model 3 |
|---|---|---|---|
| | Coef (CI) | Coef (CI) | Coef (CI) |
| Intercept | 139.41** (137.93, 140.88) | 109.11** (96.20, 122.03) | 117.59** (102.22, 132.95) |
| Individual-level variables | | | |
| Age (years) | | 0.46** (0.31, 0.63) | 0.42** (0.25, 0.59) |
| Gender | | | |
| Male (ref) | | | |
| Female | | 1.75 (-1.57, 5.07) | 2.21 (-1.14, 5.56) |
| BMI ($kg/m^2$) | | -0.03 (-0.26, 0.20) | -0.05 (-0.27, 0.18) |
| Type 2 diabetes | | | |
| Absent (ref) | | | |
| Present | | 5.79** (2.57, 9.03) | 5.73** (2.51, 8.96) |
| Education (years completed) | | | -0.44** (-0.88, -0.01) |
| Neighborhood level variable | | | |
| NSS[a] | -0.40** (-0.70, -0.10) | -0.23 (-0.52, 0.07) | -0.16 (-0.46, 0.15) |

All models fit using hierarchical linear models with random intercept components.
Model 1 is unadjusted for individual factors.
Model 2 adjusted for individual age, sex, BMI and diabetes.
Model 3 adjusted for individual age, sex, BMI, diabetes, and education.
[a]NSS = Neighborhood socioeconomic summary score. Neighborhood socioeconomic summary score derived from summation of calculated z-scores from the following indicators: Annual household income in 1999 (US dollars); Value of occupied housing units (US dollars); % of households receiving interest, dividend or net rental income; % of adults who completed high school; % of adults who completed college; % of adults in managerial or professional occupations. CI = estimated 95% confidence interval. BMI = body mass index. p-value **P<0.05; *P<0.10.

**Table 3.4. Association of neighborhood socioeconomic score with diastolic blood pressure in the African American GENOA subjects included in multilevel linear model analyses (n=948)**

| | Model 1 | Model 2 | Model 3 |
|---|---|---|---|
| | Coef (CI) | Coef (CI) | Coef (CI) |
| Intercept | 78.07** (77.21, 78.93) | 106.75** (99.80, 113.70) | 111.23** (102.96, 119.50) |
| Individual-level variables | | | |
| Age (years) | | -0.37** (-0.46, -0.29) | -0.40** (-0.49, -0.31) |
| Gender | | | |
| Male (ref) | | | |
| Female | | -2.99** (-4.78, -1.21) | -2.75** (-4.55, -0.95) |
| BMI ($kg/m^2$) | | -0.11* (-0.23, 0.01) | -0.12* (-0.24, 0.00) |
| Type 2 diabetes | | | |
| Absent (ref) | | | |
| Present | | -1.10 (-2.84, 0.64) | -1.13 (-2.87, 0.60) |
| Education (years completed) | | | -0.23* (-0.47, 0.00) |
| Neighborhood level variable | | | |
| NSS[a] | 0.06 (-0.11, 0.23) | -0.08 (-0.24, 0.08) | -0.04 (-0.20, 0.12) |

All models fit using hierarchical linear models with random intercept components.
Model 1 is unadjusted for individual factors.
Model 2 adjusted for individual age, sex, BMI and diabetes.
Model 3 adjusted for individual age, sex, BMI, diabetes, and education.
[a]NSS = Neighborhood socioeconomic summary score. Neighborhood socioeconomic summary score derived from summation of calculated z-scores from the following indicators: Annual household income in 1999 (US dollars); Value of occupied housing units (US dollars); % of households receiving interest, dividend or net rental income; % of adults who completed high school; % of adults who completed college; % of adults in managerial or professional occupations. CI = estimated 95% confidence interval. BMI = body mass index. p-value **P<0.05; *P<0.10.

**Table 3.5. Association of neighborhood socioeconomic score with combination antihypertensive pharmacologic treatment in the African American GENOA subjects included in multilevel logistic regression model analyses (n=948)**

| | Model 1 | Model 2 | Model 3 |
|---|---|---|---|
| | OR (CI) | OR (CI) | OR (CI) |
| Individual-level variables | | | |
| Age (years) | | 1.02** (1.01, 1.04) | 1.02** (1.01, 1.04) |
| Gender | | | |
| Male (ref) | | | |
| Female | | 0.81 (0.59, 1.09) | 0.79 (0.58, 1.07) |
| BMI ($kg/m^2$) | | 1.05** (1.03, 1.08) | 1.06** (1.03, 1.08) |
| Type 2 diabetes | | | |
| Absent (ref) | | | |
| Present | | 1.49** (1.10, 2.01) | 1.50** (1.11, 2.02) |
| Education (years completed) | | | 1.02 (0.98, 1.07) |
| Neighborhood level variable | | | |
| NSS[a] | 1.02 (0.99, 1.05) | 1.03** (1.00, 1.06) | 1.03* (1.00, 1.06) |

All models fit using hierarchical linear models with random intercept components.
Model 1 is unadjusted for individual factors.
Model 2 adjusted for individual age, sex, BMI and diabetes.
Model 3 adjusted for individual age, sex, BMI, diabetes, and education.
[a]NSS = Neighborhood socioeconomic summary score. Neighborhood socioeconomic summary score derived from summation of calculated z-scores from the following indicators: Annual household income in 1999 (US dollars); Value of occupied housing units (US dollars); % of households receiving interest, dividend or net rental income; % of adults who completed high school; % of adults who completed college; % of adults in managerial or professional occupations. CI = estimated 95% confidence interval. BMI = body mass index. p-value **P<0.05; *P<0.10.

**Table 3.6. Association of neighborhood socioeconomic score with blood pressure control[a] in the African American GENOA subjects included in multilevel logistic regression model analyses (n=948)**

| | Model 1 | Model 2 | Model 3 |
|---|---|---|---|
| | OR (CI) | OR (CI) | OR (CI) |
| Individual-level variables | | | |
| Age (years) | | 0.97** (0.96, 0.99) | 0.97** (0.96, 0.99) |
| Gender | | | |
| Male (ref) | | | |
| Female | | 0.82 (0.61, 1.12) | 0.80 (0.59, 1.09) |
| BMI ($kg/m^2$) | | 1.01 (0.99, 1.03) | 1.01 (0.99, 1.03) |
| Type 2 diabetes | | | |
| Absent (ref) | | | |
| Present | | 0.66** (0.49, 0.89) | 0.67** (0.50, 0.90) |
| Education (years completed) | | | 1.03 (0.99, 1.07) |
| Neighborhood level variable | | | |
| NSS[b] | 1.02 (0.99, 1.04) | 1.00 (0.98, 1.03) | 1.00 (0.97, 1.03) |

All models fit using hierarchical linear models with random intercept components.
Model 1 is unadjusted for individual factors.
Model 2 adjusted for individual age, sex, BMI and diabetes.
Model 3 adjusted for individual age, sex, BMI, diabetes, and education.
[a]Blood pressure controlled to <140/90 mmHg. [b]NSS = Neighborhood socioeconomic summary score. Neighborhood socioeconomic summary score derived from summation of calculated z-scores from the following indicators: Annual household income in 1999 (US dollars); Value of occupied housing units (US dollars); % of households receiving interest, dividend or net rental income; % of adults who completed high school; % of adults who completed college; % of adults in managerial or professional occupations. CI = estimated 95% confidence interval. BMI = body mass index. p-value **P<0.05; *P<0.10.

**Table 3.7. Use of antihypertensive drug class by poor neighborhood of residence[a]**

| | Poor neighborhood n= 584 | More advantaged neighborhood n= 364 |
|---|---|---|
| Diuretic | 57% (14%) | 57% (13%) |
| β-blocker | 15% (3%) | 17% (4%) |
| Calcium channel blocker | 33% (13%) | 39% (13%) |
| RAAS inhibitor | 34% (10%) | 37% (10%) |
| Other[b] | 24% (9%) | 21% (5%) |
| Mono-therapy | 49% | 45% |
| 2 of the above drugs in combination | 37% | 41% |
| 3 or more of the above drugs in combination | 14% | 14% |

Top portion of table data represent percentages of aware and treated hypertensive subjects taking each respective antihypertensive drug class as part of any regimen. Percentages using each class in mono-therapy form shown in parentheses; [a]Poor neighborhood based on percentage of census tract poverty, where a neighborhood was defined as "poor" if the percentage of poverty was greater than 25%, and "more advantaged" otherwise. [b]Other antihypertensive class includes alpha-blockers, vasodilators, sympatholytics, and study drugs. RAAS = renin angiotensin aldosterone system. p-value contrasts between neighborhood type groups; $p<0.05$*; $p<0.01$†; $p<0.001$‡.

**Appendix 3.1. Association of log median household income with systolic blood pressure in the African American GENOA subjects included in multilevel linear model analyses (n=948)**

| | Model 1 | Model 2 | Model 3 |
|---|---|---|---|
| | Coef (CI) | Coef (CI) | Coef (CI) |
| Intercept | 196.35** (157.43, 235.28) | 141.41** (98.23, 184.60) | 141.02** (97.90, 184.14) |
| Individual-level variables | | | |
| Age (years) | | 0.47** (0.30, 0.63) | 0.41** (0.24, 0.59) |
| Gender | | | |
| Male (ref) | | | |
| Female | | 1.67 (-1.66, 5.00) | 2.14 (-1.21, 5.50) |
| BMI ($kg/m^2$) | | -0.03 (-0.26, 0.20) | -0.05 (-0.28, 0.18) |
| Type 2 diabetes | | | |
| Absent (ref) | | | |
| Present | | 5.79** (2.56, 9.02) | 5.73** (2.50, 8.95) |
| Education (years completed) | | | -0.44** (-0.87, 0.00) |
| Neighborhood level variable | | | |
| Log median household income[a] | -12.82** (-21.62, -4.01) | -7.19 (-16.00, 1.61) | -5.23 (-14.23, 3.78) |

All models fit using hierarchical linear models with random intercept components.
Model 1 is unadjusted for individual factors.
Model 2 adjusted for individual age, sex, BMI and diabetes.
Model 3 adjusted for individual age, sex, BMI, diabetes, and education.
[a]The distribution of median household income by census tract in the study sample was right-skewed and was log-transformed to approximate a normal distribution. CI = estimated 95% confidence interval. BMI = body mass index. p-value **P<0.05; *P<0.10.

**Appendix 3.2. Association of log median household income with diastolic blood pressure in the African American GENOA subjects included in multilevel linear model analyses (n=948)**

| | Model 1 | Model 2 | Model 3 |
|---|---|---|---|
| | Coef (CI) | Coef (CI) | Coef (CI) |
| Intercept | 64.82** (42.62, 87.03) | 114.18** (90.93, 137.42) | 113.96** (90.75, 137.17) |
| Individual-level variables | | | |
| Age (years) | | -0.37** (-0.46, -0.29) | -0.40** (-0.49, -0.31) |
| Gender | | | |
| Male (ref) | | | |
| Female | | -2.99** (-4.79, -1.20) | -2.73** (-4.54, -0.93) |
| BMI ($kg/m^2$) | | -0.11* (-0.23, 0.01) | -0.12* (-0.24, 0.00) |
| Type 2 diabetes | | | |
| Absent (ref) | | | |
| Present | | -1.10 (-2.84, 0.64) | -1.13 (-2.87, 0.60) |
| Education (years completed) | | | -0.24** (-0.47, -0.01) |
| Neighborhood level variable | | | |
| Log median household income[a] | 2.99 (-2.04, 8.02) | -1.69 (-6.43, 3.05) | -0.61 (-5.45, 4.24) |

All models fit using hierarchical linear models with random intercept components.
Model 1 is unadjusted for individual factors.
Model 2 adjusted for individual age, sex, BMI and diabetes.
Model 3 adjusted for individual age, sex, BMI, diabetes, and education.
[a]The distribution of median household income by census tract in the study sample was right-skewed and was log-transformed to approximate a normal distribution. CI = estimated 95% confidence interval. BMI = body mass index. p-value **P<0.05; *P<0.10.

**Appendix 3.3. Association of log median household income with combination antihypertensive pharmacologic treatment in the African American GENOA subjects included in multilevel logistic regression model analyses (n=948)**

| | Model 1 | Model 2 | Model 3 |
|---|---|---|---|
| | OR (CI) | OR (CI) | OR (CI) |
| Individual-level variables | | | |
| Age (years) | | 1.02** (1.01, 1.04) | 1.02** (1.01, 1.04) |
| Gender | | | |
| Male (ref) | | | |
| Female | | 0.82 (0.60, 1.11) | 0.80 (0.58, 1.09) |
| BMI ($kg/m^2$) | | 1.06** (1.03, 1.08) | 1.06** (1.03, 1.08) |
| Type 2 diabetes | | | |
| Absent (ref) | | | |
| Present | | 1.49** (1.10, 2.02) | 1.50** (1.11, 2.02) |
| Education (years completed) | | | 1.02 (0.98, 1.06) |
| Neighborhood level variable | | | |
| Log median household income[a] | 1.99* (0.91, 4.32) | 2.75** (1.21, 6.24) | 2.49** (1.08, 5.77) |

All models fit using hierarchical linear models with random intercept components.
Model 1 is unadjusted for individual factors.
Model 2 adjusted for individual age, sex, BMI and diabetes.
Model 3 adjusted for individual age, sex, BMI, diabetes, and education.
[a]The distribution of median household income by census tract in the study sample was right-skewed and was log-transformed to approximate a normal distribution. CI = estimated 95% confidence interval. BMI = body mass index. p-value **P<0.05; *P<0.10.

**Appendix 3.4. Association of log median household income with blood pressure control[a] in the African American GENOA subjects included in multilevel logistic regression model analyses (n=948)**

| | Model 1 | Model 2 | Model 3 |
|---|---|---|---|
| | OR (CI) | OR (CI) | OR (CI) |
| Individual-level variables | | | |
| Age (years) | | 0.97** (0.96, 0.99) | 0.98** (0.96, 0.99) |
| Gender | | | |
| Male (ref) | | | |
| Female | | 0.83 (0.61, 1.13) | 0.81 (0.59, 1.10) |
| BMI ($kg/m^2$) | | 1.01 (0.99, 1.03) | 1.01 (0.99, 1.03) |
| Type 2 diabetes | | | |
| Absent (ref) | | | |
| Present | | 0.66** (0.50, 0.89) | 0.67** (0.50, 0.90) |
| Education (years completed) | | | 1.03 (0.99, 1.07) |
| Neighborhood level variable | | | |
| Log median household income[b] | 1.86 (0.86, 4.05) | 1.32 (0.59, 2.96) | 1.17 (0.51, 2.68) |

All models fit using hierarchical linear models with random intercept components.
Model 1 is unadjusted for individual factors.
Model 2 adjusted for individual age, sex, BMI and diabetes.
Model 3 adjusted for individual age, sex, BMI, diabetes, and education.
[a] Blood pressure controlled to <140/90 mmHg. [b]The distribution of median household income by census tract in the study sample was right-skewed and was log-transformed to approximate a normal distribution. CI = estimated 95% confidence interval. BMI = body mass index.
p-value **P<0.05; *P<0.10.

**Appendix 3.5. Association of poor neighborhood of residence with systolic blood pressure in the African American GENOA subjects included in multilevel linear model analyses (n=948)**

| | Model 1 | Model 2 | Model 3 |
|---|---|---|---|
| | Coef (CI) | Coef (CI) | Coef (CI) |
| Intercept | 136.98** (134.63, 139.32) | 108.33** (95.53, 121.13) | 117.40** (102.04, 132.76) |
| Individual-level variables | | | |
| Age (years) | | 0.46** (0.30, 0.62) | 0.41** (0.24, 0.58) |
| Gender | | | |
| Male (ref) | | | |
| Female | | 1.71 (-1.61, 5.03) | 2.15 (-1.19, 5.49) |
| BMI ($kg/m^2$) | | -0.04 (-0.27, 0.19) | -0.06 (-0.28, 0.17) |
| Type 2 diabetes | | | |
| Absent (ref) | | | |
| Present | | 5.84** (2.61, 9.07) | 5.76** (2.54, 8.99) |
| Education (years completed) | | | -0.45** (-0.88, -0.03) |
| Neighborhood level variable | | | |
| Poor neighborhood[a] | 4.51** (1.53, 7.50) | 2.81* (-0.17, 5.79) | 2.46 (-0.53, 5.45) |

All models fit using hierarchical linear models with random intercept components.
Model 1 is unadjusted for individual factors.
Model 2 adjusted for individual age, sex, BMI and diabetes.
Model 3 adjusted for individual age, sex, BMI, diabetes, and education.
[a]Poor neighborhood based on percentage of census tract poverty, where a neighborhood was defined as "poor" if the percentage of poverty was greater than 25%, and "more advantaged" otherwise. BMI = body mass index. p-value **P<0.05; *P<0.10.

**Appendix 3.6. Association of poor neighborhood of residence with diastolic blood pressure in the African American GENOA subjects included in multilevel linear model analyses (n=948)**

| | Model 1 | Model 2 | Model 3 |
|---|---|---|---|
| | Coef (CI) | Coef (CI) | Coef (CI) |
| Intercept | 78.80** (77.52, 80.08) | 106.31** (99.42, 113.20) | 111.25** (102.98, 119.52) |
| Individual-level variables | | | |
| Age (years) | | -0.37** (-0.46, -0.28) | -0.40** (-0.49, -0.31) |
| Gender | | | |
| Male (ref) | | | |
| Female | | -2.95** (-4.74, -1.16) | -2.70** (-4.50, -0.91) |
| BMI ($kg/m^2$) | | -0.11* (-0.23, 0.01) | -0.12* (-0.24, 0.00) |
| Type 2 diabetes | | | |
| Absent (ref) | | | |
| Present | | -1.09 (-2.83, 0.65) | -1.13 (-2.87, 0.61) |
| Education (years completed) | | | -0.25** (-0.48, -0.02) |
| Neighborhood level variable | | | |
| Poor neighborhood[a] | -1.31 (-2.95, 0.32) | 0.19 (-1.41, 1.80) | 0.00 (-1.61, 1.61) |

All models fit using hierarchical linear models with random intercept components.
Model 1 is unadjusted for individual factors.
Model 2 adjusted for individual age, sex, BMI and diabetes.
Model 3 adjusted for individual age, sex, BMI, diabetes, and education.
[a]Poor neighborhood based on percentage of census tract poverty, where a neighborhood was defined as "poor" if the percentage of poverty was greater than 25%, and "more advantaged" otherwise. BMI = body mass index. p-value **P<0.05; *P<0.10.

**Appendix 3.7. Association of poor neighborhood of residence with combination antihypertensive pharmacologic treatment in the African American GENOA subjects included in multilevel logistic regression model analyses (n=948)**

| | Model 1 | Model 2 | Model 3 |
|---|---|---|---|
| | OR (CI) | OR (CI) | OR (CI) |
| Individual-level variables | | | |
| Age (years) | | 1.02** (1.01, 1.04) | 1.03** (1.01, 1.04) |
| Gender | | | |
| Male (ref) | | | |
| Female | | 0.81 (0.59, 1.10) | 0.79 (0.58, 1.07) |
| BMI ($kg/m^2$) | | 1.06** (1.03, 1.08) | 1.06** (1.03, 1.08) |
| Type 2 diabetes | | | |
| Absent (ref) | | | |
| Present | | 1.48** (1.10, 2.00) | 1.49** (1.10, 2.01) |
| Education (years completed) | | | 1.03 (0.99, 1.07) |
| Neighborhood level variable | | | |
| Poor neighborhood[a] | 0.80 (0.62, 1.04) | 0.71** (0.54, 0.94) | 0.72** (0.55, 0.96) |

All models fit using hierarchical linear models with random intercept components.
Model 1 is unadjusted for individual factors.
Model 2 adjusted for individual age, sex, BMI and diabetes.
Model 3 adjusted for individual age, sex, BMI, diabetes, and education.
[a]Poor neighborhood based on percentage of census tract poverty, where a neighborhood was defined as "poor" if the percentage of poverty was greater than 25%, and "more advantaged" otherwise. BMI = body mass index. p-value **P<0.05; *P<0.10.

**Appendix 3.8. Association of poor neighborhood of residence with blood pressure control[a] in the African American GENOA subjects included in multilevel logistic regression model analyses (n=948)**

| | Model 1 | Model 2 | Model 3 |
|---|---|---|---|
| | OR (CI) | OR (CI) | OR (CI) |
| Individual-level variables | | | |
| Age (years) | | 0.97** (0.96, 0.99) | 0.98** (0.96, 0.99) |
| Gender | | | |
| Male (ref) | | | |
| Female | | 0.83 (0.61, 1.12) | 0.81 (0.59, 1.10) |
| BMI ($kg/m^2$) | | 1.01 (0.99, 1.03) | 1.01 (0.99, 1.03) |
| Type 2 diabetes | | | |
| Absent (ref) | | | |
| Present | | 0.66* (0.49, 0.89) | 0.67** (0.50, 0.90) |
| Education (years completed) | | | 1.03 (0.99, 1.07) |
| Neighborhood level variable | | | |
| Poor neighborhood[b] | 0.81 (0.62, 1.05) | 0.89 (0.68, 1.17) | 0.91 (0.69, 1.20) |

All models fit using hierarchical linear models with random intercept components.
Model 1 is unadjusted for individual factors.
Model 2 adjusted for individual age, sex, BMI and diabetes.
Model 3 adjusted for individual age, sex, BMI, diabetes, and education.
[a]Blood pressure controlled to <140/90 mmHg. [b]Poor neighborhood based on percentage of census tract poverty, where a neighborhood was defined as "poor" if the percentage of poverty was greater than 25%, and "more advantaged" otherwise. BMI = body mass index. p-value **P<0.05; *P<0.10.

**Appendix 3.9. Distribution of within-tract family relatedness across 48 census tracts in Jackson, MS tri-county area**

| Census Tract ID | # Subjects within tract | # families within tract | Relatedness within tract | # families multiple sibs per tract | # sibpairs |
|---|---|---|---|---|---|
| 28079000300 | 6 | 6 | no | 0 | NA |
| 28049000400 | 5 | 5 | no | 0 | NA |
| 28049000500 | 92 | 82 | yes | 8 | 13 |
| 28049000600 | 88 | 81 | yes | 7 | 7 |
| 28049000700 | 22 | 20 | yes | 2 | 2 |
| 28049000800 | 55 | 54 | yes | 1 | 1 |
| 28049000900 | 47 | 43 | yes | 4 | 4 |
| 28049001000 | 37 | 36 | yes | 1 | 1 |
| 28049001100 | 32 | 27 | yes | 4 | 6 |
| 28049001200 | 26 | 23 | yes | 3 | 3 |
| 28049001300 | 10 | 9 | yes | 1 | 1 |
| 28049001700 | 7 | 6 | yes | 1 | 1 |
| 28049001900 | 32 | 29 | yes | 3 | 3 |
| 28049002000 | 13 | 13 | no | 0 | NA |
| 28049002100 | 27 | 24 | yes | 2 | 4 |
| 28049002200 | 9 | 9 | no | 0 | NA |
| 28049002300 | 13 | 10 | yes | 1 | 6 |
| 28049002400 | 42 | 40 | yes | 2 | 2 |
| 28049002500 | 17 | 17 | no | 0 | NA |
| 28049002600 | 9 | 9 | no | 0 | NA |

| | | | | | |
|---|---|---|---|---|---|
| 28049002700 | 8 | 8 | no | 0 | NA |
| 28049003000 | 11 | 11 | no | 0 | NA |
| 28049003100 | 12 | 10 | yes | 1 | 3 |
| 28049003200 | 15 | 13 | yes | 2 | 2 |
| 28049003300 | 9 | 8 | yes | 1 | 1 |
| 28049003400 | 5 | 5 | no | 0 | NA |
| 28049003700 | 5 | 4 | yes | 1 | 1 |
| 28049010201 | 13 | 12 | yes | 1 | 1 |
| 28049010202 | 69 | 66 | yes | 3 | 3 |
| 28049010203 | 13 | 13 | no | 0 | NA |
| 28049010301 | 44 | 36 | yes | 7 | 9 |
| 28049010400 | 5 | 5 | no | 0 | NA |
| 28049010500 | 27 | 18 | yes | 5 | 13 |
| 28049010801 | 11 | 10 | yes | 1 | 1 |
| 28049010802 | 12 | 11 | yes | 1 | 1 |
| 28049010807 | 6 | 3 | yes | 1 | 6 |
| 28049010901 | 10 | 9 | yes | 1 | 1 |
| 28049010902 | 20 | 19 | yes | 1 | 1 |
| 28049011001 | 7 | 7 | no | 0 | NA |
| 28049011200 | 11 | 9 | yes | 2 | 2 |
| 28089030101 | 5 | 4 | yes | 1 | 1 |
| 28089030105 | 6 | 4 | yes | 1 | 3 |
| 28089030302 | 5 | 5 | no | 0 | NA |
| 28121020102 | 5 | 3 | yes | 2 | 2 |
| 28120120204 | 8 | 8 | no | 0 | NA |
| 28121020302 | 6 | 5 | yes | 1 | 1 |
| 28121020600 | 5 | 5 | no | 0 | NA |
| 28121021002 | 6 | 5 | yes | 1 | 1 |

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# Chapter 4

## Investigating Familial Correlations of Quantitative Blood Pressure Measures and the Control of Hypertension

## INTRODUCTION

In addition to a variety of individual-level sociodemographic, anthropometric, and lifestyle related factors, a positive family history of hypertension is a known risk for developing hypertension. An estimated 30% of the general population variability in blood pressure is due to genetic heritability and 60% -70% of familial aggregation of blood pressure is due to common genetic backgrounds (1). Genetic factors play key roles in inter-individual blood pressure variation and it is now widely accepted that essential hypertension results from complex interactions between genetic and environmental factors. In addition to sharing similar genetic profiles, individuals within the same family share a number of environmental factors throughout the life course, such as physical environment, dietary habits, and health beliefs and practices. These shared genetic and environmental factors may condition a common blood pressure level and, if evident, such between-family variation in blood pressure levels would suggest that genetic and environmental (or interactions between the two) effects could operate in ways that might influence individual blood pressure levels and/or the probability of hypertension control. Furthermore, evidence for familial clustering of blood pressure levels and hypertension outcomes may suggest that strategies directed for preventing hypertension should also be focused at the family level rather than on the individual level exclusively. The goal of

this study was to estimate the degree of familial clustering of quantitative blood pressure values in hypertensive sibships, and to investigate the influence of blood pressure determinants at multiple levels on such clustering.

## METHODS

### Study Population

In 1995, the National Heart, Lung and Blood Institute (NHLBI) established The Family Blood Pressure Program (FBPP) to assess the genetic influence on inter-individual blood pressure variation, hypertension, and hypertensive target organ damage. One of the four networks established by the NHLBI to meet this objective is the Genetic Epidemiology Network of Arteriopathy (GENOA). GENOA field centers in Jackson, MS, Starr County, TX, and Rochester, MN recruited hypertensive African American, Hispanic, and non-Hispanic white sibships, respectively, for linkage and family-based association studies. Subject were diagnosed with hypertension if they had a previous clinical diagnosis of hypertension by a physician with current antihypertensive treatment or an average systolic blood pressure (SBP) >=140 mmHg and/or an average diastolic blood pressure (DBP) >=90 mmHg.

In Rochester, MN and Jackson, MS, recruitment was restricted to sibships that contained a minimum of two individuals diagnosed with essential hypertension before the age of 60. Once this criterion was met, the entire sibship was invited to participate in the study. As the prevalence of diabetes among Mexican-Americans is high, the Starr County recruitment was restricted to Mexican-American sibships containing at least two individuals diagnosed with type-2 diabetes (2). Data was collected through personal

interviews, and physical and laboratory examinations. The initial phase of the GENOA study took place from September 1995 through June 2001 (3).

The primary analytic samples for the study presented here contained African American subject (n = 1123 from 598 sibships) and non-Hispanic white (n = 970 from 528 sibships) hypertensive subjects that were both aware of their hypertension status and taking antihypertensive medication(s) to lower blood pressure. Although a majority of the subjects in this cohort were diagnosed as hypertensive, a number of the sibship members invited to participate were identified as normotensive during the baseline examination and have been excluded from this analysis. Other exclusion criteria included secondary hypertension, alcoholism or drug abuse, pregnancy, insulin-dependent diabetes, or active malignancy. A second analytic sample (described below) was created to investigate the influence of neighborhood poverty concordance among African American sibpairs on the sib-sib correlations of quantitative blood pressure values and the aggregation of blood pressure control. Subjects sharing the same mother and father (assessed by concordance for both de-identified, parental personal identifier numbers) were assigned into respective sibpairs.

**Covariates**

Trained interviewers asked subjects standard questions on numerous factors, including sociodemographic, lifestyle and behavior, and cardiovascular health history. Age in years was assessed on the baseline examination date. Education was defined as the total number of years of education completed. Height was measured by stadiometer, weight by electronic balance, and body mass index (BMI) was calculated as weight in

kilograms divided by the square of height in meters. Diabetes was defined as having a fasting glucose level ≥ 126 mg/dL or currently being treated with insulin or oral agents.

**Blood Pressure Readings**

Blood pressure measurements were made with random zero sphygmomanometers and cuffs appropriate for arm size. Three readings were taken in the right arm after the subject rested in the sitting position for at least five minutes according to the Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7, 2003) guidelines (4). The SBP and DBP values were determined by the first and fifth phase Korotkoff sounds, respectively, and the last two blood pressure readings were averaged for the analyses. The diagnosis of hypertension was established based on blood pressure levels measured at the study visit (≥140/90 mmHg), or a prior diagnosis of hypertension and current treatment with antihypertensive medications.

**Blood Pressure Treatment and Antihypertensive Medications**

Based on lists of all antihypertensive medications available in the US each prescription antihypertensive drug recorded at the study visit was assigned a code number corresponding to the first 6 digits of the Medi-Span Generic Product Identifier. This number, which identifies pharmacologically equivalent drug products, was used to categorize agents with similar mechanisms of antihypertensive action.

Conditional upon being hypertensive and aware of their hypertension status, subjects were considered to be "treated" if they answered yes to the questions, "Has medication ever been prescribed by a physician to lower your blood pressure?" and "During the last month, have you used any medication that was prescribed or

recommended by a physician?" The number of prescribed antihypertensive medications was tallied for each subject. Subjects taking only one prescribed antihypertensive medication were defined as being treated with a monotherapy regimen, while those taking two or more prescribed antihypertensive medications were defined as being treated with a combination therapy regimen.

**Blood Pressure Control**

Official guidelines propose that patients with a SBP $\geq$ 140 mmHg or DBP $\geq$ 90 mmHg be considered as hypertensive (4, 5). Accordingly, in this study controlled blood pressure was defined as SBP < 140 mmHg and DBP < 90 mmHg for a treated subject with hypertension. If either one, or both, of the two requirements were not met, a hypertensive subject's blood pressure was defined as uncontrolled.

**Statistical Analysis**

**Familial Clustering of Blood Pressure and Variance Partitioning**

In order to account for the potential residual correlation between individual SBP and DBP levels that may arise from family factors that influence these quantitative measures, a multilevel analysis was conducted. Given the hierarchical nature of the data, with individuals nested within sibships, regression analyses with individuals at the first level and sibships at the second level were performed. Individual-level predictor variables included age, gender, body mass index (BMI), type 2 diabetes, and education. Age, BMI, and education were assessed as continuous variables. Gender and diabetes status were treated as dichotomous variables, with male sex and non-diabetic set as the referent groups respectively. Maternal and paternal histories of hypertension were investigated as family-level variables. Both variables were dichotomized with negative

history for hypertension set as the referent group. To examine the extent to which individual SBP and DBP variation could be attributed to a higher contextual level, four models were fit, intra-class coefficients (ICC) were calculated, and variance proportional changes were estimated.

The first model did not include any explanatory variables and aimed to partition the total SBP (and separately DBP) variance ($V_t$) into individual ($V_i$) and sibship ($V_s$) components. Doing so allows for the potential detection of a contextual effect that can be quantified as clustering of blood pressure values within sibships. The first level of this model took the following form: $Y_{ij} = \beta_{0j}+\varepsilon_{ij}$, where $Y_{ij}$ represents the predicted blood pressure level for the $i^{th}$ individual in the $j^{th}$ sibship, the intercept ($\beta_{0j}$) is constant within sibship and allowed to vary from one sibship to another, and the individual level errors are assumed to be independent and normally distributed ($\varepsilon_{ij} \sim N(0,\sigma^2)$). In the second level, the intercept defined in the first level ($\beta_{0j}$) is modeled as a function of sibships, such that $\beta_{0j} = \gamma_{00}+U_{oj}$, where $\gamma_{00}$ represents the common intercept across sibships and $U_{oj}$ is a macro error, assumed to be independent and normally distributed ($U_{oj} \sim N(0,\tau_{00})$), that measures the unique deviation of each sibship intercept from the common intercept. Applying substitution yields the full form of the null model: $Y_{ij} = \gamma_{00}+U_{oj} +\varepsilon_{ij}$.

The second model expanded the null model by including only individual-level fixed effects for age, gender, BMI, diabetes, and education. This model took the following full form: $Y_{ij} = \gamma_{00} + \gamma_{10}Age_{ij} + \gamma_{20}Gender_{ij} + \gamma_{30}BMI_{ij} + \gamma_{40}Diabetes_{ij} + \gamma_{50}Education + U_{0j} +\varepsilon_{ij}$ . The third model expanded the null model by including family-level fixed effects for maternal and paternal history of hypertension and took the

following full form: $Y_{ij} = \gamma_{00} + \gamma_{01}$Maternal history of hypertension$_j$ + $\gamma_{02}$Paternal history of hypertension$_j$ + $U_{0j}$ +$\varepsilon_{ij}$. The fourth model combined the second and third models to include fixed effects at both the individual and family levels. This model took the following full form: $Y_{ij} = \gamma_{00} + \gamma_{01}$Maternal history of hypertension$_j$ + $\gamma_{02}$Paternal history of hypertension$_j$ + $\gamma_{10}$Age$_{ij}$ + $\gamma_{20}$Gender$_{ij}$ + $\gamma_{30}$BMI$_{ij}$ + $\gamma_{40}$Diabetes$_{ij}$ + $\gamma_{50}$Education + $U_{0j}$ +$\varepsilon_{ij}$ .

In the null model (i.e. – random intercepts model), the variance partition coefficient (VPC) is equivalent to the (ICC): VPC = $(V_s/(V_s+V_i)) * 100$ = ICC = $(\tau_{00}/(\sigma^2 + \tau_{00})) *100$, where $\tau_{00}$ equals the variance of the macro error $U_{oj,}$, and $\sigma^2$ equals the variance of the individual level error $\varepsilon_{ij}$. This coefficient measures the percent of the total inter-individual variability in blood pressure that is between sibships and is a general measure of clustering of individual blood pressure in sibships. ICCs were calculated for the null models to establish a general measure of the extent of familial clustering of blood pressure. ICCs were also calculated for models 2-4 and each estimate was compared to those derived from the null models. Estimates of proportional variance explained were calculated and the degree to which the proportions of total variance in individual blood pressure levels that were within and between sibships (i.e.- families) changed as variables were added at both the individual- and family-levels was assessed. To assess the reduction in within-family variance, the following formula was applied: $(\sigma^2_1 - \sigma^2_2) / \sigma^2_1$, with $\sigma^2_1$ derived from model 1 and $\sigma^2_2$ derived from models 2-4 separately. Similarly, the reduction in between-family variance was assessed using the following formula: $(\tau_{00\ 1} - \tau_{00\ 2}) / \tau_{00\ 1}$, with $\tau_{00\ 1}$ derived from model 1 and $\tau_{00\ 2}$ derived from models 2-4 separately.

Comparing models 1 and 2 yielded estimates of the proportions of both variance components explained due to individual-level factors. Comparing models 1 and 3 yielded an estimate of the proportion of between-family variance explained due to family specific, parental histories of hypertension. Comparing models 1 and 4 allowed for the examination of how both variance components changed due to the addition of individual and family-level predictor variables.

To assess the odds and the magnitude of variation between families in hypertension control, an unconditional logistic multilevel model was fit. This model took the full form: Log odds (blood pressure control$_{ij}$) = $\gamma_{00}$ +$U_{0j}$. The estimate for the resulting $\gamma_{00}$ coefficient was interpreted as the log odds of hypertension control across families, while the variance of $U_{0j}$ ($\tau_{00}$), was interpreted as the variance between families in family-average log odds of hypertension control. Exponentiation of the estimate for $\gamma_{00}$ yielded an estimate of the odds of hypertension control and an estimate for the corresponding probability was determined by the following formula: $1 / (1 + e^{(-logit)})$. A 95% confidence interval around the odds of hypertension control across families was determined by the following formula: $\gamma_{00} \pm 1.96*\sqrt{\tau_{00}}$. Transforming these upper- and lower-bound odds into probabilities yielded a range of hypertension control probabilities across families.

**Sib-Sib Blood Pressure Correlations by Neighborhood Poverty**

To investigate the potential influence of neighborhood socioeconomic environment on sib-sib quantitative blood pressure correlations and aggregation of blood pressure control, a separate sibpair analysis, stratified by neighborhood poverty, was performed. As highlighted in Chapter 3, baseline address information was only available

for the African American GENOA subjects. As such, the sibpair analyses were restricted to African American sibpairs. The analytic sample consisted of full sibpairs only. All subjects in the analytic sample were hypertensive, aware of their hypertension status, currently taking prescribed antihypertensive medication(s) to lower blood pressure, had baseline address information that was successfully geo-coded to the census tract level and linked to tract level socioeconomic indicator data, and had at least one full sibling that met the same criteria. The final analytic sibpair sample contained 969 subjects from 387 sibships. A total of 871 possible sibpairs were analyzed. As in Chapter 3, neighborhoods were defined as poor if the percentage of poverty within a given census tract exceeded 25%, and more socioeconomically advantaged otherwise. For all possible sibpairs, concordance of neighborhood poverty was determined (i.e. - both residing in poor neighborhood(s), one residing in poor neighborhood, neither residing in poor neighborhood). Pearson's correlation coefficients (unadjusted, and age-sex adjusted) were estimated to assess sib-sib correlations of SBP and DBP levels by neighborhood concordance. Odds ratios (OR) (odds that siblings were concordant for blood pressure control divided by the odds that they were discordant) were calculated as a measure of familial aggregation blood pressure control by neighborhood concordance. All statistical analyses were performed in the R statistical package (6). An alpha-level of 0.05 was used to determine statistical significance.

## RESULTS

### Systolic Blood Pressure

Variance components and calculated ICCs for models 1 – 4, and the fixed effects from the full model (Model 4) for the African American cohort are illustrated in Table

4.1. The ICC from the null model (Table 4.1, Null model) suggests moderate clustering of SBP within families, as approximately 13.5% of the inter-individual variability in SBP was at the family-level. The addition of only individual-level variables to the null model led to a 3.6% reduction in within-family variability and a 22.3% reduction in the between-family variability. In general, the addition of group-level variables does not impact within-group variability, but can have an impact on between-group variability. The addition of only family-level variables to the null model did not lead to reductions in between-family variability (nor within-family variability as expected). The reductions in both types of variability due to the addition of both individual- and family-level variables to the null model were essentially the same as the reductions due to the addition of individual-level variables only, although the addition of family-level variables after accounting for individual-level variables (model 4) led to a slightly higher overall reduction (23.4%) in the between-family variability. The average SBP across families (i.e. - common intercept as assessed from null model) was 139.83 mmHg. In the comprehensive model including individual- and family-level variables (Table 4.1, Model 4), increasing age, female sex, diabetes, and both parental histories of hypertension were all associated with increases in SBP. Conversely, increasing levels of education was associated with decreases in SBP. Age, diabetes, and education use all reached statistical significance.

Variance components and calculated ICCs for models 1 – 4, and the fixed effects from the full model (Model 4) for the non-Hispanic white cohort are illustrated in Table 4.2. The ICC from the null model (Table 4.2, Null model) indicates that approximately 16.8% of the inter-individual variability in SBP was at the family-level. Although still

moderate, this degree of familial clustering was slightly higher compared to the African American cohort. The addition of only individual-level variables to the null model led to a 4.8% reduction in within-family variability and a 26.1% reduction in the between-family variability. The addition of only family-level variables to the null model led to a small 1% reduction in the between-family variability (and no reduction in the within-family variability as group-level variables will only reduce between-group variability). The addition of both individual- and family-level variables to the null model led to a 5.1% reduction in within-family variability and a 26.8% reduction in the between-family variability. The average SBP across families was 135.90 mmHg, slightly lower than that of the African American cohort. In the comprehensive model including individual- and family-level variables (Table 4.2, Model 4), increasing age, BMI, diabetes, and maternal history of hypertension were all associated with increases in SBP, while female sex and paternal history of hypertension were associated with decreases in SBP. Age, BMI, and maternal history of hypertension all reached statistical significance.

**Diastolic Blood Pressure**

Variance components and calculated ICCs for models 1 – 4, and the fixed effects from the full model (Model 4) for the African American cohort are illustrated in Table 4.3. Approximately 20% of the inter-individual variability in DBP was at the family-level (ICC from null model (Table 4.3, Null model) = 19.7). The addition of only individual-level variables to the null model led to a 3.6% reduction in within-family variability and a 27.0% reduction in the between-family variability in individual DBP. The addition of only family-level variables to the null model led to a 6.0% reduction in between-family variability and the fixed effect for maternal history of hypertension was

statistically significant. The addition of both individual- and family-level variables to the null model led to a 3.3% reduction in within-family variability and a 27.9% reduction in the between-family variability. The average DBP across families was 78.21 mmHg. In the comprehensive model including individual- and family-level variables (Table 4.3 Model 4), only parental histories of hypertension were associated with increases in DBP. Conversely, all individual-level fixed effects (age, female sex, BMI, diabetes, and education) were associated with decreases in DBP. The age, female sex, and education associations were statistically significant, and the BMI association was marginally significant.

Variance components and calculated ICCs for models 1 – 4, and the fixed effects from the full model (Model 4) for the non-Hispanic white cohort are illustrated in Table 4.4. As in the African American cohort, approximately 20% of the inter-individual variability in DBP was at the family-level (ICC from null model (Table 4.4, Null model) = 20.4). The addition of only individual-level variables to the null model led to a 9.5% reduction in within-family variability and a 22.7% reduction in the between-family variability in individual DBP. The addition of only family-level variables to the null model did not lead to reductions in variable components, although the fixed effect for maternal history of hypertension was statistically significant. The addition of both individual- and family-level variables (Table 4.4, Model 4) to the null model led to a 10.6% reduction in within-family variability and a 21.3% reduction in the between-family variability. The average DBP across families was 79.06 mmHg. Maternal history of hypertension was associated increased DBP. Conversely, increasing age, female sex, diabetes, and paternal history of hypertension were all associated with decreases in DBP.

The age, female sex, diabetes and maternal history of hypertension associations were statistically significant.

**Blood Pressure Control**

Among African Americans, the log odds of hypertension control across families was 0.10, corresponding to an odds of 1.11 and a probability of 0.52 (95% confidence interval (CI), 0.24, 0.80). Among non-Hispanic whites, the log odds of hypertension control across families was 0.47, corresponding to an odds of 1.60 and a probability of 0.62 (95% CI, 0.23, 0.90).

**Blood Pressure Correlations and Aggregation of Blood Pressure Control by Neighborhood Poverty**

Descriptive statistics for the hypertensive African American subjects (n=960) included in the sibpair by neighborhood poverty analyses are presented in Table 4.5. Table 4.6 presents the sib-sib correlations of SBP and DBP. Of the total 871 possible sibpairs, 313 were concordant for residing in poor neighborhoods, 365 were discordant for poor neighborhood of residence, and 193 were concordant for residing in more socioeconomically advantaged neighborhoods. In the pooled sample of all 871 possible African American sibpairs, significant sib-sib correlations were detected for both SBP ($r = 0.12$, $p < 0.001$) and DBP ($r = 0.14$, $p < 0.001$). Examination of the sib-sib correlations of quantitative blood pressure values by poor neighborhood of residence concordance revealed that SBP values among sibpairs in which both siblings resided in poor neighborhoods were statistically significant and more strongly correlated ($r = 0.20$, $p < 0.001$). Similarly, statistically significant sib-sib correlations of DBP values were detected among sibpairs in which one or both siblings resided in poor neighborhoods.

Conversely, sib-sib correlations of quantitative blood pressure values were not significantly correlated among sibpairs in which both siblings resided in more socioeconomically advantaged neighborhoods. There was statistically significant familial aggregation (sib-sib concordance) of blood pressure control among sibpairs in which both siblings resided in poor neighborhoods (OR = 1.84; 95% CI: 1.17, 2.90), but not among sibpairs in which only one (OR = 1.23; 95% CI: 0.81,1.86) or neither (OR = 0.99; 95% CI: 0.56, 1.75) sibling resided in poor neighborhoods.

**DISCUSSION**

Family aggregation of blood pressure is well recognized (1) and has been documented in numerous populations (2, 7, 8). Results from this study provided further evidence of moderate familial aggregation of quantitative blood pressure levels in both African Americans non-Hispanic Whites. For both racial/ethnic groups, the addition of individual-level variables led to significant reductions in within- and between-family variability in individual SBP and DBP, and expected relationships were detected for the individual-level fixed effects of age, BMI, and diabetes. There was also evidence of an inverse relationship between education and SBP (as reported in Chapter 2) and DBP among African Americans, after control for other individual and familial factors. Furthermore, individual-level education explained approximately 1% of the between-family variability in SBP. Maternal histories of hypertension did explain a moderate proportion of the between-family variability in SBP and DBP among non-Hispanic whites. Other studies have demonstrated similar associations between maternal history of hypertension and offspring blood pressure levels, and familial aggregation of other factors known to influence blood pressure (e.g. – dietary intake and physical activity)

may be stronger between mothers and their offspring (7). Despite this, parental history of hypertension does not seem to confer strong contextual effects that condition common blood pressure levels in non-Hispanic whites or African American families. The addition of individual- and family-level fixed effects reduced, but did not explain all of, quantitative blood pressure clustering among sibships in each racial/ethnic group. This likely reflects residual confounding that stems from the omission of potentially important predictor variables at one or multiple levels.

Previous research on the overall GENOA hypertensive sibships sample detected evidence of familial aggregation of hypertension treatment and control (2). Consistent with these earlier findings, unconditional (null) multilevel models fit in this study indicated that hypertension control among treated hypertensives aggregates in non-Hispanic white and African American families. While the range of probabilities of hypertension control were comparably wide for both ethnic groups, the odds and probability of hypertension control were greater in non-Hispanic White families, compared to African American families (as expected and previously reported in Chapter 2). Daniels et al. suggest that the familial aggregation of hypertension treatment and control are likely explained by a combination of shared environmental and genetic influences, and further point out that, "numerous environmental factors are indexed by socioeconomic status, which aggregates in families and correlates inversely with blood pressure levels (2)." Acknowledging this, the study presented here extended the previous research on familial aggregation of blood pressure control in the GENOA cohort by examining the degree to which neighborhood socioeconomic environment concordance among sibs shaped familial aggregation of blood pressure control. In general, sib-sib

correlations of quantitative blood pressure values and familial aggregation of blood pressure control were detected among sibpairs in which both siblings resided in poor neighborhoods. These findings represent a possible cross level interaction in which the degree of familial similarities in blood pressure outcomes is dependent (at least in part) on shared socioeconomic environmental context.

The present study had several limitations. First, the cross-sectional nature of the study limited the ability to make causal inferences. Second, selection bias may have been present in this study, as only families with at least two sibs with essential hypertension diagnosed before age 60 were included. Third, if the individual-level and/or group-level models were misspecified, estimates at both levels may have been biased. This brief examination of familial blood pressure correlations was particularly susceptible to misspecification of the family-level models, since parental histories of hypertension were the only variables modeled at this level and other unavailable family-level variables may have demonstrated contextual familial effects that could potentially condition common blood pressure levels among families. Furthermore, the detected moderate contextual effect of maternal history for hypertension among non-Hispanic whites may simply reflect unmeasured individual-level characteristics rather than a common familial effect. The examination of the influence of neighborhood socioeconomic environment was specifically carried out among the African American GENOA study subjects from 48 neighborhoods in the Jackson, MS tri-county area. As such, these particular findings may not be generalizable to other racial/ethnic groups, or to other individuals (regardless of race/ethnicity) residing in geographic areas marked by different socioeconomic environments.

In conclusion, this analysis provided new insights into familial aggregation of blood pressure outcomes, by specifically examining the influence of numerous factors defined at multiple levels (individual, family, and neighborhood). Significant findings across these levels suggest that combinations of family- and community-based interventions may be successful in the prevention and control of hypertension.

**Table 4.1. Familial correlation of systolic blood pressure in GENOA African Americans (n=1123)**

| Covariance parameter estimates | | | | |
|---|---|---|---|---|
| Estimate | Null model | Model 2 | Model 3 | Model 4 |
| $\tau_{00}$ | 69.65 | 54.14 | 70.31 | 53.39 |
| $\sigma^2$ | 444.81 | 429.00 | 445.03 | 430.08 |
| ICC *100% | 13.54% | 11.21% | 13.64% | 11.04% |
| **Fixed effect estimates from Model 4** | | | | |
| Effect | | Estimate | SE | p-value |
| Intercept | | 116.68 | 7.41 | **<0.0001** |
| Individual-level | | | | |
| Age (years) | | 0.43 | 0.08 | **<0.0001** |
| Gender | | | | |
| Male (ref) | | | | |
| Female | | 2.46 | 1.55 | 0.1131 |
| BMI (kg/m2) | | -0.01 | 0.11 | 0.9320 |
| Diabetes | | | | |
| No (ref) | | | | |
| Yes | | 5.56 | 1.50 | **0.0002** |
| Education (years) | | -0.58 | 0.20 | **0.0041** |
| Family-level | | | | |
| Paternal history of hypertension | | | | |
| No (ref) | | | | |
| Yes | | 1.08 | 1.44 | 0.4540 |
| Maternal history of hypertension | | | | |
| No (ref) | | | | |
| Yes | | 0.84 | 1.44 | 0.5635 |

Null model – random intercept only model; Model 2 – includes all individual-level variables only; Model 3 includes all family-level variables only; Model 4 includes all individual- and family-level variables. $\tau_{00}$ = macro error variance. $\sigma^2$ = individual error variance. ICC = intraclass correlation coefficient. BMI = body mass index. Bold type indicates $p<0.05$.

**Table 4.2. Familial correlation of systolic blood pressure in GENOA non-Hispanic whites (n=970)**

| Covariance parameter estimates | | | | |
|---|---|---|---|---|
| Estimate | Null model | Model 2 | Model 3 | Model 4 |
| $\tau_{00}$ | 45.19 | 33.40 | 44.87 | 33.07 |
| $\sigma^2$ | 224.26 | 213.42 | 223.81 | 212.91 |
| ICC *100% | 16.77% | 13.53% | 16.70% | 13.44% |
| **Fixed effect estimates from Model 4** | | | | |
| Effect | | Estimate | SE | p-value |
| Intercept | | 99.49 | 6.16 | **<0.0001** |
| Individual-level | | | | |
| Age (years) | | 0.51 | 0.06 | **<0.0001** |
| Gender | | | | |
| Male (ref) | | | | |
| Female | | -0.35 | 1.02 | 0.7353 |
| BMI (kg/m2) | | 0.17 | 0.08 | **0.0329** |
| Diabetes | | | | |
| No (ref) | | | | |
| Yes | | 2.04 | 1.56 | 0.1898 |
| Education (years) | | 0.02 | 0.23 | 0.9413 |
| Family-level | | | | |
| Paternal history of hypertension | | | | |
| No (ref) | | | | |
| Yes | | -0.13 | 1.08 | 0.9061 |
| Maternal history of hypertension | | | | |
| No (ref) | | | | |
| Yes | | 2.55 | 1.13 | **0.0243** |

Null model – random intercept only model; Model 2 – includes all individual-level variables only; Model 3 includes all family-level variables only; Model 4 includes all individual- and family-level variables. $\tau_{00}$ = macro error variance. $\sigma^2$ = individual error variance. ICC = intraclass correlation coefficient. BMI = body mass index. Bold type indicates $p<0.05$.

**Table 4.3. Familial correlation of diastolic blood pressure in GENOA African Americans (n=1123)**

| Covariance parameter estimates | | | | |
|---|---|---|---|---|
| Estimate | Null model | Model 2 | Model 3 | Model 4 |
| $\tau_{00}$ | 30.68 | 22.41 | 28.86 | 22.14 |
| $\sigma^2$ | 125.46 | 120.97 | 126.48 | 121.29 |
| ICC *100% | 19.65% | 15.63% | 18.58% | 15.44% |
| **Fixed effect estimates from Model 4** | | | | |
| Effect | | Estimate | SE | p-value |
| Intercept | | 108.49 | 4.06 | **<0.0001** |
| Individual-level | | | | |
| Age (years) | | -0.38 | 0.04 | **<0.0001** |
| Gender | | | | |
| Male (ref) | | | | |
| Female | | -2.41 | 0.84 | **0.0044** |
| BMI (kg/m2) | | -0.11 | 0.06 | 0.0624 |
| Diabetes | | | | |
| No (ref) | | | | |
| Yes | | -0.62 | 0.82 | 0.4473 |
| Education (years) | | -0.23 | 0.11 | **0.0367** |
| Family-level | | | | |
| Paternal history of hypertension | | | | |
| No (ref) | | | | |
| Yes | | 0.26 | 0.79 | 0.7465 |
| Maternal history of hypertension | | | | |
| No (ref) | | | | |
| Yes | | 0.77 | 0.79 | 0.3304 |

Null model – random intercept only model; Model 2 – includes all individual-level variables only; Model 3 includes all family-level variables only; Model 4 includes all individual- and family-level variables. $\tau_{00}$ = macro error variance. $\sigma^2$ = individual error variance. ICC = intraclass correlation coefficient. BMI = body mass index. Bold type indicates $p<0.05$.

**Table 4.4. Familial correlation of diastolic blood pressure in GENOA non-Hispanic whites (n=970)**

| Covariance parameter estimates | | | | |
|---|---|---|---|---|
| Estimate | Null model | Model 2 | Model 3 | Model 4 |
| $\tau_{00}$ | 18.05 | 13.96 | 18.20 | 14.20 |
| $\sigma^2$ | 70.36 | 63.66 | 69.89 | 62.93 |
| ICC *100% | 20.42% | 17.99% | 20.66% | 18.41% |
| **Fixed effect estimates from Model 4** | | | | |
| Effect | | Estimate | SE | p-value |
| Intercept | | 96.13 | 3.46 | **<0.0001** |
| Individual-level | | | | |
| Age (years) | | -0.28 | 0.03 | **<0.0001** |
| Gender | | | | |
| Male (ref) | | | | |
| Female | | -3.96 | 0.57 | **<0.0001** |
| BMI (kg/m2) | | 0.00 | 0.05 | 0.9356 |
| Diabetes | | | | |
| No (ref) | | | | |
| Yes | | -2.03 | 0.87 | **0.0195** |
| Education (years) | | 0.02 | 0.13 | 0.8512 |
| Family-level | | | | |
| Paternal history of hypertension | | | | |
| No (ref) | | | | |
| Yes | | -0.64 | 0.61 | 0.2903 |
| Maternal history of hypertension | | | | |
| No (ref) | | | | |
| Yes | | 1.74 | 0.64 | **0.0066** |

Null model – random intercept only model; Model 2 – includes all individual-level variables only; Model 3 includes all family-level variables only; Model 4 includes all individual- and family-level variables. $\tau_{00}$ = macro error variance. $\sigma^2$ = individual error variance. ICC = intraclass correlation coefficient. BMI = body mass index. Bold type indicates $p<0.05$.

**Table 4.5. Selected sample characteristics of the treated hypertensive African American GENOA study subjects included in the sibpair by neighborhood poverty analyses (n=960 from 871 sibpairs)**

| | |
|---|---|
| Age (years) | 60.3 (9.1) |
| BMI ($kg/m^2$) | 31.4 (6.6) |
| Education (years completed) | 11.5 (3.6) |
| SBP (mmHg) | 141.7 (22.4) |
| DBP (mmHg) | 79.1 (12.8) |
| Female (%) | 71 |
| Type 2 diabetes (%) | 26 |
| BP controlled[a] (%) | 46 |
| Residence within poor neighborhood[b] | 58 |

Quantitative variables are presented as mean (SD); categorical variables as percentages. [a]Blood pressure control defined as systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg. [b]Poor neighborhood based on percentage of census tract poverty, where a neighborhood was defined as "poor" if the percentage of poverty was greater than 25%, and "more advantaged" otherwise. BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; BP = blood pressure.

**Table 4.6. Blood pressure correlations between GENOA African American sibpairs (n=871) by neighborhood poverty concordance**

| Systolic blood pressure | | Unadjusted | | Age and sex adjusted | |
|---|---|---|---|---|---|
| | # of Sib Pairs (# of Families) | r | p-value | r | p-value |
| Both Sibs in Poor* Neighborhoods | 313 (181) | 0.206 | **0.0002** | 0.183 | **0.0012** |
| One Sib in Poor* Neighborhood | 365 (197) | 0.045 | 0.3884 | 0.022 | 0.6723 |
| Neither Sib in Poor* Neighborhood | 193 (116) | 0.101 | 0.1621 | 0.051 | 0.4757 |
| Total | 871 (387) | 0.121 | **0.0003** | 0.088 | **0.0090** |

| Diastolic blood pressure | | Unadjusted | | Age and sex adjusted | |
|---|---|---|---|---|---|
| | # of Sib Pairs (# of Families) | r | p-value | r | p-value |
| Both Sibs in Poor* Neighborhoods | 313 (181) | 0.140 | **0.0133** | 0.107 | **0.0594** |
| One Sib in Poor* Neighborhood | 365 (197) | 0.187 | **0.0003** | 0.133 | **0.0112** |
| Neither Sib in Poor* Neighborhood | 193 (116) | 0.036 | 0.6233 | -0.028 | 0.7031 |
| Total | 871 (387) | 0.137 | **0.0001** | 0.088 | **0.0094** |

*Poor Neighborhoods defined as census tracts with >25% poverty, where percent poverty is defined as the % of individuals living below the poverty level in 1999 within a given census tract. r = Pearson's correlation coefficient. Bold type indicates $p < 0.05$.

**Appendix 4.1. Calculations for familial aggregation of blood pressure control by neighborhood poverty concordance.**

Both Sibs Residing in Poor Neighborhoods

| | | Sib1 | |
|---|---|---|---|
| | | BP Controlled | BP Not Controlled |
| Sib2 | BP Controlled | 70 | 61 |
| | BP Not Controlled | 70 | 112 |

OR = (70*112)/(61*70) = 1.84
SE (log OR) = sqrt ((1/70)+(1/61)+(1/70)+(1/112)) = 0.2321496
Lower 95 % CI = 1.84 * exp - [1.96*0.2321496] = 1.17
Upper 95% CI = 1.84 * exp[1.96*0.2321496] = 2.90

One Sib Residing in Poor Neighborhood

| | | Sib1 | |
|---|---|---|---|
| | | BP Controlled | BP Not Controlled |
| Sib2 | BP Controlled | 86 | 79 |
| | BP Not Controlled | 94 | 106 |

OR = (86*106)/(79*94) = 1.23
SE (log OR) = sqrt ((1/86)+(1/79)+(1/94)+(1/106)) = 0.2106143
Lower 95 % CI = 1.23 * exp - [1.96*0.2106143] = 0.81
Upper 95% CI = 1.23 * exp[1.96*0.2106143] = 1.86

Neither Sib Residing in Poor Neighborhood

| | | Sib1 | |
|---|---|---|---|
| | | BP Controlled | BP Not Controlled |
| Sib2 | BP Controlled | 40 | 50 |
| | BP Not Controlled | 46 | 57 |

OR = (40*57)/(50*46) = 0.99
SE (log OR) = sqrt ((1/40)+(1/50)+(1/46)+(1/57)) = 0.2903153
Lower 95 % CI = 0.99 * exp - [1.96*0.2903153] = 0.56
Upper 95% CI = 0.99 * exp[1.96*0.2903153] = 1.75

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# Chapter 5

## Interactions Between Cell Adhesion Molecule Genes and Antihypertensive Drug Therapies in Determining Systolic Blood Pressure in Hypertensive Subjects

## INTRODUCTION

Hypertension affects more than 65 million adults in the United States (US) and is the most common disease for which adults seek medical attention (1, 2). Uncontrolled hypertension is an established risk factor for cardiovascular, cerebrovascular, and renal disease morbidity and mortality. In addition to lifestyle changes and behavior modifications, a variety of antihypertensive medications are commonly used as monotherapies or in combination to attempt to control hypertension. Accordingly, antihypertensive medications are among the most frequently used medications in the US. Despite this, only slightly more than half of subjects with hypertension in the US are treated pharmacologically for their condition and roughly two-thirds of those treated have their blood pressure adequately controlled (3). A contributing factor to this lack of blood pressure control is that hypertensives respond heterogeneously to antihypertensive therapies. In addition to various environmental influences, genetic variation that alters the structure, configuration, or quantity of any of the proteins involved in pharmacokinetic or pharmacodynamic mechanisms may contribute to interindividual variation in drug response (4). The goal of identifying genetic variations that influence these mechanisms regulating blood pressure response to antihypertensive therapies is to use the identified genetic predictors of response as a benchmark for ascertaining a given

drug's efficacy and toxicity prior to administering the drug to patients. If successful, the findings from antihypertensive phamacogenetic (and emerging pharmacogenomic) research could be used to tailor specific drug interventions based on an individual's biological profile. This could have major public health and economic impacts by improving the effectiveness of therapy, while concurrently reducing the occurrence of adverse events and clinical management periods.

Genetic and epidemiological research efforts, sponsored by the National Heart Lung and Blood Institute (NHLBI), have been established to identify genes influencing inter-individual blood pressure variation. Genomic regions that potentially influence blood pressure variation have been identified on several chromosomes through a variety of linkage analyses. Genome-wide linkage analyses have identified evidence of linkage on chromosome 1 with hypertension and blood pressure used as phenotypes (5, 6). Chang et al. recently conducted genome-wide linkage and candidate gene studies and identified multiple genes located on chromosome 1q that were associated with systolic blood pressure (SBP) and one positional candidate gene identified in these analyses was the *E Selectin* (*SELE*) gene (7). The *vascular cell adhesion molecule-1* (*VCAM1*) gene is also located on chromosome 1 in a different region (1p) and has been linked to cardiovascular risk factors including blood pressure (8).

Although it is not clear whether inflammation may contribute to the development of hypertension or if the two are independent phenomena interacting bi-directionally to promote vascular alterations, a growing interest in the potential pathophysiologic link between inflammation and hypertension has emerged (9-17) Recent epidemiological

studies have demonstrated that the presence of a chronic low grade inflammatory status can anticipate the future development of hypertension (9, 18-20).

Cell adhesion molecules play an integral role in the inflammatory process in general, and are involved in vascular inflammatory responses stemming from mechanical stress on the vascular walls and/or the effects of pro-inflammatory humoral factors (9). The *SELE* gene is a 13 kb gene localized to 1q22-q25 and the *VCAM1* gene is a 25 kb gene localized to 1p32-p31. Both genes encode for glycoproteins expressed by activated endothelium that mediate the adhesion of leukocytes to the vascular lining during the inflammatory process and are thought to play a role in the pathogenesis of atherosclerosis (21, 22). Hypertension is a major risk factor for atherosclerosis and is associated with endothelial cell alterations. Several studies have shown that hypertensive subjects have elevated serum levels of soluble e-selectin and vascular adhesion molecule-1 compared to normotensive controls (23-25), and positive correlations between elevated levels of soluble vascular adhesion molecule-1 and SBP have also been reported (26), suggesting that *SELE* and *VCAM1* could be involved in the pathogenesis of hypertension. The relationships between hypertension and several polymorphisms in the *SELE* gene have been studied. In particular, studies have demonstrated statistically significant associations between the L/F554 polymorphism and both SBP and diastolic blood pressure (DBP) levels (27). Associations have also been detected between arterial stiffness and polymorphisms in candidate genes, including *VCAM1* and other inflammatory molecule genes (28). Age-related arterial stiffening is thought to be a major contributor to isolated systolic hypertension (29) and the importance of SBP in the clinical management of hypertension has been recognized (30, 31).

Genes that potentially influence the risk of developing hypertension are prime candidates for influencing an individual's pharmacodynamic response to treatment. Therefore we examined whether single nucleotide polymorphisms (SNPs) in the *SELE* and *VCAM1*genes influence SBP in hypertensive subjects stratified by antihypertensive drug therapy category and tested for gene-by-drug interactions in a population-based sample of hypertensive African Americans and non-Hispanic whites from the Genetic Epidemiology Network of Arteriopathy (GENOA) study.

## METHODS

### Study Population

In 1995, the National Heart, Lung and Blood Institute (NHLBI) established The Family Blood Pressure Program (FBPP) to assess the genetic influence on inter-individual blood pressure variation, hypertension, and hypertensive target organ damage. One of the four networks established by the NHLBI to meet this objective is the Genetic Epidemiology Network of Arteriopathy (GENOA). GENOA field centers in Jackson, MS, Starr County, TX, and Rochester, MN recruited hypertensive African American, Hispanic, and non-Hispanic white sibships, respectively, for linkage and family-based association studies. Subject were diagnosed with hypertension if they had a previous clinical diagnosis of hypertension by a physician with current antihypertensive treatment or an average SBP >=140 mmHg and/or an average diastolic blood pressure (DBP) >=90 mmHg.

In Rochester, MN and Jackson, MS, recruitment was restricted to sibships that contained a minimum of two subjects diagnosed with essential hypertension before the age of 60. Once this criterion was met, the entire sibship was invited to participate in the

study. As the prevalence of diabetes among Mexican-Americans is high, the Starr County recruitment was restricted to Mexican-American sibships containing at least two subjects diagnosed with type-2 diabetes (32). Data was collected through personal interviews, and physical and laboratory examinations. The initial phase of the GENOA study took place from September 1995 through June 2001 (33). The study presented here focused on all of the hypertensive African American (n = 1329) and non-Hispanic white (n = 1129) hypertensive subjects.

**Blood Pressure Readings**

Blood pressure measurements were made with random zero sphygmomanometers and cuffs appropriate for arm size. Three readings were taken in the right arm after the subject rested in the sitting position for at least five minutes according to the Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7, 2003) guidelines (34). The SBP and DBP values were determined by the first and fifth phase Korotkoff sounds, respectively, and the last two blood pressure readings were averaged for the analyses. The diagnosis of hypertension was established based on blood pressure levels measured at the study visit ($\geq$140/90 mmHg), or a prior diagnosis of hypertension and current treatment with prescription antihypertensive medications.

**Antihypertensive Medications**

Based on lists of all antihypertensive medications available in the US, each prescription antihypertensive drug recorded at the study visit was assigned a code number corresponding to the first 6 digits of the Medi-Span Generic Product Identifier. This number, which identifies pharmacologically equivalent drug products, was used to

categorize agents with similar mechanisms of antihypertensive action. In this study, subjects on monotherapy were classified as taking a "beta-blocker", "calcium-channel blocker", "renin-angiotensin-aldosterone system (RAAS) inhibitor", "diuretic only", or "other antihypertensive" drug (e.g. research drugs). Subjects on combination therapies were classified as taking "beta-blocker + diuretic", "beta-blocker + other", "diuretic + other", or "neither beta-blocker nor diuretic". Due to both the wide variation in the types of drugs falling into the monotherapy class of "other antihypertensive" and the combination therapy class "neither beta-blocker nor diuretic", and the relatively low group sizes, subjects in these classes were excluded from the regression analyses.

**Genotyping**

SNP genotyping was conducted at the GENOA central genotyping center at the University of Texas-Houston. SNPs were selected in positional candidate genes in the region using the public National Center for Biotechnology Information (NCBI) database (35) and the private Celera database (36). SNP genotyping on a total of 11 loci in the *SELE* gene and 16 loci in the *VCAM1* gene (Table 5.3) were obtained using a combination of two genotyping platforms: mass spectrometer-based detection system implemented on a Sequenom MassARRAY system, and the fluorogenic TaqMan assay implemented on an ABI Prism 7900 Sequence Detection System.

**Statistical Analysis**

The primary goal of this analysis was to determine if there was evidence of SNP effects and gene-drug interactions on SBP levels in African American and non-Hispanic white hypertensives. Given the correlation structure inherent in sibship data of the GENOA study cohort, the distribution of subjects within each of the ten treatment groups

(no treatment, five monotherapy groups and four combination therapy groups) was assessed. Although some degree of relatedness within treatment groups was evident in both racial/ethnic groups (African Americans, Table 5.1; non-Hispanic whites Table 5.2), there were few related subjects within particular treatment groups. As such, regression analyses did not formally account for familial correlations. The parameter estimates in regression modeling are not affected by correlated data, however the standard errors of parameters are often underestimated (37). Differences in the age, BMI, SBP and DBP distributions across treatment groups were examined using an *F*-test. To determine if two SNPs were likely to be representing the same variation in the gene we used $r^2 = \frac{D^2}{p_1 p_2 q_1 q_2}$ (38) as a measure of linkage disequilibrium (LD). SNPs with high $r^2$ values are likely to have the same genotype-phenotype relationship.

Age- and sex-adjusted SNP effects on mean levels of SBP within each treatment class were estimated using linear regression modeling, where SNP genotypes were dummy coded. The dummy variables for each SNP of interest were modeled against the SBP residuals from separate multivariable regression models that included age and sex as predictor variables. Modeling the SNP genotype relationship to the resulting residuals yielded age- and sex-adjusted associations between each of the selected SNP genotypes and SBP. The regression models within each treatment class took the following basic form:

$$Y_i = \beta_0 + \beta_1 SNP_{12i} + \beta_2 SNP_{22i} + \varepsilon, \quad (1)$$

where $Y_i$ = the age- and sex-adjusted SBP residual for the $i^{th}$ subject, $SNP_{12i}$ = the heterozygous genotype of the SNP of interest for the $i^{th}$ subject, and $SNP_{22i}$ = the second alphabetically ordered, homozygous genotype of the SNP of interest for the $i^{th}$ subject.

Because of the limited sample size of some of the drug categories, a leave-one-out cross validation strategy was used to provide more accurate estimates of the percent variation in SBP explained by the SNPs and to reduce reporting of false positives. The leave-one-out cross validation procedure leaves one person out of the sample (designated as the test case) and estimates the genetic model on the N-1 remaining subjects (designated as the training cases). The estimated model was then applied to the test case, a predicted SBP was calculated, and the residual variability between observed and predicted values was estimated. A cross-validated $R^2$ value was then calculated by taking the total SBP variability in the sample minus the total residual variability divided by the total variability. The results were averaged across all test cases. The cross-validated $R^2$ will have a negative value when the model's prediction is poor (i.e. the predicted values deviate substantially from the observed values).

In order to formally evaluate whether there was evidence of gene-by-drug interactions, the effect of each SNP on SBP was compared between each treatment class. Using analysis of covariance methods, overall gene-by-drug interactions were systematically tested for using the partial *F*-test and potential SNP effect differences among each treatment class were assessed using pair-wise comparisons. The regression models used to assess each pairwise comparison between each of the treatment classes extended equation (1) above by adding SNP-treatment class interaction terms and took the following form:

$$Y_i = \beta_0 + \beta_1 SNP_{12i} + \beta_2 SNP_{22i} + \beta_3 SNP_{12} * C_i + \beta_4 SNP_{12} * C_i + \varepsilon, \quad (2)$$

where $Y_i$ = the age- and sex-adjusted SBP residual for the $i^{th}$ subject; $SNP_{12i}$ = the heterozygous genotype of the SNP of interest for the $i^{th}$ subject; $SNP_{22i}$ = the second alphabetically ordered, homozygous genotype of the SNP of interest for the $i^{th}$ subject; and C = a dichotomous treatment class variable that is assigned a value of "0" for the first treatment class of each possible treatment class pair, and a value of "1" for the second treatment class of each possible treatment class pair.

The lack of replication of genetic effects or gene-environment interactions on complex traits such as blood pressure is a major issue in the field of human genetic association studies. In order to minimize false inferences a leave one out cross validation strategy was used to estimate the extent to which gene-drug interactions improved prediction of SBP levels beyond the SNP main effects.

Because the cross-validation method provides an alternative to the adjustment of p-values (which is often conservative and can lead to type II errors), p-values were not formally adjusted for multiple testing. This issue is particularly important in susceptibility gene research since the small effects of relatively common alleles are likely to have the greatest public health impact but are unlikely to achieve p-values that withstand conservative adjustments. At the heart of the multiple testing issue is the question of how to separate out false positives from true positives. Adjusting p-values for multiple comparisons does not directly address this question, but rather aims to reduce the probability of a false positive. Cross-validation better addresses this question by

testing the predictive capability of the model on independent test cases and provides a more direct assessment of whether the result is a false positive.

All regression analyses conducted to assess (a) SNP main effects within the various treatment classes, and (b) gene-drug interactions were adjusted for age and sex. An alpha level of 0.05 was used to determine statistical significance and a cross-validated $R^2 \times 100 > 0.50$ cut point was used to identify SNPs with potential predictive capabilities based on their performance in the test cases. All analyses were performed in R (39).

**RESULTS**

The average age, BMI, SBP and DBP values for African American subjects in each treatment class are presented in Table 5.1. This table also presents analysis of variance results used to determine if the sample mean of these traits differed significantly between treatment classes. Age differed significantly ($p=0.008$) between the treatment classes, with the oldest average age among subjects in the "beta-blocker + other" class and the youngest average age among those in the "calcium-channel blocker" class. Although the mean BMI values in all treatment classes were at or above the clinical cutpoint for clinical obesity, they differed significantly ($p<0.001$) between the various treatment classes, with the highest mean BMI values among subjects in the "diuretic + other" class. Overall, there was evidence of significant variation ($p<0.001$) of SBP across treatment classes, with the highest mean level among subjects in the "beta-blocker + other" and the lowest mean level among those in the "RAAS inhibitor" class. Similar distribution information for non-Hispanic white subjects within each treatment class is presented in Table 5.2. Age differed significantly ($p<0.001$) between the treatment classes, with the oldest average age among subjects in the "beta-blocker + other" class

and the youngest average age among those in the "RAAS inhibitor" class. Statistically significant differences in BMI were not noted between the various treatment classes ($p = 0.146$), although the mean BMI values within each class nearly met or exceed the clinical cutpoint for obesity. There was also evidence of significant variation ($p<0.001$) of SBP across treatment classes, with the highest mean level among subjects in the "beta-blocker + other" and the lowest mean level among those in the "beta-blocker" class.

Table 5.3 presents a brief description of the *SELE* and *VCAM1* SNPs that were genotyped in this study. Among the *SELE* SNPs, three SNPs are located in the 5' untranslated (UTR) region, one synonymous SNP is located in exon 14, three SNPs are located in introns, three non-synonymous SNPs are located in exons 10, 9, and 5, and one SNP is located in the 3' UTR region. Among the *VCAM1* SNPs, three SNPs are located in the 5' upstream gene region, nine SNPs are located in intronic regions, two synonymous and one non-synonymous SNPs are located in exon 9, and one SNP is located in the 3' downstream region. Tables 5.4 and 5.5 present the total number of subjects that were genotyped for each *SELE* SNP, as well as the frequency and percentage of each of the corresponding three genotypes, in African Americans and non-Hispanic whites respectively. Among the non-Hispanic white sample, the rs5366 variant was monomorphic (with the exception of one subject having the heterozygous genotype at this locus) and the rs5357 SNP had a low call rate (n= 511). Similar results for each of the *VCAM1* SNPs genotyped are presented in Tables 5.6 and 5.7. The rs3786315 variant was monomorphic in the non-Hispanic white sample.

The LD pattern among variations in the *SELE* SNPs in African American and non-Hispanic white subjects are displayed in Figure 5.1 and Figure 5.2 respectively. It is

evident that the relative frequency of several of the SNPs are significantly correlated within each racial/ethnic group and thus the effects of each SNP alone is likely to represent influences from multiple SNPs in this region, either measured or unmeasured in this study. Among the African American subjects, there are two groups of SNPs that can be identified by the LD estimates ($r^2$>0.80) that are likely to be measuring the same functional variation: group 1 (rs5357 and rs5361), and group 2 (rs5368 and rs5356). Among the non-Hispanic white subjects, there are also two groups of SNPs that can be identified by the LD estimates ($r^2$>0.80) that are likely to be measuring the same functional variation: group 1 (rs5356, rs5366, and rs5368), and group 2 (rs3917436, rs932307, and rs5353). Two SNPs in particular (rs5368 and rs5356) are likely measuring the same functional variation in the *SELE* gene in both racial/ethnic groups.

The LD pattern among variations in the *VCAM1* SNPs in African American and non-Hispanic white subjects are displayed in Figure 5.3 and Figure 5.4 respectively. Among the African American subjects, strong LD ($r^2$>0.80) was not detected among the SNPs genotyped. Among the non-Hispanic white subjects, there are two groups of SNPs that can be identified by the LD estimates ($r^2$>0.80) that are likely to be measuring the same functional variation: group 1 (rs3176876 and rs3181092), and group 2 (rs3176874 and rs3917016).

**SNP effects within treatment class and gene-drug interactions**

***SELE***

**African Americans**

Figure 5.5A presents the results from the analysis of each *SELE* SNP on SBP within treatment class, as well as the results from the leave-one-out cross validation

procedure, among the African American subjects. Evidence of statistically significant and cross-validated SNP effects on SBP was demonstrated in two of the eight treatment categories. Among hypertensives taking a beta-blocker only, the rs932307 SNP was statistically significantly associated with SBP levels and predicted a substantial amount of variation in SBP (cross-validated $R^2$ x 100 = 3.2%). Among hypertensives taking a diuretic only, one SNP (rs3917436) was statistically significantly associated with SBP and cross validated, predicting approximately 0.5% of the variation in SBP.

Evidence of *SELE* SNP-drug interactions among the African American subjects is visualized in Figure 5.5B, which summarizes the results of the tests for interaction for each pair of treatment classes examined. Statistically significant and cross-validated SNP-drug interactions that predict SBP variation have been highlighted. Some of the strongest evidence for gene-by-drug interaction comes from the comparison of the SNP genotype means among subjects in the "no treatment" vs. "beta-blocker" classes, and among subjects in the "beta-blocker" class relative to the respective SNP genotype means among subjects in the other monotherapy and combination therapy treatment classes. Three separate SNPs (rs5366, rs5361, and rs932307) each demonstrated statistically significant, cross-validated differences in mean SBP between the "no treatment" and "beta-blocker" classes. The rs932307 SNP demonstrated statistically significant differences in mean SBP between the "beta-blocker" class and all 7 other classes, with cross-validated differences detected between 4 other ("calcium-channel blocker", "RAAS inhibitor", "diuretic only", and "diuretic + other") classes. The rs5366 and rs5361 SNPs also demonstrated numerous statistically significant mean SBP differences between the "beta-blocker" and the 7 other classes, although most failed to cross-validate. These

results suggest that the genotype-specific effects of particular *SELE* SNPs on SBP variation may depend upon the drug that is administered, and highlight the possibility of gene-by-beta-blocker interaction in particular. Genotype-specific mean SBP values by treatment class for the rs932307 SNP are displayed in Figure 5.6.

**Non-Hispanic Whites**

Figure 5.7A presents the results from the analysis of each *SELE* SNP on SBP within treatment class, as well as the results from the leave-one-out cross validation procedure, among the non-Hispanic white subjects. Evidence of statistically significant and cross-validated SNP effects on SBP was demonstrated in two of the eight drug categories. Among hypertensives taking a beta-blocker, four of the ten (rs5366 essentially monomorphic in sample) SNPs were statistically significantly associated with SBP levels and three of these SNPs (rs5356, rs5368, and rs1076638) each predicted a substantial amount of variation in SBP (cross-validated $R^2$ x 100 = 3.3%, 3.2%, and 2.8% respectively). Among hypertensives taking a combination therapy of a diuretic plus another antihypertensive drug, one SNP (rs932307) demonstrated a statistically significant, cross-validated association with SBP and predicted approximately 0.7% of the variation in SBP. These findings suggest possible gene-by-drug interactions between *SELE* and antihypertensive medications (particularly beta blockers) in determining SBP levels in hypertensives.

Evidence of *SELE* SNP-drug interactions among the non-Hispanic white subjects is visualized in Figure 5.7B, which summarizes the results of the tests for interaction for each pair of treatment classes examined. Statistically significant and cross-validated SNP-drug interactions that predict SBP variation have been highlighted. Similar to

results detected in the African American racial/ethnic group, some of the strongest evidence for gene-by-drug interaction comes from the comparison of SNP genotype means among subjects in the "beta-blocker" class relative to the respective SNP genotype means among subjects in the other monotherapy and combination therapy treatment classes. Since the SNPs that demonstrated significant and cross-validated effects among hypertensives taking a beta-blocker did not seem to have an influence in the other treatment classes, significant SNP-drug interactions in drug comparisons involving beta-blocker usage were expected. Accordingly, 20 of the 25 statistically significant, cross-validated comparisons of SNP effects on SBP between treatment classes involved treatment classes with beta-blocker use (in monotherapy and/or combination forms). Three separate SNPs (rs5356, rs5368, and rs1076638) each demonstrated cross-validated differences in mean SBP between the "beta-blocker" class vs. both the "diuretic only" and beta-blocker + diuretic" classes. Two of these SNPs (rs5368 and rs1076638) also demonstrated cross-validated differences in mean SBP between comparisons among the: "beta-blocker" vs. "beta-blocker + other" classes; "diuretic only" vs. "beta-blocker + other" classes; and "beta-blocker + other" vs. "diuretic + other" classes. Many of the results for the rs5356, rs5368, and rs1076638 SNPs were similar and may stem from LD relationships. In particular, rs5356 and rs5368 are in high LD ($r^2 = 0.98$) and likely represent similar functional variation within the *SELE* gene in this non-Hispanic white cohort. Still, these results suggest that the genotype-specific effect of a particular SNP on SBP variation may depend upon the drug that is administered. Furthermore, as observed in the African American cohort, *SELE* SNP genotype effects on SBP may be highly

dependent on beta-blocker use. Genotype-specific mean SBP values by treatment class for the rs5368 SNP are displayed in Figure 5.8.

***VCAM1***

**African Americans**

Figure 5.9A presents the results from the analysis of each *VCAM1* SNP on SBP within treatment class, as well as the results from the leave-one-out cross validation procedure, among the African American subjects. Evidence of statistically significant and cross-validated SNP effects on SBP was demonstrated in three of the eight treatment categories. Among hypertensives taking a beta-blocker only, the rs3176862 SNP was statistically significantly associated with SBP levels and predicted a substantial amount of variation in SBP (cross-validated $R^2$ x 100 = 4.2%). Among hypertensives taking a calcium-channel blocker only, the rs3176878 SNP was statistically significantly associated with SBP and cross-validated, predicting approximately 6.0% of the variation in SBP. Among hypertensives taking a beta-blocker + other drug, rs3176876 was statistically significantly associated with SBP and cross-validated, predicting approximately 10.5% of the variation in SBP.

Evidence of *VCAM* SNP-drug interactions among the African American subjects is visualized in Figure 5.9B, which summarizes the results of the tests for interaction for each pair of treatment classes examined. Statistically significant and cross-validated SNP-drug interactions that predict SBP variation have been highlighted. Statistically significant and cross-validated genotype effects on mean SBP differences between various treatment classes were observed for many of the SNPs investigated. Some of the strongest evidence for gene-by-drug interaction involved three SNPs in particular

(rs3176862, rs3176876, and rs3176878), with genotype effects on mean SBP differing between many treatment class comparisons. The rs317682 SNP genotypes were associated with different mean SBP profiles between the "beta-blocker" class relative to the "no treatment", "RAAS inhibitor", "beta-blocker + diuretic", and "diuretic + other" classes. The rs3176876 and rs3176878 each demonstrated statistically significant, cross-validated differences in mean SBP between the "beta-blocker + other" class and the "no treatment", "calcium-channel blocker", "diuretic only", and "diuretic + other" classes. Additionally, the rs3176876 SNP demonstrated statistically significant, cross-validated differences in mean SBP between the "beta-blocker + other" class and the remaining 3 treatment classes ("beta-blocker", "RAAS inhibitor", "diuretic only", and "beta-blocker + diuretic"). Genotype-specific mean SBP values by treatment class for the rs3176876 SNP are displayed in Figure 5.10.

**Non-Hispanic Whites**

Figure 5.11A presents the results from the analysis of each *VCAM1* SNP on SBP within treatment class, as well as the results from the leave-one-out cross validation procedure, among the non-Hispanic white subjects. Evidence of statistically significant and cross-validated SNP effects on SBP was demonstrated in two of the eight drug categories. Among hypertensives not taking a prescribed antihypertensive medication, six of the fifteen (rs3783615 monomorphic in non-Hispanic white sample) SNPs were statistically significantly associated with SBP levels and four of these SNPs (rs3170794, rs3176862, rs3176874, and rs3917016) each predicted a substantial amount of variation in SBP (cross-validated $R^2$ x 100 = 3.5%, 2.8%, 8.0%, and 2.9% respectively). However, the rs3176874 and rs3917016 SNPs were in high LD ($r^2$ = 0.95). Among

hypertensives taking a combination therapy of a diuretic + other antihypertensive drug, five of the fifteen SNPs were statistically significantly associated with SBP levels and three of these SNPs (rs3176860, rs3176862, and rs3176876) each predicted a substantial amount of variation in SBP (cross-validated $R^2$ x 100 = 6.1%, 0.9%, and 1.0% respectively).

Evidence of *VCAM1* SNP-drug interactions among the non-Hispanic white subjects is visualized in Figure 5.11B, which summarizes the results of the tests for interaction for each pair of treatment classes examined. Statistically significant and cross-validated SNP-drug interactions that predict SBP variation have been highlighted. A majority of the strongest evidence for gene-by-drug interaction comes from the comparison of SNP genotype means among subjects in the "no treatment" class relative to the respective SNP genotype means among subjects in the 4 monotherapy and 3 combination therapy treatment classes. Three separate SNPs (rs3170794, rs3176862, and rs3176874) each demonstrated cross-validated differences in mean SBP between the "no treatment" and the "beta-blocker" classes. Two of these SNPs (rs3170794 and rs3176862) and the rs1041163 SNP also demonstrated cross-validated differences in mean SBP between the "no treatment" and the "calcium-channel blocker" classes. Three SNPs (rs3176874, rs3176876, and rs3181092) each demonstrated cross-validated differences in mean SBP between the "no treatment" and the "RAAS inhibitor" classes. The rs3176876 and rs3181092 SNPs were in relatively high LD ($r^2$ = 0.81). Three SNPs (rs1409419, rs3176860, and rs3176874) each demonstrated cross-validated differences in mean SBP between the "no treatment" and the "diuretic + other" classes. 10 of the remaining 15 cross-validated results were among comparisons involving the "diuretic +

other" class. Notably, 11 of the 15 SNPs examined demonstrated statistically significant and cross-validated evidence that SNP genotype effects on mean SBP were different between one or more of the treatment classes analyzed. Genotype-specific mean SBP values by treatment class for the rs3176860 SNP are displayed in Figure 5.12.

The results illustrated in Figures 5.5-5.12 provide evidence that for certain SNPs located in the *SELE* and *VCAM1* genes, genotype-SBP phenotype associations may vary by treatment class. These findings indicate that genetic susceptibility loci for hypertension may also interact with antihypertensive therapies to influence an individual's blood pressure levels. As such, a particular genetic subgroup in the hypertensive population may benefit more from a particular drug regimen.

**DISCUSSION**

Hypertension is a major risk factor for cardiovascular, cerebrovascular, and renal disease morbidity and mortality. Despite the recognized health and economic burdens of hypertension, success in achieving and maintaining target blood pressure levels necessary to reduce cardiovascular risk has been limited. This stems largely from low hypertension awareness and treatment, as an estimated 67% of hypertensives in the US are aware of their condition and only 54% are being treated. Furthermore, in the midst of increasing prevalence, more than two-thirds of treated hypertensives in the US do not have their blood pressure adequately controlled (3).

One of the challenges in achieving broad blood pressure control is the difficulty in predicting how effective a particular antihypertensive regimen will be for a particular patient. Without a priori knowledge of how subjects will respond to a medication, a "trial-and-error" approach is typically employed to find the ideal drug for a given patient

(40). Furthermore, it is recognized that hypertension is a multifactorial disease and that combinations of antihypertensive agents, acting through different mechanisms at different sites, are often prescribed, with most patients requiring two or more drugs to achieve target blood pressure (41).

During the earlier years of phamacogenetic investigations, the focus was directed towards variants in genes (e.g.- CVP2D6 and N-acetyltransferase 2 genes) that coded for enzymes affecting drug metabolism (42). However, the variations in these genes, known to impact the pharmacokinetics (i.e.- mechanisms affecting drug concentration such as absorption, distribution, metabolism, and excretion) of particular antihypertensive agents, have decreased in importance as the agents they impacted are no longer widely prescribed and newer agents have gained widespread use. More recently, pharmacogenetic research has focused on identifying variants in candidate genes that impact the pharmacodynamic (i.e.- mechanisms governing the drug-target cell interaction and subsequent regulation of drug activity and efficacy) properties influencing individual variation in antihypertensive response (4, 40, 42). Accordingly, numerous variants in biological and positional candidate genes (mainly in the RAAS) have been predictive of blood pressure response to a variety of antihypertensive therapies, however studies have yielded conflicting results, reflecting the heterogeneous nature of hypertension and response to antihypertensive treatment (40, 43).

In the current study, we hypothesized that polymorphisms in the *SELE* and *VCAM1* genes could influence interindividual variation in blood pressure response, on the premise that hypertension is associated with endothelial cell alteration/dysfunction and that cell adhesion molecules, including *SELE* and *VCAM1*, are products of activated

endothelium. Numerous studies have demonstrated statistically significant associations between hypertension and elevated plasma levels of e-selectin (23-25, 44) and vascular adhesion molecule-1 (25, 26), suggesting that these circulating molecules are either by-products of the endothelial damage caused by hypertension or that the respective proteins encoded by the *SELE* and *VCAM1* genes are somehow involved in the determination of blood pressure. Results from recent research show that e-selectin expression correlates with vascular structural alterations, and the authors point out the possibility that e-selectin might independently contribute to such vascular changes by fostering leukocyte adhesion/accumulation (23). Previous genetic analyses using the GENOA cohort detected statistically significant associations between quantitative blood pressure values and the non-synonymous rs5368 SNP in the *SELE* gene among African American subjects (7). The common Ser128Arg (rs5361) and L/F554 (rs5355) polymorphisms in *SELE* have been investigated for their potential role in cardiovascular diseases. Associations have been detected between both variants and atherosclerosis (45), between the Ser128Arg (rs5361) variant and coronary artery disease (46-48) and recurrent venous thromboembolism (49), and between the L/F554 (rs5355) variant and blood pressure (27, 50). Furthermore, reductions in soluble selectin molecules (both e- and p-selectin) through the administration of the calcium-channel blocker benidipine (51) and variance in the degree of vascular effects derived through different antihypertensive therapies (45) have been demonstrated, suggesting that variants in genes influencing vascular tone and function may also affect blood pressure response. Administration of the angiotensin converting enzyme (ACE) inhibitor fosinopril has been shown to lower circulating vascular cell adhesion molecule-1 levels (52).

This study detected and cross-validated sets of SNPs within the *SELE* and *VCAM1* genes that may influence interindividual variation in blood pressure and blood pressure response in African American and non-Hispanic white hypertensive patients. Investigation of *SELE* SNP effects on blood pressure within treatment classes revealed that the effects that were significant and cross-validated in independent samples were primarily seen within the "beta-blocker" monotherapy class in each racial/ethnic group. Subsequent comparisons across treatment classes to investigate the potential evidence for gene-by-drug interaction revealed that most of the significant and cross-validated differences were between monotherapy and combination therapy classes relative to the beta-blocker usage, and these findings were also common to both racial/ethnic groups.

A potential explanation for the differences detected may be that certain antihypertensive therapies confer vasculoprotective properties, in addition to blood pressure lowering properties, which may improve outcomes. Studies comparing such properties between antihypertensive agents have noted improved endothelial structure and function with RAAS inhibitors (53, 54) and calcium-channel blockers (45), relative to no improvements under beta-blocker usage. Interestingly, this study provided similar evidence of gene-by-drug interaction involving the common Ser128Arg (rs5361) variant was detected between the "calcium-channel blocker" and "beta-blocker + other" treatment classes in non-Hispanic whites, and the genotypes of this SNP were associated with statistically significant different SBP profiles in several treatment classes ("calcium-channel blocker", "diuretic only", "beta-blocker + other", and "diuretic + other") relative to the "beta-blocker" class in African Americans. Although the rs5361 associations failed to cross-validate in either racial/ethnic group, these differences may have clinical

relevance as subjects with a particular allele at this locus may respond better to calcium-channel blocker administration, and simultaneously benefit from both blood pressure lowering and inhibition of e-selectin molecule expression which could reduce the rate of atherosclerotic progression (51).

The etiology of hypertension is believed to be multifactorial and polygenic, with numerous environmental and genetic factors influencing interindividual blood pressure variation. Studies investigating the role of *SELE* and *VCAM1* polymorphisms have detected that SNP effects on blood pressure may depend on environmental factors such as age and BMI (26, 27, 50). While statistically significant age differences were noted between subjects within different treatment classes in our study, the actual mean ages across classes were within a relatively tight range. While BMI differed significantly by treatment class among the African American subjects, no statistically significant BMI differences between treatment classes were observed among the non-Hispanic white subjects. Overall, mean BMI values in both racial/ethnic groups were near or above the clinical cutpoint for obesity, regardless of treatment class. This may indicate that our findings are only generalizable to over-weight and obese populations, and may reinforce the previously identified (50) BMI-specific effect of polymorphisms in inflammatory genes on blood pressure and blood pressure response.

This study had several limitations that warrant discussion. Without prospective data, genetic influence on blood pressure response to various treatment regimens could not be accurately assessed. Despite this, as illustrated in a identical analysis conducted in the GENOA non-Hispanic white cohort that investigated interactions between the *adducin2* (*ADD2*) gene and antihypertensive drug therapies on SBP, the various gene

effects observed within treatment classes were taken as a reflection of how the certain SNP genotypes responded to different antihypertensive drug environments (55). Although the within-treatment class samples were somewhat balanced and moderately sized in both racial/ethnic groups, results may have been biased by relatively small sample sizes within some classes. In particular, the "beta-blocker" monotherapy and the "beta-blocker + other" class sizes were quite small among African American subjects, and findings involving these classes (in the form of SNP main effects within these classes or SNP-drug interactions) should be interpreted with caution.

The genetic analyses carried out in these analyses were limited to a select number of SNPs within two genes in the inflammatory/endothelial dysfunction pathway(s). Genetic variants in other physiologic systems and pathways, including the RAAS, the sodium system, signal transduction pathways, the noradrenergic system, and endothelin system, influence blood pressure regulation and may be related to relationships between various antihypertensive treatments and blood pressure lowering effects. Given that hypertension is believed to be multifactorial and polygenic, further investigation of SNP main effects in other genes, as well as appropriately defined gene-environment and gene-gene interactions may provide additional insights into genetic influences on treatment response. Many ongoing genome-wide association studies have great potential to identify variants that could serve as benchmarks for individual treatment response and influence the design of novel therapies (56). Numerous statistical genetic tests were carried out in the analyses of this study, increasing the chance of false-positive findings. As used in previous research investigating the influence of *ADD2*-drug interactions on SBP (55), the cross-validation techniques used in this study reduced the number of

statistically significant findings by likely ruling out false-positive associations. Direct comparison of the various SNP effects between the African American and non-Hispanic white subject is limited due to genetic heterogeneity (i.e.- population differences in allelic distributions), although results specific to racially/ethnically homogeneous cohorts were presented. Despite these limitations, this study contributed to the developing pharmacogenetic knowledge base by demonstrating that blood pressure response to antihypertensive therapy may be modified by variations in the *SELE* and *VCAM1* genes, and presented another avenue of investigation into the potential link between inflammation and hypertension.

**Table 5.1. Distribution of antihypertensive therapies among hypertensive African Americans in GENOA**

| Antihypertensive class | N (1329) | Number of sibships (637) | Age (yrs) Mean (SD) | BMI ($kg/m^2$) Mean (SD) | SBP (mmHg) Mean (SD) | DBP (mmHg) Mean (SD) |
|---|---|---|---|---|---|---|
| No Treatment | 205 | 173 | 58.20 (9.47) | 29.80 (6.27) | 157.20 (15.20) | 88.24 (11.99) |
| **Mono Therapies** | | | | | | |
| Beta-Blocker | 42 | 39 | 59.16 (10.39) | 29.98 (6.96) | 143.98 (22.05) | 81.57 (11.51) |
| CA-Blocker | 148 | 131 | 58.24 (9.55) | 30.13 (5.13) | 142.67 (20.94) | 81.26 (12.98) |
| Diuretic | 156 | 144 | 59.87 (9.05) | 32.91 (6.48) | 133.59 (20.10) | 74.49 (10.67) |
| RAAS Inhibitors | 107 | 101 | 59.70 (10.10) | 30.17 (6.19) | 140.50 (20.97) | 80.05 (11.06) |
| Other Antihypertensive | 75 | 70 | 61.53 (8.48) | 30.48 (5.89) | 143.40 (25.09) | 79.89 (10.50) |
| **Combination Therapies** | | | | | | |
| Beta-Blocker + Diuretic | 107 | 97 | 58.98 (9.81) | 32.74 (6.54) | 134.40 (21.15) | 77.68 (13.12) |
| Beta-Blocker + Other | 32 | 30 | 62.21 (9.14) | 30.93 (5.50) | 137.59 (24.89) | 76.78 (12.69) |
| Diuretic + Other | 351 | 273 | 61.63 (9.18) | 33.62 (7.51) | 139.63 (22.28) | 77.06 (13.03) |
| Neither Beta-Blocker Nor Diuretic | 106 | 98 | 61.01 (8.83) | 32.40 (7.00) | 146.93 (27.34) | 80.72 (12.86) |
| P-value test among treatment classes* | | | 0.008 | <0.001 | <0.001 | <0.001 |

* ANOVA did not include the "No Treatment" class. BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; CA = Calcium channel; RAAS = renin angiotensin aldosterone system.

**Table 5.2. Distribution of antihypertensive therapies among hypertensive non-Hispanic whites in GENOA**

| Antihypertensive class | N (1129) | Number of sibships (548) | Age (yrs) Mean (SD) | BMI ($kg/m^2$) Mean (SD) | SBP (mmHg) Mean (SD) | DBP (mmHg) Mean (SD) |
|---|---|---|---|---|---|---|
| No Treatment | 148 | 133 | 54.99 (11.2) | 30.9 (5.6) | 149.24 (13.2) | 86.53 (9.4) |
| **Mono Therapies** | | | | | | |
| Beta-Blocker | 162 | 147 | 55.79 (10.4) | 30.69 (6.7) | 134.43 (16.1) | 79.09 (8.1) |
| CA-Blocker | 62 | 59 | 57.06 (9.3) | 29.49 (5.3) | 142.37 (15.6) | 82.56 (9.0) |
| Diuretic | 127 | 121 | 58.04 (9.6) | 32.01 (6.6) | 134.98 (12.5) | 79.17 (9.7) |
| RAAS Inhibitors | 151 | 136 | 54.87 (9.5) | 31.11 (7.3) | 133.73 (15.9) | 80.52 (8.8) |
| Other Antihypertensive | 18 | 17 | 59.97 (10.7) | 29.38 (4.8) | 141.67 (22.6) | 78.56 (8.1) |
| **Combination Therapies** | | | | | | |
| Beta-Blocker + Diuretic | 167 | 141 | 59.66 (9.4) | 32.01 (6.8) | 136.23 (16.0) | 77.34 (9.4) |
| Beta-Blocker + Other | 72 | 67 | 62.57 (8.7) | 30.66 (5.9) | 143.63 (20.8) | 78.36 (9.5) |
| Diuretic + Other | 178 | 159 | 59.13 (9.4) | 31.55 (6.3) | 134.64 (15.6) | 77.83 (10.2) |
| Neither Beta-Blocker Nor Diuretic | 44 | 42 | 58.21 (9.3) | 30.89 (6.1) | 138.64 (19.1) | 80.50 (10.5) |
| P-value test among treatment classes* | | | <0.001 | 0.146 | <0.001 | 0.004 |

* ANOVA did not include the "No Treatment" class. BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; CA = Calcium channel; RAAS = renin angiotensin aldosterone system.

**Table 5.3. Description of Cell Adhesion Molecule Candidate Genes**

| Gene Name | Gene | GENOA SNP ID | SNP rs# | SNP Type | Chromosomal Band |
|---|---|---|---|---|---|
| *selectin E* | *SELE* | SELE_012037 | rs5357 | UTR | 1q22-q25 |
| (*endothelial adhesion molecule 1*) | | SELE_010130 | rs3917436 | UTR | 1q22-q25 |
| | | SELE_010054 | rs3917434 | UTR | 1q22-q25 |
| | | SELE_009831 | rs5356 | synonymous | 1q22-q25 |
| | | SELE_007803 | rs5368 | nonsynonymous | 1q22-q25 |
| | | SELE_007532 | rs5366 | nonsynonymous | 1q22-q25 |
| | | SELE_007158 | rs1076638 | intron | 1q22-q25 |
| | | SELE_005924 | rs1534904 | intron | 1q22-q25 |
| | | SELE_003689 | rs5361 | nonsynonymous | 1q22-q25 |
| | | SELE_002043 | rs932307 | intron | 1q22-q25 |
| | | SELE_001774 | rs5353 | UTR | 1q22-q25 |
| *vascular cell adhesion molecule* 1 | *VCAM1* | VCAM1_000376 | rs1409419 | | 1p32-p31 |
| | | VCAM1_000805 | rs1041163 | | 1p32-p31 |
| | | VCAM1_001564 | rs3170794 | | 1p32-p31 |
| | | VCAM1_004199 | rs3176860 | intron | 1p32-p31 |
| | | VCAM1_004301 | rs3176861 | intron | 1p32-p31 |
| | | VCAM1_004952 | rs3176862 | intron | 1p32-p31 |
| | | VCAM1_011199 | rs3176867 | intron | 1p32-p31 |
| | | VCAM1_013438 | rs3176869 | intron | 1p32-p31 |
| | | VCAM1_015713 | rs3181088 | intron | 1p32-p31 |
| | | VCAM1_016891 | rs3176874 | intron | 1p32-p31 |
| | | VCAM1_017613 | rs3176876 | intron | 1p32-p31 |
| | | VCAM1_018152 | rs3917016 | intron | 1p32-p31 |
| | | VCAM1_020703 | rs3176878 | synonymous | 1p32-p31 |
| | | VCAM1_020770 | rs3783615 | nonsynonymous | 1p32-p31 |
| | | VCAM1_020832 | rs3176879 | synonymous | 1p32-p31 |
| | | VCAM1_021649 | rs3181092 | | 1p32-p31 |

**Table 5.4. *SELE* SNP sample size information and genotype distribution among hypertensive African Americans in GENOA**

| SNP | $N_{total}$ | $N_{11}$ $P_{11}$ | $N_{12}$ $P_{12}$ | $N_{22}$ $P_{22}$ |
|---|---|---|---|---|
| rs5357 | 616 | 572 (0.93) | 41 (0.06) | 3 (0.01) |
| rs3917436 | 1197 | 321 (0.27) | 630 (0.53) | 246 (0.20) |
| rs3917434 | 1211 | 979 (0.81) | 220 (0.18) | 12 (0.01) |
| rs5356 | 1229 | 1082 (0.88) | 144 (0.11) | 3 (0.01) |
| rs5368 | 1214 | 1059 (0.87) | 151 (0.12) | 4 (0.01) |
| rs5366 | 1211 | 1118 (0.92) | 85 (0.07) | 8 (0.01) |
| rs1076638 | 1204 | 564 (0.47) | 535 (0.44) | 105 (0.09) |
| rs1534904 | 1212 | 1088 (0.90) | 111 (0.09) | 13 (0.01) |
| rs5361 | 1239 | 1132 (0.91) | 104 (0.09) | 3 (0.01) |
| rs932307 | 1211 | 504 (0.42) | 562 (0.46) | 145 (0.12) |
| rs5353 | 1198 | 345 (0.29) | 617 (0.51) | 236 (0.20) |

N: number of subjects; P: genotype frequency; 11: homozygous major allele genotype; 12: heterozygous genotype; 22: homozygous minor allele genotype**.** SNP = single nucleotide polymorphism.

**Table 5.5. *SELE* SNP sample size information and genotype distribution among hypertensive non-Hispanic whites in GENOA**

| SNP | $N_{total}$ | $N_{11}$ $P_{11}$ | $N_{12}$ $P_{12}$ | $N_{22}$ $P_{22}$ |
|---|---|---|---|---|
| rs5357 | 511 | 4 (0.01) | 91 (0.18) | 416 (0.81) |
| rs3917436 | 965 | 52 (0.05) | 383 (0.40) | 530 (0.55) |
| rs3917434 | 994 | 425 (0.43) | 472 (0.47) | 97 (0.10) |
| rs5356 | 998 | 10 (0.01) | 159 (0.16) | 829 (0.83) |
| rs5368 | 986 | 814 (0.83) | 160 (0.16) | 12 (0.01) |
| rs5366 | 996 | 995 (0.99) | 1 (0.00) | 0 (0.00) |
| rs1076638 | 979 | 748 (0.76) | 213 (0.22) | 18 (0.02) |
| rs1534904 | 983 | 93 (0.09) | 466 (0.47) | 424 (0.43) |
| rs5361 | 994 | 787 (0.79) | 196 (0.20) | 11 (0.01) |
| rs932307 | 992 | 572 (0.58) | 372 (0.38) | 48 (0.05) |
| rs5353 | 962 | 526 (0.55) | 384 (0.40) | 52 (0.05) |

N: number of subjects; P: genotype frequency; 11: homozygous major allele genotype; 12: heterozygous genotype; 22: homozygous minor allele genotype**.** SNP = single nucleotide polymorphism.

**Table 5.6. *VCAM1* SNP sample size information and genotype distribution among hypertensive African Americans in GENOA**

| SNP | $N_{total}$ | $N_{11}$ $P_{11}$ | $N_{12}$ $P_{12}$ | $N_{22}$ $P_{22}$ |
|---|---|---|---|---|
| rs1409419 | 1218 | 471 (0.39) | 568 (0.46) | 179 (0.15) |
| rs1041163 | 1188 | 811 (0.68) | 330 (0.28) | 47 (0.04) |
| rs3170794 | 1221 | 876 (0.72) | 310 (0.25) | 35 (0.03) |
| rs316860 | 1208 | 333 (0.28) | 618 (0.51) | 257 (0.21) |
| rs3176861 | 1240 | 1126 (0.91) | 110 (0.08) | 4 (0.01) |
| rs3176862 | 1229 | 771 (0.63) | 409 (0.33) | 49 (0.04) |
| rs3176867 | 1233 | 1103 (0.89) | 123 (0.10) | 7 (0.01) |
| rs3176869 | 1169 | 1103 (0.94) | 66 (0.06) | 0 (0.00) |
| rs3181088 | 1227 | 1156 (0.94) | 68 (0.05) | 3 (0.01) |
| rs3176874 | 1202 | 1029 (0.85) | 168 (0.14) | 5 (0.01) |
| rs3176876 | 1218 | 338 (0.28) | 589 (0.48) | 291 (0.24) |
| rs3917016 | 1205 | 1060 (0.88) | 136 (0.11) | 9 (0.01) |
| rs3176878 | 1222 | 902 (0.74) | 302 (0.25) | 18 (0.01) |
| rs3783615 | 1217 | 1080 (0.89) | 128 (0.10) | 9 (0.01) |
| rs3176879 | 1230 | 591 (0.48) | 529 (0.43) | 110 (0.09) |
| rs3181092 | 1228 | 647 (0.53) | 494 (0.40) | 87 (0.07) |

N: number of subjects; P: genotype frequency; 11: homozygous major allele genotype; 12: heterozygous genotype; 22: homozygous minor allele genotype**.** SNP = single nucleotide polymorphism.

**Table 5.7. *VCAM1* SNP sample size information and genotype distribution among hypertensive non-Hispanic whites in GENOA**

| SNP | $N_{total}$ | $N_{11}$ $P_{11}$ | $N_{12}$ $P_{12}$ | $N_{22}$ $P_{22}$ |
|---|---|---|---|---|
| rs1409419 | 980 | 256 (0.26) | 485 (0.50) | 239 (0.24) |
| rs1041163 | 990 | 706 (0.71) | 268 (0.27) | 16 (0.02) |
| rs3170794 | 978 | 947 (0.97) | 31 (0.03) | 0 (0.00) |
| rs316860 | 995 | 362 (0.36) | 486 (0.49) | 147 (0.15) |
| rs3176861 | 986 | 597 (0.61) | 336 (0.34) | 53 (0.05) |
| rs3176862 | 993 | 962 (0.97) | 31 (0.03) | 0 (0.00) |
| rs3176867 | 997 | 562 (0.56) | 393 (0.40) | 42 (0.04) |
| rs3176869 | 952 | 682 (0.72) | 247 (0.26) | 23 (0.02) |
| rs3181088 | 992 | 637 (0.64) | 321 (0.32) | 34 (0.04) |
| rs3176874 | 991 | 768 (0.78) | 212 (0.21) | 11 (0.01) |
| rs3176876 | 985 | 458 (0.47) | 435 (0.44) | 92 (0.09) |
| rs3917016 | 960 | 754 (0.79) | 194 (0.20) | 12 (0.01) |
| rs3176878 | 975 | 696 (0.71) | 253 (0.26) | 26 (0.03) |
| rs3783615 | 974 | 974 (100.0) | 0 (0.00) | 0 (0.00) |
| rs3176879 | 999 | 933 (0.93) | 65 (0.67) | 1 (0.00) |
| rs3181092 | 996 | 432 (0.43) | 460 (0.46) | 104 (0.11) |

N: number of subjects; P: genotype frequency; 11: homozygous major allele genotype; 12: heterozygous genotype; 22: homozygous minor allele genotype**.** SNP = single nucleotide polymorphism.

**Figure 5.1. Linkage disequilibrium between *SELE* SNPs in GENOA African Americans**

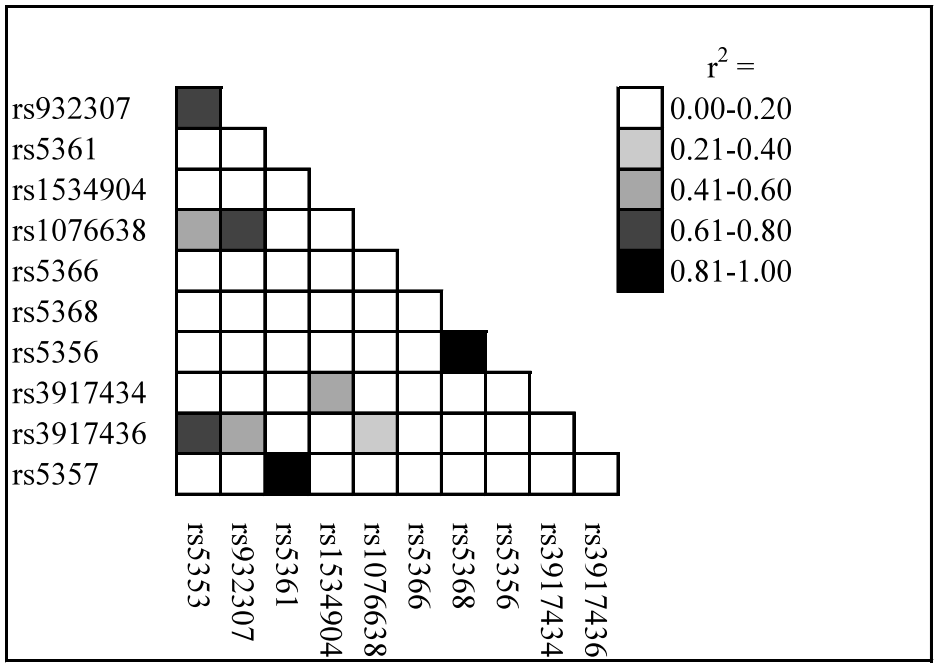


**Figure 5.2. Linkage disequilibrium between *SELE* SNPs in GENOA non-Hispanic whites**

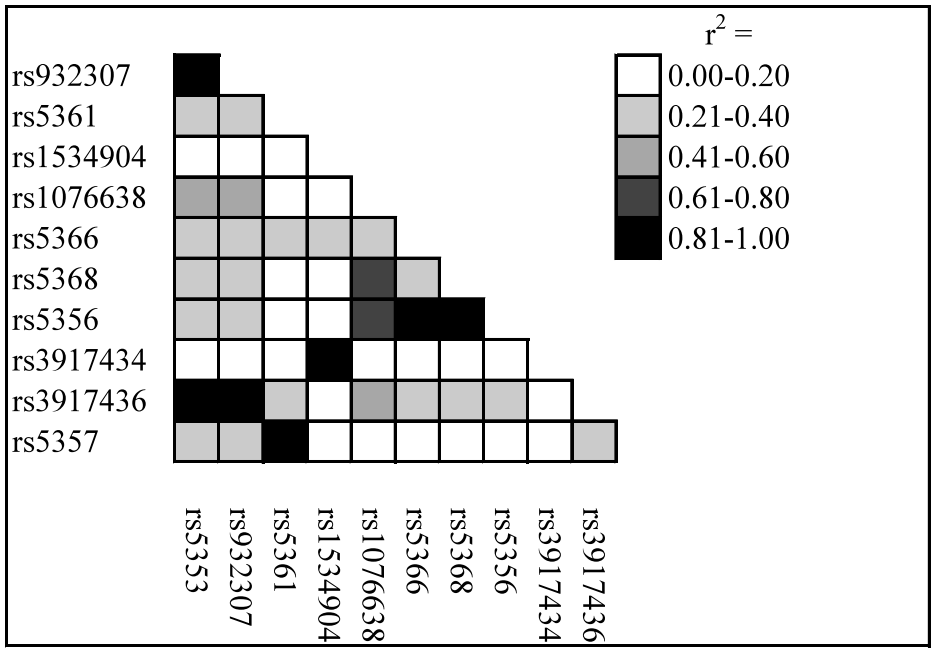


**Figure 5.3. Linkage disequilibrium between *VCAM1* SNPs in GENOA African Americans**

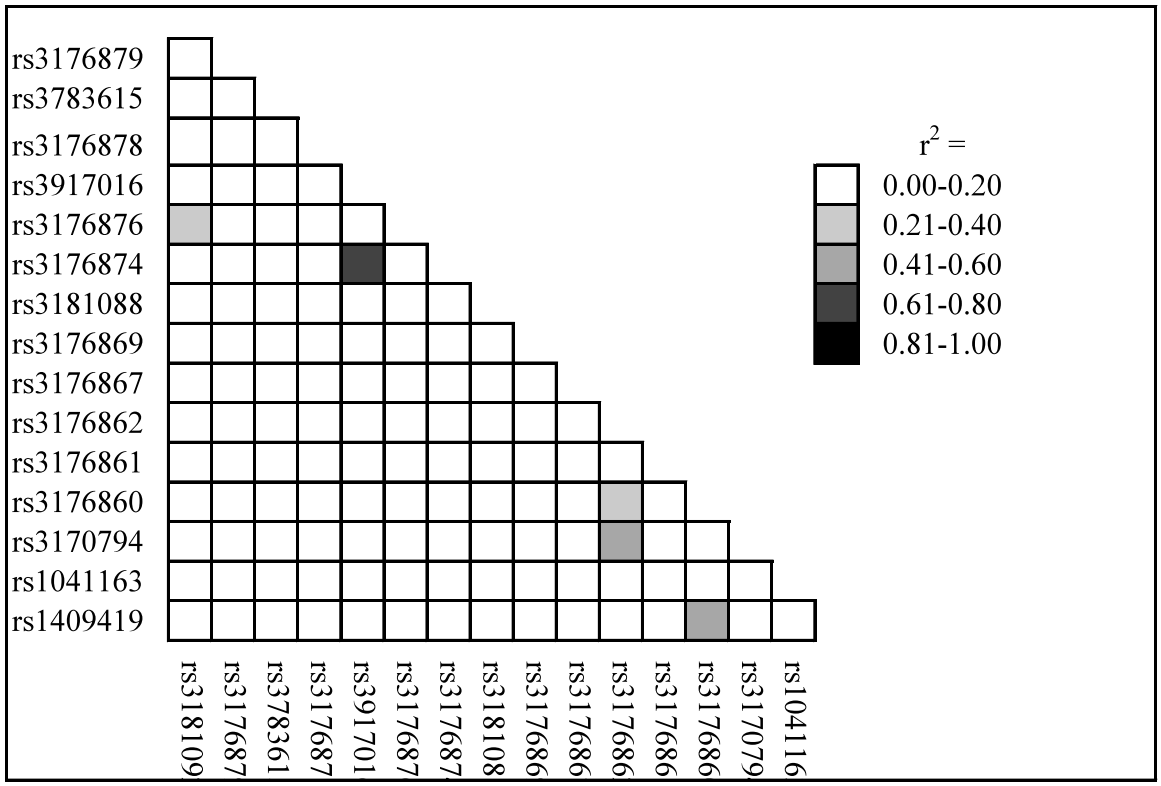
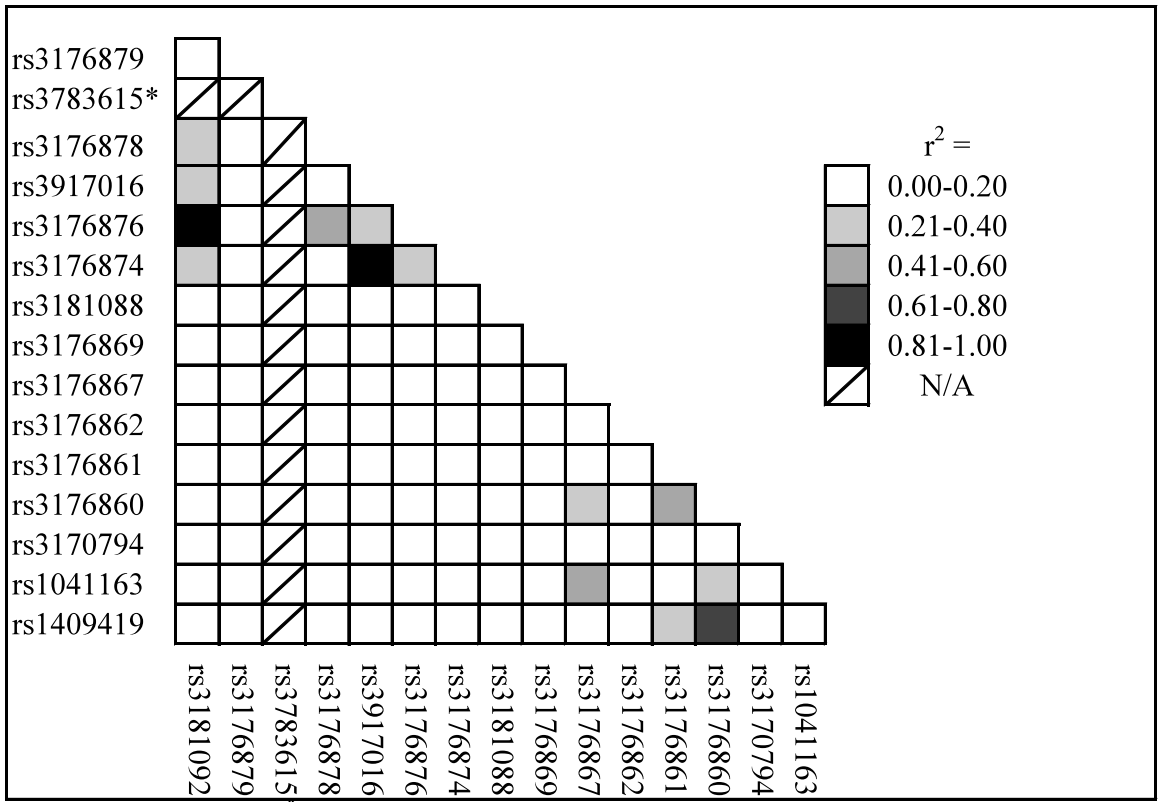
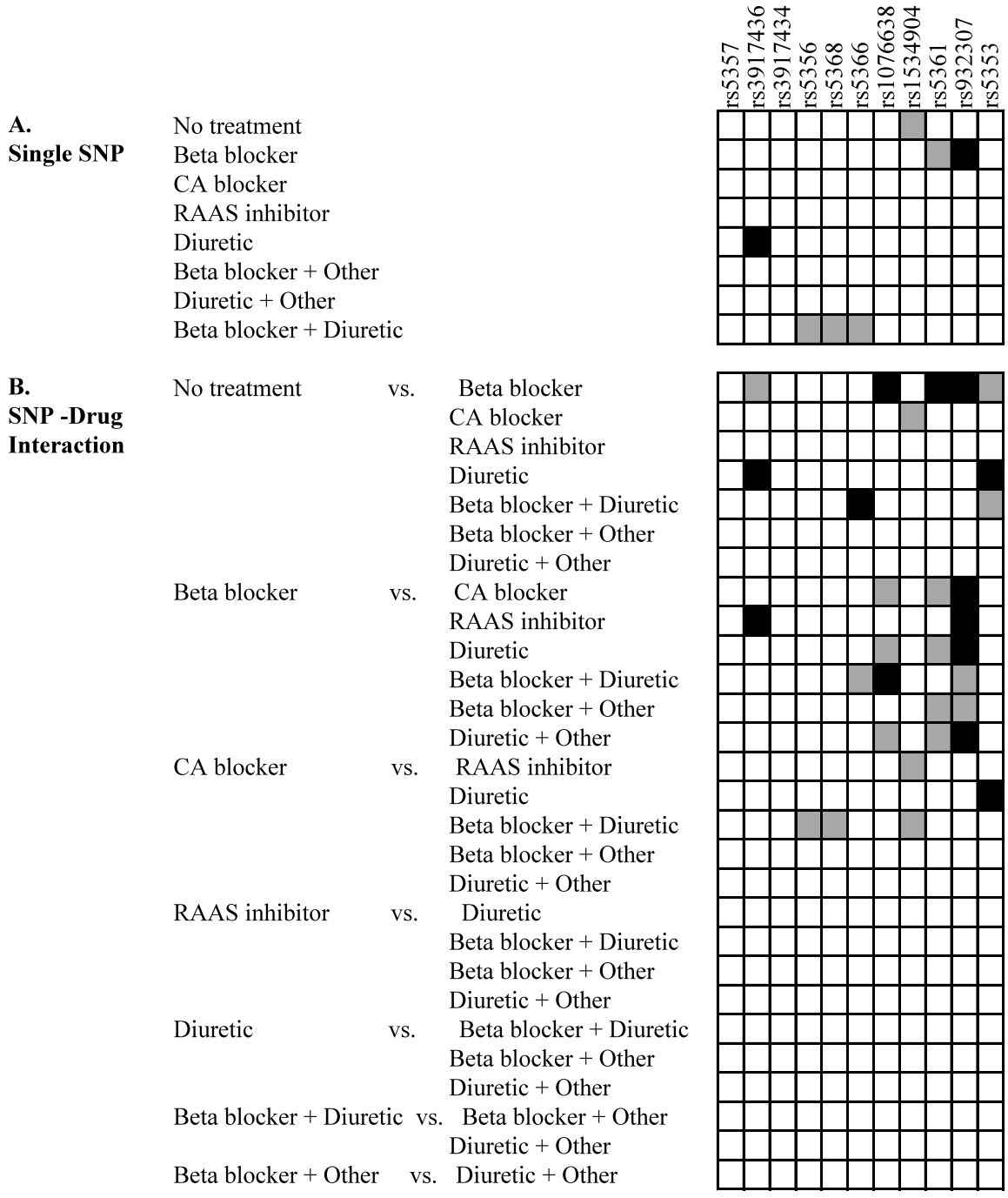


**Figure 5.4. Linkage disequilibrium between *VCAM1* SNPs in GENOA non-Hispanic whites**




*rs3783615 monomorphic in this sample.

**Figure 5.5. Single SNP and SNP-drug effects of *SELE* SNPs on systolic blood pressure in GENOA African American hypertensives (n = 1329)**



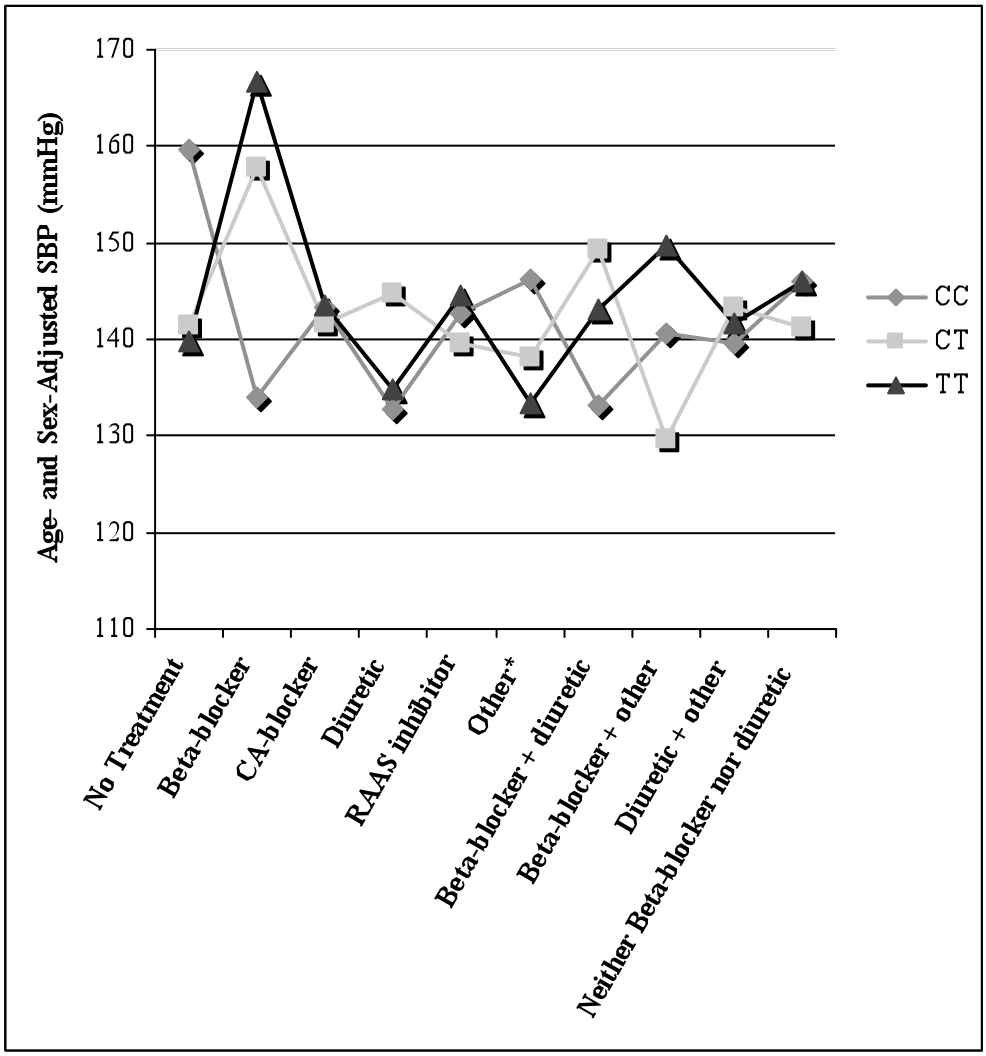

SNP rs #'s listed from left to right according to relative positions on *SELE* gene in the 5' to 3' direction. SNP = single nucleotide polymorphism; CA = Calcium channel; RAAS = renin angiotensin aldosterone system.

Statistically significant $p<0.05$ and CV $R^2 * 100 > 0.50$

Statistically significant $p<0.05$ and CV $R^2 * 100 < 0.50$

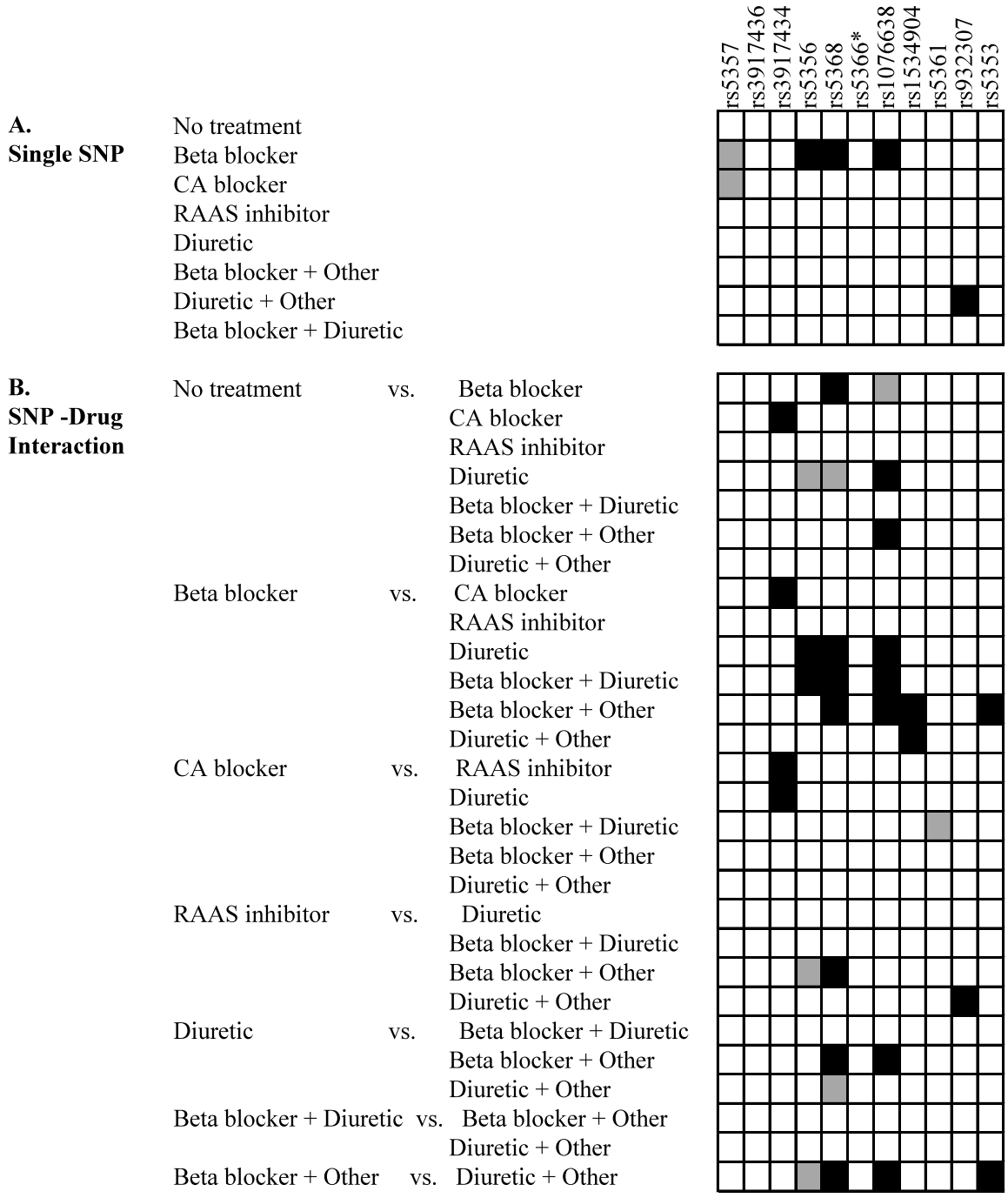
Not statistically significant

**Figure 5.6. *SELE* rs932307 genotype specific mean systolic blood pressure by treatment class in GENOA African American hypertensive subjects**




*Other antihypertensive class includes alpha-blockers, vasodilators, sympatholytics, and study drugs. SBP = systolic blood pressure; CA = calcium channel; RAAS = renin angiotensin aldosterone system.

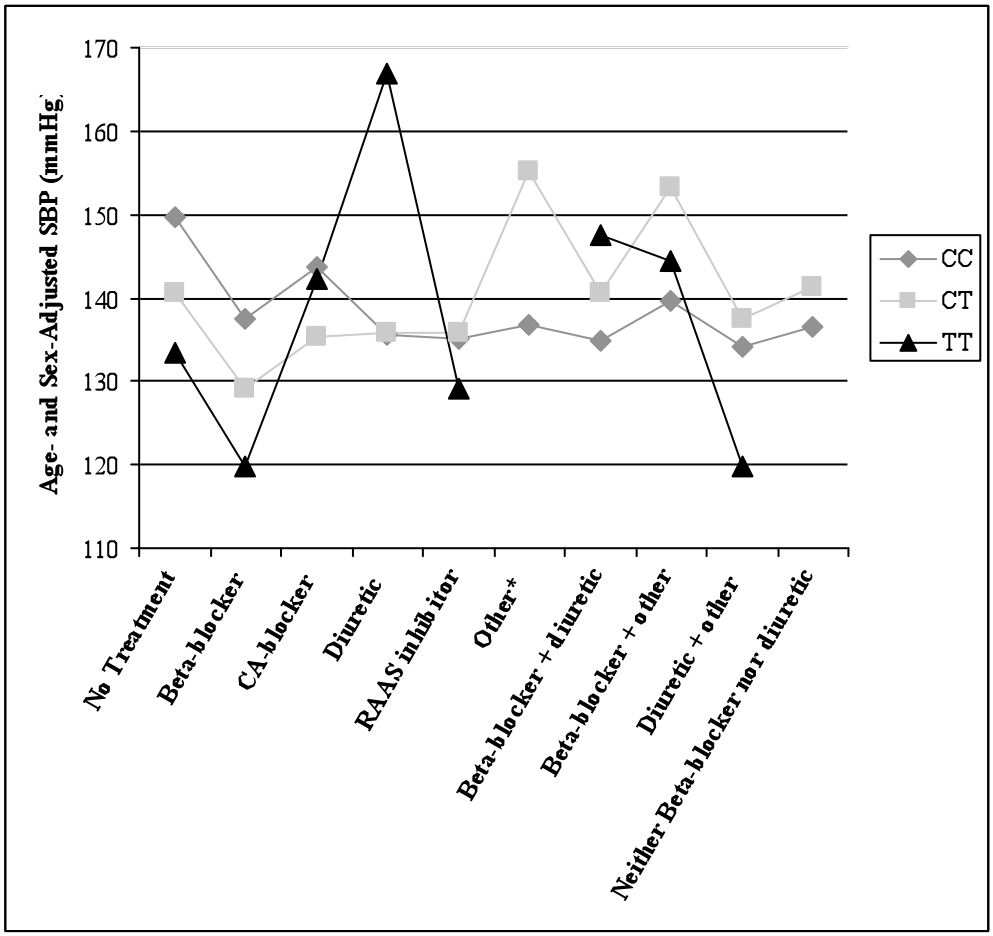
**Figure 5.7. Single SNP and SNP-drug effects of *SELE* SNPs on systolic blood pressure in GENOA non-Hispanic white hypertensives (n = 1129)**




SNP rs #'s listed from left to right according to relative positions on *SELE* gene in the 5' to 3' direction.
SNP = single nucleotide polymorphism; CA = Calcium channel; RAAS = renin angiotensin aldosterone system.

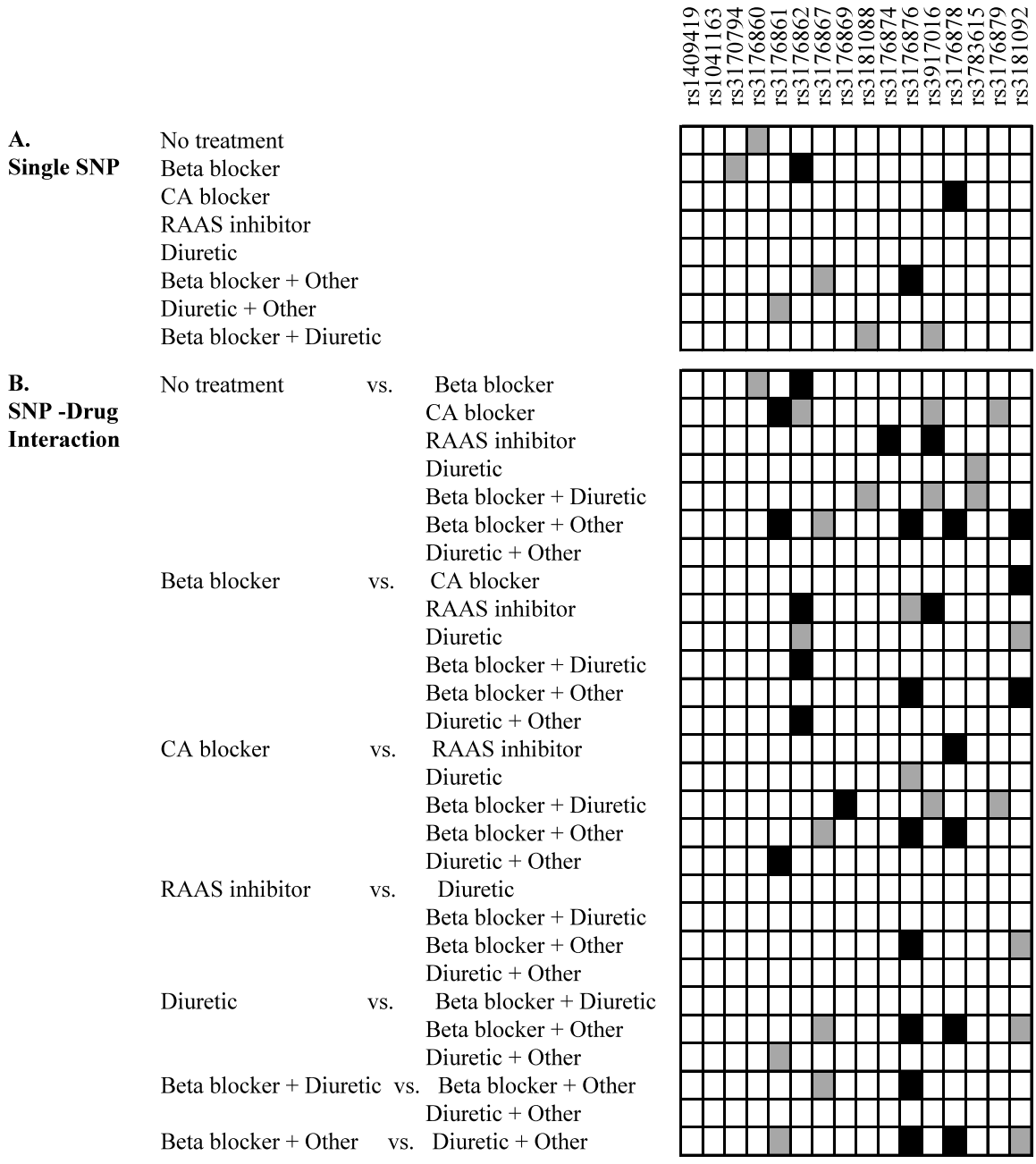
Statistically significant $p<0.05$ and CV $R^2 * 100 > 0.50$
Statistically significant $p<0.05$ and CV $R^2 * 100 < 0.50$
Not statistically significant

**Figure 5.8. *SELE* rs5368 genotype specific mean systolic blood pressure by treatment class in GENOA non-Hispanic white hypertensive subjects**




*Other antihypertensive class includes alpha-blockers, vasodilators, sympatholytics, and study drugs. SBP = systolic blood pressure; CA = calcium channel; RAAS = renin angiotensin aldosterone system.

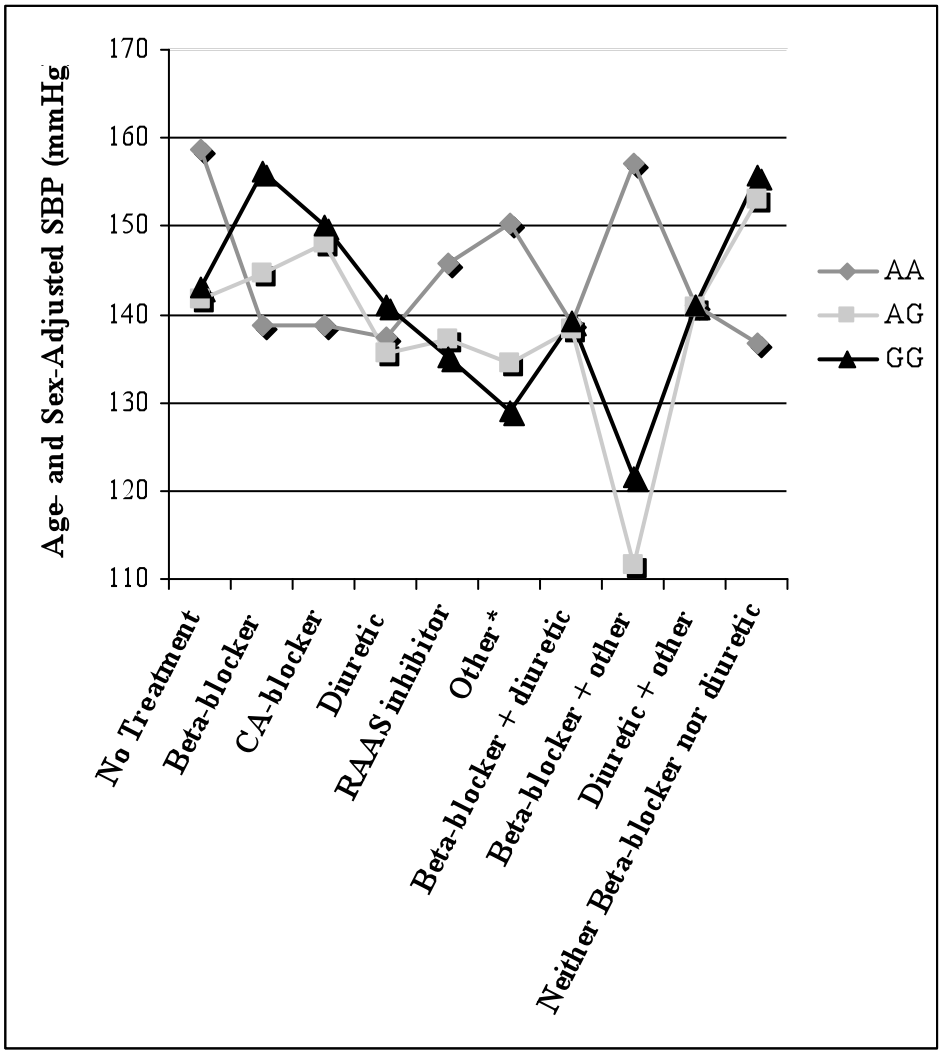
**Figure 5.9. Single SNP and SNP-drug effects of *VCAM 1* SNPs on systolic blood pressure in GENOA African American hypertensives (n = 1329)**




SNP rs #'s listed from left to right according to relative positions on *SELE* gene in the 5' to 3' direction.
SNP = single nucleotide polymorphism; CA = Calcium channel; RAAS = renin angiotensin aldosterone system.

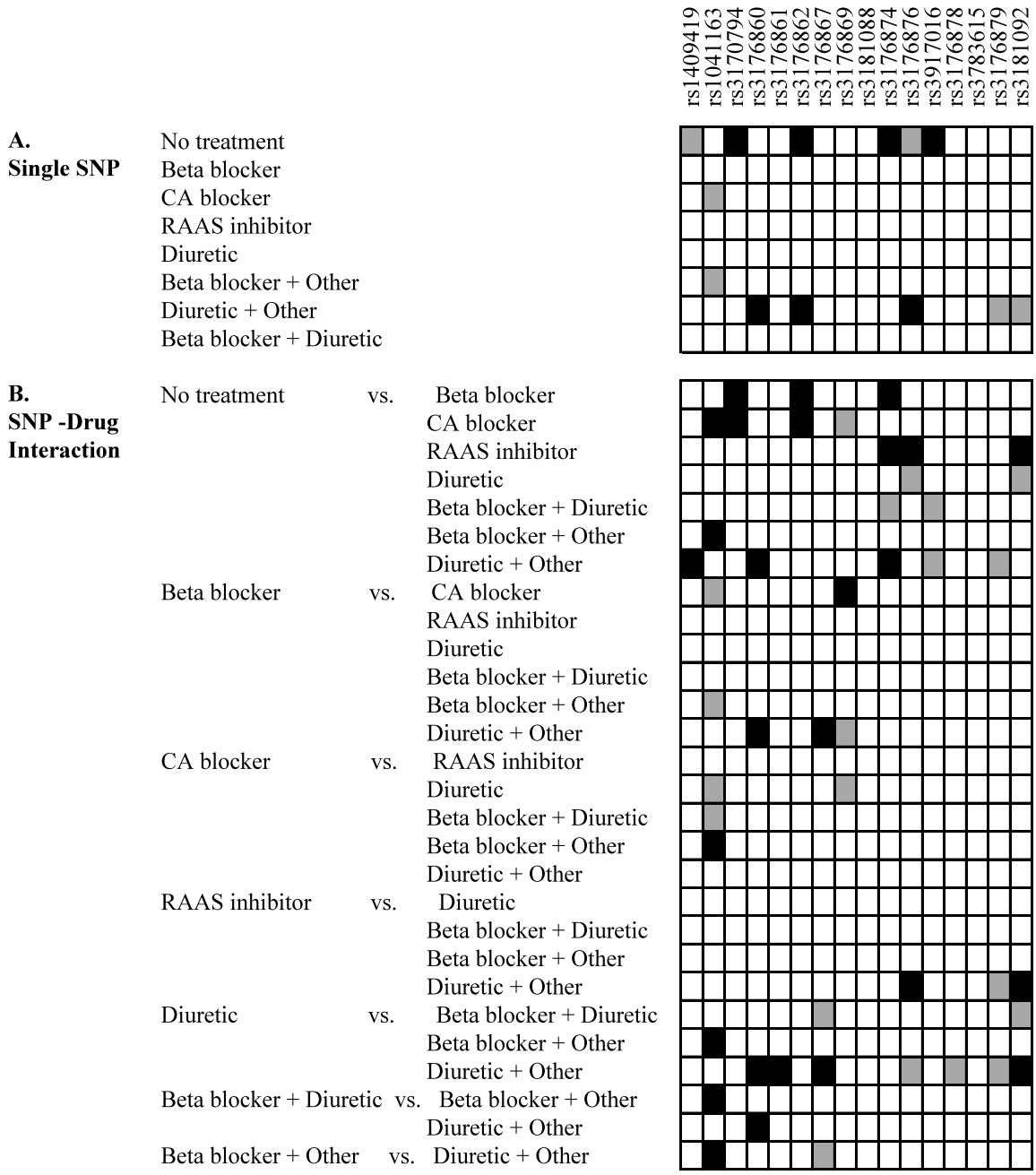
Statistically significant p<0.05 and CV $R^2$ * 100 >0.50
Statistically significant p<0.05 and CV $R^2$ * 100 <0.50
Not statistically significant

**Figure 5.10.** ***VCAM1*** **rs3176876 genotype specific mean systolic blood pressure by treatment class in GENOA African American hypertensive subjects**




*Other antihypertensive class includes alpha-blockers, vasodilators, sympatholytics, and study drugs. SBP = systolic blood pressure; CA = calcium channel; RAAS = renin angiotensin aldosterone system.

**Figure 5.11. Single SNP and SNP-drug effects of *VCAM1* SNPs on systolic blood pressure in GENOA non-Hispanic white hypertensives (n = 1129)**



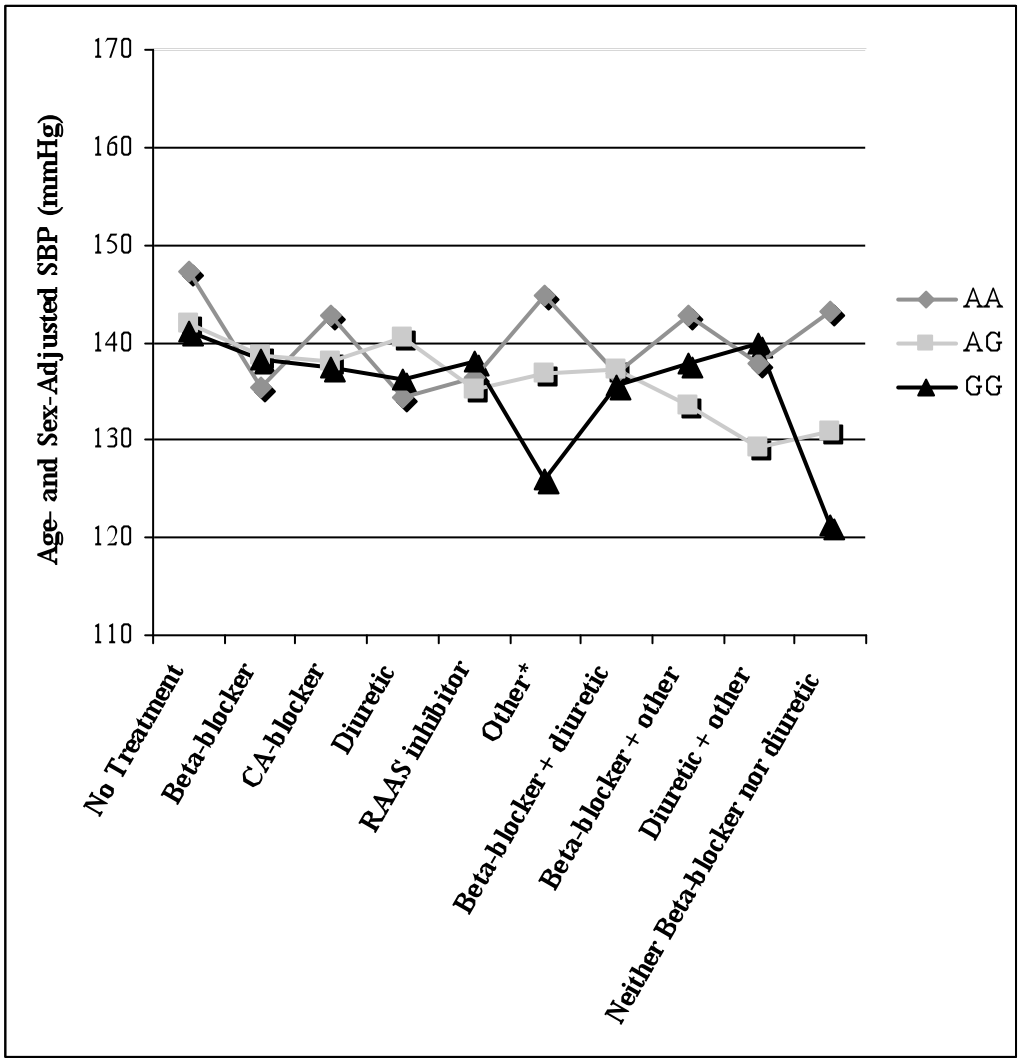

SNP rs #'s listed from left to right according to relative positions on *SELE* gene in the 5' to 3' direction. SNP = single nucleotide polymorphism; CA = Calcium channel; RAAS = renin angiotensin aldosterone system.

Statistically significant $p<0.05$ and CV $R^2 * 100 > 0.50$

Statistically significant $p<0.05$ and CV $R^2 * 100 < 0.50$

Not statistically significant

**Figure 5.12. VCAM1 rs3176860 genotype specific mean systolic blood pressure by treatment class in GENOA non-Hispanic white hypertensive subjects**




*Other antihypertensive class includes alpha-blockers, vasodilators, sympatholytics, and study drugs. SBP = systolic blood pressure; CA = calcium channel; RAAS = renin angiotensin aldosterone system.

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# Chapter 6

# Conclusion

## SUMMARY OF FINDINGS

The need for a shift in epidemiology to a paradigm that considers many levels of organization (molecular, individual, and societal) in the design, analysis, and interpretation of epidemiological studies has been described (1). The purpose of this dissertation was to investigate factors across multiple levels that likely shape the distribution of quantitative blood pressure (BP) measures and the relative odds of BP treatment and control in a bi-ethnic sample of hypertensive subjects from the Genetic Epidemiology Network of Arteriopathy (GENOA) study.

Findings from Chapter 2 indicated that BP control rates were suboptimal, even among treated hypertensives, and BP control rates were lower among African American (particularly female) subjects, compared to non-Hispanic white subjects. These findings were in accordance with national data on BP control (2-4). The distributions of the types of antihypertensive drug therapies utilized within each racial/ethnic group suggested that prescribing patterns may generally comply with recommended treatment guidelines (5). As expected, age was the strongest predictor of both continuous BP measures and the probability of BP control in both racial/ethnic groups. The presence of co-morbidities was strongly associated with the relative odds of receiving more aggressive BP treatment in both racial/ethnic groups, as expected. Positive histories of coronary heart disease

(CHD) and/or cerebrovascular disease (CBVD) were relatively low and comparable in each racial/ethnic group. In non-Hispanic whites, a positive history of CHD was associated with a decreased odds of BP control (unadjusted OR: 0.55, 95% CI: 0.36, 0.84). The African American sample had a significantly higher percentage of diabetic individuals compared to their non-Hispanic white counter parts (28% vs. 13%). The presence of diabetes was a strong univariate predictor of BP control among African Americans (OR: 0.59, 95% CI: 0.45, 0.77) and this effect remained upon adjustment for age and sex (OR: 0.61, 95% CI: 0.46, 0.81). Low levels of education were significantly associated with decreased odds of BP control in both racial/ethnic groups in unadjusted analyses. Upon controlling for potential confounders, the education effect was attenuated towards non-significance in non-Hispanic whites. In contrast, the education effect remained statistically significant in African Americans, even after adjustment for age, sex, BMI, and diabetes (OR: 1.04, 95% confidence interval (CI): 1.00-1.08), providing additional supporting evidence that factors indexed by SES may influence BP control and contribute to observed disparities in BP control rates between racial/ethnic groups.

The main finding in Chapter 3 suggested that residing in a socioeconomically disadvantaged neighborhood might reduce the likelihood of being treated for hypertension more aggressively with multiple medications among treated African Americans. This finding was consistent regardless of the neighborhood-level variable used to capture neighborhood socioeconomic environments (neighborhood socioeconomic summary score (increasing score represented greater affluence), OR: 1.03, 95% CI: 1.00, 1.06; poor neighborhood of residence (defined as a neighborhood with >25% poverty), OR: 0.72, 95% CI: 0.55, 0.96) and the associations detected withstood

adjustment for individual age, sex, BMI, diabetes, and education. Neighborhood socioeconomic environment, as measured using census-derived proxy variables, was not associated with BP control, and this finding corroborates findings from similar previous investigations in other studies (6).

Findings from Chapter 4 provided further evidence of moderate familial aggregation of quantitative BP levels in both African Americans non-Hispanic Whites. Adjustment for individual level variables led to significant reductions in both the within- and between-family variance in BP levels in both racial/ethnic groups. Parental histories of hypertension were the only family-level variables available and, in general, did not seem to confer strong contextual effects on individual BP levels. Among African subjects, sib-sib correlations of quantitative BP values and familial aggregation of BP control were detected among sibpairs in which both siblings resided in poor neighborhoods. These findings suggest that sibs living in similar types of neighborhoods may be more likely to demonstrate similar BP outcomes, as opposed to sibs living in dissimilar types of neighborhoods.

The main finding from Chapter 5 was that *SELE* and *VCAM1* single nucleotide polymorphism (SNP) main effects, as well as gene-drug interaction effects, were associated with SBP in both African Americans and non-Hispanic whites. These findings suggest that SBP response to antihypertensive drug therapies may be partially dependent on the effects of SNPs within genes, namely *SELE* and *VCAM1,* in the inflammation/endothelial dysfunction pathway. These findings add to the growing body of pharmacogenetic knowledge and the promise of developing "personalized medicine" approaches that tailor clinical management decisions based on genetic profiles.

## LIMITATIONS

The high percentages of hypertension awareness and treatment in the GENOA subjects may pose a couple of issues. First, greater awareness and more frequent treatment in our sample may reflect selection bias since hypertension (in at least two sibs), with or without prior use of antihypertensive medication, was a criterion for study participation. Second, as a result of such high percentages there was not much variation in these hypertension outcomes, which limited the ability to assess/detect significant predictors. Given that the GENOA study was based on hypertensive sibships, data correlations may have potentially affected the standard errors of effect estimates in this dissertation work. Multi-level modeling strategies were used to account for familial (and neighborhood) correlation in this dissertation. As the GENOA subjects were generally older hypertensives, inferences may not be generalizable to individuals who are younger, normotensive.

All analyses in this dissertation were based on cross-sectional data. Establishing causality from such data can be difficult, since exposure(s) and disease are measured at the same time. This may not be an issue for some exposures (e.g. - individual genotypes) that are relatively constant within individuals. However, it is important to note that an individual's exposure to certain risk factors (e.g. - neighborhood of residence) at the time of enrollment in a cross-sectional study may not equal exposure status when the disease process began. This latter point was a particular limitation in the proposed study, as residential histories of the GENOA participants are unavailable. The influence of genetic variation (and other factors) on BP response was limited in the absence of longitudinal data on BP measures, treatment adherence, and treatment dosage.

The quantitative BP measure and BP control outcomes of this study were all based on BP measurements taken during one short time period. As BP continually fluctuates in individuals, the measurements taken at the time of examination may have been artificially higher (white coat hypertension phenomenon) or lower than a normal average for a given individual. As a result, cross-sectional classifications of BP control, for example, may not reflect a given individual's typical BP control status. Furthermore, although efforts were made to obtain accurate office BP measurements, calibration errors, inappropriately sized arm cuffs, or operator digit preference may have led to measurement errors. Despite this, it is likely that such errors are distributed evenly across the study samples and may not have biased findings. There is also the potential for similar measurement errors of the various exposures that were based on physical examinations at one time point. In addition, some exposure variables are based on information ascertained from questionnaires and are prone to response bias.

Census tracts were used as proxies for neighborhoods in this research. Census tracts have been commonly employed as an area measure in health research and previous studies indicate that differences between census tracts and smaller area measures (block-groups) are likely small (7). Still, defining neighborhoods in this way had limitations, as the boundaries used to define them may not have corresponded with what people define/perceive as their neighborhoods. The census-derived socioeconomic proxies used may not have accurately represented the neighborhood construct(s) most relevant to the BP outcomes tested, and failed to investigate specific mechanisms/characteristics that may be causally related to BP levels, treatment, and/or control. Socioeconomic environments (based on the various indicator variables used) were relatively

homogeneous across the census tracts investigated in this research, which may have limited the ability to parse out important neighborhood socioeconomic contextual effects.

Several of the analyses conducted in this dissertation (chiefly those in Chapter 5) involved many association tests and the results were vulnerable to false positive findings. Acknowledging this, cross-validation methods were employed to reduce the possibility of Type I errors, increase the internal validity of findings within samples, and assess the predictive ability of factors considered.

The genetic analytic approach used in Chapter 5 was based on the premise that susceptibility alleles for common diseases, such as cardiovascular disease (and related subclinical disease measures such as BP), are not under strong negative selection, and common variants contribute to common disease traits (i.e., the 'common disease/common variant' hypothesis) (8). However, the allelic spectrum for complex quantitative traits such as BP is not fully delineated, and it is possible that multiple rare variants (not assessed) influence BP. While many genome-wide association studies (GWAS) on BP are ongoing (9-12) and have the great potential to identify genomic regions that influence BP (and BP response to therapeutic interventions), genome-wide data was not available on the GENOA subjects at the time analyses in Chapter 5 were conducted. Particular investigation of SNPs in the *SELE* and *VCAM1* candidate genes was based on previously detected associations between SNPs in these genes and cardiovascular outcomes (including hypertension), and the hypothesis that inflammation may independently promote the development of hypertension. Although this possible pathogenic direction has sparked recent interest, reverse causation (i.e. - inflammation is a response to hypertension induced endothelial dysfunction) is equally likely. Insufficient sample sizes in each treatment class or random measurement error may have limited the power to detect genotype–phenotype associations.

## SIGNIFICANCE AND FUTURE DIRECTIONS

Strengthening our understanding of common chronic diseases is a difficult challenge given their complex and multi-factorial nature. It is well accepted that many genes influence the risk of developing chronic disease through their additive and interactive effects, and that such risk also depends on lifetime environmental exposures, as well as interactions between genetic and environmental influences. Although many studies have made (and continue to make) valuable contributions towards the identification of important health determinants of chronic diseases, they remain largely rooted within scientific disciplines and a need for transdisciplinary approaches exists.

The work presented in this dissertation was part of a key project with the Center for Integrative Approaches to Health Disparities (a collaboration between the University of Michigan and the Jackson Heart Study through its partners the University of Mississippi Medical Center and Jackson State University) (13). The future development and continuation of such transdisciplinary research is perfectly aligned with the aforementioned call for a paradigm shift in epidemiological research (1). A transdisciplinary focus on the determinants of chronic diseases holds the promise of yielding new etiological insights, identifying reasons for observed health disparities in chronic disease outcomes that persist along racial/ethnic and socioeconomic lines, and would help to identify key intervention points to reduce the overall health and economic burdens stemming from common chronic diseases.

A natural future direction of such integrative research will be to thoroughly investigate the ways in which health determinants at different levels interact to influence the risk of chronic disease development. In 2006, the Institute of Medicine (IOM) drafted

a consensus report containing recommendations that were "designed to explicate and facilitate research on the impact on health of interactions among social, behavioral, and genetic factors (14)." The primary recommendations the IOM set forth in this report include: the promotion and development of transdisciplinary and collaborative research and research training; the development of rich databases containing life course social, behavioral, and genetic information in diverse populations; the development and implementation of new and innovative modeling strategies (including pattern recognition models, multivariate statistics, and pathway analysis) that will yield more comprehensive predictions of disease; the investigation of biological signatures as a means of discovering biological systems that interact with social and behavioral factors; testing gene-environment interactions and pathways of human diseases using controllable animal models; and attending to the ethical, legal, and social implications of conducting transdisciplinary research (14).

The IOM report reminds that, "health outcomes are multidetermined and result from complex interactions of many factors over time (14)." It is intuitive then that approaches aimed to further our etiological understanding of disease should be integrated and reasonably consider the multitude of factors acting in concert to give rise to the development of common chronic disease. This dissertation research took important novel first steps in constructing interconnections between factors across a broad framework of health determinants that jointly influence BP outcomes. Significant findings from this research highlight the importance of mutually considering factors defined at multiple levels in developing a richer etiological understanding of common chronic diseases.

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