8-9-2014

A BIOECOLOGICAL APPROACH TO UNDERSTANDING THE INTERACTION OF ENVIRONMENTAL STRESS AND GENETIC SUSCEPTIBILITY IN INFLUENCING CORTISOL AND BLOOD PRESSURE IN AFRICAN AMERICAN ADULTS

Sandra Marie Coulon
University of South Carolina

A Bioecological Approach to Understanding the Interaction of Environmental Stress and Genetic Susceptibility in Influencing Cortisol and Blood Pressure in African American Adults

by

Sandra Marie Coulon

Bachelor of Science
Louisiana State University, 2005

Master of Arts
University of South Carolina, 2011

Submitted in Partial Fulfillment of the Requirements

For the Degree of Doctor of Philosophy in

Clinical-Community Psychology

College of Arts and Sciences

University of South Carolina

2014

Accepted by:

Dawn K. Wilson, Major Professor

Brent M. Egan, Committee Member

Amanda J. Fairchild, Committee Member

Greg A. Hand, Committee Member

Lacy K. Ford, Jr., Vice Provost and Dean of Graduate Studies

DEDICATION

This work is dedicated with deep admiration and love to my grandparents, Marie Antoinette Sumich Charbonnet, John William Charbonnet, Neva Cecile Ducote Coulon, and Kermit Joseph Coulon; not only did you create my wonderful parents, but without your living examples of hard work, and your encouragement of my education above other things, I would not have felt free and able to do this. And especially, to MaRie for your matter-of-fact strength, poise, and wisdom in the face of both joy and hardship, PaPa John for first showing me what it is to find excitement in progress and truth in beauty, MaMa Nevie for your intelligence and constant perceptive kindness toward others, and PaPa Kermit for ambition, charisma, and luck that must have come not from the world loving you but from you loving it.

ACKNOWLEDGMENTS

This research was supported by the National Institute on Aging (NIH F31AG039930 to Sandra M. Coulon, M.A., and Dawn K. Wilson, Ph.D), the National Institute of Digestive and Kidney Diseases (NIH R01 DK067615 to Dawn K. Wilson, Ph.D.), the University of South Carolina (Advanced Support Program for Integration of Research Excellence-II Grant), and the American Psychological Association (Health Psychology Division 38 Research Addressing Health Disparities Graduate Student Research Award).

ABSTRACT

African Americans are disproportionately affected by high blood pressure, a precursor to cardiovascular disease. Bioecological, biomedical, and gene-environment interaction theories were integrated to test the impact of environmental stress and genetic susceptibility on stress-related outcomes, including waking cortisol, perceived stress, and blood pressure in African-American adults. The primary aim of the study was to investigate the effects of neighborhood socioeconomic status (SES), neighborhood satisfaction, and neighborhood collective efficacy on waking cortisol, perceived stress, and blood pressure and to determine whether genetic risk for increased glucocorticoid receptor sensitivity moderated those relations in a gene-by-environment (GxE) interaction. A secondary aim was to investigate a potential mechanistic model whereby cortisol and perceived stress were expected to mediate the influence of neighborhood factors on BP, and also expected to interact with genetic risk to influence BP in a moderated mediation design. Blood pressure, saliva cortisol, buccal swab gene samples, psychosocial surveys, and geographic census data were collected from 450 African American adult participants. Three glucocorticoid receptor polymorphisms (*Bcl*1, FHBP5, and 9β) that have been linked to cortisol and blood pressure outcomes were genotyped and indexed into a single genetic risk factor. Aims were tested statistically using path analysis for estimating interaction effects, and for testing moderated mediation effects using the product of coefficients method with bootstrapped confidence intervals.

The sample was 70% female and results of the primary and secondary models indicated that neighborhood SES was negatively related to waking cortisol and that waking cortisol was negatively related to systolic blood pressure. Follow-up analyses revealed a significant GxE interaction predicting perceived stress, and a trend for predicting afternoon cortisol, and systolic blood pressure. The pattern was consistent across the interaction models and indicated that individuals with high genetic risk had poorer outcomes in poorer environments and better outcomes in better environments; individuals with low genetic risk showed almost no environmental interaction. The pattern was consistent with a differential susceptibility/plasticity GxE effect, in contrast to more traditional dual risk or diathesis-stress effects. These findings are the first to assess gene-by-neighborhood interactions in African-American adults, as they impact cortisol and BP, and they may contribute to a comprehensive and contextually relevant understanding of high BP and cardiovascular health disparity. Conclusions may inform the development of innovative, targeted prevention efforts, and public policy efforts to decrease BP health disparity through greater consideration of neighborhood factors, and differential susceptibility to both more and less positive environments.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ACort..... afternoon cortisol

BMI.....body mass index

BP..... blood pressure

CVD .....cardiovascular disease

CE ..... collective efficacy

DBP.....diastolic blood pressure

GxE ..... gene-by-environment

GR ..... glucocorticoid receptor

HR.....heart rate

NSat..... neighborhood satisfaction

NSES..... neighborhood socioeconomic status

PS ..... perceived stress

SBP .....systolic blood pressure

SES..... socioeconomic status

SNP .....single nucleotide polymorphism

WCort.....waking cortisol

CHAPTER 1

INTRODUCTION

Socioeconomically disadvantaged groups in the U.S., and in particular African-American adults, experience the highest rates of cardiovascular disease (CVD) as part of a long-standing and substantial health disparity (Burt et al., 1995; Collins & Winkleby, 2002; Lloyd-Jones, et al., 2009; Roger et al., 2012; Schocken, et al., 2008; M. Wong, Shapiro, Boscardin, & Ettner, 2002). Over the past century CVD has disproportionately affected African-American adults with mortality risk due to high blood pressure (BP) increasing from about 8% to 14% since the 1970's (Ford, Li, Zhao, Pearson, & Capewell, 2009; Gill, Vythilingam, & Page, 2008). African American mortality rates due to high BP are approximately 44 deaths annually per 100,000 individuals, versus 15 deaths annually for European Americans (Lloyd-Jones et al., 2009). Rates of fatal stroke and CVD deaths are 1.8 and 1.5 times greater, respectively (Chobanian et al., 2003). Additionally, BP-related increases in mortality of 20% have primarily affected minority populations, with about 44% of African Americans currently classified as having high BP, in contrast to 28% of European Americans (Cutler et al., 2008; Lloyd-Jones et al., 2009; Roger et al., 2012). Prevention efforts have had only modest effects on high BP in African American populations, likely because high BP is a complex, multifactorial disease for which the etiology is not fully understood, and may vary across demographic groups (Gadegbeku, Lea, & Jamerson, 2005; Kuzawa & Sweet, 2009; Ofili, 2001).

Achieving national health equity and creating physical and social environments that promote health and reduce health disparity are top priorities for the *Healthy People 2020* initiative, under the U.S. Department of Health and Human Services (Koh, 2010; U.S. Department of Health and Human Services, 2011). Thus, a better understanding of how environmental factors influence BP is necessary, especially in at-risk populations, and may provide insight into how socioeconomic disadvantage influences or perpetuates CVD-related health disparities (Adler et al., 1994; Andresen & Miller, 2005; Matthews & Gallo, 2011). Additionally, it is estimated that high BP is up to 30-40% heritable and that genetic risk and environmental factors likely interact to influence its development (Arnett et al., 2007; Franks, 2008; Imumorin et al., 2005; Levy et al., 2000; Pausova, Tremblay, & Hamet, 1999).

Theoretically, socioeconomically disadvantaged persons can experience greater chronic environmental stress, or more specifically greater distress (Selye, 1975), which in turn may lead to adverse physiologic functioning, cardiovascular "wear and tear", and ultimately high BP and CVD (Anderson, 1998; Clark, Anderson, Clark, & Williams, 1999; Dowd, Simanek, & Aiello, 2009; Matthews & Gallo, 2011; Steptoe & Marmot, 2002). Population-level reductions in BP as small as 2 mm Hg (millimeters of mercury) may reduce the prevalence of high BP by 17% (Cardiology, 1995), and reductions in stress have been associated with 3-10 mm Hg decreases in BP (Linden & Moseley, 2006; Rainforth et al., 2007). However, reports of interactions among stress-related gene-by-environment (GxE) risk factors are lacking in African-American populations. A better understanding of associations among these factors may inform and facilitate public health initiatives (e.g. *Healthy People 2020*) that aim to address the BP health disparity

experienced by African-American adults. A solid rationale can therefore be established for research, such as the current study, which aims to assess how stress-related GxE interactions influence basal cortisol as a marker of physiologic stress, and BP as a relevant cardiovascular outcome, in African-American adults.

1.1 SOCIOECONOMIC DISADVANTAGE AND ENVIRONMENTAL FACTORS

The impact of socioeconomic disadvantage on health has been thoroughly investigated as a function of individual socioeconomic indicators, termed *compositional* socioeconomic status (e.g. index of an individual's income, occupation, education; Shavers, 2007). However, it has less frequently been studied in relation to environmental or contextual stressors, such as *contextual* socioeconomic status (SES), neighborhood satisfaction, and neighborhood collective efficacy. Contextual SES differs from compositional SES in that it characterizes the socioeconomic environment that surrounds the individual (e.g., neighborhood resources), rather than characterizing the specific individual level of resources (Shavers, 2007). Given complex relations between socioeconomic stressors and health, and potential genetic and population-specific moderators, the traditional exclusion of these environmental factors from SES research considerably limits a comprehensive understanding of high BP and its etiology (Matthews & Gallo, 2011; Shavers, 2007).

Compositional SES demonstrates a reliable positive association with better health outcomes and often accounts for meaningful proportions of outcome variation (Adler & Ostrove, 1999). However, it has been noted that compositional measures are likely overly simplistic, and do not capture heterogeneity in the structure and influence of SES within and between populations (Adler et al., 1994; Cox, McKevitt, Rudd, & Wolfe, 2006;

Johnson et al., 1995; LaVeist, 2005). Alternatively, measures of contextual SES, sometimes referred to as ecological SES (Andresen & Miller, 2005) or neighborhood SES (Matthews & Gallo, 2011), aim to characterize socioeconomic *contexts* to which people are exposed, and may account for variation in health outcomes such as BP, above and beyond compositional SES. Indeed, a growing body of literature supports this notion (Matthews & Gallo, 2011; Merlo et al., 2001; Pickett & Pearl, 2001). Neighborhood SES and related factors such as neighborhood satisfaction and collective efficacy may, therefore, provide insight into etiologic processes for which SES operates uniquely, as has been suggested for high BP in African Americans (Gadegbeku et al., 2005; Kuzawa & Sweet, 2009; Ofili, 2001). Additionally, neighborhood environmental stress has been linked to cardiovascular outcomes (Diez Roux et al., 2002b; Kapuku, Treiber, & Davis, 2002; Morenoff et al., 2007; Petersen et al., 2006; Thomas, Nelesen, Ziegler, Natarajan, & Dimsdale, 2009; Thorpe Jr, Brandon, & LaVeist, 2008), indicating a growing need to further explore these associations and potential moderating genetic risk factors.

1.2 INTEGRATED CONCEPTUAL FRAMEWORK

Bioecological theory, an adaptation of Bronfenbrenner's original ecological systems theory (Bronfenbrenner, 1979, 2005), asserts that human health, behavior, and development are embedded within graded micro- and macro-level ecological contexts. Within and between these ecological levels, complex processes occur which facilitate the interacting influence of more proximal biological and more distal ecological factors on human health (Tudge, Mokrova, Hatfield, & Karnik, 2009). Bioecological approaches can provide a contextual foundation for the interdisciplinary study of cardiovascular health, which may not be afforded by traditional biomedical approaches that often apply

reductionistic, or symptom-based conceptualizations of etiology and treatment (Hayman & Hughes, 2006; Stokols, 1996; Tu & Ko, 2008).

Anderson (Anderson & Armstead, 1995; Johnson et al., 1995) and Matthews (Matthews & Gallo, 2011; Matthews, Gallo, & Taylor, 2010) both present conceptual models specific to the impact of SES on cardiovascular health in African Americans (Anderson & Armstead, 1995; Johnson et al., 1995; Matthews & Gallo, 2011; Matthews et al., 2010). Consistent with a bioecological approach, they theorize that SES-related health disparities can be understood only by studying multiple levels of analysis that can collectively detect unique relations between environmental stress and health. For example, by integrating the study of social-environmental, organ system, and molecular levels of analysis, interactions among neighborhood environments and genetic factors can be investigated to provide a more comprehensive understanding of the determinants of high BP (Anderson, 1998). Similarly, biopsychosocial approaches to understanding health focus on analytic levels containing biological, psychological, and social influences (Anderson & Armstead, 1995; Taylor, 2011). It should be noted that application of this "multiple levels of analysis," which refers to an ecological systems approach, does not necessarily imply the simultaneous statistical modeling of multiple levels.

Bioecological, multiple levels of analysis, and biopsychosocial approaches provide comprehensive frameworks for investigating high BP in African Americans, and they may be further specified through the integration of biomedical models. Biomedical models operate to inform expectations of specific physiological processes, and directional hypotheses for stress and disease pathways. When individuals are faced with environmental stress, one physiologic process initiated is the neuroendocrine stress

response. This response involves the secretion of cortisol steroid hormones through the hypothalamic-pituitary-adrenal (HPA) axis. Cortisol steroid hormones are chemical messengers that travel through blood/plasma to communicate information between bodily tissues. HPA processes and cortisol secretion directly impact acute functioning and general regulation of cardiovascular, metabolic, immune, and cellular systems in the human body. The HPA axis and cortisol also impact the nervous system via mediating autonomic functioning, with sympathetic arousal working in conjunction with HPA responding to adapt an individual's biological state to acute and chronic stressors, respectively. Cortisol binds to intracellular glucocorticoid receptors (GRs) that occur in nearly every cell of the human body. It then translocates into the cell nucleus to combine with DNA molecules, and thus it has a powerful impact on the tissues and organs of the systems noted above (Constanti, 1998). A cell's response to cortisol or its secretion of cortisol can depend therefore on the sensitivity of GRs, with increased sensitivity conferring increased binding and subsequent impact on tissue.

Additionally, receptor sensitivity and cortisol binding activities impact regulation of the HPA system, as well as other tissue-specific systems, thereby influencing overall or basal stress response patterns. When secreted, cortisol prompts the neuroendocrine system to physiologically adapt the body to internal, behavioral, or environmental acute and chronic stimuli/stressors. Circulating cortisol therefore produces physiologic hyper-arousal (e.g. increased BP) which is adaptive for acute stress and helps to preserve homeostasis (Zhu et al., 2005), but maladaptive in the presence of chronic stress (Anderson, 1989; Matthews, Schwartz, Cohen, & Seeman, 2006; Seeman & McEwen, 1996; Troxler, Sprague, Albanese, Fuchs, & Thompson, 1977). Thus, chronic stress, such

as the environmental stress likely experienced by individuals experiencing at-risk levels of neighborhood SES, neighborhood satisfaction, and collective efficacy, can contribute largely to systemic physiological, neurological, and psychological dysfunction. Generally, systemic dysfunction can influence the development of high BP, atherosclerosis, immunosuppression, memory loss, and depression (Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003; Phillips et al., 2006).

Though the term "stress" is often used to describe adverse or overwhelming experiences within both physical/health and psychological domains, its measurement and presentation is distinct for each domain. As a physical phenomenon, the term characterizes any objective change in functioning that is a response to an environmental stimulus, regardless of whether that stimulus is perceived as positive or negative by the individual. As a psychological phenomenon, the term characterizes any subjective or cognitive experience of stress, and importantly captures the experience of distress perceived by the individual. In contrast to physiologic stress, cognitive perceptions of stress or distress, characterize changes in functioning that are a response to stimuli for which the valence is negative and adverse. The construct of perceived stress therefore captures subjective distress-related cognitive components and coping responses that impact health and well-being (Lazarus, 1991), whereas physical measures of stress such as adrenaline or cortisol capture physiologic arousal (Selye, 1975). It is therefore important to assess both physiologic and subjective cognitive indicators of stress when considering the extent to which stress is associated with or influences by environmental risk. These indicators, in turn, are associated with or influence chronic disease outcomes such as high BP (King & Hegadoren, 2002). For this study, the general term "stress" is

used to characterize cortisol as a marker of physical stress that is elevated or dysregulated with chronic exposure to adverse environments, as well as cognitive perceptions of distress.

Environmental stress and neuroendocrine processes do not influence health independently of genetic risk factors, and high BP is estimated to be partially heritable as a complex, polygenic (versus Mendelian) disease (Arnett et al., 2007; Levy et al., 2000). "Gene-by-environment" (GxE) interaction frameworks capture both components of the classic "nature-nurture" debate, asserting that genetic factors interact with contextual, environmental factors to influence physiologic processes, BP, and health (Imumorin et al., 2005; Pausova et al., 1999; Zhu et al., 2005). GxE frameworks for understanding high BP are supported by evidence that genetic factors alter the sensitivity of GRs, and therefore are associated with variation in glucocorticoid functioning and the impact of cortisol on tissues and organs (Arnett et al., 2007; Imumorin et al., 2005; Pausova et al., 1999; Wust et al., 2004). Specifically, it may be theorized from a public health and dual risk standpoint that genetic and environmental factors interact to influence stress-related outcomes of cortisol, perceived stress, and BP (Figure 1.1). From a mechanistic standpoint, it may be theorized that environmental risk influences cortisol secretion and perceived stress, which is regulated/moderated in part by genetic risk, which in turn influences BP (Figure 1.2).

Common gene polymorphisms characterize genetic heterogeneity associated with phenotypic variation and are known as single nucleotide polymorphisms (SNPs). SNPs indicate variation in a DNA sequence that occurs when a single nucleobase (adenine [A], thymine [T], cytosine [C], guanine [G]) for a given gene location, or locus, differs

between individuals or between pairs of chromosomes. SNPs are defined as affecting at least 1% of the population (i.e. having a minor allele frequency ≥ 1%), though SNPs that are relatively common (e.g. minor allele frequency of 25%) are often targeted for the investigation of complex health outcomes. Theoretically, GxE interaction models suppose that the impact of environmental stress on health outcomes such as BP varies as a function of genetic risk. Specific to this study, it asserts that the impact of neighborhood SES on blood pressure will be greater in individuals with SNPs that confer increased glucocorticoid receptor sensitivity; the environment affects cortisol stress hormones and perceptions of stress, and genetic factors moderate the effect of those stress factors on the cardiovascular system. Similarly, environmental stress models of health indicate pathways in which ambient, or stable, features of the physical environment interact with individual differences to influence health outcomes (Taylor, 2011; Wandersman & Nation, 1998), and the current research is congruent with such a model.

Integration of bioecological, biomedical, and GxE interaction theories guide hypotheses of relations among environmental stress, GR SNPs, cortisol, perceived stress, and BP. For the GxE interaction a dual risk approach is assumed through which conceptually, the impact of a poor neighborhood environment on health is expected to be worse with increasing genetic risk (Figure 1.3). This is equivalent to diathesis–stress models for the development of psychopathology, which theorize that individuals who are predisposed to develop a given condition, or to adopting a given environmental response, will do so in the presence of a particular environmental trigger or context (Hankin & Abela, 2005). The relevance of this integrated approach is underscored by evidence that environmental and physiologic processes may influence cardiovascular health in African

Americans in a way that is functionally unique (Anderson, 1989; Green & Darity Jr, 2010; Minor, Wofford, & Jones, 2008; Ofili, 2001; Williams, Yu, Jackson, & Anderson, 1997). While differential susceptibility theory also provides a framework that may be relevant to the associations targeted in the current research, it has not been targeted as it is more often linked to developmental processes in childhood (Belsky & Pluess, 2009). Thus, this study aims to expand upon our understanding of how dual risk of environmental and genetic processes may uniquely influence stress-related outcomes and BP in African Americans.

1.3 BACKGROUND LITERATURE

Neighborhood SES, Neighborhood Perceptions, Cortisol and Cardiovascular Outcomes. Compositional SES has been linked to high BP (Dressler, 1990a; Hawkley, Masi, Berry, & Cacioppo, 2006; Lehman, Taylor, Kiefe, & Seeman, 2009; Strogatz et al., 1997), other measures of cardiovascular health such as vascular inflammation (Hong, Nelesen, Krohn, Mills, & Dimsdale, 2006), and nocturnal BP dipping (Spruill et al., 2009). These relations have been demonstrated both in general populations (Gasperin, Netuveli, Dias-da-Costa, & Pattussi, 2009; James, 1987; Rainforth et al., 2007) and in African Americans (Dressler, 1990a; Hawkley et al., 2006; Lehman et al., 2009; Strogatz et al., 1997). However, they have not always been supported (Hawkley et al., 2006; Kapuku et al., 2002; Pointer, Livingston, Yancey, McClelland, & Bukoski, 2008), and at most they account for 30% of BP variation (Dressler, 1990a). Nonetheless, studies of contextual SES, neighborhood satisfaction, and collective efficacy may add to the existing literature by focusing on broader contextual factors.

Contextual SES. A handful of studies have assessed associations of contextual SES and environmental stress with BP and cardiovascular health outcomes in African Americans (Diez Roux et al., 2002b; Kapuku et al., 2002; Merlo et al., 2001; Morenoff et al., 2007; Petersen et al., 2006; Thomas et al., 2009; Thorpe Jr et al., 2008). Findings from most investigators (Merlo et al., 2001; Morenoff et al., 2007; Petersen et al., 2006; Thomas et al., 2009; Thorpe Jr et al., 2008), but not all (Diez Roux et al., 2002b) supported hypotheses that contextual factors influence BP and cardiovascular health outcomes. Geographically aggregated data provided by the U.S. Census Bureau are most frequently used as measures of contextual SES in the U.S., with sets of variables capturing contextual income, education, and occupation included. One study assessed the relation of neighborhood SES to cardiovascular health outcomes in African-American and European-American men with untreated hypertension. The study used variables of median household income, median values of owner-occupied housing units, percentage of households on public assistance, percentage of households beneath the federally designated poverty level, percentage of adults in the work force who were unemployed, median gross rent, and proportion of residents greater than age 25 years lacking a high school diploma. These variables were aggregated at the census tract level as a measure of contextual SES (Petersen et al., 2006). The study found that lower neighborhood SES was linked to the presence of preclinical atherosclerosis, a thickening of the arteries that can result in part due to high blood pressure (*OR* = 1.5), above and beyond the influence of individual SES (Petersen et al., 2006). Similar results have been found in international populations (Merlo et al., 2001).

Another study that equally represented African-American and European-American adults, used the block-level percentage of individuals living in poverty as an indicator of contextual SES. The study found that lower neighborhood SES interacted with individual education level (individual SES) to predict healthier BP reactivity (Thomas et al., 2009). It is worth again noting considering however that reactivity is physiologically distinct from resting BP, in that it is an acute cardiovascular response rather than a marker of systemic functioning. In a multi-ethnic study, neighborhood SES scores for those who died of CVD were lower (-3.5) than those who died of other causes (-2.7), and those who did not die (-1.8), though the trend was not significant (Diez Roux, Borrell, Haan, Jackson, & Schultz, 2004). As has been done previously, neighborhood SES was quantified using data aggregated at the block level and included variables of median household income, median value owner-occupied housing, proportion of households receiving interest, dividend, or net rental income, proportion of adults with a high school diploma, proportion of adults with a college education, and proportion of adults employed in executive, managerial, or professional occupations. Another study conducted using the same neighborhood SES index and within a similar population demonstrated that contextual SES was not associated with hazard rations for high BP, or receiving a diagnosis of high BP (Diez Roux et al., 2002b).

A study by Jones-Webb and colleagues (2004) enrolled African American and European American men and indexed contextual SES using census poverty data. They found that contextual SES predicted CVD mortality over 6 years for African American men living in low SES neighborhoods (Jones-Webb et al., 2004). However, a study in young (M_{age} = 18.8) African American men demonstrated no relation between

neighborhood SES (median household income, median monthly housing cost, mean home value, percentage of households below the poverty line, percentage of single-women headed households, parental education level, and percentage unemployed individuals) and basal cortisol and resting BP (Kapuku et al., 2002). An investigation of neighborhood SES using the Townsend Deprivation Index (percentage of households that own a car, percentage of households with one or more persons per room, percentage of people living in owner-occupied housing, and proportion of unemployed individuals aged 16 and older) found that it was inversely related to systolic BP in a large sample of African American men and women (Cubbin, Hadden, & Winkleby, 2001). Finally, using census-derived estimates of poverty by zip code it was found that neighborhood SES was not related to having a diagnosis of high BP in African American women (Tanaka et al., 2007). It should be noted that for all studies neighborhood SES characterized the objective quantification of participants' contexts or neighborhood (e.g. using census blocks as proxies for neighborhood context). Because self-reported perceptions of context are likely to affect the HPA stress response and BP, it is important to understand the role of both, and thus the current research assessed subjective perceptions of the neighborhood environment and objective indicators of neighborhood SES.

Few studies have examined the effects of socioeconomic factors on cortisol or HPA activity in African American adults, or of contextual SES in African American adults. One study of African American children found that neighborhood SES, which they termed neighborhood disorder (percent unemployment, poverty, female-headed households, and vacant housing by zip code), was inversely related to cortisol levels immediately upon waking, unexpectedly; the opposite was true for European American

children (Dulin-Keita, Casazza, Fernandez, Goran, & Gower, 2012). Another however found no relation between the neighborhood SES and cortisol (Kapuku et al., 2002).

Of studies that have examined the effects of compositional SES, perceived stress, or job stress in African Americans, results have been mixed. Studies have typically hypothesized an inverse relation of socioeconomic factors and cortisol concentrations. One multi-ethnic study found that lower compositional SES (education and income) was related to higher total cortisol concentration (seven samples collected in one day), as hypothesized, and accounted for 3% of cortisol variance, independent of race (S. Cohen, Doyle, & Baum, 2006). Another found that survey-assessed material hardship was related to a larger negative slope for diurnal cortisol variation over the day (Ranjit, Young, & Kaplan, 2005).

However, positive or more complex relations can be found as well, likely given the complexities of SES and of HPA functioning, and potential for dysregulation and burnout in the context of chronic stress or adversity during early-life development (Anisman, Griffiths, Matheson, Ravindran, & Merali, 2001; Kajantie et al., 2007; Kumari, Chandola, Brunner, & Kivimaki, 2010). One study found that African American adults with lower SES (educational attainment) had waking cortisol values approximately 4 nmol/L (1.45 ng/mL) lower than higher SES adults, though the inverse was true for European American adults (Bennett, Merritt, & Wolin, 2004). In a sample of female family caregivers, African-American women showed greater cortisol and SBP reactivity after completing an interview during which they discussed caregiver stress; at the same time however, they reported greater perceived meaning in their roles as caregivers (Wilcox, Bopp, Wilson, Fulk, & Hand, 2005).

Another study demonstrating the interplay between physiological and psychological stress showed that in work-stressed teachers there were differential patterns of cortisol hyper-reactivity and hypo-reactivity (Wolfram, Bellingrath, Feuerhahn, & Kudielka, 2013). These different forms of dysregulation depended on the individual stress condition. Interestingly, the emotion-related stressor (perceived emotional exhaustion) was linked to hyper-reactivity, whereas the functional/problem-related stressor (perceived over-commitment to responsibilities) was linked to hypo-reactivity.

In other studies, hypothesized inverse relations have been found between socioeconomic factors and cortisol, though the effect may be moderated by demographic factors such as gender (Pruessner, Hellhammer, & Kirschbaum, 1999; Steptoe et al., 2003). Findings provide evidence that socioeconomic stressors relate to HPA functioning and cortisol in African-American populations, and relate in unique patterns of cortisol secretion in African Americans, or that African Americans may experience unique stressors that lead to HPA dysfunction.

The Neighborhood Environment. Neighborhood satisfaction can be conceptualized as broadly capturing an individual's perceptions of happiness with the overall environment in which he/she lives (Parkes, Kearns, & Atkinson, 2002). Neighborhood collective efficacy characterizes individuals' or sets of individuals' perceptions of mutual trust and willingness to intervene for the common good within their neighborhoods (Sampson, Raudenbush, & Earls, 1997), fostering resilience to adversity or stress (Bandura, 2000). Thus, collective efficacy captures the extent to which individual's contexts are supportive versus stressful, or convey a sense of community.

Those experiencing low collective efficacy are likely exposed to increased environmental stress (McMillan & Chavis, 1986; Sampson et al., 1997; Sarason, 1974).

Little research has been done to investigate the role of specific environmental stressors, such as low perceived neighborhood satisfaction and low perceived collective efficacy, in effecting health outcomes such as cortisol and BP. Though some studies have provided evidence for the relation of related factors such as perceived stress and low social support (S. Cohen et al., 2006; Dowd et al., 2009; Kumari, Badrick, et al., 2010; Steptoe, Siegrist, Kirschbaum, & Marmot, 2004; Wright & Steptoe, 2005), these constructs likely do not capture variation in neighborhood-specific contextual factors. Additionally, neighborhood satisfaction has primarily been investigated in relation to health behaviors, in particular physical activity, and has not been conceptualized within a bioecological model of environmental stressors and high BP. Nevertheless, investigations of the construct as a determinant of PA are promising, and one study demonstrated that health explained 26% of the variance in neighborhood satisfaction in black South Africans (Westaway, 2007). Another study which included a large proportion of African American adults (57%) demonstrated that perceptions of crime but not neighborhood satisfaction mediated the effect of neighborhood deprivation on perceptions of well-being (Kruger, Reischl, & Gee, 2007). However, neighborhood satisfaction was assessed with only one item, and it was in fact correlated significantly with depressive symptoms (r = .15). A study by Morris, McAuley, and Motl (2008) demonstrated an indirect link between neighborhood satisfaction and self-reported physical activity using a 17-item subscale of the Neighborhood Environment Walkability Survey, though the sample was comprised of mostly European-American women. Finally, one study did examine the

influence of neighborhood satisfaction on BP in a large sample of African American adults (Coulon et al., 2011). It was found that satisfaction was positively related to both SBP and DBP for individuals perceiving their neighborhoods as having a higher threat of crime.

Similarly, little research has attempted to link collective efficacy to high BP or cardiovascular dysfunction. Sampson and colleagues' original development and assessment of the collective efficacy construct and assessment tool indicated that it was inversely related to violent crime in an urban, multi-ethnic city, after accounting for individual characteristics (Sampson et al., 1997). In another multiethnic study it was found that collective efficacy was positively associated with parks and negatively associated with the presence of alcohol outlets (D. A. Cohen, Inagami, & Finch, 2008). Finally, in a study conducted within a large, predominantly European American sample, it was demonstrated that collective efficacy was significantly associated with perceived gang activity (Duncan, Duncan, Okut, Strycker, & Hix-Small, 2003). Studies of relations between neighborhood environmental stress and cortisol or HPA functioning in African Americans have not been conducted.

Thus, the role of contextual SES has been investigated to a larger degree than perceived neighborhood environmental factors, however neighborhood satisfaction and collective efficacy have been linked to outcomes related to socioeconomic disadvantage and health and warrant further investigation within a bioecological framework. The current research therefore included measures of neighborhood SES as an operationalization of contextual SES, neighborhood satisfaction, and collective efficacy.

Genetic Risk, the HPA Response, Perceived Stress, and Blood Pressure. GR functioning has been implicated as a central factor in associations of stress, cortisol, and high BP. Gene association studies have identified receptor and stress-related polymorphisms that account for some individual variation in the HPA stress response, basal and reactive cortisol levels, perceived stress, high BP, and related chronic disease such as obesity and type II diabetes (DeRijk & de Kloet, 2005; Manenschijn, van den Akker, Lamberts, & van Rossum, 2009; Rietschel et al., 2013; Wust et al., 2004). An understanding of how GR polymorphisms affect receptor functioning by interacting with environmental factors can provide important insight into high BP etiology and health disparities.

Briefly, the human genome is comprised of deoxyribonucleic acid (DNA). DNA contains nucleotide codes that are responsible for building proteins and passing genetic traits to offspring. DNA is stored within 23 pairs of chromosome structures, with one chromosome in each pair contributed by an individual's maternal or paternal parent, resulting in 46 chromosomes total. Genes comprise sets of DNA, which code for assembly of function-specific proteins. Maternal and paternal chromosomes each contribute a code, or an A, T, C, or G base, known as an allele. Individuals who carry the same base for both alleles are homozygous, and those carrying different bases are heterozygous. Individuals carrying a SNP for one less common base in a pair, typically referred to as the minor allele, may be susceptible to related adverse health outcomes.

As noted previously, SNPs are polymorphisms that characterize common variation in the genotype and its physical expression (i.e. phenotype). SNPs account for about 90% of variation in the human genome and are identified when a single nucleobase

or “base” (adenine [A], thymine [T], guanine [G], or cytosine [C]) differs among alleles in at least 1% of the population. Thus, individuals with SNPs carry a base substitution, a specific type of mutation, which results in a genotype that can increase risk for adverse health outcomes. While SNPs may affect protein function and gene expression, they typically are not the single cause of disease development. Rather, they establish a role for genetics by indicating or serving as proxies for regions of vulnerability associated with polygenic disease.

The GR gene influences the body’s physiologic response to stress through HPA activation, both through potential increased tissue sensitivity and differential regulation of the system (e.g. via feedback mechanisms). The targeted GR regulatory genes are located on chromosomes 5 and 6 (see Figure 1.4 for a representation of the human genome and the targeted GR SNPs). Three SNPs in the glucocorticoid regulatory genes, *Bcl*1 (rs41423247), FHBP5 (rs1360780), and 9β (rs6198), have been targeted in association studies of the HPA stress response, cortisol, cardiovascular outcomes, and chronic disease vulnerability. Descriptive information for each of these SNPs, including the nucleotide variant, common, minor, and risk alleles, ancestral allele, SNP location and functionality, and minor allele frequency based on the 1000 Genomes Project (Genomes Project et al., 2010), is included in Table 1.1.

The *Bcl*1 SNP is a C to G intron substitution that likely is not functional but may be a marker, or tag SNP, for vulnerability to inflammation that characterizes cardiovascular dysfunction. Its common allele has been consistently associated with relevant outcomes such as high cholesterol, a trend for higher BP (Di Blasio et al., 2003), HTN status (Watt et al., 1992), and cortisol response to psychosocial stress (Kumsta et

al., 2007; Stevens et al., 2004), as well as increased abdominal obesity (van Rossum & Lamberts, 2004). However, one study found that a small subsample of homozygotes for the G allele (n = 8) exhibited cortisol hypo-reactivity in response to the Trier Social Stress Test (Wust et al., 2004). Minor allele frequency in African Americans is > 25% (Sherry et al., 2001), demonstrating adequate genetic variation to investigate potential GxE interactions.

FHBP5 is functionally linked to differences in sensitivity and HPA glucocorticoid regulation, with SNPs in this region associated with increased stress reactivity and the development of chronic stress conditions such as depression and post-traumatic stress disorder (Binder et al., 2008; Ising et al., 2008; Kirchheiner et al., 2008; Roy, Gorodetsky, Yuan, Goldman, & Enoch, 2010). Importantly, this SNP has been studied predominantly in relation to affective and anxiety disorders of psychiatric stress, though its potential effects on biomarkers of stress such as cortisol and BP remain largely unknown (Binder, 2009). Thus, investigation of an FHBP5 SNP most consistently associated with chronic stress conditions (rs1360780) is novel and can potentially provide a functional genetic link across physical (high BP) and psychiatric chronic stress conditions. Minor allele frequency in African Americans is estimated at 39-44% (Roy et al., 2010; Sherry et al., 2001; Xie et al., 2010).

The 9β SNP functionally increases stabilization of receptor mRNA through an A to G substitution, changing protein expression and leading to decreased glucocorticoid sensitivity and moderating inflammatory processes. Its common allele has been associated with increased heart attack and coronary heart disease risk of 2.2 and 2.8-fold, respectively (van den Akker et al., 2008), as well as increased adrenocorticotropin

hormone secretion (a precursor to cortisol) in response to psychosocial stress (Kumsta et al., 2007), though one linkage study did not find an association of 9β with BP (Syed et al., 2006). Thus, its minor allele is actually protective of increased stress responding. The 9β SNP has been associated with BP in a dose-dependent relation, with individuals homozygous for the common allele and homozygous for the minor allele having mean systolic BP (SBP) of 138 and 122 mm Hg, respectively. The 9β SNP is also a tag SNP for a haplotype that is associated with categorical HTN status (Chung et al., 2008), meaning that it also able to represent the effects of those SNPs on BP. Specifically, its haplotype contains another SNP (rs10482605) that has been independently associated with GR dysfunction and stress (Kumsta et al., 2009). The minor allele frequency in African Americans likely is not high (7%), though investigation of the influence of this SNP is warranted given its functional significance and consistent predictive utility for BP and HPA stress outcomes. Additionally, it is possible that factors that have been controlled in the proposed study, such as SES and BP medication status, have previously masked effects of 9β in African Americans. It is also important that previous studies have not accounted for environmental stress that might be characterized by low neighborhood SES, neighborhood satisfaction, and collective efficacy. Other SNPs associated with variation in GC functioning (e.g. N363S, ER22/23EK) are not targeted in the proposed study due to low allele frequency and/or less consistent evidence for their relations to cortisol and BP.

Most studies either explicitly or implicitly assume a diathesis-stress model, or rather a pattern of dual risk whereby individuals with greater heritable risk have worse outcomes in worse environmental conditions. Thus, they are predisposed to poorer health

outcomes under poorer environmental conditions (Ingram & Luxton, 2005). This assumption likely is perpetuated in part by the notion that in general, minor alleles or mutation are always associated with worse outcomes, and this is not the case. Findings that a given allele may operate as a risk factor in one population or experimental design and a protective factor in another (Kumsta et al., 2007; Wust et al., 2004), further convey the caution that should be taken in considering the dual risk or stress-diathesis assumption.

The HPA Stress Response, Cortisol, and Blood Pressure. The causal role of the HPA stress response, as represented by cortisol secretion, in influencing BP is relevant to the secondary aim of the proposed research (described below). The role of excess cortisol in the development of high BP and cardiovascular dysfunction has been established through experimental trials and clinical studies (Whitworth, Mangos, & Kelly, 2000; Whitworth, Williamson, Mangos, & Kelly, 2005), though mechanisms are complex and not fully understood (Whitworth et al., 2000; Whitworth et al., 2005). Cortisol secretion results in physiological arousal that is characterized by increases in BP, heart rate, gluconeogenesis, immunosuppression, renal sodium retention, and metabolic activity. Chronic cortisol elevation, often associated with stress or genetic factors, has been linked to atherosclerosis and reduced plasticity of the arterial system, high BP, obesity, and high cholesterol. GCs bind to GRs in the hippocampus and provide regulatory feedback to the HPA axis, allowing the system to recover from cortisol-mediated physiological arousal, and maintain homeostasis. Thus, dysfunction or sensitivity of GR receptors results in excess plasma cortisol, and negative health outcomes as noted (Gunnar & Vazquez, 2006; Phillips et al., 2006). Participants injected with cortisol in experimental designs

experience dose-dependent increases in BP acutely and over time (Pirpiris, Yeung, Dewar, Jennings, & Whitworth, 1993; Whitworth, Brown, Kelly, & Williamson, 1995), and also within 24 hours (Kelly, Mangos, Williamson, & Whitworth, 1998). Accordingly, treatment for hypercortisolemia attenuates high BP and cardiovascular dysfunction. Cortisol is also implicated in the development of high BP in individuals diagnosed with Cushing's Syndrome (Whitworth et al., 2000), a disease marked by endogenous hypercortisolism due to pituitary or adrenal tumors that cause endocrine dysfunction (Magiakou, Smyrnaki, & Chrousos, 2006). High BP is present in 80-95% of adults with Cushing's and thus is highly correlated with hypercortisolism. Cushing's patients therefore have a CVD mortality rate that is at least 4 times that of the general population (Fraser, Davies, & McConnell, 1989; Magiakou et al., 2006; Stewart, Walker, Holder, O'Halloran, & Shackleton, 1995). Indeed only 50% of those with untreated Cushing's survive 5 years beyond their initial diagnosis (Whitworth et al., 2005). When Cushing's is treated through surgery or hormone therapy, high BP is resolved (Magiakou et al., 2006), but is only partially resolved if complete relief of hypercortisolism is not achieved (Magiakou et al., 2006). This provides strong evidence that cortisol is causally related to high BP, underscoring the need to understand cortisol and BP associations within a bioecological framework and as they are influenced by environmental stress within the neighborhood context.

Perceptions of Stress, Cortisol, and Health. As an individual-level risk factor, perceived stress captures distress experienced by an individual due to overwhelming responsibilities, circumstances, or adverse events. This construct has been linked to health-related outcomes such as blood pressure and cortisol patterns, above and beyond

the effects of socioeconomic risk or compositional SES (Dressler, 1990b; Pruessner et al., 1999). Thus, perceived stress has been linked to cortisol outcomes, and conceptually, provides a subjective measure of stress as a supplement to assessing physiologic stress.

Genetic risk factors have been linked to variations in perceived stress, though studies have focused on SNPs regulated inflammatory processes (Peace et al., 2012), or the overall variance accounted for by genetics rather than specific candidate genes (Rietschel et al., 2013). One study however produced null findings when assessing whether perceived stress moderated the impact of genetic risk, based on targeted receptor SNPs that regulate corticotropin-releasing hormone, a precursor to cortisol in the HPA axis, on irritable bowel syndrome flare-ups (Sato et al., 2012). Another study in a small sample of African- and European-Americans ($N = 49$), found no association between the Bcl1 SNP and perceived stress (Melcescu et al., 2012). Finally, two studies that assessed links between perceived stress and serotonin transporter SNPs showed that genetic risk was related to increased symptoms of depression with greater perceived stress (Tsuboi et al., 2011) and also predicted greater perceived stress in women (Mizuno et al., 2006).

1.4 STUDY AIMS AND HYPOTHESES

Broadly, the current research aimed to assess associations among environmental stress, genetic, physiologic, and cardiovascular factors as they represent relations among stress processes and cardiovascular health in African Americans.

Primary Aim. The primary aim was to test the conceptual risk model (Figure 1.1) assessing whether genetic risk, which may produce a heightened physiological and psychological response to stress, moderates the association of environmental stress with

cortisol, perceived stress, and BP, in a GxE interaction (Figure 1.5). In consideration of the primary aim to examine moderation, it was hypothesized that:

1. For main effects, neighborhood SES, neighborhood satisfaction, collective efficacy, and genetic risk would be inversely and linearly associated with waking cortisol, BP, and perceived stress, such that lower levels of neighborhood SES, neighborhood satisfaction, collective efficacy, and genetic risk would predict higher levels of waking cortisol, systolic BP, diastolic BP, and perceived stress.
2. For interaction effects, the inverse associations of neighborhood SES, neighborhood satisfaction, and collective efficacy with outcomes would be stronger for individuals with increased genetic risk. Thus, the slopes relating lower neighborhood SES, neighborhood satisfaction, and collective efficacy to higher BP, cortisol, and perceived stress would be steepest for individuals with greater genetic risk.

Secondary Aim. Given evidence that increases in stress lead to increases in blood pressure, a secondary aim was to investigate the conceptual mechanistic model (Figure 1.2), assessing whether waking cortisol partially mediates the effect of environmental stress on BP, and whether genetic risk moderates the impact of the cortisol mediator on BP. In contrast to the risk conceptualization, the mechanistic conceptualization focuses on testing biomedical theory that posits that genetic GR factors that increase glucocorticoid sensitivity moderate the impact of cortisol on cardiovascular tissues throughout the body, leading to poorer BP outcomes. A gene-by-waking cortisol interaction term was therefore included in this model, instead of the gene-by-

neighborhood SES term included in the risk model (Figure 1.6). In consideration of the secondary aim, which tested moderated mediation pathways, it was hypothesized that:

1. For direct effects, lower neighborhood SES, satisfaction, collective efficacy, and higher genetic risk would be linearly associated with higher waking cortisol concentrations, as well as higher SBP and DBP. As a mediator, higher cortisol would be associated with higher SBP and DBP outcomes.
2. For the indirect effect, that relations between neighborhood and genetic risk, and BP, would be weaker with cortisol included as a mediator, indicating that cortisol was partially responsible for the relation of risk factors to BP.
3. For interaction effects, genetic risk would moderate the association of cortisol and BP outcomes, such that individuals with greater genetic risk would have poorer BP outcomes, or larger slopes for the regression of cortisol on SBP and DBP. Thus, the slopes relating higher waking cortisol to higher SBP and DBP would be steepest for individuals with greater genetic risk.

It should be noted that models for the aims focus on testing the interaction of genetic risk with neighborhood SES. Neighborhood satisfaction and collective efficacy were tested, and the results are reported; however, they were of secondary interest relative to the GxE interaction. The rationale for this approach was based on findings that, of those three factors, neighborhood SES has been most consistently linked to BP and cardiovascular outcomes, and sampling and statistical limitations indicate that three interaction terms should not be included in the same model. It should also be noted that given mixed findings regarding patterns of association among socioeconomic factors and cortisol in African Americans, hypotheses of positive, linear relations between

neighborhood variables and cortisol were tentative. Follow-up analyses and sensitivity analyses aimed also to supplement findings of the primary and secondary aims, by investigating perceived stress as a cognitive construct theoretically and empirically linked to outcomes, and by exploring patterns of results for which differential findings may have been possible (BP medication status, timing of the cortisol measure, targeted SNPs).

In summary, this investigation aimed to contribute to a comprehensive and contextually relevant understanding of high BP and related health disparity in African Americans through the integrated study of multiple systems. Results are intended to inform bioecological conceptualizations of BP etiology, the development of innovative selective prevention efforts, and public policy.

Table 1.1
Genetic Characteristics of Targeted SNPs.

SNP	Gene	CA → MA	AA[a]	RA	Gene Function	Location	SNP Function	dbSNP [b]
*Bcl*1 [c] rs41423247	NR3C1	G → C	G	G	GR sensitivity	5q	intron variant	> 25%
FHBP5 rs1360780	NR3C1	C → T	T	T	Binding protein 5 modulates GR	6p	intron variant	39-44%
9β [c] rs6198	NR3C1	A → G	A	A	GR sensitivity	5q	utr variant 3 prime	7%

Note: AA, ancestral allele; CA, common allele; GR, glucocorticoid receptor; MA, minor allele; RA, risk allele; SNP, single nucleotide polymorphism.

[a]Ancestral allele, identified based on allele frequency in chimpanzees, per NCBI dbSNP database.

[b]Frequency of carrying either one or two copies of the minor allele based on the National Center for Biotechnology Information's central database.

[c]Minor alleles for these SNPs are protective, such that the common alleles have been linked to increased risk for poorer cardiovascular health outcomes, see Background Literature.

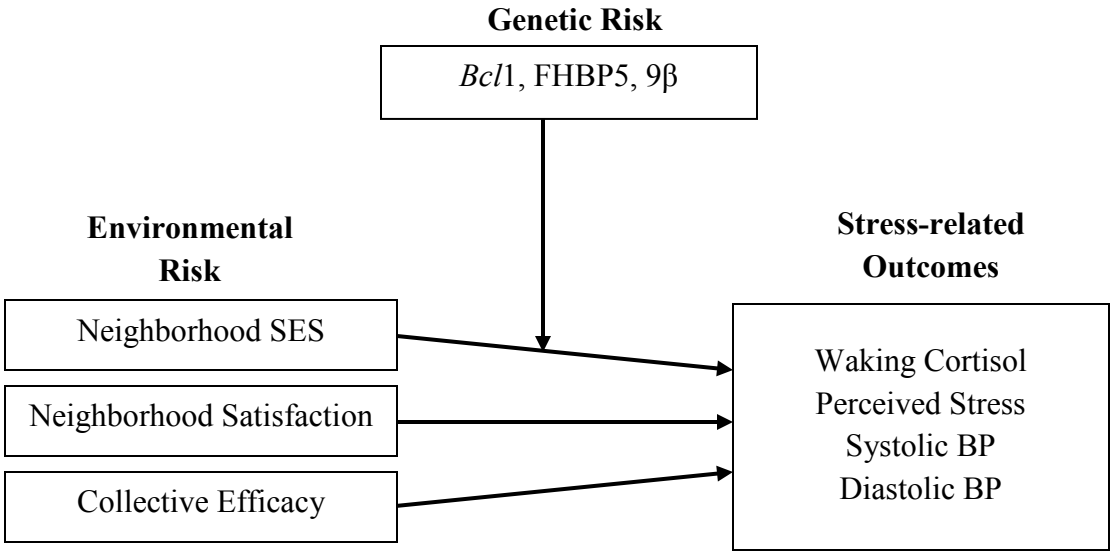


Figure 1.1 Conceptual risk model of interacting GxE risk predicting cortisol, perceived stress, and blood pressure for the primary aim.

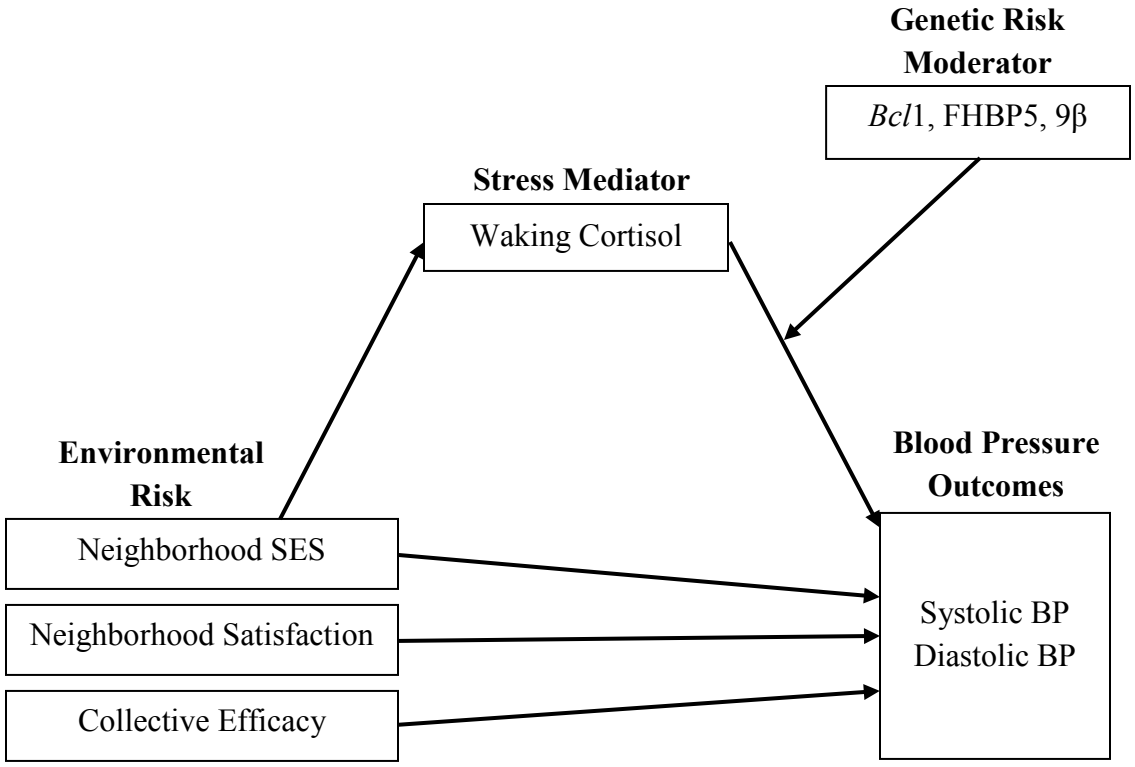
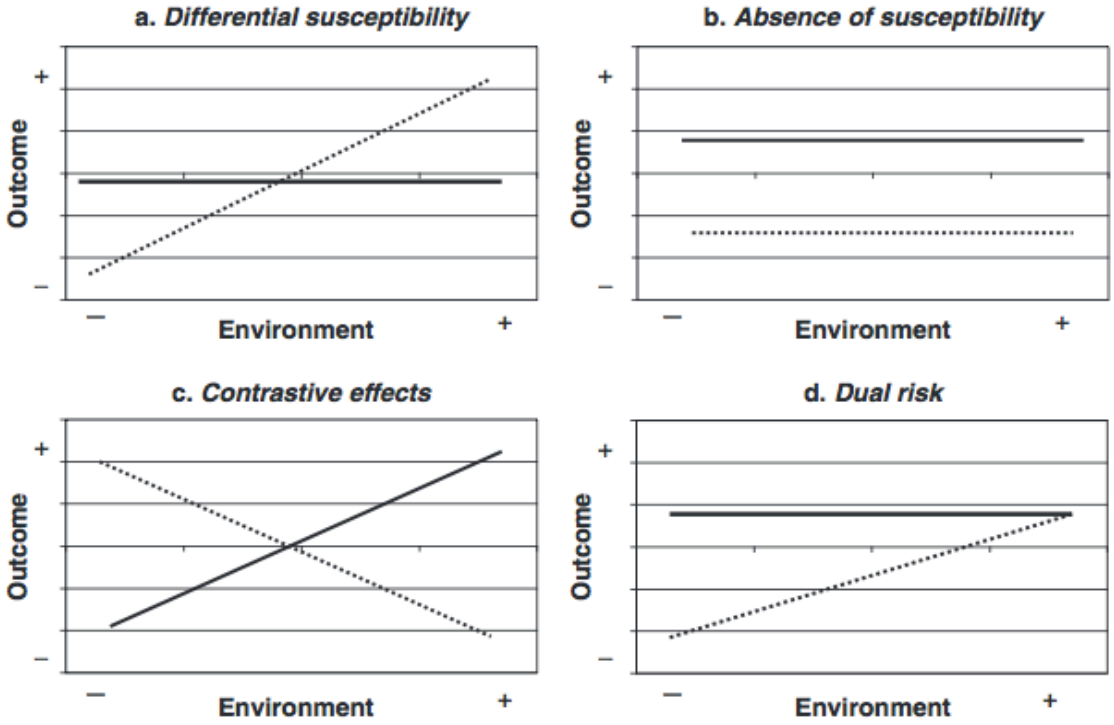


Figure 1.2. Conceptual mechanistic model of interacting genetic-by-waking cortisol risk predicting blood pressure for the secondary aim.



Graphical display of different moderation effects. The x-axis indicates variation in the environmental factor from negative to positive; the y-axis indicates the outcome from negative to positive; and the lines depict the two groups differing on the susceptibility factor. Model a represents differential susceptibility. Model b depicts absence of susceptibility (fixed strategies)—that is, the two groups show different outcomes but variation in the environmental factor does not affect the outcome. In model c, the regression lines reflect contrastive effects. Model d represents a fan-shaped interaction, with the moderator affecting the outcome in just one direction.

Figure 1.3. Explanation of moderating genetic effects, including dual risk, differential susceptibility, and diathesis-stress, figure taken from Belsky, Bakermans-Kranenburg, and van IJzendoorn (2007).

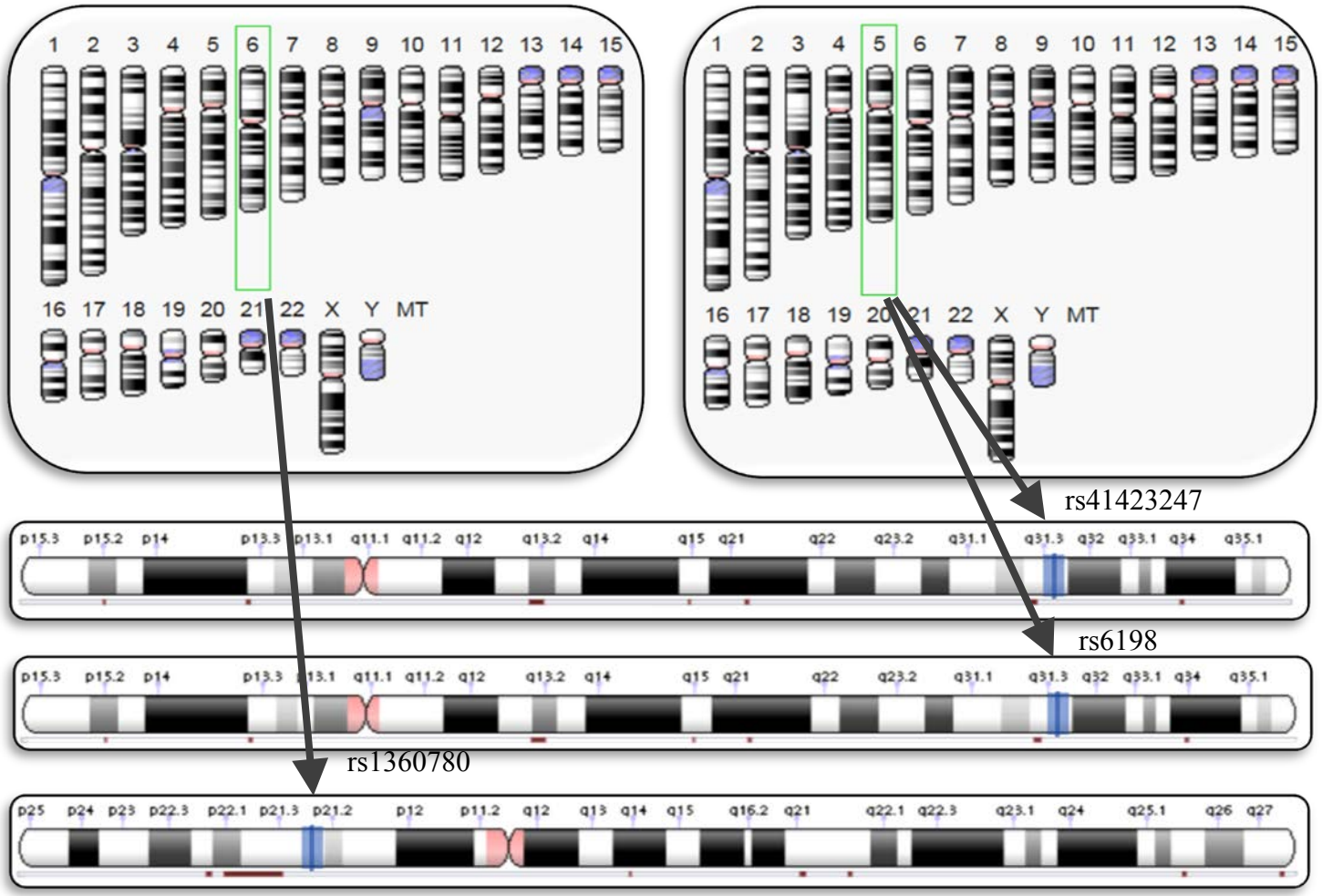


Figure 1.4. Targeted GR genes at locus 5q31 and example heterozygous genotype for *Bcl*I SNP, with images taken from the 1,000 Genomes Project.

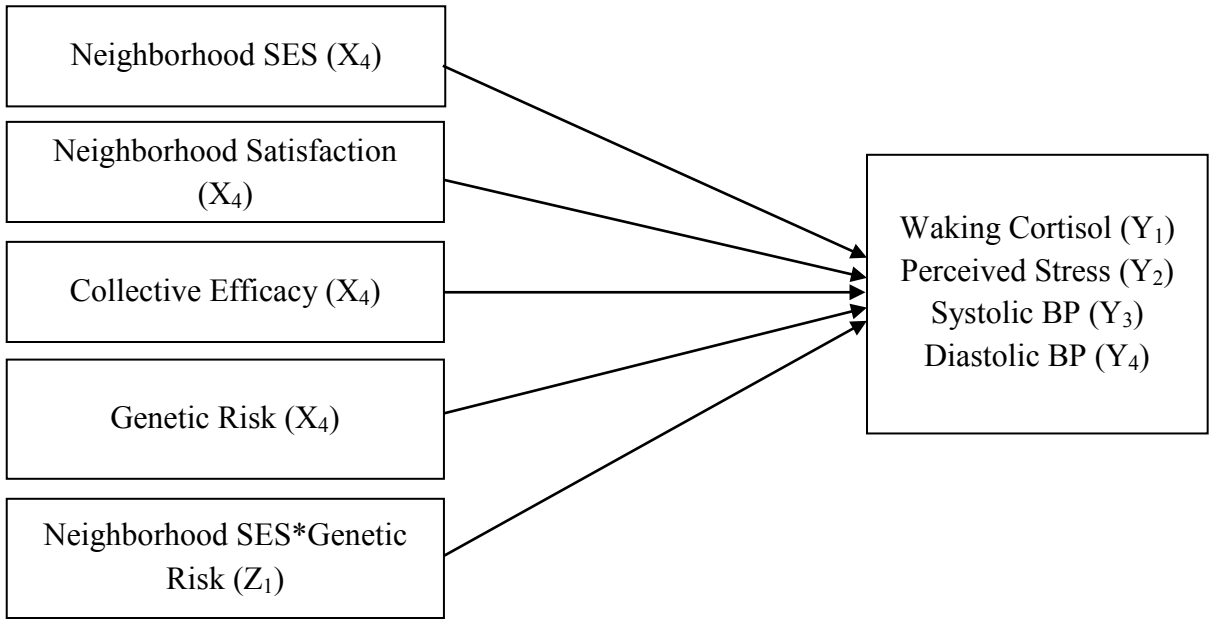


Figure 1.5. Statistical model of interacting GxE risk predicting cortisol, blood pressure, and perceived stress for testing the primary aim.

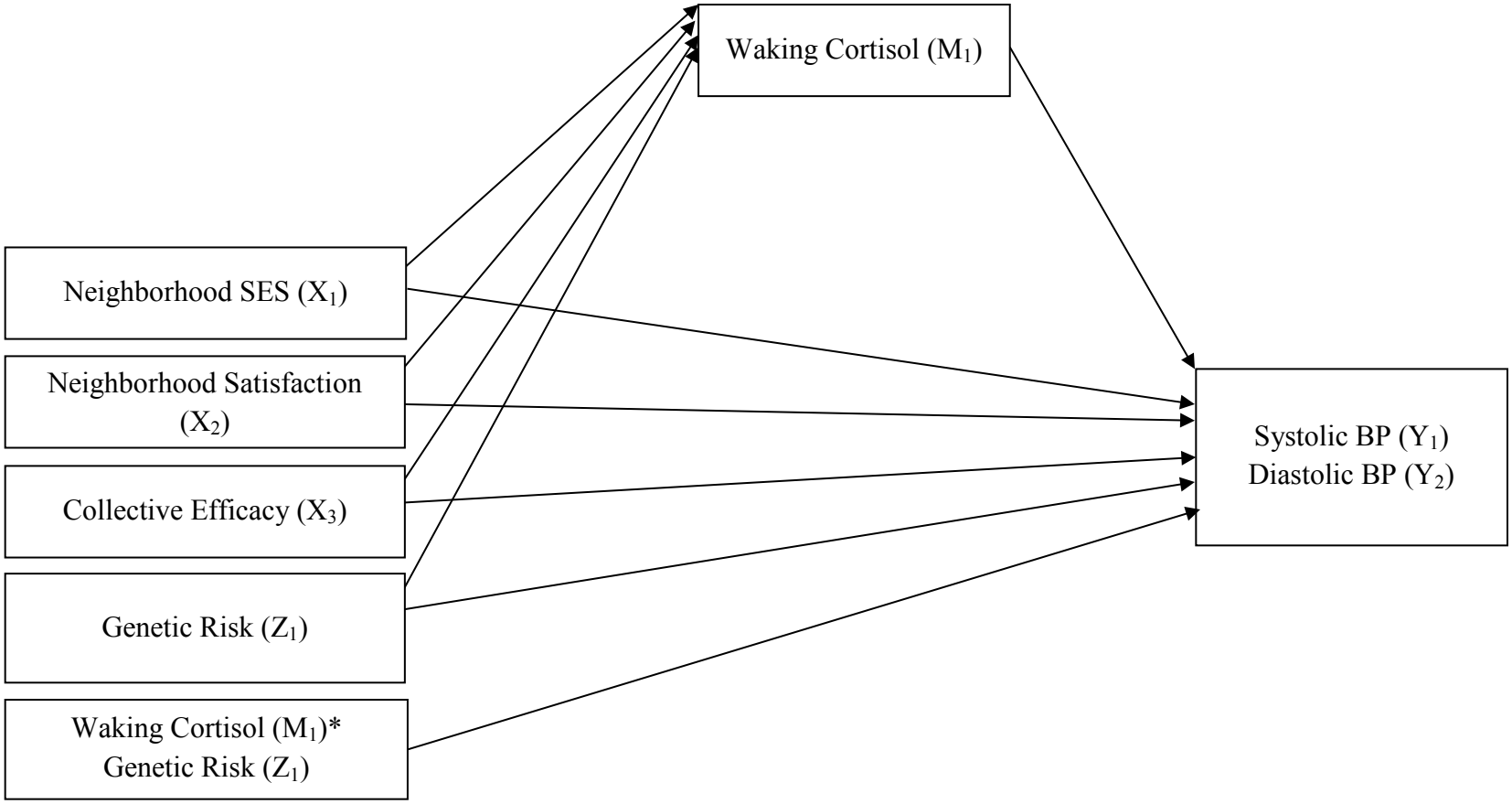


Figure 1.6. Statistical model of interacting gene-by-waking cortisol risk predicting blood pressure for testing the secondary aim.

CHAPTER 2
METHODS

2.1 PARTICIPANTS

Participants included African American male and female adults who were recruited from a number of obesity intervention studies (described below), as well as from local community events and word-of-mouth (Table 2.1). Individuals were given the option to enroll if they were: 1) African-American (self-identified, with data collected on number of grandparents of African or African-American heritage), 2) $\geq$ 18 years of age, and 3) residing within or nearby four cities in South Carolina that were targeted by the various obesity intervention studies. Individuals who expressed interest in completing the study were screened and enrolled on-site if permitted by the time and setting, or they were contacted by phone by trained study staff to schedule a follow-up appointment. Approval from the Independent Review Board of the University of South Carolina was obtained, and informed consent procedures were completed prior to enrollment.

A majority of participants were recruited into the present study as part of the Positive Action for Today's Health (PATH) parent trial (n = 245), which enrolled African American adults residing in three low-income, demographically-matched communities. The trial aimed to examine the effects of a 24-month environmental intervention on physical activity, and data were collected during the PATH 24-month, post-intervention measurement period (Coulon et al., 2012; Lawson et al., 2014; Wilson et al., 2010). Controls for potential treatment effects are discussed in the *Data Analytic Plan*. However,

given this study's cross-sectional design and focus on environmental and genetic factors, versus behavioral factors, it was anticipated that intervention effects would minimally impact the proposed research. Data were also collected from parents participating in the Supporting Health Interactively through Nutrition and Exercise (SHINE) trial (*n*=57), which enrolled African American adolescent-parent dyads (St George, Wilson, Schneider, & Alia, 2013). The SHINE trial aimed to examine the effects of an 8-week family-based intervention on physical activity and intake of fruits and vegetables, and data were collected during the 8-week, post-intervention measurement period. As mentioned previously, controls for potential treatment effects are discussed in the *Data Analytic Plan*. Participants were also independently recruited for the present study (*n* = 99), as part of the Understanding Heredity and the Environment in African-American Risk of HyperTension (HEART) trial. Finally, participants were recruited from the Families Improving Together (FIT) trial (*n* = 49), which implements an 8-week family-based weight loss intervention plus an 8-week online maintenance program, to obtain a final sample of *N* = 450. See Table 2.1 for a summary of these studies and recruitment efforts.

2.2 PROCEDURES

Informed consent procedures were conducted by the doctoral candidate or by selected staff members. All completed research and ethics trainings and were selected due to demonstrating skill and sensitivity in working with vulnerable populations. During consenting procedures participants were encouraged to ask questions about the study and their involvement. Given potential concerns around the collection of genetic and physiologic data, and the fact that many individuals who were given the opportunity to

enroll were already enrolled in another research study, special care was taken to ensure that participants fully understood their rights as research participants, the study design and purpose, potential risks and benefits of the study, and confidentiality.

To this end, participants were first told that their participation was optional, that they had the right to choose not to participate at any time, and that their decision to participate or not to participate would have no effect on their involvement in any other research study. Second, participants were told that they were being targeted because African Americans are most affected by high BP in the southeastern U.S. They were told that the study aimed to better understand how environmental factors, such as how a person feels about his or her neighborhood, and hereditary factors, such as very specific variations in genetic risk, impacted stress hormone and BP levels. Third, participants were told that they would be participating in one 45-90 minute study visit. They were told that they would complete surveys asking about their health and environment, and that by providing saliva and buccal swab samples they would provide measures of cortisol, a stress hormone, and small parts of DNA that have been linked to high BP and related health outcomes. Fourth, participants were told that any samples that they provided would be used only for the research purposes specified, and would not be used to measure behaviors or activities; participants were given a detailed account of what would happen to their samples once they provided them. Fifth, participants were told that there was minimal risk involved with providing saliva and buccal swab samples. They were told that though their study participation may not benefit them personally, it may contribute to positive strides in public health and African American communities by helping to explain how environmental and genetic factors contribute to health disparity.

Upon completion of informed consent procedures, study visits were then scheduled to occur between 2pm and 6:30pm on another day. During scheduling, participants were shown how to collect a saliva sample using the Salivette© (SARSTEDT AG & Co., Nümbrecht, Germany), and were instructed to collect a sample the morning of their study visit, immediately upon waking. They were also asked to fast for 30 minutes prior to their scheduled appointment time to promote collection of cleaner samples. Participants who completed the study visit on the same day that they were enrolled, were asked to collect the sample the following morning, and return it by mail to the research staff, using an addressed and stamped envelope that was provided.

During their primary study visit, participants first completed an assessment of BP, and they were then provided an afternoon saliva sample and a buccal swab gene sample. They then completed demographic and environmental surveys. Surveys were completed last to ensure that their content did not impact physiologic factors prior to saliva collection and BP assessment. Anthropometric data were collected as part of the ongoing trials from which the sample was recruited, or, after all other study assessments have been completed, during the same visit. Upon completion of the study, participants were compensated for their time with a gift bag or $10. Participants with uncontrolled high BP were referred to seek medical care immediately.

2.3 MEASURES

Anthropometrics. Height, weight, and waist circumference were measured and body mass index (BMI) was calculated. BMI is a correlate of BP and cortisol (Nilsson, Klasson, & Nyberg, 2001), and stress-induced cortisol secretion can vary as a function of central adiposity (Epel et al., 2000).

Demographics. Information regarding age, sex, education level, income, marital status was collected via self-report questionnaire. These variables are risk factors for high BP, as identified by the American Heart Association (Lloyd-Jones et al., 2009), and have been associated with cortisol elevation (Dowd et al., 2009; Masi, Rickett, Hawkley, & Cacioppo, 2004).

Blood Pressure Medication. Participants were asked to report whether they had been prescribed medications, and whether they were taking their medications regularly, and as directed by their physician (i.e. whether they were compliant).

Perceived Stress. The individual-level construct of perceived stress was measured via the 10-item version of the Perceived Stress Scale (PSS; Appendix A; S. Cohen, Kamarck, & Mermelstein, 1983). The PSS has demonstrated convergent validity as it has been associated with biomarkers of stress (van Eck, Berkhof, Nicolson, & Sulon, 1996), and internal consistency ranges 0.75-0.92 (S. Cohen, Kamarck, & Mermelstein, 1983; Glaser, Kiecolt-Glaser, Marucha, MacCallum, Laskowski, & Malarkey, 1999). In this sample internal consistency was good with $\alpha = .81$. The measure has been associated with biomarkers of stress, such as cortisol (S. Cohen, Kamarck, & Mermelstein, 1983; van Eck et al., 1996). Differential item functioning within a large multiethnic sample has been assessed, with results demonstrating that all items of the 10-item version of the PSS were invariant across demographic groups (Cole, 1999), and did not vary by ethnicity with factor analytic work demonstrating strong loadings for most items (Sharp, Kimmel, Kee, Saltoun, & Chang, 2007). This measure was included to provide an individual-level control for perceptions of stress, and was included as an auxiliary outcome variable to better estimate missing data (Acock, 2005).

Neighborhood Socioeconomic Status (NSES). Using 2010 census data, an index of contextual SES was calculated by geocoding participants' addresses using latitude and longitude coordinates on a map, using ArcGIS® software by Esri, and then these were linked to census data for those addresses/participants at the block-level. Census blocks are the smallest geographic entities for which the U.S. Census bureau collects and quantifies data for all census variables (U.S. Census Bureau, 2010). Sets of census blocks comprise census tracts, with blocks representing statistical areas bounded by visible, geographic features such as roads, streams, railroad tracks, or city blocks. They may also be bound by nonvisible boundaries such as property lines, county limits, etc. and short line-of-sight extensions of roads. The are delineated every 10 years (Rossiter, 2011), with blocks identified using 4-digit numbers and tracts identified using 3-digit numbers (see Appendix D for a census block map).

Census variables included: 1) median household income, 2) median value owner-occupied housing, 3) proportion of households receiving interest, dividend, or net rental income, 4) proportion of adults with a high school diploma, 5) proportion of adults with a college education, and 6) proportion of people employed in executive, managerial, or professional occupations. These census variables comprise a factor of contextual SES (factor loadings $\geq$0.60) within high internal consistency at the block level (α = 0.92; Diez-Roux et al., 2001). In this sample, internal consistency was good with α = .80. Additionally, this set of variables has been used in previous studies assessing links among contextual SES and cardiovascular health in African Americans (Borrell, Diez Roux, Rose, Catellier, & Clark, 2004; Diez Roux et al., 2004; Diez Roux et al., 2002b),

after reviewing other indices that have been used previously to assess relations between SES and cardiovascular health (Appendix E).

Neighborhood Satisfaction. All items from the Neighborhood Satisfaction subscale of the Neighborhood Environment Walkability Survey (NEWS) were used to assess perceived neighborhood satisfaction (Saelens, Sallis, Black, & Chen, 2003). The Neighborhood Satisfaction subscale consists of 17 items with 4-point Likert response options (Appendix F). Internal consistency of the scale is in this sample was $\alpha = .87$, and in others it has been high, with $\alpha > 0.86$ (Morris, McAuley, & Motl, 2008). Factorial and criterion validity of the survey for measuring a number of neighborhood environment constructs with the NEWS has been established (Cerin, Conway, Saelens, Frank, & Sallis, 2009).

Collective Efficacy. The collective efficacy scale aims to assess individuals' perceptions of mutual trust and willingness to intervene for the common good within their neighborhoods (Sampson et al., 1997). The scale was comprised of two 5-item subscales of *informal social control* and *social cohesion and trust,* which prompted responses to questions such as "What is the likelihood that your neighbors could be counted on to intervene in various ways if children were skipping school and hanging out on a street corner?" (Appendix G). Responses to the two scales demonstrated high internal consistency ($r = 0.77$-0.80), suggesting that they collectively assess collective efficacy (D. A. Cohen et al., 2008; Sampson et al., 1997). Internal consistency for the total scale in this samples was $\alpha = .83$. The scale has demonstrated validity, with responses correlated with assessments of neighborhood services, friendship and kinship ties, and organizational participation through a Community Survey (CS). Correlation

coefficients ranged from 0.21 to 0.49. The scale has also been demonstrated to have a strong inverse relation to violent crime rates (r = -.53), within the same sample (Sampson et al., 1997).

Genetic Risk. DNA collected via buccal swabs were delivered without subject identification to the biochemistry laboratory for genotyping. Extra precautions were taken to ensure the confidentiality of genetic data. For example, gene samples received identification codes that were distinct from all other study identification codes, and which were available to only the study Principle Investigator and Laboratory Director. DNA were isolated using QIAGEN kits (QIAGEN, Valencia, CA) and stored at -80^{o}C until analysis. Genotypes for *Bcl*1 (rs41423247), FKBP5 (rs1360780), and 9β (rs6198) variants were obtained with the use of a TaqMan allelic discrimination assay that employs the 5' nuclease activity of Taq polymerase to detect a fluorescent reporter (VIC and FAM) signal-generated during polymerase chain reactions. Two methods of quality control for genotyping were used: negative controls, and genotyping of replicate samples (at least 5% of total). Replicate samples were checked. If there was no match the genotyping was repeated. Genotype analysis was performed using the latest version of the 7900HT Sequence Detection Software (SDS v2.3).

Once genotypes were obtained, genetic risk was quantified in a single variable by indexing the presence of nucleotides that have previously been linked to increased GC stress-responding and/or cardiovascular outcomes for each of the three targeted SNPs. For example, individuals received an index score of 0, 1, or 2 for each SNP, corresponding to the genotypes homozygous for the low-risk allele, heterozygous, and homozygous for the high-risk allele, respectively. A mean of these three SNP indices was

calculated for each patient to obtain the final genetic risk score. This ensured that varying levels of risk were captured, and was considered appropriate given that each SNP is theorized to directly or indirectly (e.g. by operating as a tag SNP) influence either HPA stress responding through the same GR mechanisms. Such a cumulative indexing of genetic risk has been previously indicated within samples assessing SNPs that are linked not only to the same outcomes but also to the same underlying DNA methylation processes (Wickrama, O'Neal, & Lee, 2013). For the purposes of the current research, the effects of individual SNPs on outcomes was not be tested.

Cortisol. Saliva was collected as a measure of HPA cortisol activity, once immediately upon waking, and between 2:00pm and 7:30pm within 24 hours and at least 30 minutes after eating. Saliva sampling provides a valid measure of basal cortisol activity (Levine, Zagoory-Sharon, Feldman, Lewis, & Weller, 2007). Salivette collection devices were used. For collection of the waking samples, participants were given verbal and written instructions to collect the sample immediately upon waking the following morning, without rising or rinsing their mouths, and to return the sample to the study staff that same afternoon, during their scheduled appointment. Studies of adherence indicate that individuals asked to collect waking samples typically do so approximately 6 minutes after waking, with samples collected 1-15 minutes after waking providing stable values of cortisol concentrations (Dockray, Bhattacharyya, Molloy, & Steptoe, 2008). For collection of afternoon samples, participants reported for their appointments and worked directly with study staff. Participants were instructed to rinse their mouths with distilled water, and chew the sterile cotton swab for 3 minutes to stimulate and collect saliva. All

samples were collected during the regular working week, with some evidence that average cortisol concentrations between weekdays and weekends (Maina et al, 2012).

The distribution for waking cortisol was positively skewed, and this issue was addressed in three ways. First, cortisol concentrations that were physiologically implausible were removed (e.g. 125.2 ng/mL upon waking). Second, values that were plausible but were greater than 3 standard deviations above the mean or that were greater than the highest possible value detectable via the ELISA assay (>7.185ng/mL for afternoon concentrations, > ng/mL for waking concentrations) were truncated at that highest value. Third, the data were transformed using a natural log function, which has been common with measures of cortisol (Champaneri et al., 2013; Godfrey et al., 2014; Hackman, Betancourt, Brodsky, Hurt, & Farah, 2012; Vreeburg et al., 2009). Analyses were run both with and without outliers, and with and without transformed data.

Study staff then collected the Salivettes and transported them to the biochemistry laboratory. Samples were centrifuged for 5 minutes at 2,000rpm. After centrifugation, saliva was aliquotted and stored. Cortisol concentrations within the samples were measured within one year of sample collection using a radioimmunoassay procedure per manufacturer's directions (R&D Systems, Minneapolis, MN, USA), in which a 1ml volume of cortisol was added to a 50 microliter sample of saliva which will then incubate for 2 hours at room temperature. Tubes were decanted and read on the Gamma counter. Average interassay and intraassay variation was less than 5-6%. Assays and/or samples not meeting these criteria were included in additional radioimmunoassays. The cortisol-specific assay had extremely high specificity and low cross-reactivity (<1%), and cortisol concentration was determined in ng per mL of saliva collected, based on a sigmoidal

four-parameter curve at a fit of r $\leq$ .9632. Assays that were completed with cortisol measured in nmol/L (Universitaet Trier) were converted to ng/mL for quantification and interpretation, based on a division by 2.759 that is specific to saliva cortisol (Hay & John AH Wass, 2009).

Once values for cortisol concentrations were obtained, HPA cortisol activity was quantified with waking cortisol concentrations used to indicate basal cortisol levels. Afternoon samples were considered as part of follow-up analyses. Cortisol levels that are highest upon waking, peak within an hour of waking, and gradually decrease over the course of the day with lowest values just prior to sleep typically indicate healthy HPA diurnal patterns. Though the pattern of diurnal cortisol is not truly linear, a steeper negative slope can provide a gross indicator decent HPA functioning. Positive or flatter slopes (i.e. lower levels of waking cortisol and higher levels of afternoon/evening cortisol) indicate HPA dysfunction, which has been demonstrated in chronically stressed African Americans (Knight, Avery, Janssen, & Powell, 2010; Skinner, Shirtcliff, Haggerty, Coe, & Catalano, 2011). Thus, cortisol slope from waking to afternoon was calculated, though not targeted in this study.

Blood Pressure. Dinamap BP equipment (model 8100; Critikon Inc., Tampa, FL) was used with a standard research protocol outlined by National High Blood Pressure Education Program ("Update on the 1987 Task Force Report on High Blood Pressure in Children and Adolescents: a working group report from the National High Blood Pressure Education Program. National High Blood Pressure Education Program Working Group on Hypertension Control in Children and Adolescents," 1996). BP readings from Dinamaps used in the PATH study have been compared to manual BP readings, with

typical measurement differences < 5 mm Hg. During BP assessments, participants were seated in a relaxed position with legs uncrossed. Based on upper-arm diameter the appropriately sized cuff was placed on the left arm and participants rested for 5 minutes before 3-4 BP assessments were taken. One minute passed between assessments with results from the first discarded from analyses (Calhoun et al., 2008). Thus, BP was quantified as mean systolic and diastolic BP values for the second and third assessments for PATH participants, and the second, third, and fourth assessments for SHINE, HEART, and FIT participants. Additionally, assessment of mean differences within the present sample indicated that initial readings were significantly higher than second readings of SBP, $t(492) = 135.96$, $p<.001$, and DBP, $t(490) = 147.93$, and higher than the averages of subsequent readings of SBP, $t(492) = 139.98$, $p< .001$, and DBP, $t(492) = 153.181$, $p < .001$, by a difference of 1-2 mmHg. Mean BP (MBP) was also calculated as DBP plus one-third of pulse pressure (PP), with PP determined by subtracting DBP from SBP, given evidence of it's independent relevance to clinical outcomes (Yoshitomi, Nagakura, & Miyauchi, 2005).

2.4 STATISTICAL ANALYSES

Missing Data. Full information maximum likelihood (FIML) estimation was implemented to address missing data (Enders & Bandalos, 2001). FIML accommodates data which are Missing at Random (MAR) or data that are Missing Completely at Random (MCAR). Thus FIML was considered appropriate given assumptions that missing data are MAR, or that missingness in a model variable was not due to a participant's score on that variable, after controlling for other variables in the study (Acock, 2005). Multiple imputation would not better address the issue than FIML, and

regardless, estimates for variables with missing data ≥20% can be biased up to 20% if assuming MAR (Schlomer, Bauman, & Card, 2010). Thus addressing substantial missing data for waking cortisol (31%), MAR was assumed based on reasons for missingness (e.g. lost to follow-up), and variables that were theoretical correlates of missingness for waking cortisol were included as auxiliary variables in the statistical models (perceived stress, afternoon cortisol), if they were not already being included in the model (e.g. neighborhood SES, age). This approach has been shown to improve FIML estimations for addressing missing data, reduce potential bias in parameter estimates, and ensure validity of the MAR assumption (Acock, 2005; Schlomer et al., 2010).

Assumptions. Tests for potential violations of regression and mediation assumptions were completed prior to running the primary analysis. Normality of the variable distributions was examined with histograms and measures of skewness and kurtosis. Homoscedasticity of the variables was examined with scatter plots and conditional distributions of residuals. Multiple regressions were conducted to ensure that predictor-predictor and predictor-mediator interactions were not present. Autocorrelation plots were examined to test for independence of residuals, and case diagnostics were conducted to assess the presence and influence of outliers in the data. Variance inflation factors and estimates of tolerance were computed to assess the degree of multicolinearity among the predictors. In the absence of temporal precedence of the mediator to the outcome or the predictors to the mediator, a methodological assumption of statistical mediation, relational rather than causal pathways were interpreted for results of the secondary aim.

Clustering. Preliminary examination of block-level clustering within PATH communities indicated that ICC's for BP are small (.004). Data for 156 unique block groups were generated with substantial variability in the size in the number of study participants that each block group contained; most block groups contained only 1 or 2 participants, and within this data structure block group intraclass correlation coefficients as estimators of potential clustering of outcomes by block group could not be estimated, nor modeled within a multilevel structure. Nesting that would have occurred by community for block groups containing larger numbers of participants was therefore addressed through a combined, categorical study-by-treatment control variable. Because the final sample included participants recruited from four studies, of which two exposed participants to treatment conditions, the study-by-treatment control variable included 7 categories, the first 3 of which captured the three PATH conditions, the second two capturing the two SHINE conditions, and the final two capturing the HEART and FIT studies, within which participants were not exposed to an intervention prior to data collection for the current study.

Power. Because effect sizes for GxE interactions of neighborhood SES and target SNPs are not available for African Americans, it was assumed that effect sizes for interactions will be small (r^2 = .02). To address the primary aim of the current research, it was therefore estimated 392 participants will need to complete the study to achieve .80 power (α = .05) for testing the interaction of neighborhood SES and genetic risk in predicting cortisol and BP (Aiken, West, & Reno, 1991; J Cohen, 1988). Additionally, estimates of sample sizes needed for GxE interaction designs range from 300 to 450 (Luan, Wong, Day, & Wareham, 2001).

To address the secondary aim of the proposed research, it was estimated that 435 participants were needed to complete the study to achieve .80 power ($\alpha = .05$) for testing whether cortisol mediates the interaction of neighborhood SES and genetic risk in predicting BP (i.e. to test for moderated mediation), again assuming small effect sizes ($r^2 = .02$; Preacher, Rucker, & Hayes, 2007).

Data Analytic Plan. Primary analyses were conducted using the MPlus statistical software package (Muthén & Muthén, Los Angeles, LA), with model assumptions and case diagnostics completed with SAS and SPSS statistical software packages (SAS Institute, Cary, NC, U.S.A.; SPSS Inc., Chicago, IL, U.S.A). The primary risk-related aim was assessed through multiple linear regression within a path analysis for estimating direct effects and interaction effects among measured variables. Thus, the following model regressed cortisol and BP outcomes on relevant control variables (not shown), neighborhood factors, genetic risk, and the interaction of neighborhood SES with genetic risk:

Cortisol and BP = β_0+ β_1Neighborhood SES + β_2Neighorhood Satisfaction + β_3Neighborhood Collective Efficacy + β_4Genetic Risk + β_5Genetic Risk * Neighborhood SES + ε

In this equation, $\beta_1 - \beta_3$ represent the direct effects of neighborhood factors on cortisol and BP, β_4 represents the direct effect of genetic risk to physiologic stress responding on cortisol and BP, β_5 represents the effect of neighborhood SES on cortisol and BP at varying levels of genetic risk, and ε represents variation in cortisol and BP that is not

explained by $\beta_1 - \beta_5$ (i.e. model error). Control variables that were included (age, sex, BMI, BP medication status, study-by-treatment) are not depicted.

The secondary mechanism-related aim was assessed by estimating direct, interaction, and mediated effects through a set of multiple linear regressions, consistent with a moderated mediation conceptual model. The product of coefficients method for estimating the mediated effect (Iacobucci, Saldanha, & Deng, 2007; MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002) was applied. This method relies on estimating direct effects for an *a* path, which regresses the mediator on the predictors, a *b* path, which regresses the outcomes on the mediator, and a *c'* path, which regresses the outcomes on the mediator and predictors, as in (MacKinnon, 2008). The mediated or indirect effect will then be estimated by multiplying coefficients of the *a* and *b* paths together to obtain their product (αβ). The r^2 measure of the mediated effect was calculated to determine the amount of variance in the dependent variable that is explained by both the mediator and predictors, but not by either alone. The r^2 measure is a better estimate of effect size in samples of $N<500$ than the proportion mediated of the total effect measure (MacKinnon, 2008).

The distribution of the product or empirical resampling method has greater power and more accurate type 1 error rates than other methods when bootstrapping corrections are applied (Fairchild & MacKinnon, 2009; Fairchild & McQuillin, 2009; MacKinnon et al., 2002; MacKinnon & Luecken, 2008). Bias-corrected bootstrapping with 2,000 estimation draws was therefore applied to form asymmetric confidence limits (Fairchild & McQuillin, 2009; MacKinnon et al., 2002; Preacher et al., 2007).

Thus, the following models which regressed the cortisol mediator on relevant control variables (not shown), neighborhood factors and genetic risk, and the interaction of cortisol with genetic risk, and which regressed BP outcomes on relevant control variables (not shown), neighborhood factors, genetic risk, and the interaction of cortisol with genetic risk, were estimated:

$$\text{Waking Cortisol} = \beta_0 + \beta_1 \text{Neighborhood SES} + \beta_2 \text{Neighborhood Satisfaction} + \beta_3 \text{Collective Efficacy} + \beta_4 \text{Genetic Risk} + \varepsilon$$

$$\text{Blood Pressure} = \beta_0 + \beta_1 \text{Neighborhood SES} + \beta_2 \text{Neighborhood Satisfaction} + \beta_3 \text{Collective Efficacy} + \beta_4 \text{Cortisol} + \beta_5 \text{Genetic Risk} + \beta_6 \text{Genetic Risk} * \text{Cortisol} + \varepsilon$$

In the first equation, $\beta_1 - \beta_4$ represent the direct effects (*a* paths) of neighborhood and genetic risk factors on the cortisol mediator, and ε represents variation in cortisol and BP that was not explained by $\beta_1 - \beta_4$ (i.e. model error). In the second equation $\beta_1 - \beta_4$ represent the direct effect of neighborhood factors and the cortisol mediator on BP outcomes (*c'* paths), β_5 represents the direct effect of genetic risk to glucocorticoid sensitivity on BP (*b* path), β_6 represents the effect of cortisol on BP at varying levels of genetic risk (conditional *b* path), and ε represents variation in cortisol and BP that was not explained by $\beta_1 - \beta_6$ (i.e. model error). Control variables that were included (age, sex, BMI, BP medication status, study-by-treatment) are not depicted.

Model Fit. Indices of fit were calculated to examine whether the relations among model variables were correctly specified. The chi-square goodness-of-fit test was

examined; failure to reject the null hypothesis (i.e. non-significant p-value) indicates appropriate model fit. Given that this test has been associated with inflated Type I error rates for samples $\geq$ 400, descriptive fit indices were also estimated and interpreted (Hu & Bentler, 1998). Root Mean Square Error of Approximation (RMSEA), for which values less than .10 are adequate fit, and Standardized Root Mean Square Residual (SRMR), for which models approaching 0.000 approach perfect fit, indices were used to assess the absolute fit of primary and secondary aim models, and Akaike Information Criterion (AIC) was used to assess comparative fit across models, with lower numbers indicating relatively better fit (Kenny & McCoach, 2003); (Kenny, 2011).

Follow-up Analyses. Follow-up sensitivity analyses were conducted to assess if patterns of results differed when other potential influencing factors on model outcomes were considered. Sensitivity analyses focused on three variable sets for which differential findings may have been possible: 1) BP medication status, inclusion of all participants versus inclusion of only participants not prescribed/taking BP medications, 2) Timing of the cortisol measure, inclusion of waking cortisol as the target outcome (primary aim) or mediator (secondary aim) for which there was smaller sample, versus inclusion of afternoon cortisol while controlling for waking cortisol, for which there was a larger sample, and 3) Targeted SNPs included in the genetic risk score, inclusion of all three targeted SNPs, versus inclusion only of the two SNPs which had adequate variability in allele frequencies (rs41423247 and rs1360780) and exclusion of the SNP for which only 7% of the total sample had one or two copies of the minor allele (rs6198). Such an approach has been used in the past with the 9β (rs6198) and *Bcl*1 (rs41423247 SNPs, given little variation in allele frequencies (Velders et al., 2012). Additionally,

inconsistent findings for neighborhood SES-waking cortisol-blood pressure relations resulted in examination of perceived stress as a potential moderator of neighborhood SES, in considering alternative hypotheses.

Table 2.1
Summary of Studies and Cortisol and Genetic Data Collection Conditions.

	PATH	SHINE	HEART	FIT	Totals
Study Trials	Positive Action for Today's Health (PATH)	Supporting Health Interactively through Nutrition and Exercise (SHINE)	Understanding Heredity and the Environment in African-American Risk of HyperTension (HEART)	Families Improving Together (FIT)	---
Total Sample (%)	245 (54)	57 (13)	99 (22)	49 (11)	450 (100)
Unmedicated Sample (%)	109 (47)	32 (14)	61 (26)	30 (13)	232 (100)
Study PI and Funding	Dawn Wilson, Ph.D. NIH R01 DK067615	Sara St. George, M.A. NIH F31 HD066944	Sandra Coulon, M.A. NIH F31 AG039930	Dawn Wilson, Ph.D. NIH R01 HD072153	---
Data Collection Year and Season	Fall 2010	Spring 2011 - Summer 2012	Fall 2012 - Spring 2013	Summer 2013 - Fall 2013	Fall 2010 - Fall 2013
Study Design	Randomized Intervention Trial, 3 conditions/groups	Randomized Intervention Trial, 2 conditions	Cross-sectional Study	Randomized Intervention Trial, 2 conditions	3 Randomized Trials and 1 Cross-sectional Study
Intervention	12-month environmental programs targeting increased PA, with12-months maintenance	8-week family-based program targeting increase PA and fruit and vegetable intake	---	16-week family- and web-based program for weight loss	Physical activity and obesity prevention programs
Data Collection Time Point	Post-intervention at 24-month follow-up	Post-intervention	---	Pre-intervention	Pre- and post-intervention
Cortisol Collection Time Point	Optional Waking [a] Afternoon (2pm-6:30pm)	Waking, Afternoon (4pm-7:30pm)	Waking, Afternoon (2pm-6:00pm)	Waking, Afternoon (2pm-7:30pm)	Waking Afternoon (2pm-7:30pm)

[a] Collection of a waking cortisol sample was presented as an optional self-collection measure in the PATH trial, due to concerns related to participant burden.

CHAPTER 3
RESULTS

3.1 DEMOGRAPHIC AND DESCRIPTIVE DATA

Sample. The final sample consisted of 450 African-American adults who enrolled as part of the PATH, SHINE, HEART, and FIT trials. These individuals were recruited and enrolled in the study between September 2010 and December 2013. Of the total sample, 193 individuals had been prescribed BP medications (43%), 232 individuals reported not having been prescribed medications (52%), and data were missing for 25 individuals (6%). Of the 193 medicated individuals, only 14 (7%) reported not "taking medications regularly and as instructed." Follow-up sensitivity analyses were conducted to examine if patterns of results change across the total sample and the unmedicated sample of 232 adults.

Statistical Assumptions. Distributions for predictor variables indicated good variability (Figure 3.1), with no concerns related to restriction of range or significant skew or kurtosis (Table 3.1). Blood pressure outcomes were normally distributed. Waking cortisol showed high estimates for positive skewness (1.26) and kurtosis (1.197). A natural log transformation was done to generate a normal distribution, as this particular transformation was appropriate for positively skewed dependent variables for which residuals increase as the dependent variable increases (J. Cohen, Cohen, West, & Aiken, 2003). This transformation has also been applied in previous studies that included cortisol

as an outcome (Champaneri et al., 2013; Godfrey et al., 2014; Hackman et al., 2012; Vreeburg et al., 2009). Homoscedasticity of the variables was examined with scatter plots and conditional distributions of residuals. The Durbin-Watson statistic was used to test for independence of error for SBP (d = 1.866, SE = 19.02), DBP (d = 1.775, SE = 11.08), transformed waking cortisol (d = 1.873, SE = 2.868), and perceived stress (d = 1.866, SE = 11.08) outcomes, with all values approaching 2.00 and indicating little-to-no autocorrelation of residuals in this cross-sectional design (J. Cohen et al., 2003). Multiple regressions were conducted and confirmed that predictor-predictor and predictor-mediator interactions were not present. Autocorrelation plots were examined to test for independence of residuals, and case diagnostics were conducted to assess the presence and influence of outliers in the data. Variance inflation factors and estimates of tolerance were computed to assess the degree of multicolinearity among the predictors. In the absence of temporal precedence of the mediator to the outcome or of the predictors to the mediator, which is a methodological assumption of statistical mediation, pathway results for the secondary aim were interpreted as relational rather than causal.

Final control variables were selected due to being significantly correlated with or predictive of outcomes in preliminary models, and also because they have been mechanistically and/or empirically linked to outcomes. Control variables included were age, sex, BMI, BP medication compliance status, and a study-by-treatment variable. Physical activity was tested in the model, but ultimately was not included as a control variable because it was not predictive of outcomes and was only available for a subset of the sample (n = 242). Compositional SES (individual income and education) was not predictive of model outcomes and was therefore not included as a control variable.

Missing Data. Each model variable had less than 10% missing data with the exception of waking and afternoon cortisol samples (Table 3.2). Missingness for psychosocial variables was typically due to participants being lost to follow-up. Missingness for genetic data was due to inability to amplify or genotype DNA samples, data being unavailable at the time of genotyping, and for 6 participants, refusing to provide the sample. Missingness for waking cortisol data was due primarily to participants not returning waking samples (*note:* as previously referenced, participants in the PATH trial were told provision of this sample was optional, due to concerns related to participant burden), and missingness for afternoon cortisol was due primarily to data being unavailable at the time of completing bioassay procedures, given that these afternoon samples were not the target cortisol variable in this study. Specifically, missing data for waking cortisol affected 35%, 19%, 39%, and 29% of the PATH, SHINE, HEART, and FIT samples, respectively.

Clustering. Broadly, participants were nested within studies, with the PATH trial contributing the majority of participants to the total sample (54%), and the SHINE, HEART, and FIT trials contributing 13%, 22%, and 11% to the total sample, respectively. Geographically, participants were also nested within block groups, with block group-level census data extracted for 429 participants (95.3% of the total sample). Data for 156 unique block groups were generated with substantial variability in the size of the number of study participants that each block group contained (Table 3.3), with 83% of block groups containing only 1 or 2 participants.

Descriptive Data. Demographic, psychosocial, environmental, and biological data are described in detail in Table 3.4. Mean values for age, sex, BMI, neighborhood

SES, perceived collective efficacy, systolic BP, and afternoon cortisol differed significantly by study, confirming the need to include a study-by-treatment control variable in the statistical analyses. In general, the overall sample was predominantly female (70%) and the average participant age was 50 years (SD = 14). The sample was largely at-risk for the development of cardiovascular disease and other chronic diseases based on a high average BMI of 33.53 (SD = 9.16). There were no differences between men and women for waking cortisol or neighborhood. Average genetic risk scores indicated that the majority of the sample had increased risk for tissue sensitivity to glucocorticoid binding, with the major alleles for two of the three targeted SNPs being linked to increased risk as noted in Table 1.1. Systolic BP was normally distributed with a mean reading of 126.25 (*SD* = 19.86), indicating that most participants fell into the prehyptensive status range of 120-139 mmHg. Diastolic BP was normally distributed also with an average of 78.08 (*SD* = 11.33) indicating a majority of participants falling at the upper end of the normal range of 60-80 mmHg. Cortisol was significantly and positively skewed, with an average 3.53 ng/mL (*SD* = 2.87) of cortisol upon waking, and 1.98 ng/mL (*SD* = 2.04) in the afternoon.

Genetic Data. Genotype frequencies are presented by study and for the total sample in Table 3.5. Results showed that allele frequencies for the minor alleles of *Bcl*1 (rs41423247) and 9β (rs6198) were consistent with nationally representative samples (Sherry et al., 2001). However, allele frequencies for the T risk allele FHBP5 (rs1360780) were higher than those typically seen in the literature, with 71% of the present sample carrying one or two copies of the G allele, compared to the 39-44% cited in the National Center for Biotechnology Information SNP database (Sherry et al., 2001).

3.2 CORRELATIONS

Correlations among model variables were calculated, with alpha set at .05 for two-tailed significance testing (Table 3.6). Results indicated that SBP was positively related to DBP, age and BMI, and inversely related to waking cortisol (Figure 3.2). DBP was positively related to perceived stress and inversely related to age. Though consistently statistically significant, it is worth noting that in terms of clinical significance, the effect is not large; for every 1-year increase in age, there would be a .133 decrease in DBP, such that an increase in age of 10 years would equate to a decrease in DBP of 1.33. Waking cortisol was positively related to afternoon cortisol, and inversely related to perceived stress, and neighborhood SES. Neighborhood satisfaction and collective efficacy were both inversely related to perceived stress, and positively related to age, and to each other. The correlation was less than .50, and a statistical test for multicolinearity was run that also indicated no significant redundancy. Lower neighborhood satisfaction was also related to being female. Additionally, neighborhood SES was significantly correlated with compositional SES at $r(448) = .252$, $p<.001$.

3.3 NEIGHBORHOOD SES, GENETIC RISK, CORTISOL, AND BLOOD PRESSURE

The primary aim was to test whether genetic risk for greater physiologic sensitivity to cortisol moderated the association of environmental stress (neighborhood SES) with cortisol and BP, in a GxE interaction (Figure 1.1).

Results from the path model assessing the primary GxE interaction, (Table 3.7) for which waking cortisol, SBP, and DBP were outcomes, indicated direct effects of study-by-treatment, $b = -1.084$, $t(439) = -2.261$, $p = .024$, and BMI, $b = .311$, $t(439) =$

2.867, p = .004, on SBP, and effects of BP medication status, b = 1.590, t(439) = 2.491, p = .013, being female, b = -3.165, t(439) = -2.543, p = .011, and age, b = -.132, t(439) = -2.922, p = .003, on DBP. The model also indicated that neighborhood SES predicted waking cortisol, b = -.025, t(439) = -2.029, p = .042, such that lower SES was related to higher waking cortisol values, consistent with hypotheses. The primary aim models were saturated and fit indices therefore could not be interpreted (df=0).

Perceived Stress. Neighborhood risk and GxE effects predicted perceived stress, indicating direct inverse relations of neighborhood satisfaction, b = .168, t(439) = -3.386, p = .001, and collective efficacy, b = -.122, t(439) = .043, p = .005, such that individuals with less perceived satisfaction and less neighborhood efficacy had greater perceived stress (Table 3.10). The GxE interaction was also statistically significant, b = -.046, t(439) = -2.871, p<.001, and the pattern of relations indicated interval differences in slope magnitude by genetic risk (Figure 3.3), such that individuals with greater genetic risk had higher perceived stress with lower SES conditions, and lower perceived stress with higher SES conditions.

Sensitivity Analyses. Results did not differ for model estimations within the unmedicated sample (Table 3.8). With afternoon cortisol as an outcome in the model (Table 3.9), instead of waking cortisol, the GxE interaction showed a trend toward statistical significance, b = -.054, t(439) = -1.722, p = .085, with the pattern of relations indicating interval differences in slope magnitude by genetic risk, such that individuals with greater genetic risk had higher afternoon cortisol in lower neighborhood SES conditions, and lower afternoon cortisol with higher SES conditions. Waking cortisol also predicted afternoon cortisol, b = .243, t(439) = 4.338, p < .001.

3.3 MODERATED MEDIATION MODEL

The secondary aim was to test a potential mechanism through which environmental and genetic risk, and cortisol impact BP. Specifically it was assessed whether waking cortisol partially mediated the effects of environmental stress on BP, conditional on genetic risk, in an expanded GxE interaction (Figure 1.6). The moderated mediation model (Table 3.11) indicated unexpectedly that lower waking cortisol was related to higher SBP, b = -2.622, $t(438)$ = -2.203, p = .028 (Figure 3.5), and there was a trend for a similar relationship with neighborhood SES, b = -.025, $t(438)$ = -1.780, p = .075. RMSEA for the model was .093 and the SRMR was 0.024, indicating moderate fit (df=5).

Indirect effects assessed with αβ estimates were not significant, with R^2 for the mediated effect of neighborhood SES; neighborhood satisfaction, and collective efficacy through waking cortisol on SBP with R^2 ranging = -.077 to -.030; and for the mediated effect on DBP with R^2 ranging = -.044 to -.047; negative estimates are a mathematical artifact, and indicate no mediated effect or 0% variance accounted for by an indirect effect (manual calculations not shown).

Sensitivity Analyses. Results for model estimations within the unmedicated sample (Table 3.12) differed such that the prediction of SBP by waking cortisol was no longer statistically significant, b = -2.656, $t(438)$ = -1.645, p = .100. The AIC was 25050.519 for the model with the total sample, and 12262.568 for the model with unmedicated individuals, again indicating better fit when medicated individuals were excluded (df=5). RMSEA for the unmedicated model was 0.062 was and the SRMR was .036. The model assessing moderated mediation with afternoon cortisol as the mediator

while controlling for waking cortisol indicated a trend for a GxE interaction, b = -.0546, $t(437)$ = -1.722, p = .085 (Table 3.13), though neighborhood SES did not predict afternoon cortisol. The pattern of the interaction suggested that individuals with high genetic risk had the highest values of afternoon cortisol in low neighborhood SES contexts, and the lowest values of afternoon cortisol in high neighborhood SES contexts. The slope for individuals with medium genetic risk as smaller, and the slope for individuals with the least genetic risk was virtually flat (Figure 3.4).

When the two-gene risk factor variable was included in the total sample, there was a marginal trend in the prediction of SBP by the gene-by-cortisol interaction, b = 4.033, $t(438)$ = 1.651, p = .099 (Table 3.14). AIC for the model was 27000.252, which was 2% lower than the model with the three-gene risk factor. Consistent with results of the primary aim for afternoon cortisol, the pattern of relations indicated interval differences in slope magnitude by genetic risk (Figure 3.5), such that individuals with greater genetic risk had higher SBP with higher waking cortisol, and lower SBP with lower waking cortisol. In contrast, individuals with medium genetic risk showed a slope in the same direction but with a smaller magnitude, and individuals with the least genetic risk had virtually no slope relation with SBP across low and high levels of waking cortisol.

Perceived Stress. A follow-up analysis was conducted with inclusion of perceived stress as the mediator predicting waking cortisol (Table 3.15). Consistent with findings of the primary aim, results indicated that the GxE interaction predicted the perceived stress mediator, b = -.044, $t(451)$ = -2.551, p = .012, perceived stress predicted waking cortisol, b = -.216, $t(451)$ = -2.505, p = .012, and neighborhood SES predicted

waking cortisol, b = -.026, $t(451)$ = -1.926, p = .054 (Figure 3.6). Though there were significant relations across both *a* and *b* paths, such that the GxE interaction predicted perceived stress (*a* path) and the perceived stress predicted SBP, DBP, and waking cortisol (*b* paths), there was also a direct effect neighborhood SES on waking cortisol (*c'* path). Despite the presence of significant direct effects in each of the mediation pathways, there were no significant indirect effects (αβ estimators). The mediated effect of neighborhood SES through perceived stress on waking cortisol, SBP, and DBP with R^2 ranging = -.074 to -.036, indicating no mediated effect and no variance accounted for by an indirect path. Fit statistics did not provide empirical support for the model, as the RMSEA was .108 and the SRMR was 0.065 (*df*=27).

Table 3.1
Estimates of Skewness and Kurtosis of Model Outcome Variables.

	Skewness		Kurtosis	
	Estimate	*SE*	*Estimate*	*SE*
SBP	.630	.116	.453	.232
DBP	.394	.116	.136	.232
PS	.085	.118	-.012	.235
Untransformed WCort	1.264	.141	1.197	.281
Transformed WCort	-.843	.141	.534	.281

Note. DBP, diastolic blood pressure; PS, perceived stress; SBP, systolic blood pressure; WCort, waking cortisol.

Table 3.2
Missing Data and Reasons for Missingness by Model Variable.

	n	Total Missing	Percent Missing	Reasons for Missingness				
				Error in Measure	Lost to Follow-Up	Out of Range Value	Refused Collection	Data Not Available
GeR	411	39	8.7%	---	---	---	6	33
NSES	429	21	4.7%	---	---	5	---	16
CE	431	19	4.2%	---	19	---	---	---
NSat	418	32	7.1%	---	32	---	---	---
PS	428	22	4.9%	---	14	---	---	8
BPMed	425	25	5.6%	---	25	---	---	---
SBP	440	10	2.2%	10	---	---	---	---
DBP	440	10	2.2%	10	---	---	---	---
WCort	299	151	33.6%	4	143	4	---	---
ACort	378	72	16.0%	5	4	6	---	57

Note. ACort, afternoon cortisol; BP Med, blood pressure medication status; CE, collective efficacy; DBP, diastolic blood pressure; GeR, genetic risk; NSat, neighborhood satisfaction; NSES, neighborhood socioeconomic status; PS, perceived stress; SBP, systolic blood pressure; WCort, waking cortisol.

Table 3.3
Block Group Subsamples by Number of Participants and Proportions of Total.

X Ppts per BG	No. of BGs with X Ppts	Total Ppts	Proportion of BGs (N=155)	Proportion of Geocoded Sample (N=429)
1	94	94	61%	22%
2	34	68	22%	16%
3	11	33	7%	8%
4	3	12	2%	3%
5	2	10	1%	2%
6	1	6	.6%	1%
10	1	10	.6%	2%
14	3	42	2%	10%
19	1	19	.6%	4%
20	1	20	.6%	5%
21	1	21	.6%	5%
23	1	23	.6%	5%
26	1	26	.6%	6%
45	1	45	.6%	10%

Note. BG, block group; No., number; Ppts, participants.

Table 3.4
Descriptive Data for Model Variables by Project (N=450).

	Mean (SD), Range				
	PATH (n=245)	***SHINE (n=57)***	***HEART (n=99)***	***FIT (n=49)***	***Total (n=450)***
Age*	55.80 (15.56) [a] 21-89	41.91 (8.59) [ab] 30.00-72.00	44.44 (9.34) [a] 27.00-68.00	43.82 (7.51) [b] 29.00-61.00	50.23 (14.26) 21.00-89.00
Female*	64% [a]	91% [b]	60% [a]	92% [b]	70%
BMI*	32.45 (8.65) [a] 17.7-59.6	36.68 (8.60) [b] 23.60-55.49	31.77 (8.94) [a] 17.77-57.83	38.82 (10.19) [b] 24.77-60.32	33.53 (9.16) 17.65-60.32
BP Med	1.04 (1.00) 0-2	0.65 (0.89) 0-2	0.70 (0.93) 0-2	0.73 (0.94) 0-2	0.89 (0.98) 0-2
GeR	1.49 (0.37) 0.00-2.00	1.45 (0.38) 0.67-2.00	1.53 (0.30) 0.67-2.00	1.49 (0.31) 0.67-2.00	1.49 (0.35) 0.00-2.00
NSES*	-0.98 (5.79) [a] -20.8-15.2	3.61 (3.73) [b] -9.96-9.79	2.76 (3.44) [b] -6.28-10.66	2.97 (4.73) [b] -15.31-9.45	0.82 (5.40) -20.79-15.17
CE*	3.58 (0.78) [a] 0.80-4.80	3.41 (0.82) [ab] 0.80-4.70	3.38 (0.82) [ab] 0.80-4.80	3.10 (0.96) [b] 1.30-4.60	3.46 (0.83) 0.80-4.80
NSat	3.79 (0.65) 1.53-5.00	3.74 (0.71) 1.47-5.00	3.49 (0.72) 1.94-5.00	3.58 (0.76) 2.12-4.82	3.69 (0.70) 1.47-5.00
PS*	2.27 (0.64) [a] 0.60-4.20	2.47 (0.65) [ab] 1.00-4.00	2.56 (0.69) [b] 0.80-4.30	2.44 (0.72) [ab] 0.80-3.70	2.38 (0.67) 0.60-4.30
PMSS*	5.51 (1.07) [a] 1.50-7.00	5.51 (1.36) [a] 1.92-7.00	4.72 (1.52) [b] 1.00-7.00	5.19 (1.25) [ab] 2.33-7.00	5.30 (1.28) 1.00-7.00
SBP* (mmHg)	129.24 (20.69) [a] 74.50-201.50	125.20 (17.25) [ab] 93.00-173.00	121.98 (18.19) [ab] 82.33-175.67	120.87 (19.27) [b] 91.67-179.33	126.25 (19.86) 74.50-201.50
DBP (mmHg)	77.76 (11.26) 50.50-118.50	79.67 (9.97) 60.00-103.50	78.70 (11.81) 57.00-113.00	76.60 (12.22) 54.00-110.67	78.08 (11.33) 50.50-118.50
MBP (mmHg)	94.91 (13.28) 62.16-141.98	94.83 (11.36) 75.82-121.32	93.12 (13.43) 66.33-130.76	90.66 (14.61) 64.14-132.98	94.05 (13.27) 62.16-141.98
HR (bpm)	77.20 (12.24) 44.50-105.50	76.71 (11.25) 55.00-109.00	77.47 (12.09) 49.00-113.67	77.15 (13.53) 53.00-112.67	77.19 (12.20) 44.50-113.67
WCort (ng/mL)	4.16 (3.33) 0.13-12.08	3.20 (2.44) 0.39-12.08	2.59 (1.90) 0.13-8.60	2.72 (1.65) 0.36-6.43	3.53 (2.87) 0.13-12.08
ACort* (ng/mL)	2.41 (2.30) [a] 0.05-9.25	1.13 (1.44) [b] 0.14-8.88	1.65 (1.54) [a] 0.12-9.25	1.63 (1.76) [ab] 0.22-9.25	1.98 (2.04) 0.05-9.25
Cortisol Decline	1.95 (3.27) -6.21-9.79	2.20 (2.77) -5.82-11.45	1.06 (2.17) -5.83-5.87	1.53 (1.82) -1.62-5.16	1.76 (2.87) -6.21-11.45

Note. ACort, afternoon cortisol; BMI, body mass index; BP Med, blood pressure medication status; bpm, beats per minute; CE, collective efficacy; DBP, diastolic blood pressure; GeR, genetic risk; HR, heart rate; mmHg, millimeters of mercury; ng/mL, nanogram per millileter; MBP, mean blood pressure; NSat, neighborhood satisfaction; NSES, neighborhood socioeconomic status; PMSS, perceived multidimensional social support; PS, perceived stress; SBP, systolic blood pressure; WCort, waking cortisol.

*Indicates statistically significant mean differences across studies, and study means that did not differ share the same letter superscript (^{a}, ^{b}, or ^{c}).

Table 3.5
SNP Risk Allele Frequencies by Project.

SNP	Genotypes	PATH n (%)	SHINE n (%)	HEART n (%)	FIT n (%)	Total n (%)
*Bcl*1 rs41423247	CC	12 (6)	6 (13)	3 (3)	2 (6)	23 (6)
	C**G**	52 (24)	14 (29)	29 (32)	11 (33)	106 (27)
	GG	151 (70)	28 (58)	60 (65)	20 (61)	259 (67)
	Total	215 (100)	48 (100	92 (100)	33 (100)	388 (100)
FHBP5 rs1360780	CC	69 (32)	14 (29)	24 (26)	8 (25)	115 (30)
	C**T**	105 (49)	24 (49)	44 (48)	16 (50)	189 (49)
	TT	42 (19)	11 (22)	24 (26)	8 (25)	85 (22)
	Total	216 (100)	49 (100)	92 (100)	32 (100)	389 (100)
9β* rs6198	GG	1 (.5)	0 (0)	1 (1)	0 (0)	2 (1)
	G**A**	10 (5)	5 (10)	6 (7)	3 (9)	24 (6)
	AA	209 (95)	46 (90)	85 (92)	30 (91)	370 (93)
	Total	220 (100)	51 (100)	92 (100)	33 (100)	396 (100)

Note: Risk alleles are bolded. There were no significant differences in rates of genetic risk by study. Rs, reference sequence; SNP, single nucleotide polymorphism.

Table 3.6
Correlation Table for Model Variables (N=450).

	WCort	SBP	DBP	ACort	PS	Age	Female	BMI	NSES	GeR	BP Med	NSat
SBP	-0.11*	---	---	---	---	---	---	---	---	---	---	---
DBP	-0.05	0.73**	---	---	---	---	---	---	---	---	---	---
ACort	0.26**	0.02	0.02	---	---	---	---	---	---	---	---	---
PS	-0.14**	0.05	0.16**	-0.00	---	---	---	---	---	---	---	---
Age	0.01	0.15**	-0.11*	0.07	-0.23**	---	---	---	---	---	---	---
Female	-0.05	0.01	-0.08	-0.17**	0.09	0.02	---	---	---	---	---	---
BMI	0.00	0.12*	0.07	-0.17**	-0.02	-0.12*	0.33**	---	---	---	---	---
NSES	-0.16**	-0.07	0.04	-0.08	0.01	-0.05	0.04	-0.03	---	---	---	---
GeR	-0.00	-0.03	-0.02	0.05	-0.03	0.09	0.01	0.00	0.08	---	---	---
BP Med	-0.00	0.17**	0.05	0.04	-0.09*	0.46**	0.17**	0.10*	-0.01	0.02	---	---
NSat	0.06	0.05	0.05	0.02	-0.30**	0.12*	-0.13**	-0.04	0.03	0.04	0.02	---
CE	0.03	0.02	-0.00	0.03	-0.27**	0.16**	-0.07	-0.06	0.03	0.04	0.06	0.47**

*p<.05, **p<.01

Note: ACort, afternoon cortisol; BMI, body mass index; BP Med, blood pressure medication status; CE, collective efficacy; CortD, cortisol decline with more positive numbers indicating greater decline; DBP, diastolic blood pressure; GeR, genetic risk; NSat, neighborhood satisfaction; NSES, neighborhood socioeconomic status; PS, perceived stress; SBP, systolic blood pressure; WCort, waking cortisol.

Table 3.7
Primary Aim, Risk Model, Total Sample (N=450).

	Estimate	SE	Est/SE	Two-tailed *p*-value
Waking Cortisol				
Intercept	0.818	0.536	1.528	0.127
Age	-0.001	0.005	-0.259	0.796
Female	-0.093	0.143	-0.651	0.515
BMI	0.002	0.007	0.293	0.769
BP Med	-0.004	0.074	-0.054	0.957
Study-Tx	-0.031	0.03	-1.004	0.315
CE	-0.002	0.082	-0.021	0.984
NSat	0.073	0.095	0.768	0.442
NSES	-0.025	0.013	-2.029	0.042*
GeR	0.025	0.168	0.149	0.881
GeRxNSES	0.002	0.036	0.066	0.948
Systolic BP				
Intercept	113.461	8.296	13.677	0.000
Age	0.113	0.079	1.43	0.153
Female	-2.216	2.159	-1.026	0.305
BMI	0.311	0.109	2.867	0.004**
BP Med	2.14	1.146	1.867	0.062
Study-Tx	-1.084	0.479	-2.261	0.024*
CE	-0.939	1.304	-0.72	0.472
NSat	1.002	1.56	0.642	0.521
NSES	-0.027	0.191	-0.142	0.887
GeR	-2.272	2.825	-0.804	0.421
GeRxNSES	-0.274	0.506	-0.541	0.588
Diastolic BP				
Intercept	79.292	4.780	16.587	0.000
Age	-0.132	0.045	-2.922	0.003**
Female	-3.165	1.245	-2.543	0.011*
BMI	0.099	0.063	1.587	0.113
BP Med	1.59	0.638	2.491	0.013*
Study-Tx	0.003	0.276	0.011	0.991
CE	-0.357	0.754	-0.474	0.636
NSat	1.124	0.9	1.249	0.212
NSES	0.071	0.11	0.643	0.520
GeR	-0.79	1.653	-0.478	0.633
GeRxNSES	-0.342	0.297	-1.153	0.249

Note: BMI, body mass index; BP, blood pressure; BP Med, blood pressure medication status; CE, collective efficacy; GeR, genetic risk; GeRxNSES, genetic risk-by-neighborhood socioeconomic status; NSat, neighborhood satisfaction; NSES, neighborhood socioeconomic status, Tx, treatment.

*$p \leq .05$

Table 3.8
Primary Aim, Risk Model, Unmedicated Sample (N=232).

	Estimate	SE	Est/SE	Two-tailed *p*-value
Waking Cortisol				
Intercept	0.694	0.535	1.297	0.195
Age	-0.001	0.005	-0.119	0.906
Female	-0.105	0.144	-0.734	0.463
BMI	0.003	0.007	0.500	0.617
BP Med	-0.005	0.074	-0.066	0.947
Study-Tx	-0.026	0.030	-0.866	0.386
CE	0.006	0.083	0.074	0.941
NSat	0.074	0.095	0.777	0.437
NSES	-0.025	0.013	-1.974	0.048*
GeR	0.030	0.168	0.179	0.858
GeRxNSES	0.001	0.036	0.015	0.988
Systolic BP				
Intercept	114.131	8.310	13.734	0.000
Age	0.110	0.079	1.397	0.162
Female	-2.210	2.160	-1.023	0.306
BMI	0.311	0.109	2.868	0.004**
BP Med	2.139	1.147	1.865	0.062
Study-Tx	-1.103	0.479	-2.301	0.021*
CE	-0.983	1.306	-0.753	0.451
NSat	0.912	1.563	0.584	0.559
NSES	-0.026	0.191	-0.135	0.893
GeR	-2.327	2.827	-0.823	0.410
GeRxNSES	-0.271	0.507	-0.535	0.592
Diastolic Blood Pressure				
Intercept	79.563	4.787	16.621	0.000
Age	-0.133	0.045	-2.944	0.003**
Female	-3.151	1.245	-2.531	0.011*
BMI	0.100	0.063	1.597	0.110
BP Med	1.591	0.639	2.492	0.013*
Study-Tx	-0.007	0.276	-0.024	0.981
CE	-0.373	0.755	-0.495	0.621
NSat	1.081	0.902	1.199	0.231
NSES	0.071	0.111	0.644	0.519
GeR	-0.850	1.654	-0.513	0.608
GeRxNSES	-0.342	0.297	-1.151	0.250

Note: BMI, body mass index; BP, blood pressure; BP Med, blood pressure medication status; CE, collective efficacy; GeR, genetic risk; GeRxNSES, genetic risk-by-neighborhood socioeconomic status; NSat, neighborhood satisfaction; NSES, neighborhood socioeconomic status.

*$p \leq .05$

Table 3.9

Primary Aim, Risk Model, Afternoon Cortisol Outcome, Total Sample (N=450).

	Estimate	SE	Est/SE	Two-tailed *p*-value
Afternoon Cortisol				
Intercept	0.880	0.450	1.957	0.050*
Age	0.000	0.004	0.016	0.987
Female	-0.294	0.116	-2.539	0.011*
BMI	-0.014	0.006	-2.456	0.014*
BP Med	0.067	0.061	1.095	0.274
Study-Tx	-0.022	0.026	-0.835	0.404
WCort	0.243	0.056	4.338	0.000*
CE	-0.006	0.072	-0.083	0.934
NSat	-0.044	0.084	-0.527	0.598
NSES	-0.005	0.011	-0.501	0.617
GeR	0.096	0.148	0.648	0.517
GeRxNSES	-0.054	0.031	-1.722	0.085

Note: BMI, body mass index; BP, blood pressure; BP Med, blood pressure medication status; CE, collective efficacy; GeR, genetic risk; GeRxNSES, genetic risk-by-neighborhood socioeconomic status; NSat, neighborhood satisfaction; NSES, neighborhood socioeconomic status.

*$p \leq .05$

Table 3.10
Primary Aim, Risk Model, Perceived Stress Outcome, Total Sample (N=450).

	Estimate	SE	Est/SE	Two-tailed *p*-value
Perceived Stress				
Intercept	3.889	0.269	14.467	0.000
Age	-0.008	0.002	-3.201	0.001**
Female	0.103	0.069	1.49	0.136
BMI	-0.006	0.003	-1.721	0.085
BP Med	0.01	0.036	0.268	0.789
Study-Tx	0.028	0.016	1.782	0.075
CE	-0.122	0.043	-2.808	0.005**
NSat	-0.168	0.05	-3.386	0.001**
NSES	-0.005	0.006	-0.749	0.454
GeR	-0.037	0.09	-0.418	0.676
GeRxNSES	-0.046	0.016	-2.871	0.004**

Note: BMI, body mass index; BP, blood pressure; BP Med, blood pressure medication status; CE, collective efficacy; GeR, genetic risk; GeRxNSES, genetic risk-by-neighborhood socioeconomic status; NSat, neighborhood satisfaction; NSES, neighborhood socioeconomic status.

*$p \leq .05$

Table 3.11
Secondary Aim, Mechanistic Model, Total Sample (N=450).

Variable	B	SE	t	Two-tailed *p*	LCL	UCL	R^2
Systolic Blood Pressure							
Intercept (I_1)	113.043	8.019	14.096	0.000	97.323	128.982	
Age (X_1)	0.098	0.080	1.227	0.220	-0.064	0.249	
Female (X_2)	-2.460	2.188	-1.124	0.261	-7.063	1.554	
BMI (X_3)	0.327	0.115	2.843	0.004**	0.104	0.549	
BP Med (X_4)	2.235	1.201	1.861	0.063	-0.136	4.541	
Study-Tx (X_5)	-1.191	0.481	-2.475	0.013*	-2.130	-0.240	.091
NSat (X_6)	1.228	1.567	0.784	0.433	-2.038	4.164	
CE (X_7)	-0.826	1.376	-0.601	0.548	-3.503	1.982	
NSES (X_8)	-0.083	0.186	-0.448	0.654	-0.439	0.273	
WCort (X_9)	-2.622	1.190	-2.203	0.028*	-4.973	-0.256	
GeR (Z_1)	-1.660	2.770	-0.599	0.549	-6.682	3.982	
GeRxWCort (XZ_1)	3.303	3.747	0.881	0.378	-3.282	10.703	
Diastolic Blood Pressure							
Intercept (I_1)	79.079	4.651	17.001	0.000	69.917	88.364	
Age (X_1)	-0.133	0.045	-2.929	0.003**	-0.231	-0.048	
Female (X_2)	-3.102	1.219	-2.544	0.011*	-5.416	-0.684	
BMI (X_3)	0.099	0.067	1.477	0.140	-0.040	0.224	
BP Med (X_4)	1.574	0.651	2.419	0.016*	0.335	2.831	
Study-Tx (X_5)	-0.015	0.285	-0.052	0.959	-0.571	0.564	.049
NSat (X_6)	1.129	0.915	1.234	0.217	-0.736	2.865	
CE (X_7)	-0.293	0.804	-0.364	0.716	-1.868	1.301	
NSES (X_8)	0.068	0.106	0.642	0.521	-0.146	0.264	
WCort (X_9)	-0.483	0.760	-0.635	0.526	-1.976	1.007	
GeR (Z_1)	-0.416	1.671	-0.249	0.803	-3.491	2.965	
GeRxWCort (XZ_1)	0.457	2.700	0.169	0.865	-4.126	6.059	
Waking Cortisol							
Intercept (I_1)	-0.167	0.549	-0.304	0.761	-1.24	0.878	
Age (X_1)	-0.001	0.005	-0.145	0.885	-0.011	0.009	
Female (X_2)	-0.096	0.155	-0.618	0.536	-0.411	0.187	
BMI (X_3)	0.005	0.007	0.634	0.526	-0.009	0.020	
BP Med (X_4)	-0.007	0.074	-0.094	0.925	-0.147	0.148	.039
Study-Tx (X_5)	-0.032	0.031	-1.038	0.299	-0.101	0.024	
NSat (X_6)	0.074	0.091	0.814	0.416	-0.104	0.260	
CE (X_7)	0.003	0.091	0.033	0.974	-0.178	0.176	
NSES (X_8)	-0.025	0.014	-1.780	0.075	-0.051	0.003	
GeR (X_9)	0.006	0.184	0.033	0.974	-0.365	0.345	
Variable	B	SE	t	*p*	LCL	UCL	R^2

Mediated/Indirect Effects							
NSES→Cort→SBP	0.065	0.053	1.231	0.218	-0.002	0.215	
NSat→Cort→SBP	-0.194	0.283	-0.687	0.492	-1.009	0.216	
CE→Cort→SBP	-0.008	0.276	-0.028	0.978	-0.630	0.535	
NSES→Cort→DBP	0.012	0.023	0.528	0.598	-0.018	0.082	---
NSat→Cort→DBP	-0.036	0.100	-0.358	0.720	-0.395	0.072	
CE→Cort→DBP	-0.001	0.085	-0.017	0.987	-0.208	0.158	
Direct Effects							
NSES→SBP	-0.083	0.186	-0.448	0.654	-0.439	0.273	
NSat→SBP	1.228	1.567	0.784	0.433	-2.038	4.164	
CE→ SBP	-0.826	1.376	-0.601	0.548	-3.503	1.982	
NSES→DBP	0.068	0.106	0.642	0.521	-0.146	0.264	---
NSat→DBP	1.129	0.915	1.234	0.217	-0.414	2.865	
CE→ DBP	-0.293	0.804	-0.364	0.716	-1.868	1.301	

Note: BMI, body mass index; BP, blood pressure; BP Med, blood pressure medication status; CE, collective efficacy; GeR, genetic risk; GeRxNSES, genetic risk-by-neighborhood socioeconomic status; NSat, neighborhood satisfaction; NSES, neighborhood socioeconomic status.

* = $p < .05$, ** = $p < .01$

Table 3.12

Secondary Aim, Mechanistic Model, Unmedicated Sample (N=232).

Variable	B	SE	t	Two-tailed *p*	LCL	UCL	R^2
Systolic Blood Pressure							
Intercept (I_1)	129.248	19.484	6.634	0.000	89.542	166.201	
Age (X_1)	0.030	0.123	0.240	0.810	-0.216	0.257	
Female (X_2)	-3.379	3.678	-0.919	0.358	-10.527	3.569	
BMI (X_3)	0.001	0.186	0.006	0.995	-0.36	0.378	
BP Med (X_4)	-1.062	6.862	-0.155	0.877	-14.592	12.623	
Study-Tx (X_5)	0.032	0.873	0.036	0.971	-1.594	1.879	
NSat (X_6)	0.105	2.697	0.039	0.969	-5.229	5.388	.043
CE (X_7)	1.049	2.473	0.424	0.671	-3.456	6.174	
NSES (X_8)	-0.515	0.286	-1.797	0.072	-1.06	0.042	
WCort (X_9)	-2.656	1.615	-1.645	0.100	-5.548	0.635	
GeR (Z_1)	1.830	4.195	0.436	0.663	-5.974	10.134	
GeRxWCort (XZ_1)	3.062	4.444	0.689	0.491	-4.124	13.289	
Diastolic Blood Pressure							
Intercept (I_1)	96.322	10.13	9.509	0.000	75.087	115.904	
Age (X_1)	-0.298	0.064	-4.647	0.000**	-0.433	-0.176	
Female (X_2)	-2.796	1.812	-1.543	0.123	-6.530	0.442	
BMI (X_3)	-0.084	0.104	-0.807	0.420	-0.282	0.119	
BP Med (X_4)	-0.500	3.707	-0.135	0.893	-7.355	7.151	
Study-Tx (X_5)	0.238	0.471	0.505	0.614	-0.640	1.211	
NSat (X_6)	0.424	1.352	0.313	0.754	-2.177	2.964	.152
CE (X_7)	0.849	1.193	0.712	0.477	-1.462	3.258	
NSES (X_8)	0.030	0.149	0.200	0.842	-0.276	0.310	
WCort (X_9)	-0.708	0.962	-0.736	0.462	-2.536	1.214	
GeR (Z_1)	0.481	2.415	0.199	0.842	-3.788	5.63	
GeRxWCort (XZ_1)	0.292	3.230	0.090	0.928	-5.104	7.181	
Waking Cortisol							
Intercept (I_1)	0.255	1.188	0.214	0.830	-2.448	2.217	
Age (X_1)	-0.002	0.009	-0.276	0.782	-0.018	0.015	
Female (X_2)	-0.301	0.266	-1.131	0.258	-0.817	0.242	
BMI (X_3)	0.006	0.011	0.503	0.615	-0.015	0.028	
BP Med (X_4)	0.015	0.497	0.031	0.975	-0.928	0.958	
Study-Tx (X_5)	-0.028	0.047	-0.587	0.557	-0.122	0.065	.0544
NSat (X_6)	0.076	0.147	0.516	0.606	-0.213	0.354	
CE (X_7)	-0.075	0.158	-0.474	0.635	-0.349	0.269	
NSES (X_8)	-0.037	0.020	-1.844	0.065	-0.075	0.006	
GeR (X_9)	-0.042	0.301	-0.141	0.888	-0.709	0.486	

Variable	B	SE	t	*p*	LCL	UCL	R^2
Mediated/Indirect Effects							
NSES→Cort→SBP	0.099	0.095	1.045	0.296	-0.015	0.347	
NSat→Cort→SBP	-0.201	0.493	-0.408	0.683	-1.532	0.487	
CE→Cort→SBP	0.199	0.532	0.375	0.708	-0.62	1.511	
NSES→Cort→DBP	0.026	0.045	0.581	0.561	-1.06	0.042	
NSat→Cort→DBP	-0.054	0.198	-0.270	0.787	-5.229	5.388	
CE→Cort→DBP	0.053	0.206	0.257	0.797	-3.456	6.174	
Direct Effects							
NSES→SBP	-0.515	0.286	-1.797	0.072	-0.033	0.154	
NSat→SBP	0.105	2.697	0.039	0.969	-0.732	0.175	
CE→ SBP	1.049	2.473	0.424	0.671	-0.177	0.745	
NSES→DBP	0.030	0.149	0.200	0.842	-0.276	0.31	---
NSat→DBP	0.424	1.352	0.313	0.754	-2.177	2.964	
CE→ DBP	0.849	1.193	0.712	0.477	-1.462	3.258	

* = p < .05, ** = p < .01

Table 3.13
Secondary Aim, Mechanistic Model, Afternoon Cortisol Mediator, Total Sample (N=450).

Variable	B	SE	t	*p*	LCL	UCL	R^2
Systolic BP (Y_1) on Control Variables (X_{1-6}) and Predictors (X_{7-10}; Z_1; XZ_1)							
Intercept (I_1)	115.259	8.017	14.376	0.000	99.694	131.035	
Age (X_1)	0.108	0.080	1.348	0.178	-0.055	0.262	
Female (X_2)	-2.178	2.238	-0.973	0.331	-7.016	1.937	
BMI (X_3)	0.324	0.117	2.775	0.006**	0.093	0.556	
BP Med (X_4)	2.122	1.205	1.761	0.078	-0.216	4.466	
Study-Tx (X_5)	-1.152	0.483	-2.385	0.017*	-2.113	-0.180	
WCort (X_6)	-2.952	1.224	-2.411	0.016*	-5.384	-0.630	.081
NSat (X_7)	1.210	1.573	0.769	0.442	-2.043	4.137	
CE (X_8)	-0.897	1.360	-0.659	0.510	-3.610	1.867	
NSES (X_9)	-0.086	0.188	-0.457	0.648	-0.453	0.276	
ACort (X_{10})	0.733	1.169	0.627	0.530	-1.524	3.017	
GeR (Z_1)	-1.965	2.789	-0.704	0.481	-7.411	3.563	
GeRxACort (XZ_1)	0.205	2.762	0.074	0.941	-5.584	5.439	
Diastolic BP (Y_1) on Control Variables (X_{1-5}) and Predictors (X_{6-9}; Z_1; XZ_1)							
Intercept (I_1)	79.500	4.690	16.949	0.000	70.365	88.585	
Age (X_1)	-0.132	0.046	-2.885	0.004**	-0.227	-0.047	
Female (X_2)	-3.021	1.251	-2.415	0.016*	-5.523	-0.581	
BMI (X_3)	0.101	0.067	1.500	0.134	-0.033	0.232	
BP Med (X_4)	1.555	0.659	2.360	0.018*	0.322	2.854	
Study-Tx (X_5)	-0.009	0.284	-0.030	0.976	-0.573	0.547	.069
WCort (X_6)	-0.715	0.787	-0.909	0.363	-2.239	0.873	
NSat (X_7)	1.145	0.912	1.256	0.209	-0.780	2.879	
CE (X_8)	-0.303	0.790	-0.384	0.701	-1.810	1.321	
NSES (X_9)	0.064	0.106	0.610	0.542	-0.143	0.263	
ACort (X_{10})	0.327	0.654	0.500	0.617	-0.905	1.665	
GeR (Z_1)	-0.498	1.777	-0.280	0.779	-3.826	3.108	
GeRxWCort (XZ_1)	-0.146	1.533	-0.095	0.924	-3.028	2.971	
Afternoon Cortisol (M_1) on Control Variables (X_{1-5}) and Predictors (X_{6-9})							
Intercept (I_1)	0.594	0.479	1.238	0.216	-0.377	1.496	
Age (X_1)	0.001	0.005	0.141	0.888	-0.008	0.010	
Female (X_2)	-0.272	0.116	-2.337	0.019*	-0.514	-0.054	.069
BMI (X_3)	-0.014	0.005	-2.653	0.008**	-0.026	-0.004	
BP Med (X_4)	0.059	0.063	0.929	0.353	-0.057	0.186	
Study-Tx (X_5)	-0.017	0.026	-0.666	0.505	-0.068	0.034	
WCort (X_6)	0.243	0.060	4.071	0.000**	0.125	0.357	
NSat (X_7)	-0.042	0.088	-0.474	0.636	-0.222	0.123	
CE (X_8)	-0.001	0.075	-0.018	0.986	-0.148	0.159	
NSES (X_9)	-0.007	0.011	-0.618	0.537	-0.027	0.016	

GeR (X_{10})	0.089	0.176	0.508	0.611	-0.261	0.434

Table 3.14
Secondary Aim, Mechanistic Model, Two-Gene Interaction, Total Sample (N=450).

Variable	B	SE	t	Two-tailed *p*	LCL	UCL	R^2
Systolic BP (Y_1) on Control Variables (X_{1-5}) and Predictors (X_{6-9}; Z_1; XZ_1)							
Intercept (I_1)	113.314	8.098	13.993	0.000	97.030	128.539	
Age (X_1)	0.087	0.079	1.092	0.275	-0.072	0.241	
Female (X_2)	-2.444	2.196	-1.113	0.266	-7.024	1.604	
BMI (X_3)	0.332	0.115	2.886	0.004**	0.103	0.55	
BP Med (X_4)	2.371	1.189	1.994	0.046*	0.008	4.707	
Study-Tx (X_5)	-1.239	0.481	-2.577	0.010*	-2.160	-0.263	.100
NSat (X_6)	-0.095	0.186	-0.512	0.609	-1.921	4.23	
CE (X_7)	1.184	1.575	0.752	0.452	-3.372	2.081	
NSES (X_8)	-0.716	1.370	-0.523	0.601	-0.452	0.266	
WCort (X_9)	-2.790	1.156	-2.413	0.016*	-4.920	-0.25	
GeR2 (Z_1)	-2.125	1.911	-1.112	0.266	-5.809	1.729	
GeR2xWCort (XZ_1)	4.033	2.442	1.651	0.099	-1.278	8.295	
Diastolic BP (Y_1) on Control Variables (X_{1-5}) and Predictors (X_{6-9}; Z_1; XZ_1)							
Intercept (I_1)	79.119	4.692	16.864	0.000	69.690	88.037	
Age (X_1)	-0.142	0.046	-3.090	0.002**	-0.238	-0.054	
Female (X_2)	-3.110	1.225	-2.539	0.011*	-5.468	-0.688	
BMI (X_3)	0.104	0.067	1.557	0.119	-0.034	0.228	
BP Med (X_4)	1.667	0.646	2.581	0.010*	0.417	2.941	
Study-Tx (X_5)	-0.046	0.288	-0.160	0.873	-0.595	0.545	.055
NSat (X_6)	0.061	0.106	0.576	0.565	-0.695	2.91	
CE (X_7)	1.128	0.916	1.232	0.218	-1.781	1.381	
NSES (X_8)	-0.213	0.801	-0.266	0.790	-0.139	0.262	
WCort (X_9)	-0.650	0.746	-0.871	0.384	-1.965	1.074	
GeR (Z_1)	-0.763	1.206	-0.633	0.527	-2.968	1.744	
GeRxWCort (XZ_1)	1.716	1.888	0.909	0.364	-2.307	4.907	
Waking Cortisol (M_1) on Control Variables (X_{1-5}) and Predictors (X_{6-9})							
Intercept (I_1)	-0.179	0.548	-0.327	0.744	-1.244	0.872	
Age (X_1)	-0.001	0.005	-0.121	0.904	-0.011	0.009	
Female (X_2)	-0.101	0.155	-0.654	0.513	-0.412	0.189	
BMI (X_3)	0.005	0.007	0.672	0.502	-0.009	0.02	
BP Med (X_4)	-0.007	0.073	-0.100	0.920	-0.144	0.15	.039
Study-Tx (X_5)	-0.032	0.031	-1.045	0.296	-0.099	0.025	
NSat (X_6)	-0.024	0.014	-1.741	0.082	-0.105	0.262	
CE (X_7)	0.073	0.091	0.805	0.421	-0.178	0.178	
NSES (X_8)	0.004	0.091	0.043	0.966	-0.051	0.003	
GeR (X_9)	-0.047	0.121	-0.385	0.701	-0.293	0.187	

Table 3.15
Secondary Aim, Mechanistic Model, Perceived Stress Mediator and Waking Cortisol Outcome, Total Sample (N=450).

Variable	B	SE	t	Two-tailed *p*	LCL	UCL	R^2
Systolic BP (Y_1) on Control Variables (X_{1-5}) and Predictors (X_{6-9}; Z_1; XZ_1)							
Intercept (I_1)	104.051	7.208	14.436	0.000	91.058	119.055	
Age (X_1)	0.144	0.083	1.744	0.081	-0.020	0.301	
Female (X_2)	-2.832	2.191	-1.293	0.196	-7.574	1.262	
BMI (X_3)	0.335	0.115	2.918	0.004**	0.097	0.553	
BP Med (X_4)	2.074	1.180	1.757	0.079	-0.206	4.401	.081
Study-Tx (X_5)	-1.245	0.483	-2.577	0.010**	-2.263	-0.367	
PS (X_6)	3.588	1.442	2.488	0.013*	0.499	6.253	
NSES (X_8)	0.005	0.186	0.026	0.979	-0.357	0.362	
GeR (Z_1)	-2.016	2.734	-0.737	0.461	-7.437	3.355	
GeRxNSES (XZ_1)	-0.070	0.452	-0.155	0.877	-0.919	0.838	
Diastolic BP (Y_1) on Control Variables (X_{1-5}) and Predictors (X_{6-9}; Z_1; XZ_1)							
Intercept (I_1)	74.674	4.064	18.376	0.000	67.003	82.638	
Age (X_1)	-0.105	0.045	-2.330	0.020*	-0.199	-0.022	
Female (X_2)	-3.762	1.227	-3.067	0.002**	-6.252	-1.427	
BMI (X_3)	0.119	0.065	1.828	0.068	-0.013	0.246	
BP Med (X_4)	1.541	0.639	2.411	0.016*	0.385	2.788	.069
Study-Tx (X_5)	-0.170	0.277	-0.613	0.540	-0.718	0.382	
PS (X_6)	2.784	0.799	3.484	0.000**	1.129	4.295	
NSES (X_8)	0.108	0.100	1.079	0.281	-0.098	0.301	
GeR (Z_1)	-0.562	1.722	-0.326	0.744	-3.827	2.895	
GeRxNSES (XZ_1)	-0.190	0.243	-0.782	0.434	-0.663	0.302	
Waking Cortisol (Y_1) on Control Variables (X_{1-5}) and Predictors (X_{6-9})							
Intercept (I_1)	0.839	0.456	1.841	0.066	-0.097	1.665	
Age (X_1)	-0.003	0.005	-0.629	0.529	-0.013	0.007	
Female (X_2)	-0.071	0.151	-0.470	0.638	-0.380	0.197	
BMI (X_3)	0.001	0.007	0.099	0.921	-0.012	0.015	
BP Med (X_4)	-0.005	0.070	-0.077	0.939	-0.137	0.14	.081
Study-Tx (X_5)	-0.027	0.030	-0.903	0.367	-0.090	0.03	
PS (X_6)	-0.216	0.086	-2.505	0.012*	-0.393	-0.056	
NSES (X_8)	-0.026	0.014	-1.926	0.054*	-0.053	0.001	
GeR (Z_1)	0.016	0.178	0.091	0.927	-0.349	0.34	
GeRxNSES (XZ_1)	-0.005	0.034	-0.136	0.892	-0.077	0.057	
Perceived Stress (M_1) on Control Variables (X_{1-5}) and Predictors (X_{6-9})							
Intercept (I_1)	2.766	0.202	13.697	0.000**	2.369	3.181	
Age (X_1)	-0.009	0.003	-3.352	0.001**	-0.014	-0.003	
Female (X_2)	0.149	0.074	2.025	0.043*	0.007	0.301	

BMI (X_3)	-0.006	0.004	-1.513	0.130	-0.013	0.002	.107
BP Med (X_4)	0.006	0.040	0.142	0.887	-0.074	0.084	
Study-Tx (X_5)	0.044	0.017	2.573	0.010**	0.012	0.079	
NSES (X_8)	-0.009	0.006	-1.602	0.109	-0.021	0.001	
GeR (Z_1)	-0.056	0.102	-0.548	0.584	-0.266	0.147	
GeRxNSES (XZ_1)	-0.044	0.017	-2.551	0.011*	-0.082	-0.012	

* = $p < .05$, ** = $p < .01$

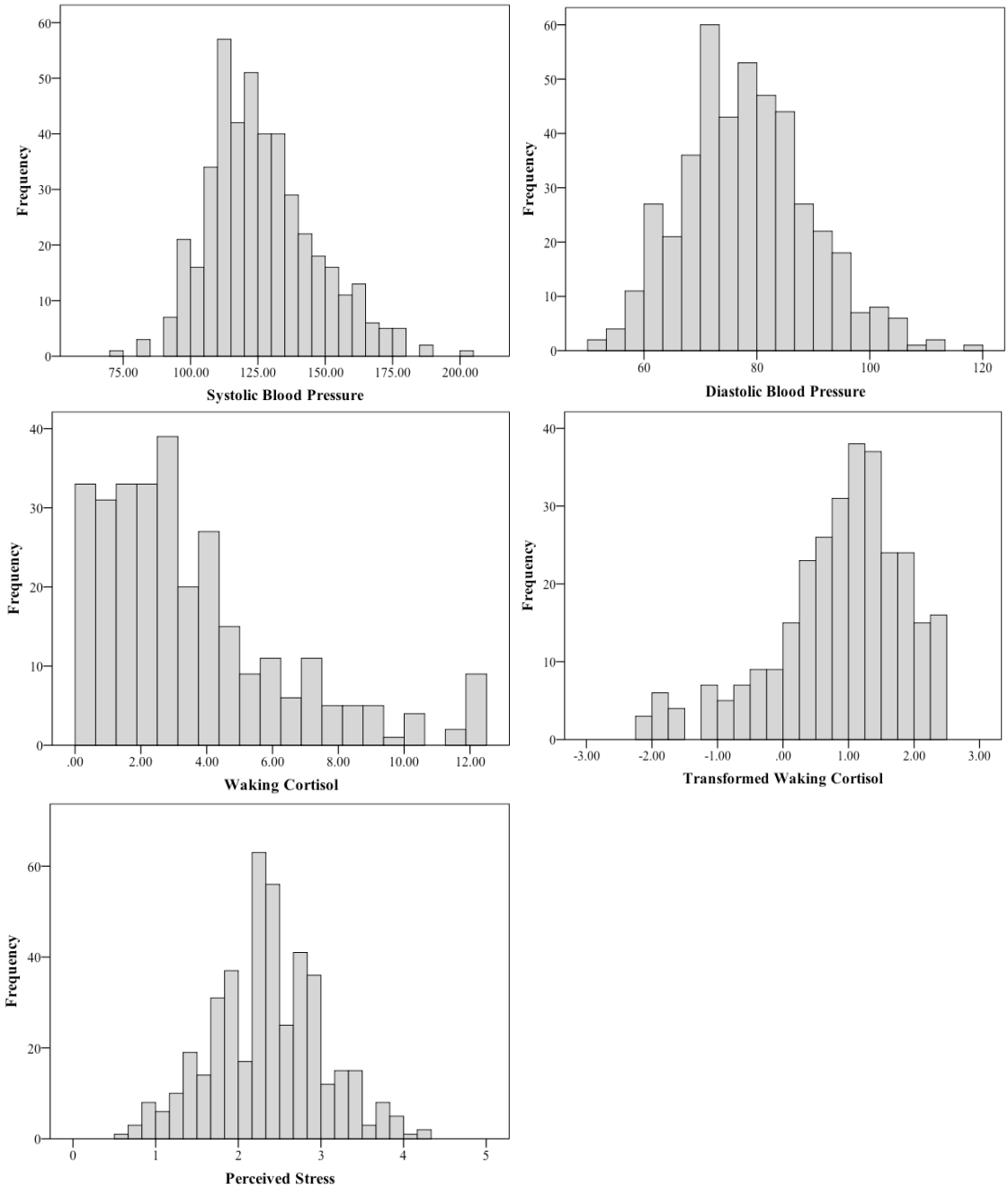


Figure 3.1. Frequency distributions of model outcome variables.

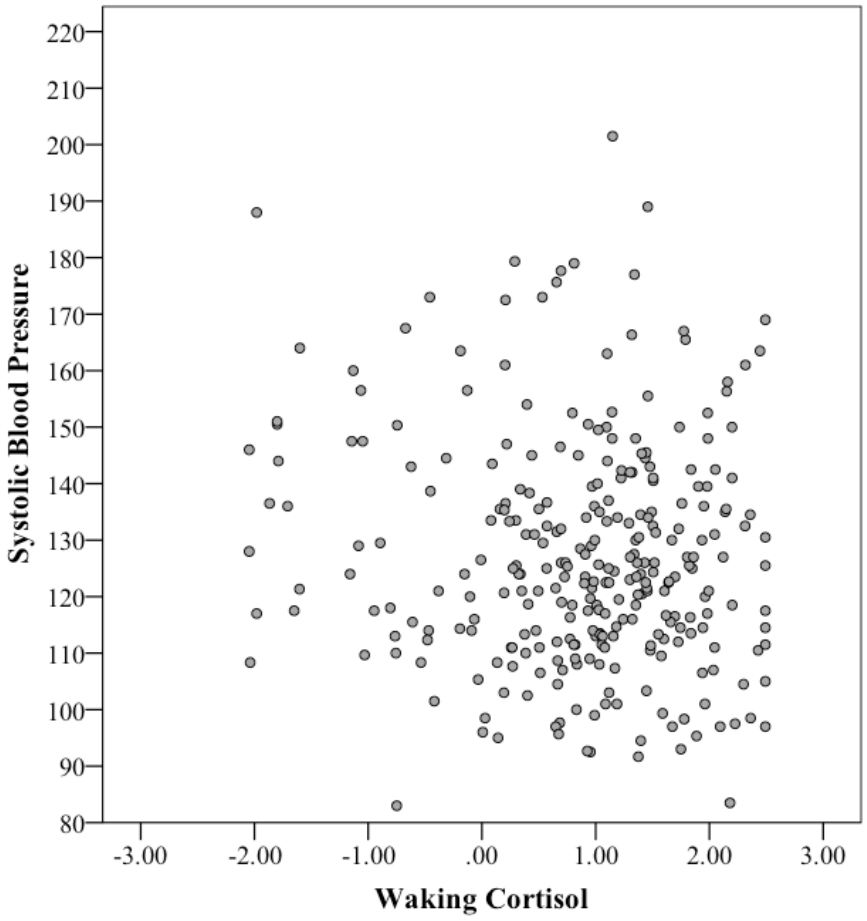


Figure 3.2. Systolic blood pressure plotted as a function of waking cortisol in the total sample.

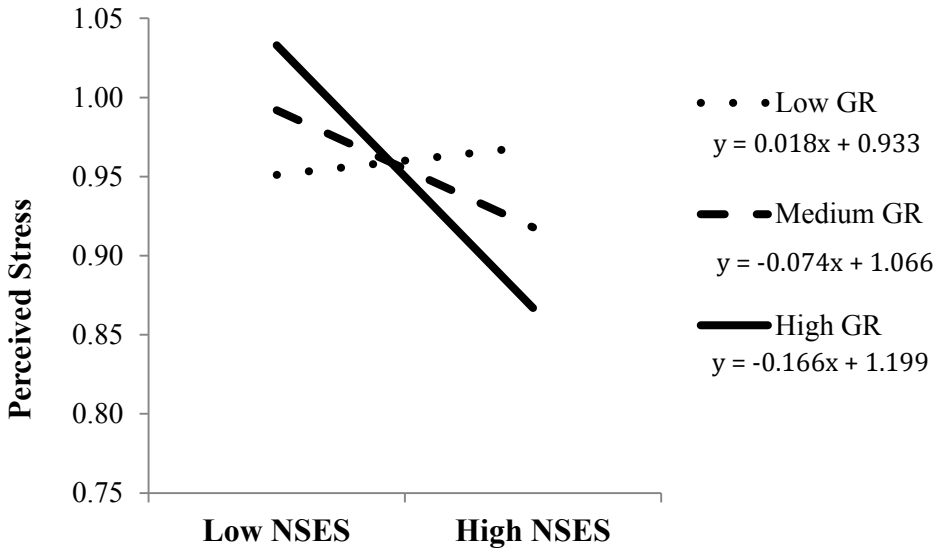


Figure 3.3. Gene-by-neighborhood socioeconomic status interaction predicting perceived stress in the total sample (b=-.046, t=-2.871, p<.001), with a differential susceptibility pattern.

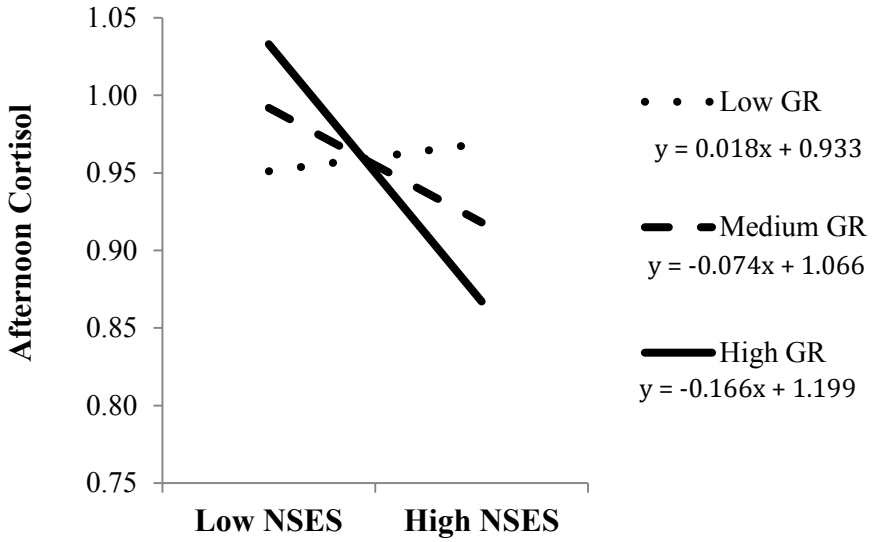


Figure 3.4. Trend (*b*=-.054, *t*=-1.722, *p*=.085) for gene-by-neighborhood socioeconomic status interaction predicting afternoon cortisol in the total sample, with a differential susceptibility pattern.

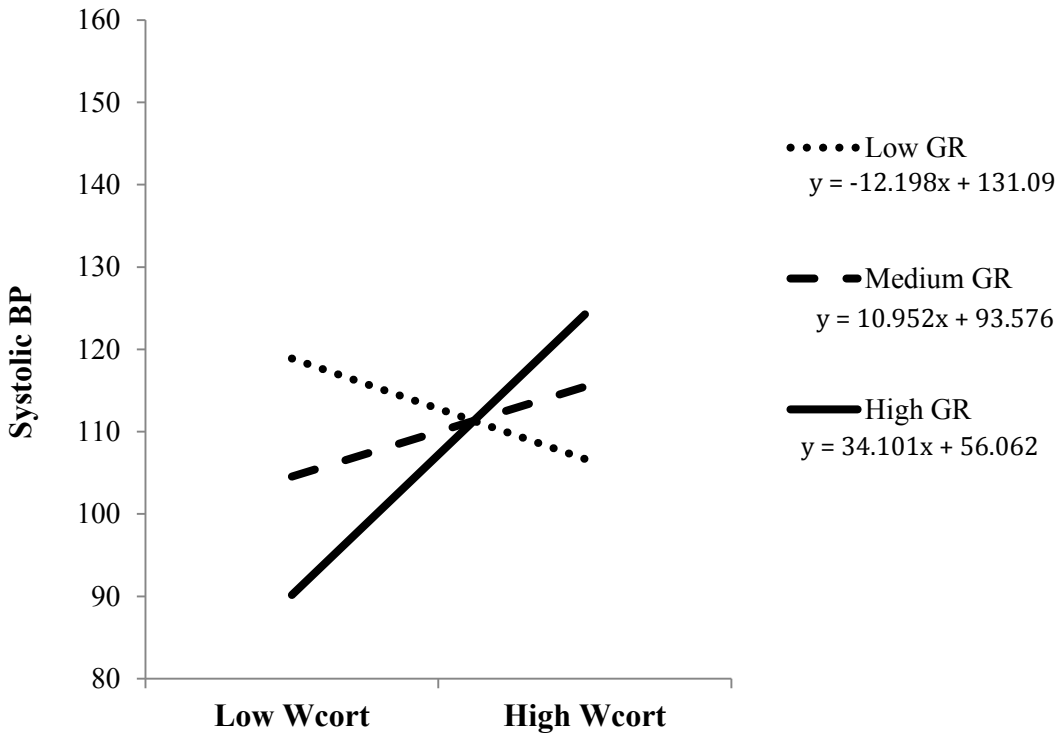


Figure 3.5. Gene-by-waking cortisol interaction predicting systolic blood pressure in the total sample (*b*=4.033, *t*=1.651, *p*=.099), with a two-gene model and a differential susceptibility pattern.

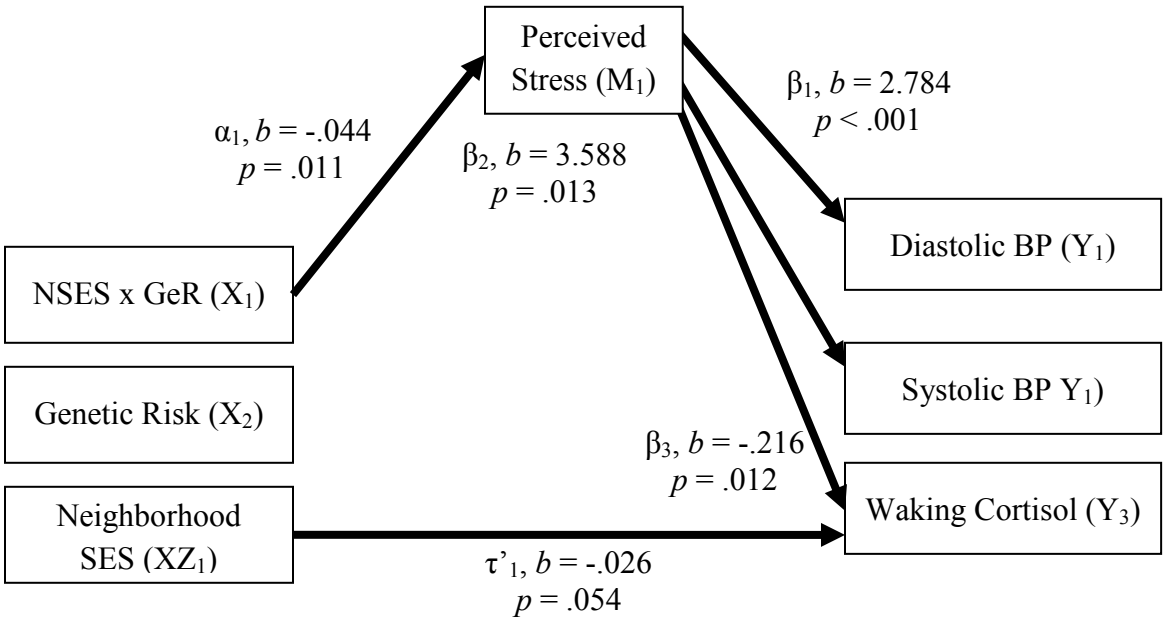


Figure 3.6. Model of relations of GxE risk with perceived stress as a mediator and cortisol and blood pressure as outcomes. Only statistically significant relations are indicated. Mediated effects (αβ) were not significant and are not depicted.

CHAPTER 4

DISCUSSION

4.1 SUMMARY OF FINDINGS

This cross-sectional study investigated relations among environmental stressors, genetic risk, waking cortisol, and blood pressure in African-American adults. Primary and secondary aims focused on detecting gene-by-neighborhood SES and gene-by-cortisol interactions as part of risk- and mechanism-focused models. Results supported hypotheses for some of the direct effects and interactions. In summary, this study found the following: 1) significant direct pathways linking neighborhood SES to waking cortisol, waking cortisol to systolic blood pressure, and perceived stress to waking cortisol and both SBP and DBP; lower neighborhood SES was related to higher waking cortisol, and lower waking cortisol was related to higher BP, 2) trends for GxE effects across SBP, afternoon cortisol, and perceived stress outcomes; a consistent pattern of higher genetic risk was associated with worse outcomes in higher-risk environments, and with better outcomes in lower risk environments, 3) no support for the mediated pathways hypothesized, with no significant indirect effects, and 4) unexpected inverse relations between age and diastolic blood pressure.

4.2 DIRECT EFFECTS AND BIVARIATE RELATIONS

Neighborhood SES, Waking Cortisol and Blood Pressure. Lower

neighborhood SES was related to higher waking cortisol in this study's primary risk model. Regarding the size of the effect, an increase of one standard deviation in neighborhood SES was equivalent to a .14 ng/mL increase in waking cortisol using untransformed data. Put in other words, a neighborhood would need a 24-unit increase in neighborhood SES to relay a one standard deviation decrease in waking cortisol (3.33 ng/mL). This effect size is small but may be clinically meaningful, given that .14 ng/mL is not insubstantial with a mean of 4.16 and 68% of the sample having values ranging from .13 to 4.16. The 24-unit increase in neighborhood SES equates to a 1 SD increase in waking cortisol, and is also meaningful because neighborhood SES values in this study had a range of 36 units (-20.8 – 15.2; Table 3.3). Thus, individuals at the lower end of the neighborhood SES distribution may have waking cortisol values that are a full standard deviation higher than those at the higher end of the SES distribution. It is also worth noting here that this study sample included primarily underserved communities, and the "higher end" of this distribution is therefore relative to a more underserved sample.

While the relation between neighborhood SES and waking cortisol was in the hypothesized direction, its meaning must also be considered relative to other direct effects found in this study. Most salient, it was hypothesized that with an inverse association between neighborhood SES and waking cortisol, there would be a positive association between waking cortisol and BP as part of a potential mechanistic pathway. However, that was not the case, and instead lower waking cortisol was related to higher SBP. This presents a challenge conceptually because it was theorized that if lower SES confers higher cortisol in this study, then higher cortisol should confer higher SBP, rather than lower SBP as was found. However, with mixed findings relating BP and cortisol to

each other, these results are not necessarily inconsistent with the literature (Whitworth et al., 2000; Whitworth et al., 2005), or inconsistent with biomedical models of HPA dysregulation due to chronic stress exposure.

A number of studies have examined relevant direct pathways, and indeed relations have been detected among neighborhood SES, cortisol, and BP in both inverse and positive directions. One multi-ethnic study found that lower compositional SES (education and income) was inversely related to cortisol concentrations as hypothesized, and accounted for 3% of cortisol variance, independent of race (S. Cohen et al., 2006). Another found that survey-assessed material hardship was related to a larger negative slope for diurnal cortisol variation over the day (Ranjit et al., 2005). Inconsistent with the findings of this study, Chen and Paterson found in an ethnically diverse sample (47% African American) that living in a lower SES neighborhoods had lower basal cortisol levels (Chen & Paterson, 2006), however participants were adolescents, and thus the relations of these risk factors may naturally differ from those in adults. Thomas and colleagues found that lower neighborhood SES predicted healthier BP reactivity, with the relation moderated by individual SES (Thomas et al., 2009). Another study found that African-American adults with lower SES had waking cortisol values approximately 4 nmol/L (1.45 ng/mL) lower than higher SES adults, though there was an inverse relation for European American adults (Bennett et al., 2004). Similar results were found in African-American children, with greater neighborhood disorder related to lower waking cortisol levels immediately upon waking, though again the opposite was true for European American children (Dulin-Keita et al., 2012). Citing HPA dysregulation as an explanation for findings in the unexpected direction, a final study found in the Whitehall

II cohort that neighborhood socioeconomic deprivation was related to blunted cortisol reactivity (Barrington et al., 2014). Two distinct studies found that quicker rates of reactivity recovery of cortisol were related to greater neighborhood disadvantage in African-American children (Rudolph et al., 2014), with effects sometimes present for boys only (Hackman et al., 2012).

Findings that are not wholly consist across studies suggest that the relation of cortisol to neighborhood stress is complicated and may vary across demographic groups and measures, but also that previous research has shown both positive and inverse effects to be valid. In particular, the relationship between cortisol and exposure to stressors seems complex due to: 1) the nature of the cortisol measurement (e.g. basal, diurnal, reactivity), 2) measurement of stressors (e.g. perceived, experimentally-induced, neighborhood risk), 3) developmental considerations of the HPA system both long-term and short-term, and in particular when considering dysregulation due to chronic stress or habituation to stressors, and 4) state-specific confounds in measurement of cortisol related to eating, drinking, substance use, physical activity, sleep behaviors, and hormonal factors (e.g. female triphasic menstrual cycle). Indeed, the complexity of the cortisol diurnal rhythm may account for much of the variability in findings linking neighborhood factors to cortisol (Almeida, Piazza, & Stawski, 2009). Additionally, objective (e.g. neighborhood SES) and subjective (e.g. perceived stress) indices of stress may relate to physiology and health outcomes through different, independent mechanisms, and may respectively be subject to different confounds.

Genetic Risk, Cortisol, and Blood Pressure. No direct effects of genetic risk on cortisol or BP outcomes were found. This is not entirely surprising as studies finding

direct effects of GR genes on complex disease such as high BP often investigate a wide array of biomarkers, use experimental designs, or include very large samples (DeRijk & de Kloet, 2005; Manenschijn et al., 2009; Wust et al., 2004), which this study did not do, relatively speaking. Additionally, the premise of the primary aim of this study was that the greatest influence of genetic risk would exist as a function of environmental risk. It is worth noting however that for one of the targeted SNPs, the current sample had a much higher frequency of the G risk allele than that of the general population, 71% compared to approximately 40% (Sherry et al., 2001; Wust et al., 2004).

4.3 GxE INTERACTIONS AND DIFFERENTIAL SUSCEPTIBILITY

The GxE trends found in this study did not show the dual risk pattern that was hypothesized in Figure 1.3. Rather, a differential susceptibility pattern was supported, in which risk alleles are better conceptualized as plasticity alleles, because they relate to both better and worse outcomes given varied environmental exposures.

The slope for individuals with medium risk was less steep, and the slope for individuals with low risk was nearly flat (Figures 3.3 - 3.5). This is consistent with the patterns defined by Belsky, Bakermans-Kranenburg, & van Ijzendoorn (2007), that indicate differential susceptibility. Differential susceptibility theory proposes that individuals carrying a minor allele variation are not only at risk for poorer outcomes in poorer conditions, but that they are also "at risk" for better outcomes in better conditions. The term genetic "risk" is therefore more accurately conceptualized as genetic "susceptibility," "vulnerability," "sensitivity," or "plasticity" (Belsky, Bakermans-Kranenburg, & Van IJzendoorn, 2007; Belsky & Pluess, 2009; Wickrama et al., 2013). Though the term "plasticity" seems most parsimonious and least susceptible to confusion

with other more general concepts, the term "susceptibility" is most often associated with this particular pattern of GxE influence, and will therefore be used herein.

Belsky and colleagues (2007) outline four patterns through which genetic factors may moderate the impact of the environment on health outcomes, including the diathesis-stress or "dual risk" approach, and another which is the differential susceptibility pattern that was in fact found in this study. Consistent with the differential susceptibility model, each pattern in this study demonstrated a cross-over interaction pattern, and the absence of a direct gene effect. These nuances of the GxE interactions provide further support that differential susceptibility is truly represented, rather than dual risk or diathesis-stress (Belsky et al., 2007; Roisman et al., 2012).

GxE Pathways and Perceived Stress. In relation specifically to the GxE findings for perceived stress, it is difficult to determine what the underlying mechanism may be within cross-sectional data. Models indicated that perceived stress was significantly predicted by the GxE neighborhood interaction, with a differential susceptibility pattern. When included as a mediator in the mechanistic model, higher perceived stress was predicted by the GxE interaction, and in turn it was related to higher SBP, with all findings in the expected directions.

Perceived stress has been consistently linked to cardiovascular health outcomes such as high BP (Dressler, 1990a; Hawkley et al., 2006; Lehman et al., 2009; Strogatz et al., 1997), vascular inflammation (Hong et al., 2006), and nocturnal BP dipping (Spruill et al., 2009), and these relations have been demonstrated in African-American populations (Dressler, 1990a; Hawkley et al., 2006; Lehman et al., 2009; Strogatz et al.,

1997). These results therefore add to this literature through incorporation of the genetic and neighborhood susceptibility factors.

It is possible that perceived stress is an indicator of coping-related mediators, such that increased genetic susceptibility would make an individual more prone to stress-related cognitions that are more intense or more frequent, or that are more susceptible to related negative mood and poor coping. This is consistent with Lazarus' stress-appraisal model, in which perceptions of stress mediate the impact of contextual risk on health (Lazarus, 1991). One study did show that high responses on the Perceived Stress Scale were related to higher depression scores, a correlate of distorted cognitions related to adversity, though not to plasma waking cortisol (Salacz, Csukly, Haller, & Valent, 2012). Similarly, another study found links between perceived stress and symptoms of disordered mood, but with neither relating to cortisol (Jasim, Louca, Christidis, & Ernberg, 2014). Underscoring the potential complexities of these relations, one study in breast cancer patients found that depressive symptoms were negatively related to basal cortisol levels but positively related to rate of change in cortisol, and perceived stress was not related to cortisol at all (Saxton et al., 2014). These studies taken together with the present findings provide support for integrating a cognitive component (e.g. perceived stress) in understanding the GxE interactions on health outcomes (Lazarus, 1991).

Findings Relative to the Current Literature. In the past few years there has been increased investigation and reporting on glucocorticoid GxE interactions as they impact stress-related health outcomes (e.g. BMI, post-traumatic stress disorder, suppression of adrenocorticotropin hormone). Few have reported differential susceptibility and the majority have focused on youth samples, with early childhood

adversity most often targeted as environmental risk. While they differ from the present study by their GxE patterns, targeted populations, and focus on developmental rather than ecological/neighborhood factors, they provide invaluable insight for interpretation of the GxE patterns found in this study.

A study of the Bcl1 SNP found that it, but not other glucocorticoid SNPs, moderated the effect of prenatal maternal psychological symptoms on child emotional and behavioral problems in children homozygous for the C allele (Velders et al., 2012). In the current study the G allele was conceptualized as the risk allele because studies in adults have show that it is related to high cholesterol and a trend for higher BP (Di Blasio et al., 2003), HTN status (Watt et al., 1992), increased cortisol response to psychosocial stress (Kumsta et al., 2007; Stevens et al., 2004), and increased abdominal obesity (van Rossum & Lamberts, 2004). However, one study did find a hypo-reactive effect of cortisol to psychosocial stress in a small sample of homozygotes for the G allele, and the authors propose that discrepant findings for GxE effects may result if glucocorticoid SNP affects vary by type of stressor experienced, and the duration of the experience (Wust et al., 2004). As with the relation of neighborhood SES and cortisol, results are mixed and indicated underlying mechanisms that may be more complicated than what can be captured by simple bidirectional risk models.

Recent GxE studies related to glucocorticoid receptor sensitivity in the FKBP5 SNP have focused largely on stress-related mental health disorders. Klengel and colleagues found that the SNP moderated the impact of childhood trauma on adult symptoms of post-traumatic stress disorder, while there was no direct genetic effect (Klengel et al., 2013). Compared to healthy controls, another study reported that

depressed patients with a copy of the T allele had reduced ACTH suppression following dexamethasone administration, indicating HPA dysregulation (Menke et al., 2013). Additionally, these links between FKBP5 and HPA functioning seem to have been confirmed in both humans and rats (Suderman et al., 2012). Finally, another investigation of FKBP5 relative to mental health indicated that individuals with the risk allele, though it is unclear which nucleobase was coded for risk, were more likely to have attempted to commit suicide if they also had high levels of childhood trauma (Roy et al., 2010). Thus, a number of studies have reported GxE effects for the GR SNPs investigated in this study, but a consistent pattern is not evident. It seems a dual risk or diathesis-stress pattern has been assumed, but other mechanisms may be at play (e.g. differential susceptibility) when considering complex findings.

Wickrama and colleagues (2013) report research most relevant to the current study (Wickrama et al., 2013). Their recent study provides initial evidence of significant gene-by-neighborhood effects, as well as evidence of a differential susceptibility pattern, in contrast to a dual-risk. Their study assessed whether dopamine and serotonin receptor SNPs moderated the impact of census-derived community socioeconomic adversity on BMI trajectories. They found that community adversity interacted with genetic factors to predict variable BMI trajectories, with the interaction pattern showing that higher genetic susceptibility and environmental risk was related to worse trajectories, but that lower genetic susceptibility and environmental risk was related to better trajectories. Notably, this pattern was stronger in African-American versus Caucasian adolescents (Wickrama et al., 2013). Similar again to the present study, this study found a GxE interaction effect, in the absence of a direct genetic effect.

Implications for Differential Susceptibility. These results further provide support for a true effect of the glucocorticoid gene-by-neighborhood and gene-by-waking cortisol trends found in the present study, and it is worth noting novel findings. First, the pattern of interactions in the present study was consistent across perceived stress, afternoon cortisol, and blood pressure outcomes ($p<.10$). The pattern indicated a susceptibility or plasticity role for genetics that may ultimately help to explain inconsistent findings across studies, and may be an overall better fit for the complexities of stress-related GxE processes. Second, this study provides the first evidence of a role for FKBP5 beyond mental health outcomes. Given the overlap between HPA processes that contribute to the development of health conditions traditionally categorized as "mental" and "physical," such as anxiety and high blood pressure, it will be important that careful consideration be paid in the future to potential multifinality in genetic susceptibility (i.e. that the same GxE processes may result in varied but related outcomes). Third, this study was one of the first to focus on neighborhood-level environmental risk, whereas most studies investigating differential glucocorticoid gene effects have assessed childhood adversity, or individual-level risk factors. Fourth, this study included an objective measure of neighborhood socioeconomic status as an indicator of chronic contextual stress, as well as subjective measures of the neighborhood context; this seems to be the second study to assess both within a GxE framework, building on the work of Wickrama and colleagues (2013).

Thus, the findings in the present study build uniquely on a small body of work that suggests a more hopeful message, with genetic variation related potentially not just to worse outcomes, but to better outcomes too. As such, this concept challenges

traditional conceptualizations of gene polymorphisms or mutations as being inherently "risk-y" for their human carriers (Belsky et al., 2007). The susceptibility versus risk pattern suggests also that future investigations expand beyond the study of negative outcomes (e.g. HPA dysfunction, higher perceived stress) conferred via stress-related gene-by-environment interactions, and also consider positive outcomes that may develop under more nurturing environmental conditions, such as resilience, or effective coping.

4.4 LIMITATIONS AND CONSIDERATIONS.

Design. Perhaps the greatest limitation of this study is its cross-sectional design paired with single timepoint measures of cortisol and blood pressure outcomes. The cross-sectional design cannot inform causal relations among environmental, physiologic, genetic, and BP factors. Single timepoint measures of BP and cortisol may also be confounded by reactivity and lability, thus not providing a fully accurately measure of basal functioning. Additionally, neuroendocrine regulation of stress hormones in response to the environment is complex, with associations between cortisol and stress sometimes not positive and/or linear due to habituation and chronic dysregulation of the HPA system (Knight et al., 2010; Skinner et al., 2011), or to the unforeseen presence of recent acute stressors.

Though mediation is often tested in cross-sectional study designs, bias in parameter estimates and standard errors are introduced by this approach (Maxwell & Cole, 2007). Maxwell and Cole (2007) note that statistical tests and estimates for mediation are conducted within cross-sectional samples in a majority of studies. Additionally they note that while tests of mediation aim to understand mechanisms of change over time, even studies with access to longitudinal data do not appropriately

match the data to the analyses (Maxwell & Cole, 2007). Thus, conceptually and methodologically "some amount of time must elapse between the cause and its effect," and thus a causal mediation model with a cause (*X*), mediator (*M*), and effect (*Y*) necessitates a minimum of three waves of data. Additionally, Maxwell and Cole note that bias in cross-sectional mediation most often affects the direct effect of X on Y (*c'*), consistent with findings of only a marginal direct effect of neighborhood SES on waking cortisol and relatively stronger predictor-mediator and mediator-outcome effects, in this study. The potential bias in an *X*-*Y* estimate (over- or under-estimation of the presence, magnitude, and direction of the effect) for which the true population value is zero also cannot be known in cross-sectional mediation without assessment of the stability of *X* and *M*.

With causal inferences tenable only when independent variables are manipulated (Holland, 1988), the proposed study design does not allow causal inference, and therefore does not provide true tests of mediation as an indicator of a causal pathway, for the secondary mechanistic aim of this research. The majority of participants who enrolled in this trial were exposed to interventions aiming to influence health behaviors; appropriate statistical strategies were applied to address this issue however, and it should be considered that this cross-sectional design did not target any behaviors in the models.

Finally, limitations related to geographic clustering and generalizing from neighborhood-level risk to individual-level outcomes must be considered relative to known ecological bias. This "ecological fallacy" carries the risk of making inferences about an individual based on data that represent a group (Piantadosi, Byar, & Green, 1988; Schwartz, 1994), and its threat due to the use of spatially-aggregated areal units is

more specifically referred to as the modifiable areal unit problem (Flowerdew, Manley, & Sabel, 2008; Openshaw, 1984). Flowerdew and colleagues (2008) have proposed that studies trying to identify neighborhood effects have used convenient or arbitrary ward or census delineations, and showed that the effects of neighborhood on chronic disease status depends in part on the areal unit selected. In this study, block groups were used as the spatial aggregate, and they were the smallest unit for which the targeted neighborhood socioeconomic data are published by the U.S. Census Bureau, though census block divisions are the smallest defined areal unit (*Urban Area Criteria for the 2010 Census*, 2011). Block groups contain an average or spatial equivalent of 39 blocks across the U.S.

Alternatively however, Schwartz (1994) proposes that the ecological fallacy should be not be used to characterize "crude attempts" to understand individuals using ecological data, but rather as a general validity problem. Specifically, Schwartz challenges three key assumptions that perpetuate the notion of ecological fallacy (that individual-level models are more perfectly specified, that ecological correlations are intended to substitute for individual correlations, and that group-level variables do not cause individual disease), and asserts instead that cross-level inferences be approached with care in any direction. Schwartz notes also that the risks of the ecological fallacy be considered relative to the benefits of understanding systems and context by assessing multiple levels of influence (Schwartz, 1994).

In this study, given that the ecological socioeconomic context was of interest, selection of a smaller unit of ecological analysis (e.g. blocks instead of block groups) may have missed a large potion of the neighborhood context to which a participant was exposed. While this ecological fallacy often refers to situations in which ecological (e.g.

neighborhood-level) data are collected in place of individual-level data as a matter of necessity, in this study, these data were of substantive interest. Nonetheless, the risk of remains to be considered, and future investigations may look not only at ecological risk factors (e.g. neighborhood SES), but also at ecological outcomes (e.g. aggregated neighborhood BP). It is also worth noting that in this study, the majority of block groups (83%), the ecological aggregate from which neighborhood SES was derived, contained only 1-2 participants. Additionally, given the modifiable areal unit problem, future work may consider assessing the effects of neighborhood on health, with neighborhoods measured and related data quantified using more than one areal unit, or may use zone design software to determine the most valid spatial boundaries and then aggregate data.

Measures. The collection of only one morning cortisol sample is a limitation. A higher response rate for the return of waking samples, as well as collection of a greater number of samples throughout the day, across multiple days, would provide the best estimate of the relation of cortisol to gene-environment risk and blood pressure outcomes. This study collected only waking and afternoon samples from participants, though additional samples (1- and 2-hour post-waking) have been collected in a subsample of participants (n>70), as part of an ongoing research program, with the timing based on previous work (Dudgeon et al., 2012). Additional morning samples will allow estimation of the cortisol awakening response (CAR), with variable patterns in cortisol rise and decline over the course of the first few waking hours, and then later in the day, being linked consistently to various health outcomes, including high blood pressure. However, a number of studies have shown that CAR in particular is more unstable than waking cortisol level, relative to daily stressors versus chronic stressors (Maina, Bovenzi,

Palmas, Rossi, & Filon, 2012; Polk, Cohen, Doyle, Skoner, & Kirschbaum, 2005; Stalder, Hucklebridge, Evans, & Clow, 2009; Vreeburg et al., 2009). Collection of a bed-time sample as well would provide a final data point to estimate near-complete diurnal patterns, and collection of all of these samples over the course of multiple days would ensure that CAR estimates are not the result of acute state versus chronic trait HPA functioning. However, for studies limited to 1-day cortisol assessments, there are a number of reasons that a single waking sample may be more appropriate than CAR, in certain populations or when focusing on chronic versus acute stress and disease.

One study which concluded that CAR was more state-dependent than waking or overall diurnal cortisol patterns found that CAR was more strongly linked to day of the week and whether participants were working that day (Maina et al., 2012). These findings would therefore suggest that use of the single waking cortisol measure has advantages for the study of chronic versus acute stressors. Other studies have reported similar findings, with CAR linked to wake time, sleep duration, and season/number of daylight hours (Polk, Cohen, Doyle, Skoner, & Kirschbaum, 2005; Stalder, Hucklebridge, Evans, & Clow, 2009; Vreeburg et al., 2009). For studies assessing acute stressors and outcomes this may be ideal, however for studies assessing more chronic stressors and outcomes, such as neighborhood environment, genetic risk, and high blood pressure, basal or diurnal indicators of cortisol functioning are likely a better fit.

4.5 FUTURE DIRECTIONS

Experimental Exploration and the Social Competence Interview. Given the cross-sectional design of this study, investigation of gene-by-neighborhood stress interactions as they impact cortisol and blood pressure within an experimental design

would greatly supplement these findings. Collection of blood pressure values before, during, and after the introduction of a relevant neighborhood stressor would inform the presence and magnitude of an acute stress response on blood pressure reactivity. Additionally, the genetic susceptibility factors examined in this study may again be investigated as potential moderators of both the reactivity response, as well as perceptions related to the experiencing the stressor. To this end, a small pilot study has been initiated in which adults from the present study also opted to complete an additional experimental study (*N*=19). The Social Competence Interview paradigm was used (Ewart, Jorgensen, Suchday, Chen, & Matthews, 2002), with the stressor manipulation relying on participants to select a chronic stressor and tell of a recent event in which it was problematic, while reliving as many of the feelings, thoughts, and observations of the event that they are able to recall. Confirmation of direct effects of neighborhood impact on cortisol decline pre- and post-stressor, and a direct relation of cortisol to blood pressure trajectory throughout the interview, may supplement findings of direct effects that resulted from this study. Additionally, assessment of variable GxE relations to more acute (Social Competence Interview) or less acute (Perceived Stress Scale) subjective stress experiences may inform potential underlying mechanisms that could not be elucidated based on this cross-sectional study.

Multimorbidities. Over 1 in 4 adults has multiple chronic conditions (hypertension, coronary heart disease, stroke, diabetes, cancer, arthritis, hepatitis, weak or failing kidneys, asthma, and COPD), and also stress-related mental health problems such as depression (Ward, Schiller, & Goodman, 2014; Wolff, Starfield, & Anderson, 2002). However, a recent review of chronic disease randomized controlled trials indicated that

only 2.5% of trials consider multiple chronic conditions, or the whole health of the individual (Jadad, To, Emara, & Jones, 2011). Because chronic conditions not only co-occur but also overlap in their etiologies (e.g. HPA dysfunction), and in what may be indicated for effective treatment (e.g. stress management, physical activity), examining the direct, indirect, and GxE effects on multiple outcomes or on indexed outcomes may be both valid and efficient. Sometimes termed the study of "multimorbidities" or "multiple chronic conditions," investigation of multiple health outcomes is more consistent with bioecological or biopsychosocial approach than the traditional "disease silos," or biomedical model (Ahn et al., 2013; Ory et al., 2013). In the case of high blood pressure, a multimorbidity approach may provide unique insight not only on the potential "ripple effect" of effective hypertension management to other chronic diseases (Wilson, 2014), but also on disease-disease interactions that may be impacted by neighborhood stress and genetic susceptibility factors. For example, it is possible that the GxE impact on perceived stress influences physical activity, which then influences weight as an obesity-related outcome, which then has a positive impact on BP; such relations likely will not be detected with focus on a single chronic condition.

4.6 IMPLICATIONS AND PUBLIC HEALTH SIGNIFICANCE

This study aimed to provide a more comprehensive, bioecological understanding of associations among stress-related neighborhood risk factors, genetic susceptibility, stress-induced physiologic processes, and cardiovascular outcomes in African American adults. Findings that neighborhood SES, which falls within the more distal outer ring of the bioecological framework, related to waking cortisol at the innermost, individual point of the framework, provides confirmation that traditional biomedical approaches miss

much of the story, as well as potential opportunities for public health intervention. Findings that neighborhood SES may further influence health through a gene interaction that relates to an individual's perceived stress further underscores the importance of a comprehensive approach. Neighborhood factors may be amenable to intervention and can be targeted to facilitate progress in public health (Adler & Newman, 2002), consistent with the *Healthy People 2020* initiative under the U.S. Department of Health and Human Services (Koh, 2010; U.S. Department of Health and Human Services, 2011).

Using a bioecological framework, the findings from this interdisciplinary study contribute to an increased understanding of how neighborhood and genetic risk and susceptibility factors potentially impact HPA functioning and cardiovascular health, in a novel sample of African-American adults. Moreover, investigation of potential interactions among these factors may build upon a growing knowledge of cardiometabolic health, and provide a better understanding of how underserved and high-stress environments negatively impact public health and health equity (Blakemore & Froguel, 2010; Fister, Vuletic, & Kern, 2012). Specific opportunities for prevention and intervention may ultimately include 1) broadening the perspective through which behaviorally-based approaches to personalized medicine may be responsibly implemented, 2) integrating common disease risk assessment into clinical practice, using genome sequencing technologies, and 3) advocating for public policy intervention based on increased risk experienced by African American adults (Meisel, Walker, & Wardle, 2012; Salari, Watkins, & Ashley, 2012). Thus, significant scientific and policy implications may result from a better understanding of GxE interactions as they influence

health in at-risk populations, and findings from this work may promote progress in attenuating cardiovascular health disparity experienced by African-American adults.

REFERENCES

Acock, A. C. (2005). Working with missing values. *Journal of Marriage and Family, 67*(4), 1012-1028.

Adler, N. E., Boyce, T., Chesney, M., Cohen, S., Folkman, S., Kahn, R., & Syme, S. (1994). Socioeconomic status and health: The challenge of the gradient. *American Psychologist, 49*(1), 15-24.

Adler, N. E., & Newman, K. (2002). Socioeconomic disparities in health: pathways and policies. *Health Aff (Millwood), 21*(2), 60-76.

Adler, N. E., & Ostrove, J. M. (1999). Socioeconomic status and health: what we know and what we don't. *Ann N Y Acad Sci, 896*, 3-15.

Ahn, S., Basu, R., Smith, M. L., Jiang, L., Lorig, K., Whitelaw, N., & Ory, M. G. (2013). The impact of chronic disease self-management programs: healthcare savings through a community-based intervention. *BMC Public Health, 13*, 1141. doi: 10.1186/1471-2458-13-1141

Aiken, L., West, S., & Reno, R. (1991). *Multiple regression: Testing and interpreting interactions*: Sage Publications, Inc.

Almeida, D. M., Piazza, J. R., & Stawski, R. S. (2009). Interindividual differences and intraindividual variability in the cortisol awakening response: an examination of age and gender. *Psychol Aging, 24*(4), 819-827. doi: 10.1037/a0017910

Anderson, N. B. (1989). Racial differences in stress-induced cardiovascular reactivity and hypertension: current status and substantive issues. *Psychol Bull, 105*(1), 89-105.

Anderson, N. B. (1998). Levels of analysis in health science. A framework for integrating sociobehavioral and biomedical research. *Ann N Y Acad Sci, 840*, 563-576.

Anderson, N. B., & Armstead, C. A. (1995). Toward understanding the association of socioeconomic status and health: a new challenge for the biopsychosocial approach. *Psychosom Med, 57*(3), 213-225.

Andresen, E. M., & Miller, D. K. (2005). The future (history) of socioeconomic measurement and implications for improving health outcomes among African Americans. *J Gerontol A Biol Sci Med Sci, 60*(10), 1345-1350. doi: 60/10/1345 [pii]

Anisman, H., Griffiths, J., Matheson, K., Ravindran, A. V., & Merali, Z. (2001). Posttraumatic stress symptoms and salivary cortisol levels. *Am J Psychiatry, 158*(9), 1509-1511.

Arnett, D., Baird, A., Barkley, R., Basson, C., Boerwinkle, E., Ganesh, S., . . . McDermott, D. (2007). Relevance of genetics and genomics for prevention and treatment of cardiovascular disease: a scientific statement from the American Heart Association Council on Epidemiology and Prevention, the Stroke Council, and the Functional Genomics and Translational Biology Interdisciplinary Working Group. *Circulation, 115*(22), 2878.

Bandura, A. (2000). Exercise of human agency through collective efficacy. *Current Directions in Psychological Science, 9*(3), 75.

Barrington, W. E., Stafford, M., Hamer, M., Beresford, S. A., Koepsell, T., & Steptoe, A. (2014). Neighborhood socioeconomic deprivation, perceived neighborhood factors, and cortisol responses to induced stress among healthy adults. *Health Place, 27*, 120-126. doi: 10.1016/j.healthplace.2014.02.001

Belsky, J., Bakermans-Kranenburg, M. J., & Van IJzendoorn, M. H. (2007). For better and for worse differential susceptibility to environmental influences. *Current Directions in Psychological Science, 16*(6), 300-304.

Belsky, J., & Pluess, M. (2009). Beyond diathesis stress: differential susceptibility to environmental influences. *Psychol Bull, 135*(6), 885-908. doi: 2009-19763-005 [pii]10.1037/a0017376

Bennett, G. G., Merritt, M. M., & Wolin, K. Y. (2004). Ethnicity, education, and the cortisol response to awakening: a preliminary investigation. *Ethn Health, 9*(4), 337-347. doi: 10.1080/1355785042000285366

Binder, E. B. (2009). The role of FKBP5, a co-chaperone of the glucocorticoid receptor in the pathogenesis and therapy of affective and anxiety disorders. *Psychoneuroendocrinology, 34 Suppl 1*, S186-195. doi: S0306-4530(09)00185-1 [pii]10.1016/j.psyneuen.2009.05.021

Binder, E. B., Bradley, R. G., Liu, W., Epstein, M. P., Deveau, T. C., Mercer, K. B., . . . Ressler, K. J. (2008). Association of FKBP5 polymorphisms and childhood abuse with risk of posttraumatic stress disorder symptoms in adults. *JAMA, 299*(11), 1291-1305. doi: 299/11/1291 [pii]10.1001/jama.299.11.1291

Blakemore, A. I., & Froguel, P. (2010). Investigation of Mendelian forms of obesity holds out the prospect of personalized medicine. *Ann N Y Acad Sci, 1214*, 180-189. doi: 10.1111/j.1749-6632.2010.05880.x

Borrell, L. N., Diez Roux, A. V., Rose, K., Catellier, D., & Clark, B. L. (2004). Neighbourhood characteristics and mortality in the Atherosclerosis Risk in Communities Study. *Int J Epidemiol, 33*(2), 398-407. doi: 10.1093/ije/dyh063

Bronfenbrenner, U. (1979). The Ecology of Human DevelopmentCambridge. *MA: Harvard*.

Bronfenbrenner, U. (2005). The Bioecological Theory of Human Development (2001).

Calhoun, D., Jones, D., Textor, S., Goff, D., Murphy, T., Toto, R., . . . Sica, D. (2008). Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. *Circulation, 117*(25), e510.

Cardiology, S. (1995). Implications of small reductions in diastolic blood pressure for primary prevention. *Arch Intern Med, 155*, 701.

Cerin, E., Conway, T. L., Saelens, B. E., Frank, L. D., & Sallis, J. F. (2009). Cross-validation of the factorial structure of the Neighborhood Environment Walkability Scale (NEWS) and its abbreviated form (NEWS-A). *Int J Behav Nutr Phys Act, 6*, 32. doi: 1479-5868-6-32 [pii]10.1186/1479-5868-6-32

Champaneri, S., Xu, X., Carnethon, M. R., Bertoni, A. G., Seeman, T., DeSantis, A. S., . . . Golden, S. H. (2013). Diurnal salivary cortisol is associated with body mass index and waist circumference: the Multiethnic Study of Atherosclerosis. *Obesity (Silver Spring), 21*(1), E56-63. doi: 10.1002/oby.20047

Chen, E., & Paterson, L. (2006). Neighborhood, family, and subjective socioeconomic status: How do they relate to adolescent health? *Health psychology, 25*(6), 704-714.

Chobanian, A., Bakris, G., Black, H., Cushman, W., Green, L., Izzo Jr, J., . . . Wright Jr, J. (2003). Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension, 42*(6), 1206.

Chung, C., Shimmin, L., Natarajan, S., Hanis, C., Boerwinkle, E., & Hixson, J. (2008). Glucocorticoid receptor gene variant in the 3'untranslated region is associated with multiple measures of blood pressure. *Journal of Clinical Endocrinology & Metabolism*.

Clark, R., Anderson, N. B., Clark, V. R., & Williams, D. R. (1999). Racism as a stressor for African Americans: A biopsychosocial model. *American Psychologist, 54*(10), 805.

Cohen, D. A., Inagami, S., & Finch, B. (2008). The built environment and collective efficacy. *Health Place, 14*(2), 198-208. doi: S1353-8292(07)00051-2 [pii]10.1016/j.healthplace.2007.06.001

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences*: Lawrence Erlbaum.

Cohen, J., Cohen, P., West, S., & Aiken, L. (2003). *Applied multiple regression/correlation analysis for the behavioral sciences* (3rd ed.). Mahwah, New Jersey: Lawrence Erlbaum Associates.

Cohen, S., Doyle, W., & Baum, A. (2006). Socioeconomic status is associated with stress hormones. *Psychosom Med, 68*(3), 414-420. doi: 10.1097/01.psy.0000221236.37158.b9

Cohen, S., Kamarck, T., & Mermelstein, R. (1983). A global measure of perceived stress. *Journal of health and social behavior, 24*(4), 385-396.

Constanti, A. (1998). *Basic endocrinology for students of pharmacy and allied health sciences*: CRC Press.

Coulon, S., Wilson, D., Griffin, S., St George, S., Alia, K., Trumpeter, N., . . . Gadson, B. (2012). Formative Process Evaluation for Implementing a Social Marketing Intervention to Increase Walking Among African Americans in the Positive Action for Today's Health Trial. *Am J Public Health, 102*(12), 2315-2321. doi: 10.2105/AJPH.2012.300758

Coulon, S., Wilson, D., St. George, S., Trumpeter, N., Acenbrak, A., Lopez, M., & Egan, B. (2011). *Associations of Social-Environmental Factors with Hypertension and Blood Pressure in Underserved African Americans in the Positive Action for Today's Health (PATH) Trial* Paper presented at the Society of Behavioral Medicine, Washington D.C.

Cox, A., McKevitt, C., Rudd, A., & Wolfe, C. (2006). Socioeconomic status and stroke. *The Lancet Neurology, 5*(2), 181-188.

Cubbin, C., Hadden, W. C., & Winkleby, M. A. (2001). Neighborhood context and cardiovascular disease risk factors: the contribution of material deprivation. *Ethn Dis, 11*(4), 687-700.

Cutler, J., Sorlie, P., Wolz, M., Thom, T., Fields, L., & Roccella, E. (2008). Trends in hypertension prevalence, awareness, treatment, and control rates in United States adults between 1988-1994 and 1999-2004. *Hypertension*.

DeRijk, R., & de Kloet, E. (2005). Corticosteroid receptor genetic polymorphisms and stress responsivity. *Endocrine, 28*(3), 263-269.

Di Blasio, A., van Rossum, E., Maestrini, S., Berselli, M., Tagliaferri, M., Podestà, F., . . . Lamberts, S. (2003). The relation between two polymorphisms in the glucocorticoid receptor gene and body mass index, blood pressure and cholesterol in obese patients. *Clinical endocrinology, 59*(1), 68-74.

Diez Roux, A. V., Borrell, L. N., Haan, M., Jackson, S. A., & Schultz, R. (2004). Neighbourhood environments and mortality in an elderly cohort: results from the cardiovascular health study. *J Epidemiol Community Health, 58*(11), 917-923. doi: 10.1136/jech.2003.019596

Diez Roux, A. V., Chambless, L., Merkin, S., Arnett, D., Eigenbrodt, M., Nieto, F., . . . Sorlie, P. (2002a). Socioeconomic disadvantage and change in blood pressure associated with aging. *Circulation*, 10000025.

Diez Roux, A. V., Chambless, L., Merkin, S. S., Arnett, D., Eigenbrodt, M., Nieto, F. J., . . . Sorlie, P. (2002b). Socioeconomic disadvantage and change in blood pressure associated with aging. *Circulation, 106*(6), 703-710.

Diez-Roux, A. V., Kiefe, C. I., Jacobs, D. R., Jr., Haan, M., Jackson, S. A., Nieto, F. J., . . . Schulz, R. (2001). Area characteristics and individual-level socioeconomic position indicators in three population-based epidemiologic studies. *Ann Epidemiol, 11*(6), 395-405.

Dockray, S., Bhattacharyya, M. R., Molloy, G. J., & Steptoe, A. (2008). The cortisol awakening response in relation to objective and subjective measures of waking in the morning. *Psychoneuroendocrinology, 33*(1), 77-82. doi: S0306-4530(07)00219-3 [pii]10.1016/j.psyneuen.2007.10.001

Dowd, J., Simanek, A., & Aiello, A. (2009). Socio-economic status, cortisol and allostatic load: a review of the literature. *Int J Epidemiol*.

Dressler, W. W. (1990a). Lifestyle, stress, and blood pressure in a southern black community. *Psychosomatic medicine, 52*(2), 182.

Dressler, W. W. (1990b). Lifestyle, stress, and blood pressure in a southern black community. *Psychosom Med, 52*(2), 182-198.

Dudgeon, W. D., Jaggers, J. R., Phillips, K. D., Durstine, J. L., Burgess, S. E., Lyerly, G. W., . . . Hand, G. A. (2012). Moderate-Intensity Exercise Improves Body Composition and Improves Physiological Markers of Stress in HIV-Infected Men. *ISRN AIDS, 2012*, 145127. doi: 10.5402/2012/145127

Dulin-Keita, A., Casazza, K., Fernandez, J. R., Goran, M. I., & Gower, B. (2012). Do neighbourhoods matter? Neighbourhood disorder and long-term trends in serum cortisol levels. *J Epidemiol Community Health, 66*(1), 24-29. doi: jech.2009.092676 [pii]10.1136/jech.2009.092676

Duncan, T. E., Duncan, S. C., Okut, H., Strycker, L. A., & Hix-Small, H. (2003). A multilevel contextual model of neighborhood collective efficacy. *Am J Community Psychol, 32*(3-4), 245-252.

Enders, C., & Bandalos, D. (2001). The relative performance of full information maximum likelihood estimation for missing data in structural equation models. *Structural Equation Modeling: A Multidisciplinary Journal, 8*(3), 430-457.

Epel, E. S., McEwen, B., Seeman, T., Matthews, K., Castellazzo, G., Brownell, K. D., . . . Ickovics, J. R. (2000). Stress and body shape: stress-induced cortisol secretion is consistently greater among women with central fat. *Psychosom Med, 62*(5), 623-632.

Ewart, C. K., Jorgensen, R. S., Suchday, S., Chen, E., & Matthews, K. A. (2002). Measuring stress resilience and coping in vulnerable youth: the Social Competence Interview. *Psychol Assess, 14*(3), 339-352.

Fairchild, A., & MacKinnon, D. (2009). A general model for testing mediation and moderation effects. *Prevention Science, 10*(2), 87-99.

Fairchild, A., & McQuillin, S. (2009). Evaluating mediation and moderation effects in school psychology: A presentation of methods and review of current practice. *Journal of School Psychology*.

Fister, K., Vuletic, S., & Kern, J. (2012). Paving the way for personalised behaviourally based prevention of obesity: systematic search of the literature. *Coll Antropol, 36 Suppl 1*, 201-210.

Flowerdew, R., Manley, D. J., & Sabel, C. E. (2008). Neighbourhood effects on health: does it matter where you draw the boundaries? *Soc Sci Med, 66*(6), 1241-1255. doi: 10.1016/j.socscimed.2007.11.042

Ford, E., Li, C., Zhao, G., Pearson, W., & Capewell, S. (2009). Trends in the prevalence of low risk factor burden for cardiovascular disease among United States adults. *Circulation*.

Franks, P. (2008). Identifying genes for primary hypertension: methodological limitations and gene–environment interactions. *Journal of human hypertension, 23*(4), 227-237.

Fraser, R., Davies, D., & McConnell, J. (1989). Hormones and hypertension. *Clinical endocrinology, 31*(6), 701-746.

Gadegbeku, C., Lea, J., & Jamerson, K. (2005). Update on disparities in the pathophysiology and management of hypertension: focus on African Americans. *The Medical clinics of North America, 89*(5).

Gasperin, D., Netuveli, G., Dias-da-Costa, J., & Pattussi, M. (2009). Effect of psychological stress on blood pressure increase: a meta-analysis of cohort studies. *Cadernos de Saúde Pública, 25*, 715-726.

Genomes Project, C., Abecasis, G. R., Altshuler, D., Auton, A., Brooks, L. D., Durbin, R. M., . . . McVean, G. A. (2010). A map of human genome variation from population-scale sequencing. *Nature, 467*(7319), 1061-1073. doi: 10.1038/nature09534

Gill, J., Vythilingam, M., & Page, G. G. (2008). Low cortisol, high DHEA, and high levels of stimulated TNF-alpha, and IL-6 in women with PTSD. *J Trauma Stress, 21*(6), 530-539. doi: 10.1002/jts.20372

Godfrey, K. M., Strachan, E., Dansie, E., Crofford, L. J., Buchwald, D., Goldberg, J., . . . Afari, N. (2014). Salivary cortisol and cold pain sensitivity in female twins. *Ann Behav Med, 47*(2), 180-188. doi: 10.1007/s12160-013-9532-4

Green, T., & Darity Jr, W. (2010). Under the Skin: Using Theories From Biology and the Social Sciences to Explore the Mechanisms Behind the Black-White Health Gap. *Am J Public Health, 100*(S1), S36.

Gunnar, M., & Vazquez, D. (2006). Stress neurobiology and developmental psychopathology. *Developmental psychopathology, 2*, 533–577.

Hackman, D. A., Betancourt, L. M., Brodsky, N. L., Hurt, H., & Farah, M. J. (2012). Neighborhood disadvantage and adolescent stress reactivity. *Frontiers in human neuroscience, 6*.

Hankin, B. L., & Abela, J. R. (2005). *Development of psychopathology: A vulnerability-stress perspective*: Sage Publications.

Hawkley, L., Masi, C., Berry, J., & Cacioppo, J. (2006). Loneliness is a unique predictor of age-related differences in systolic blood pressure. *Psychol Aging, 21*(1), 152.

Hay, I. D., & John AH Wass (Eds.). (2009). *Clinical Endocrine Oncology*: John Wiley & Sons.

Hayman, L., & Hughes, S. (2006). Progress in Prevention: Prevention of Cardiovascular Disease A Life Course Ecological Perspective. *Journal of Cardiovascular Nursing, 21*(6), 500.

Heinrichs, M., Baumgartner, T., Kirschbaum, C., & Ehlert, U. (2003). Social support and oxytocin interact to suppress cortisol and subjective responses to psychosocial stress. *interactions, 54*, 1389-1398.

Holland, P. W. (1988). Causal inference, path analysis, and recursive structural equations models. *Sociological methodology*, 449-484.

Hong, S., Nelesen, R., Krohn, P., Mills, P., & Dimsdale, J. (2006). The association of social status and blood pressure with markers of vascular inflammation. *Psychosomatic medicine, 68*(4), 517.

Hu, L., & Bentler, P. M. (1998). Fit indices in covariance structure modeling: Sensitivity to underparameterized model misspecification. *Psychological methods, 3*(4), 424.

Iacobucci, D., Saldanha, N., & Deng, X. (2007). A meditation on mediation: Evidence that structural equations models perform better than regressions. *Journal of Consumer Psychology, 17*(2), 139.

Imumorin, I., Dong, Y., Zhu, H., Poole, J., Harshfield, G., Treiber, F., & Snieder, H. (2005). A gene-environment interaction model of stress-induced hypertension. *Cardiovascular Toxicology, 5*(2), 109-132.

Ingram, R. E., & Luxton, D. D. (2005). Vulnerability-stress models. *Development of psychopathology: A vulnerability-stress perspective*, 32-46.

Ising, M., Depping, A. M., Siebertz, A., Lucae, S., Unschuld, P. G., Kloiber, S., . . . Holsboer, F. (2008). Polymorphisms in the FKBP5 gene region modulate recovery from psychosocial stress in healthy controls. *Eur J Neurosci, 28*(2), 389-398. doi: EJN6332 [pii]10.1111/j.1460-9568.2008.06332.x

Jadad, A. R., To, M. J., Emara, M., & Jones, J. (2011). Consideration of multiple chronic diseases in randomized controlled trials. *JAMA, 306*(24), 2670-2672. doi: 10.1001/jama.2011.1886

James, S. (1987). Psychosocial precursors of hypertension: a review of the epidemiologic evidence. *Circulation, 76*(1 Pt 2), I60.

Jasim, H., Louca, S., Christidis, N., & Ernberg, M. (2014). Salivary cortisol and psychological factors in women with chronic and acute oro-facial pain. *J Oral Rehabil, 41*(2), 122-132. doi: 10.1111/joor.12118

Johnson, K. W., Anderson, N. B., Bastida, E., Kramer, B. J., Williams, D., & Wong, M. (1995). Macrosocial and environmental influences on minority health. *Health Psychol, 14*(7), 601-612.

Jones-Webb, R., Yu, X., O'Brien, J., Hannan, P., Wall, M., & Oswald, J. (2004). Does socioeconomic position moderate the effects of race on cardiovascular disease mortality? *Ethn Dis, 14*(4), 489-496.

Kajantie, E., Feldt, K., Raikkonen, K., Phillips, D., Osmond, C., Heinonen, K., . . . Eriksson, J. (2007). Body size at birth predicts hypothalamic-pituitary-adrenal axis response to psychosocial stress at age 60 to 70 years. *Journal of Clinical Endocrinology & Metabolism, 92*(11), 4094.

Kapuku, G., Treiber, F. A., & Davis, H. C. (2002). Relationships among socioeconomic status, stress induced changes in cortisol, and blood pressure in African American males. *Ann Behav Med, 24*(4), 320-325.

Kelly, J., Mangos, G., Williamson, P., & Whitworth, J. (1998). Cortisol and hypertension. *Clinical and Experimental Pharmacology and Physiology, 25*(S1), S51-S56.

Kenny, D. A. (2011, September 4, 2011). Measuring Model Fit. Retrieved March 11, 2012, 2012, from http://davidakenny.net/cm/fit.htm

Kenny, D. A., & McCoach, D. B. (2003). Effect of the number of variables on measures of fit in structural equation modeling. *Structural Equation Modeling, 10*(3), 333-351.

King, S. L., & Hegadoren, K. M. (2002). Stress hormones: how do they measure up? *Biol Res Nurs, 4*(2), 92-103.

Kirchheiner, J., Lorch, R., Lebedeva, E., Seeringer, A., Roots, I., Sasse, J., & Brockmoller, J. (2008). Genetic variants in FKBP5 affecting response to antidepressant drug treatment. *Pharmacogenomics, 9*(7), 841-846. doi: 10.2217/14622416.9.7.841

Klengel, T., Mehta, D., Anacker, C., Rex-Haffner, M., Pruessner, J. C., Pariante, C. M., . . . Binder, E. B. (2013). Allele-specific FKBP5 DNA demethylation mediates gene-childhood trauma interactions. *Nat Neurosci, 16*(1), 33-41. doi: 10.1038/nn.3275

Knight, J. M., Avery, E. F., Janssen, I., & Powell, L. H. (2010). Cortisol and depressive symptoms in a population-based cohort of midlife women. *Psychosom Med, 72*(9), 855-861. doi: PSY.0b013e3181f4ab87 [pii]10.1097/PSY.0b013e3181f4ab87

Koh, H. K. (2010). A 2020 vision for healthy people. *N Engl J Med, 362*(18), 1653-1656. doi: 362/18/1653 [pii]10.1056/NEJMp1001601

Kruger, D. J., Reischl, T. M., & Gee, G. C. (2007). Neighborhood social conditions mediate the association between physical deterioration and mental health. *Am J Community Psychol, 40*(3-4), 261-271. doi: 10.1007/s10464-007-9139-7

Kumari, M., Badrick, E., Chandola, T., Adler, N. E., Epel, E., Seeman, T., . . . Marmot, M. G. (2010). Measures of Social Position and Cortisol Secretion in an Aging Population: Findings From the Whitehall II Study. *Psychosomatic medicine, 72*(1), 27.

Kumari, M., Chandola, T., Brunner, E., & Kivimaki, M. (2010). A nonlinear relationship of generalized and central obesity with diurnal cortisol secretion in the Whitehall II study. *J Clin Endocrinol Metab, 95*(9), 4415-4423. doi: jc.2009-2105 [pii]10.1210/jc.2009-2105

Kumsta, R., Entringer, S., Koper, J., van Rossum, E., Hellhammer, D., & Wüst, S. (2007). Sex specific associations between common glucocorticoid receptor gene variants and hypothalamus-pituitary-adrenal axis responses to psychosocial stress. *Biological psychiatry, 62*(8), 863-869.

Kumsta, R., Moser, D., Streit, F., Koper, J., Meyer, J., & Wüst, S. (2009). Characterization of a glucocorticoid receptor gene (GR, NR3C1) promoter polymorphism reveals functionality and extends a haplotype with putative clinical relevance. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 150*(4), 476-482.

Kuzawa, C., & Sweet, E. (2009). Epigenetics and the embodiment of race: developmental origins of US racial disparities in cardiovascular health. *American Journal of Human Biology, 21*(1), 2-15.

LaVeist, T. (2005). Disentangling race and socioeconomic status: a key to understanding health inequalities. *Journal of Urban Health, 82*.

Lawson, A., Ellerbe, C., Carroll, R., Alia, K., Coulon, S., Wilson, D., . . . St. George, S. (2014). Bayesian latent structure modeling of walking behavior in a physical activity intervention. *Stat Methods Med Res*. doi: 10.1177/0962280214529932

Lazarus, R. S. (1991). Progress on a cognitive-motivational-relational theory of emotion. *Am Psychol, 46*(8), 819-834.

Lehman, B., Taylor, S., Kiefe, C., & Seeman, T. (2009). Relationship of early life stress and psychological functioning to blood pressure in the CARDIA study. *Health Psychol, 28*(3), 338-346.

Levine, A., Zagoory-Sharon, O., Feldman, R., Lewis, J., & Weller, A. (2007). Measuring cortisol in human psychobiological studies. *Physiology & behavior, 90*(1), 43-53.

Levy, D., DeStefano, A., Larson, M., O'Donnell, C., Lifton, R., Gavras, H., . . . Myers, R. (2000). Evidence for a gene influencing blood pressure on chromosome 17: genome scan linkage results for longitudinal blood pressure phenotypes in subjects from the Framingham Heart Study. *Hypertension, 36*(4), 477.

Linden, W., & Moseley, J. (2006). The efficacy of behavioral treatments for hypertension. *Applied psychophysiology and biofeedback, 31*(1), 51-63.

Lloyd-Jones, D., Adams, R., Brown, T., Carnethon, M., Dai, S., De Simone, G., . . . Gillespie, C. (2009). Heart disease and stroke statistics--2010 update. A report from the American Heart Association. *Circulation*.

Luan, J., Wong, M., Day, N., & Wareham, N. (2001). Sample size determination for studies of gene-environment interaction. *Int J Epidemiol, 30*(5), 1035.

MacKinnon, D. (2008). *Introduction to statistical mediation analysis*: Erlbaum Psych Press.

MacKinnon, D., Lockwood, C., Hoffman, J., West, S., & Sheets, V. (2002). A comparison of methods to test mediation and other intervening variable effects. *Psychological methods, 7*(1), 83-104.

MacKinnon, D., & Luecken, L. (2008). How and for whom? Mediation and moderation in health psychology. *Health psychology, 27*(2), S99-S100.

Magiakou, M., Smyrnaki, P., & Chrousos, G. (2006). Hypertension in Cushing's syndrome. *Best Practice & Research Clinical Endocrinology & Metabolism, 20*(3), 467-482.

Maina, G., Bovenzi, M., Palmas, A., Rossi, F., & Filon, F. L. (2012). Psychosocial environment and health: methodological variability of the salivary cortisol measurements. *Toxicol Lett, 213*(1), 21-26. doi: 10.1016/j.toxlet.2011.08.019

Manenschijn, L., van den Akker, E., Lamberts, S., & van Rossum, E. (2009). Clinical features associated with glucocorticoid receptor polymorphisms. *Ann N Y Acad Sci, 1179*(Glucocorticoids and Mood Clinical Manifestations, Risk Factors, and Molecular Mechanisms), 179-198.

Masi, C., Rickett, E., Hawkley, L., & Cacioppo, J. (2004). Gender and ethnic differences in urinary stress hormones: the population-based Chicago Health, Aging, and Social Relations Study. *Journal of applied physiology, 97*(3), 941.

Matthews, K. A., & Gallo, L. C. (2011). Psychological perspectives on pathways linking socioeconomic status and physical health. *Annu Rev Psychol, 62*, 501-530. doi: 10.1146/annurev.psych.031809.130711

Matthews, K. A., Gallo, L. C., & Taylor, S. E. (2010). Are psychosocial factors mediators of socioeconomic status and health connections? A progress report and blueprint

for the future. *Ann N Y Acad Sci, 1186*, 146-173. doi: NYAS5332 [pii]10.1111/j.1749-6632.2009.05332.x

Matthews, K. A., Schwartz, J., Cohen, S., & Seeman, T. (2006). Diurnal cortisol decline is related to coronary calcification: CARDIA study. *Psychosomatic medicine, 68*(5), 657.

Maxwell, S. E., & Cole, D. A. (2007). Bias in cross-sectional analyses of longitudinal mediation. *Psychol Methods, 12*(1), 23-44. doi: 2007-03329-002 [pii]10.1037/1082-989X.12.1.23

McMillan, D. W., & Chavis, D. M. (1986). Sense of community: A definition and theory. *Journal of community psychology, 14*(1), 6-23.

Meisel, S. F., Walker, C., & Wardle, J. (2012). Psychological responses to genetic testing for weight gain: a vignette study. *Obesity (Silver Spring), 20*(3), 540-546. doi: 10.1038/oby.2011.324

Melcescu, E., Griswold, M., Xiang, L., Belk, S., Montgomery, D., Bray, M., . . . Koch, C. A. (2012). Prevalence and cardiometabolic associations of the glucocorticoid receptor gene polymorphisms N363S and BclI in obese and non-obese black and white Mississippians. *Hormones (Athens), 11*(2), 166-177.

Menke, A., Klengel, T., Rubel, J., Bruckl, T., Pfister, H., Lucae, S., . . . Binder, E. B. (2013). Genetic variation in FKBP5 associated with the extent of stress hormone dysregulation in major depression. *Genes Brain Behav, 12*(3), 289-296. doi: 10.1111/gbb.12026

Merlo, J., Ostergren, P. O., Hagberg, O., Lindstrom, M., Lindgren, A., Melander, A., . . . Berglund, G. (2001). Diastolic blood pressure and area of residence: multilevel

versus ecological analysis of social inequity. *J Epidemiol Community Health, 55*(11), 791-798.

Minor, D., Wofford, M., & Jones, D. (2008). Racial and ethnic differences in hypertension. *Current atherosclerosis reports, 10*(2), 121-127.

Mizuno, T., Aoki, M., Shimada, Y., Inoue, M., Nakaya, K., Takahashi, T., . . . Endo, Y. (2006). Gender difference in association between polymorphism of serotonin transporter gene regulatory region and anxiety. *Journal of psychosomatic research, 60*(1), 91-97.

Morenoff, J., House, J., Hansen, B., Williams, D., Kaplan, G., & Hunte, H. (2007). Understanding social disparities in hypertension prevalence, awareness, treatment, and control: the role of neighborhood context. *Soc Sci Med, 65*(9), 1853-1866.

Morris, K. S., McAuley, E., & Motl, R. W. (2008). Neighborhood satisfaction, functional limitations, and self-efficacy influences on physical activity in older women. *Int J Behav Nutr Phys Act, 5*, 13. doi: 1479-5868-5-13 [pii]10.1186/1479-5868-5-13

Nilsson, P., Klasson, E., & Nyberg, P. (2001). Life-style intervention at the worksite-reduction of cardiovascular risk factors in a randomized study. *Scandinavian Journal of Work Environment and Health, 27*(1), 57-62.

Ofili, E. (2001). Ethnic disparities in cardiovascular health. *Ethnicity & disease, 11*(4), 838.

Openshaw, S. (1984). Ecological fallacies and the analysis of areal census data. *Environ Plan A, 16*(1), 17-31.

Ory, M. G., Ahn, S., Jiang, L., Smith, M. L., Ritter, P. L., Whitelaw, N., & Lorig, K. (2013). Successes of a national study of the Chronic Disease Self-Management

Program: meeting the triple aim of health care reform. *Med Care, 51*(11), 992-998. doi: 10.1097/MLR.0b013e3182a95dd1

Parkes, A., Kearns, A., & Atkinson, R. (2002). What makes people dissatisfied with their neighbourhoods? *Urban Studies, 39*(13), 2413-2438.

Pausova, Z., Tremblay, J., & Hamet, P. (1999). Gene-environment interactions in hypertension. *Current Hypertension Reports, 1*(1), 42-50.

Peace, R. M., Majors, B. L., Patel, N. S., Wang, D., Valle-Pinero, A. Y., Martino, A. C., & Henderson, W. A. (2012). Stress and gene expression of individuals with chronic abdominal pain. *Biol Res Nurs, 14*(4), 405-411. doi: 10.1177/1099800412458350

Petersen, K., Bleil, M., McCaffery, J., Mackey, R., Sutton-Tyrrell, K., Muldoon, M., & Manuck, S. (2006). Community socioeconomic status is associated with carotid artery atherosclerosis in untreated, hypertensive men. *American journal of hypertension, 19*(6), 560-566.

Phillips, L., McGorry, P., Garner, B., Thompson, K., Pantelis, C., Wood, S., & Berger, G. (2006). Stress, the hippocampus and the hypothalamic-pituitary-adrenal axis: implications for the development of psychotic disorders. *Australian and New Zealand Journal of Psychiatry, 40*(9), 725-741.

Piantadosi, S., Byar, D. P., & Green, S. B. (1988). The ecological fallacy. *Am J Epidemiol, 127*(5), 893-904.

Pickett, K. E., & Pearl, M. (2001). Multilevel analyses of neighbourhood socioeconomic context and health outcomes: a critical review. *J Epidemiol Community Health, 55*(2), 111-122.

Pirpiris, M., Yeung, S., Dewar, E., Jennings, G., & Whitworth, J. (1993). Hydrocortisone-induced hypertension in men: the role of cardiac output. *American journal of hypertension, 6*(4), 287-294.

Pointer, M., Livingston, J., Yancey, S., McClelland, M., & Bukoski, R. (2008). Psychosocial factors contribute to resting blood pressure in African Americans. *Ethnicity & disease, 18*(3), 289.

Polk, D. E., Cohen, S., Doyle, W. J., Skoner, D. P., & Kirschbaum, C. (2005). State and trait affect as predictors of salivary cortisol in healthy adults. *Psychoneuroendocrinology, 30*(3), 261-272. doi: 10.1016/j.psyneuen.2004.08.004

Preacher, K. J., Rucker, D. D., & Hayes, A. F. (2007). Addressing moderated mediation hypotheses: Theory, methods, and prescriptions. *Multivariate Behavioral Research, 42*(1), 185-227.

Pruessner, J. C., Hellhammer, D. H., & Kirschbaum, C. (1999). Burnout, perceived stress, and cortisol responses to awakening. *Psychosom Med, 61*(2), 197-204.

Rainforth, M., Schneider, R., Nidich, S., Gaylord-King, C., Salerno, J., & Anderson, J. (2007). Stress reduction programs in patients with elevated blood pressure: a systematic review and meta-analysis. *Current Hypertension Reports, 9*(6), 520-528.

Ranjit, N., Young, E. A., & Kaplan, G. A. (2005). Material hardship alters the diurnal rhythm of salivary cortisol. *Int J Epidemiol, 34*(5), 1138-1143. doi: dyi120 [pii]10.1093/ije/dyi120

Rietschel, L., Zhu, G., Kirschbaum, C., Strohmaier, J., Wust, S., Rietschel, M., & Martin, N. G. (2013). Perceived Stress has Genetic Influences Distinct from Neuroticism and Depression. *Behav Genet*. doi: 10.1007/s10519-013-9636-4

Roger, V. L., Go, A. S., Lloyd-Jones, D. M., Benjamin, E. J., Berry, J. D., Borden, W. B., . . . Turner, M. B. (2012). Executive summary: heart disease and stroke statistics--2012 update: a report from the American Heart Association. *Circulation, 125*(1), 188-197. doi: 125/1/188 [pii]10.1161/CIR.0b013e3182456d46

Roisman, G. I., Newman, D. A., Fraley, R. C., Haltigan, J. D., Groh, A. M., & Haydon, K. C. (2012). Distinguishing differential susceptibility from diathesis-stress: recommendations for evaluating interaction effects. *Dev Psychopathol, 24*(2), 389-409. doi: 10.1017/S0954579412000065

Rossiter, K. (2011). What are census blocks? In U. S. C. Bureau (Ed.), *Random Samplings- The official blog of the U.S. Census Bureau* (Vol. 2012).

Roy, A., Gorodetsky, E., Yuan, Q., Goldman, D., & Enoch, M. A. (2010). Interaction of FKBP5, a stress-related gene, with childhood trauma increases the risk for attempting suicide. *Neuropsychopharmacology, 35*(8), 1674-1683. doi: npp2009236 [pii]10.1038/npp.2009.236

Rudolph, K. E., Gary, S. W., Stuart, E. A., Glass, T. A., Marques, A. H., Duncko, R., & Merikangas, K. R. (2014). The association between cortisol and neighborhood disadvantage in a U.S. population-based sample of adolescents. *Health Place, 25*, 68-77. doi: 10.1016/j.healthplace.2013.11.001

Saelens, B. E., Sallis, J. F., Black, J. B., & Chen, D. (2003). Neighborhood-based differences in physical activity: an environment scale evaluation. *Am J Public Health, 93*(9), 1552-1558.

Salacz, P., Csukly, G., Haller, J., & Valent, S. (2012). Association between subjective feelings of distress, plasma cortisol, anxiety, and depression in pregnant women. *Eur J Obstet Gynecol Reprod Biol, 165*(2), 225-230. doi: 10.1016/j.ejogrb.2012.08.017

Salari, K., Watkins, H., & Ashley, E. A. (2012). Personalized medicine: hope or hype? *Eur Heart J, 33*(13), 1564-1570. doi: 10.1093/eurheartj/ehs112

Sampson, R. J., Raudenbush, S. W., & Earls, F. (1997). Neighborhoods and violent crime: a multilevel study of collective efficacy. *Science, 277*(5328), 918-924.

Sarason, S. B. (1974). *The psychological sense of community: Prospects for a community psychology*: Jossey-Bass.

Sato, N., Suzuki, N., Sasaki, A., Aizawa, E., Obayashi, T., Kanazawa, M., . . . Fukudo, S. (2012). Corticotropin-releasing hormone receptor 1 gene variants in irritable bowel syndrome. *PLoS One, 7*(9), e42450. doi: 10.1371/journal.pone.0042450

Saxton, J. M., Scott, E. J., Daley, A. J., Woodroofe, M. N., Mutrie, N., Crank, H., . . . Coleman, R. E. (2014). Effects of an exercise and hypocaloric healthy eating intervention on indices of psychological health status, hypothalamic-pituitary-adrenal axis regulation and immune function after early-stage breast cancer: a randomised controlled trial. *Breast Cancer Res, 16*(2), R39. doi: 10.1186/bcr3643

Schlomer, G. L., Bauman, S., & Card, N. A. (2010). Best practices for missing data management in counseling psychology. *J Couns Psychol, 57*(1), 1-10. doi: 10.1037/a0018082

Schwartz, S. (1994). The fallacy of the ecological fallacy: the potential misuse of a concept and the consequences. *Am J Public Health, 84*(5), 819-824.

Seeman, T., & McEwen, B. (1996). Impact of social environment characteristics on neuroendocrine regulation. *Psychosomatic medicine, 58*(5), 459.

Selye, H. (1975). Confusion and controversy in the stress field. *J Human Stress, 1*(2), 37-44. doi: 10.1080/0097840X.1975.9940406

Shavers, V. L. (2007). Measurement of socioeconomic status in health disparities research. *J Natl Med Assoc, 99*(9), 1013-1023.

Sherry, S., Ward, M., Kholodov, M., Baker, J., Phan, L., Smigielski, E., & Sirotkin, K. (2001). dbSNP: the NCBI database of genetic variation. *Nucleic acids research, 29*(1), 308.

Skinner, M. L., Shirtcliff, E. A., Haggerty, K. P., Coe, C. L., & Catalano, R. F. (2011). Allostasis model facilitates understanding race differences in the diurnal cortisol rhythm. *Dev Psychopathol, 23*(4), 1167-1186. doi: S095457941100054X [pii]10.1017/S095457941100054X

Spruill, T., Gerin, W., Ogedegbe, G., Burg, M., Schwartz, J., & Pickering, T. (2009). Socioeconomic and psychosocial factors mediate race differences in nocturnal blood pressure dipping. *American journal of hypertension, 22*(6), 637-642.

St George, S. M., Wilson, D. K., Schneider, E. M., & Alia, K. A. (2013). Project SHINE: effects of parent-adolescent communication on sedentary behavior in African

American adolescents. *J Pediatr Psychol, 38*(9), 997-1009. doi: 10.1093/jpepsy/jst027

Stalder, T., Hucklebridge, F., Evans, P., & Clow, A. (2009). Use of a single case study design to examine state variation in the cortisol awakening response: relationship with time of awakening. *Psychoneuroendocrinology, 34*(4), 607-614. doi: 10.1016/j.psyneuen.2008.10.023

Steptoe, A., Kunz-Ebrecht, S., Owen, N., Feldman, P. J., Willemsen, G., Kirschbaum, C., & Marmot, M. (2003). Socioeconomic status and stress-related biological responses over the working day. *Psychosom Med, 65*(3), 461-470.

Steptoe, A., & Marmot, M. (2002). The role of psychobiological pathways in socio-economic inequalities in cardiovascular disease risk. *Eur Heart J, 23*(1), 13-25. doi: 10.1053/euhj.2001.2611S0195668X01926119 [pii]

Steptoe, A., Siegrist, J., Kirschbaum, C., & Marmot, M. (2004). Effort--Reward Imbalance, Overcommitment, and Measures of Cortisol and Blood Pressure Over the Working Day. *Psychosomatic medicine, 66*(3), 323.

Stevens, A., Ray, D., Zeggini, E., John, S., Richards, H., Griffiths, C., & Donn, R. (2004). Glucocorticoid sensitivity is determined by a specific glucocorticoid receptor haplotype. *Journal of Clinical Endocrinology & Metabolism, 89*(2), 892.

Stewart, P., Walker, B., Holder, G., O'Halloran, D., & Shackleton, C. (1995). 11 beta-Hydroxysteroid dehydrogenase activity in Cushing's syndrome: explaining the mineralocorticoid excess state of the ectopic adrenocorticotropin syndrome. *Journal of Clinical Endocrinology & Metabolism, 80*(12), 3617.

Stokols, D. (1996). Translating social ecological theory into guidelines for community health promotion. *American Journal of Health Promotion, 10*, 282-298.

Strogatz, D. S., Croft, J., James, S., Keenan, N., Browning, S., Garrett, J., & Curtis, A. (1997). Social support, stress, and blood pressure in black adults. *Epidemiology, 8*(5), 482-487.

Suderman, M., McGowan, P. O., Sasaki, A., Huang, T. C., Hallett, M. T., Meaney, M. J., . . . Szyf, M. (2012). Conserved epigenetic sensitivity to early life experience in the rat and human hippocampus. *Proc Natl Acad Sci U S A, 109 Suppl 2*, 17266-17272. doi: 10.1073/pnas.1121260109

Syed, A., Irving, J., Redfern, C., Hall, A., Unwin, N., White, M., . . . Weaver, J. (2006). Association of Glucocorticoid Receptor Polymorphism A3669G in Exon 9 with Reduced Central Adiposity in Women&ast. *Obesity (Silver Spring), 14*(5), 759-764.

Tanaka, M., Jaamaa, G., Kaiser, M., Hills, E., Soim, A., Zhu, M., . . . McNutt, L. A. (2007). Racial disparity in hypertensive disorders of pregnancy in New York State: a 10-year longitudinal population-based study. *Am J Public Health, 97*(1), 163-170. doi: 10.2105/ajph.2005.068577

Taylor, S. (2011). The Future of Social‐ Health Psychology: Prospects and Predictions. *Social and Personality Psychology Compass, 5*(5), 275-284.

Thomas, K., Nelesen, R., Ziegler, M., Natarajan, L., & Dimsdale, J. (2009). Influence of education and neighborhood poverty on pressor responses to phenylephrine in African-Americans and Caucasian-Americans. *Biological psychology, 82*(1), 18-24.

Thorpe Jr, R., Brandon, D., & LaVeist, T. (2008). Social context as an explanation for race disparities in hypertension: findings from the Exploring Health Disparities in Integrated Communities (EHDIC) Study. *Soc Sci Med, 67*(10), 1604-1611.

Troxler, R., Sprague, E., Albanese, R., Fuchs, R., & Thompson, A. (1977). The association of elevated plasma cortisol and early atherosclerosis as demonstrated by coronary angiography. *Atherosclerosis, 26*(2), 151-162.

Tsuboi, H., Sakakibara, H., Yamakawa-Kobayashi, K., Tatsumi, A., Inamori, T., Hamamoto, R., . . . Shimoi, K. (2011). Val1483Ile polymorphism in the fatty acid synthase gene was associated with depressive symptoms under the influence of psychological stress. *J Affect Disord, 134*(1-3), 448-452. doi: 10.1016/j.jad.2011.05.010

Tu, J., & Ko, D. (2008). Ecological studies and cardiovascular outcomes research. *Circulation, 118*(24), 2588.

Tudge, J. R. H., Mokrova, I., Hatfield, B. E., & Karnik, R. B. (2009). Uses and misuses of Bronfenbrenner's bioecological theory of human development. *Journal of Family Theory & Review, 1*(4), 198-210.

U.S. Census Bureau. (2010). 2010 Census Constituent FAQs. http://2010.census.gov/partners/pdf/ConstituentFAQ.pdf

U.S. Department of Health and Human Services. (2011). About Healthy People. Retrieved August 9, 2011, from http://www.healthypeople.gov/2020/about/default.aspx

Update on the 1987 Task Force Report on High Blood Pressure in Children and Adolescents: a working group report from the National High Blood Pressure

Education Program. National High Blood Pressure Education Program Working Group on Hypertension Control in Children and Adolescents. (1996). *Pediatrics, 98*(4 Pt 1), 649-658.

Urban Area Criteria for the 2010 Census. (2011). Commerce.

van den Akker, E., Koper, J., van Rossum, E., Dekker, M., Russcher, H., de Jong, F., . . . Witteman, J. (2008). Glucocorticoid receptor gene and risk of cardiovascular disease. *Arch Intern Med, 168*(1), 33.

van Eck, M., Berkhof, H., Nicolson, N., & Sulon, J. (1996). The effects of perceived stress, traits, mood states, and stressful daily events on salivary cortisol. *Psychosomatic medicine, 58*(5), 447.

van Rossum, E., & Lamberts, S. (2004). Polymorphisms in the glucocorticoid receptor gene and their associations with metabolic parameters and body composition. *Recent Progress in Hormone Research, 59*(1), 333.

Velders, F. P., Dieleman, G., Cents, R. A., Bakermans-Kranenburg, M. J., Jaddoe, V. W., Hofman, A., . . . Tiemeier, H. (2012). Variation in the glucocorticoid receptor gene at rs41423247 moderates the effect of prenatal maternal psychological symptoms on child cortisol reactivity and behavior. *Neuropsychopharmacology, 37*(11), 2541-2549. doi: 10.1038/npp.2012.118

Vreeburg, S. A., Kruijtzer, B. P., van Pelt, J., van Dyck, R., DeRijk, R. H., Hoogendijk, W. J., . . . Penninx, B. W. (2009). Associations between sociodemographic, sampling and health factors and various salivary cortisol indicators in a large sample without psychopathology. *Psychoneuroendocrinology, 34*(8), 1109-1120. doi: 10.1016/j.psyneuen.2009.04.024

Wandersman, A., & Nation, M. (1998). Urban neighborhoods and mental health. Psychological contributions to understanding toxicity, resilience, and interventions. *Am Psychol, 53*(6), 647-656.

Ward, B. W., Schiller, J. S., & Goodman, R. A. (2014). Multiple chronic conditions among US adults: a 2012 update. *Prev Chronic Dis, 11*, E62. doi: 10.5888/pcd11.130389

Watt, G., Harrap, S., Foy, C., Holton, D., Edwards, H., Davidson, H., . . . Fraser, R. (1992). Abnormalities of glucocorticoid metabolism and the renin-angiotensin system: a four-corners approach to the identification of genetic determinants of blood pressure. *Journal of hypertension, 10*(5), 473.

Westaway, M. S. (2007). Life and neighborhood satisfaction of black and white residents in a middle-class suburb of Johannesburg. *Psychol Rep, 100*(2), 489-494.

Whitworth, J., Brown, M., Kelly, J., & Williamson, P. (1995). Experimental studies on cortisol-induced hypertension in humans. *Journal of human hypertension, 9*(6), 395-399.

Whitworth, J., Mangos, G., & Kelly, J. (2000). Cushing, cortisol, and cardiovascular disease. *Hypertension, 36*(5), 912.

Whitworth, J., Williamson, P., Mangos, G., & Kelly, J. (2005). Cardiovascular consequences of cortisol excess. *Vascular health and risk management, 1*(4), 291.

Wickrama, K. K., O'Neal, C. W., & Lee, T. K. (2013). Early community context, genes, and youth body mass index trajectories: an investigation of gene-community interplay over early life course. *J Adolesc Health, 53*(3), 328-334. doi: 10.1016/j.jadohealth.2013.04.004

Wilcox, S., Bopp, M., Wilson, D., Fulk, L., & Hand, G. (2005). Race differences in cardiovascular and cortisol responses to an interpersonal challenge in women who are family caregivers. *Ethnicity & disease, 15*(1), 17-24.

Williams, D. R., Yu, Y., Jackson, J. S., & Anderson, N. B. (1997). Racial differences in physical and mental health. *Journal of Health Psychology, 2*(3), 335-351.

Wilson, D. (2014). *Presidential Keynote Address: The Relevance, Impact, and Reach of Behavioral*

Medicine Paper presented at the 35th Annual Meeting of the Society of Behavioral Medicine Philadelphia, PA.

Wilson, D., Trumpeter, N., St George, S., Coulon, S., Griffin, S., Van Horn, M., . . . Gadson, B. (2010). An overview of the "Positive Action for Today's Health" (PATH) trial for increasing walking in low income, ethnic minority communities. *Contemp Clin Trials, 31*(6), 624-633. doi: S1551-7144(10)00155-2 [pii]10.1016/j.cct.2010.08.009

Wolff, J. L., Starfield, B., & Anderson, G. (2002). Prevalence, expenditures, and complications of multiple chronic conditions in the elderly. *Arch Intern Med, 162*(20), 2269-2276.

Wolfram, M., Bellingrath, S., Feuerhahn, N., & Kudielka, B. M. (2013). Emotional exhaustion and overcommitment to work are differentially associated with hypothalamus-pituitary-adrenal (HPA) axis responses to a low-dose ACTH1-24 (Synacthen) and dexamethasone-CRH test in healthy school teachers. *Stress, 16*(1), 54-64. doi: 10.3109/10253890.2012.683465

Wright, C., & Steptoe, A. (2005). Subjective socioeconomic position, gender and cortisol responses to waking in an elderly population. *Psychoneuroendocrinology, 30*(6), 582-590.

Wust, S., van Rossum, E., Federenko, I., Koper, J., Kumsta, R., & Hellhammer, D. (2004). Common polymorphisms in the glucocorticoid receptor gene are associated with adrenocortical responses to psychosocial stress. *Journal of Clinical Endocrinology & Metabolism, 89*(2), 565.

Xie, P., Kranzler, H. R., Poling, J., Stein, M. B., Anton, R. F., Farrer, L. A., & Gelernter, J. (2010). Interaction of FKBP5 with childhood adversity on risk for post-traumatic stress disorder. *Neuropsychopharmacology, 35*(8), 1684-1692. doi: npp201037 [pii]10.1038/npp.2010.37

Yoshitomi, Y., Nagakura, C., & Miyauchi, A. (2005). Significance of mean blood pressure for blood pressure control. *Int Heart J, 46*(4), 691-699.

Zhu, H., Poole, J., Lu, Y., Harshfield, G., Treiber, F., Snieder, H., & Dong, Y. (2005). Sympathetic nervous system, genes and human essential hypertension. *Current Neurovascular Research, 2*(4), 303-317.

APPENDIX A

Perceived Stress Scale

1. In the last month, how often have you been upset because of something that happened unexpectedly?
2. In the last month, how often have you felt that you were unable to control the important things in your life?
3. In the last month, how often have you felt nervous and "stressed"?
4. In the last month, how often have you felt confident about your ability to handle your personal problems?
5. In the last month, how often have you felt that things were going your way?
6. In the last month, how often have you found that you could not cope with all the things that you had to do?
7. In the last month, how often have you been able to control irritations in your life?
8. In the last month, how often have you felt that you were on top of things?
9. In the last month, how often have you been angered because of things that were outside of your control?
10. In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?

***Likert Response Options*:**

1. never
2. almost never
3. sometimes
4. fairly often
5. very often

APPENDIX B

Multidimensional Scale of Perceived Social Support

1. There is a special person who is around when I am in need.
2. There is a special person with whom I can share my joys and sorrows.
3. My family really tries to help me.
4. I get the emotional help and support I need from my family.
5. I have a special person who is a real source of comfort for me.
6. My friends really try to help me.
7. I can count on my friends when things go wrong.
8. I can talk about my problems with my family.
9. I have friends with whom I can share my joys and sorrows.
10. There is a special person in my life who cares about my feelings.
11. My family is willing to help me make decisions.
12. I can talk about my problems with my friends.

***Likert Response Options*:**

1. very strongly disagree
2. strongly disagree
3. mildly disagree
4. neither agree nor disagree
5. mildly agree
6. strongly agree
7. very strongly agree

APPENDIX C

Census Map Delineating Blocks and Tracts

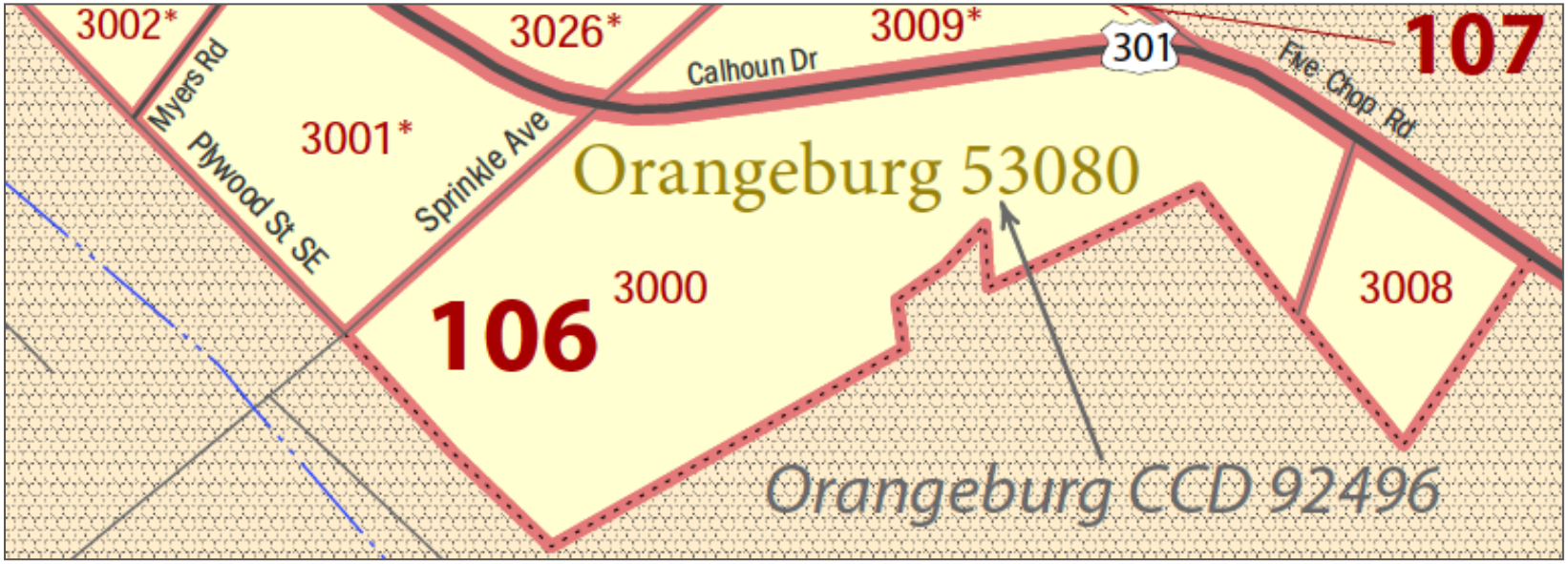


Figure C.1. Census Map Example Delineating Block Groups and Tracts.

Note. Map taken from the website of the U.S. Census Bureau:
http://www2.census.gov/geo/maps/dc10map/GUBlock/st45_sc/place/p4553080_orangeburg/DC10BLK_P4553080_003.pdf

APPENDIX D

Table D.1
Neighborhood SES Measures Considered

SES Variable Domains	Atherosclerosis Risk In Communities	Townsend Material Deprivation	Neighborhood Poverty	(Kapuku et al., 2002) Neighborhood SES
Income	1. Median household income 2. Median value owner-occupied housing 3. Proportion households receiving interest, dividend, or net rental income	1. Percentage households own car 2. Percentage households with 1 or more persons per room 3. Percentage people living in owner-occupied housing	1. Percentage households below the poverty line	1. Median household income 2. Median monthly housing cost 3. Mean home value 4. Percentage households below the poverty line 5. Percentage single-women headed households
Education	4. Proportion adults with a high school diploma 5. Proportion adults with a college education	X	X	6. Parental education level
Occupation	6. Proportion people employed in executive, managerial, or professional occupations	4. Proportion of unemployed aged 16 and older	X	7. Percentage unemployed individuals
Links to Cardiovascular Health	Linked inversely to CVD mortality (Borrell et al., 2004; Diez Roux et al., 2004) but not HTN (Diez Roux et al., 2002a)	Linked inversely to systolic BP (Cubbin et al., 2001)	Linked inversely to CVD mortality (Jones-Webb et al., 2004) but not HTN (Tanaka et al., 2007)	Not linked to resting BP or cortisol

APPENDIX E

Neighborhood Satisfaction Survey

1. How satisfied are you with how many friends you have in your neighborhood?
2. How satisfied are you with the number of people you know in your neighborhood?
3. How satisfied are you with how easy and pleasant it is to walk in your neighborhood?
4. How satisfied are you with the amount and of speed of traffic in your neighborhood?
5. How satisfied are you with your neighborhood as a good place to raise children?
6. How satisfied are you with your neighborhood as a good place to live?
7. How satisfied are you with the highway access from your home?
8. How satisfied are you with the access to public transportation in your neighborhood?
9. How satisfied are you with your commuting time to work/school?
10. How satisfied are you with the access to shopping in your neighborhood?
11. How satisfied are you with how easy and pleasant it is to bicycle in your neighborhood?
12. How satisfied are you with quality of the schools in your neigbhborhood?
13. How satisfied are you with the access to entertainment in your neighborhood (restaurants, movies, clubs, etc)?
14. How satisfied are you with the safety from threat of crime in your neighborhood?
15. How satisfied are you with the noise from traffic in your neighborhood?
16. How satisfied are you with the number and quality of food stores in your neighborhood?
17. How satisfied are you with the number and quality of restaurants in your neighborhood?

***Likert Response Options*:**

1. strongly dissatisfied
2. somewhat dissatisfied
3. somewhat satisfied
4. strongly satisfied

APPENDIX F

Collective Efficacy Measure

Informal Social Control Subscale:

What is the likelihood that your neighbors could be counted on to intervene in various ways if:

1. Children were skipping school and hanging out on a street corner
2. Children were spray-painting graffiti on a local building
3. Children were showing disrespect to an adult
4. A fight broke out in front of their house*
5. The fire station closets to their home was threatened with budget cuts*

***Likert Response Options*:**

1. very unlikely
2. unlikely
3. neither likely or unlikely
4. likely
5. very likely

Social Cohesion and Trust Subscale:

How much do you agree with the following statements:

1. People around here are willing to help their neighbors
2. This is a close-knit community
3. People in this neighborhood can be trusted
4. People in this neighborhood generally don't get along with each other (reverse coded)
5. People in this neighborhood do not share the same values (reverse coded)

***Likert Response Options*:**

1. strongly disagree
2. disagree
3. neither agree nor disagree
4. agree
5. strongly agree

APPENDIX G

Contact and Demographic Information

Please answer the following questions as best you can. There are no right or wrong answers. All of your information will be kept confidential, and will be secure electronically and physically

1. **What is the best phone number to reach you at?**
   _____Other_____

2. **What is your current address?**

   _____

   _____

3. **How long have you lived there for?**

   _____

4. **Is there any other address we should have on file for you?**

   _____

5. **Are you an American citizen (circle)?** Yes No

6. **Which of the following best describes you (circle ONLY ONE)?**
   ____ Black or African American
   ____ White or European American
   ____ Hispanic or Latino
   ____ Other, Describe:
   _____

7. **If you consider yourself to be African American, please put an "X" next to the following statement which describes your heritage:**
   ____ 3 or more grandparents of African or African American descent
   ____ 2 grandparents of African or African American descent
   ____ 1 grandparent of African or African American descent
   ____ None of the above
   ____ Unsure

8. **How old are you? _____ What is your date of birth (DD/MM/YYYY) _____**

9. **What is your sex (circle)?** Male Female

10. Please indicate your employment status (put an "X"):

_____ Working
_____ Temporarily Laid Off
_____ Unemployed
_____ Retired
_____ Permanently Disabled
_____ Homemaker
_____ Student
_____ Other

What is the highest grade of school or year of college you have completed?

____ Never attended school or only attended kindergarten
____ Grades 1-8 (elementary)
____ Grades 9-11 (some high school)
____ Grades 12 or GED (high school graduate)
____ College 1 year to 3 years (some college or technical school)
____ College 4 years or more (college graduate)
____ Graduate training or professional degree

11. If you added together the yearly incomes, before taxes, of all members of your household for the last year, would the total be (put an "X"):

____ Less than $10,000
____ $10,000 to $24,999
____ $25,000 to $39,999
____ $40,000 to $54,999
____ $55,000 to $69,999
____ $70,000 to $84,999
____ $85,000 or more
____ Other, Describe:
_____

12. What is your marital status (put an "X")?

____ Married
____ Separated
____ Divorced
____ Widowed
____ Never Married
____ In an unmarried couple
____ Other, Describe: _____

13. How many children, aged 17 or younger, live in your house? _____

14. Do you or your family own the place where you are living now, or do you rent (put an "X")?

____ Own
____ Rent
____ Don't know
____ Other, Describe: _____

15. How did you find out about us?

____ By word of mouth, from a friend or family member
____ Got a flyer at an event I attended
____ Received a phone call from HEART staff
____ Other [please tell us more…] _____