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Gene By Environment Interaction On Weight-Related Outcomes Over Time In Underserved African-American Adults

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GENE BY ENVIRONMENT INTERACTION ON WEIGHT-RELATED OUTCOMES
OVER TIME IN UNDERSERVED AFRICAN-AMERICAN ADULTS

by

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ABSTRACT

Obesity research in the area of prevention has become a national priority given the increasingly high prevalence rate of this condition among US adults, and subsequent health risks that are associated. The etiology of obesity is complex, so a more comprehensive understanding of the interaction between genetic predisposition and the social environment in regards to obesity in adults would advance our knowledge for future public health and prevention efforts. This study's aim was to assess the impact of a gene by neighborhood social environment interactions on weight-related (i.e., waist circumference) and stress-related (i.e. cortisol) outcomes in underserved African-American adults. A bioecological framework was used in the present study to integrate factors, including social environmental factors (i.e. perceptions of safety from crime, neighborhood satisfaction, neighborhood social life, and collective efficacy) and genetic risk (Sympathetic Nervous System and Hypothalamic-Pituitary-Adrenal axis related genes) to better understand the gene by environment interactions on weight-related and stress-related outcomes in adults. This study utilized participants from the Positive Action for Today's Health (PATH) trial. Based on a dual risk model, it is hypothesized that those with the highest genetic risk and who experienced negative neighborhood environment conditions would have the worst outcomes (i.e. highest waist circumference and highest cortisol levels). There were no significant three-way interactions with gene by environment interactions predicting change over time. However, results did indicate three significant gene by environment interactions on weight related outcomes, all within the

SNS pathway. These significant results included two interactions that support the dual risk model, which were the SNS genetic risk by neighborhood social life interaction ($b=-0.108$, $t(618)=-2.018$, $p=0.04$), and SNS genetic risk by informal social control (collective efficacy) interaction ($b=-0.510$, $t(618)=-1.95$, $p=0.05$) on waist circumference outcomes. Further, there was a significant SNS genetic risk by neighborhood satisfaction interaction ($b=1.481$, $t(618)=2.233$, $p=0.02$) on waist circumference outcomes, which did not match the dual risk hypothesis. For the secondary aims, however, there was only one SNS by social cohesion and trust interaction ($b=0.59$, $p=0.02$) on cortisol in the unexpected direction for the linear regression. Implications of these findings, limitations of the study and future directions are discussed.

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CHAPTER 1

SIGNIFICANCE

Obesity prevention has become a national priority given the increasing prevalence of this condition among US adults (U.S. Department of Health and Human Services, 2011; Desai, Miller, Staples, et al., 2008), but there continues to be a necessity to expand the understanding of determinants of obesity for future prevention programs. In addition, obesity has become a global problem and it is estimated that approximately 500 million adults are obese, with nearly 1.5 billion identified as either overweight or obese worldwide (Finucane, Stevens, Cowan, et al., 2011). Even more alarming is the projection that given current trends, by 2030 there may be more than 2.1 billion overweight adults, and 1.1 billion obese adults worldwide (Kelly, Yang, Chen, et al., 2008). Further, Finkelstein, Khavjou, Thompson, et al. (2012) utilized a more conservative model, which projected estimates of obesity rates leveling off by 2030 with 42% of the population classified as obese. Obesity is associated with several health risks, including and increased risk for coronary heart disease, high blood pressure, stroke, and type 2 diabetes (Schoenborn & Stommel, 2011). Research has also shown overweight/obesity is associated with the development of abnormal blood fats, metabolic syndrome, cancer, osteoarthritis, sleep apnea, and reproductive issues (National Heart, Lung, and Blood Institute, 2012). The high prevalence rates of obesity also greatly impacts the US economy, as obesity and associated health complications are estimated to incur costs in excess of \$215 billion annually (Hammond & Levine, 2010), and at the current rate it is estimated that by 2030 annual economic productivity loss due to obesity

could reach \$580 billion (Levi, Segal, St. Lauren, et al., 2012). Until this chronic disease is better understood, it will continue to severely impact individual's lives, and economically burden the US healthcare system.

There has been limited previous research focused specifically on underserved populations (ethnic minorities) and understanding how social environmental factors relate to stress and obesity. Specifically, with regards to the obesity trends in America, currently, 68.5% of American adults (≥ 20 years old) are overweight or obese, while 35% are obese (Ogden, Carroll, Kit et al., 2014). However, this disparity in overweight/obesity rates for African Americans is greatest in comparison to Caucasians (67.2%), with over three fourths of all African-American adults either classified as overweight or obese (76.2%, including 69% of men and 82% of women; Ogden, Carroll, Kit, et al., 2014). Further, nearly half (48.1%) of all African-American adults are obese (37.1% of men and 56.6% of women; Ogden et al., 2014), compared to obesity rates of 42% for Hispanic, 35% for Non-Hispanic white and 11.7% for Non-Hispanic Asian (Ogden et al., 2015). African Americans are approximately 1.5 times more likely to be obese than their Caucasian counterparts (Ogden, et al., 2014). Masters, et al. (2013) found almost one in five deaths were associated with excess body weight for Americans, which was concluded after examining 19 National Health Interview Survey cohorts that were directly linked to the national mortality records. Further, they found African Americans mortality rates for men (5%) and women (27%) were positively associated with high body mass index (Masters, et al., 2013). Overall, based on the high prevalence rates of overweight and obesity, especially for African Americans, prevention efforts are a national priority.

The determinants of obesity are not well understood given the complexity of this potentially life threatening chronic illness. The etiology of obesity and related health issues are complex (Patakey, Bobbioni-Harsch, & Golay, 2010), which may be driven by social environmental factors (i.e. social capital, collective efficacy, and crime; Suglia et al., 2016) in addition to genetic risk. This has led to a national initiative aimed at reducing the health disparities, which includes targeting social environments such as the neighborhood environment. The “Healthy People 2020” initiative (U.S. Department of Health and Human Services, 2011), organized by the Department of Health and Human Services, has aspirational goals, including achieving health equity for all racial groups in America, and in doing so reducing and eventually eliminate disparities. Additionally, they state that by creating more positive social environments (i.e. neighborhoods, work, etc) that promote health there should be improvements in eliminating health disparities (U.S. Department of Health and Human Services, 2011). Therefore, one avenue to explore is the influence that social environmental factors (such as neighborhood social environmental factors) have on obesity, especially for at-risk populations such as African-Americans adults.

An increasing interest in the field has been to expand understanding of the complexity of gene by environment interactions on health outcomes, such as obesity. There are fundamental genetic and environmental factors that influence these complex, multifactorial relationships in understanding weight related outcomes (Karnehed, Tynelius, Heitmann et al. 2006). Thus, it is important to develop a better understanding of determinants of the disease in order to develop effective prevention and intervention programs. However, research that specifically investigates the role of the gene by

environment interactions in adults has been limited. Most likely, this is because obesity is a complex chronic illness where the etiology is only partially understood. Specifically, the development of obesity most likely involves multiple systems (i.e. neuroendocrine, genetics, immune system, stress regulation, etc.) but the exact impact of each system is still unknown (Patakay, Bobbioni-Harsch, & Golay, 2010). The current study expands on previous research specifically by assessing gene by neighborhood social environment interactions on weight-related and stress-related outcomes in underserved African-American adults.

CHAPTER 2

INTRODUCTION

2.1 Ecological Systems, Stress and Obesity

Previous genetic research has had a strong emphasis on Genome Wide Association Studies (GWAS) and little focus on theory or mechanisms. Utilizing a theory to better understand the complexity of obesity may be appropriate, especially when integrating multiple systems that include both the broader environment (neighborhood) and key genetic pathways (i.e. stress related pathways). Theoretically, the bioecological theory (Bronfenbrenner, 2005), as well as stress and coping theories (Anderson, 1998; Cohen, 2006; Selye, 1975) are important frameworks to utilize when trying to identify potential causal pathways of gene and environmental interactions on obesity. The Bioecological model is used in the present study as a framework for integrating multiple factors, specifically social environmental factors, biological underpinnings, and genetic risk to better understand their influence on weight-related outcomes in African-American adults. Bioecological theory is an adaptation of Bronfenbrenner's ecological systems theory (Bronfenbrenner, 1979; Bronfenbrenner, 2005) that suggests that human development, behavior, and health are not only influenced by many microsystemic (family, places of work, etc.), mesosystemic (interactions between the microsystemic factors), exosystemic (churches, neighborhoods, communities, policies, etc.) and macrosystemic (culture and subculture related to all systems) contexts, but also includes characteristics of the individual (genetics and biology) in understanding health outcomes.

It is through assessing multiple systemic levels of an individual's environment that the current study expands on past research in advancing our understanding of the development of obesity.

This study specifically examines genetic and biological underpinnings (physiological stress), as well as neighborhood social interactions that may impact weight-related and stress-related outcomes. Tudge, et al. (2009) have argued that there are many complex processes occurring between and within the ecological levels that enable the proximal biological and distal ecological factors to influence human health such as weight-related outcomes. Furthermore, utilizing Bronfenbrenner's bioecological theory, this study assessed several individual level predictors including genetic, and neighborhood social environmental factors such as neighborhood perceived safety from crime and perceived neighborhood social interaction. Each of these factors will be assessed at the microsystem level over time in order to better understand gene by environmental interactions on adiposity in African-American adults. Based on this theoretical framework, bioecological theory provides a model for understanding multiple systems to be assessed in an effort to better understand the complexity of obesity.

Historically, African Americans have been shown to be more likely to live in high stress environments (e.g. poverty, high crime), and they also have been shown to have a genetic predisposition to physiologically respond to stress that leads to chronic diseases that are commonly associated with obesity (Anderson & Armstead 1995). One theory that highlights the importance of stress on obesity outcomes specifically in African Americans is Anderson's stress model (Anderson & Armstead, 1995). Anderson and Armstead (1995) and Matthews and Gallo (2011) have highlighted the importance that

socioeconomic status (SES) has on cardiovascular health, particularly in African Americans. Compositional SES (i.e. individual's income, occupation and education; Shavers, 2007) has shown consistent positive associations with health outcomes (Adler & Ostrove, 1999). Utilizing SES and other related neighborhood social environmental factors may provide insight into etiology of obesity, and how stress plays an important role. Neighborhood environmental stress has also been consistently negatively linked to cardiovascular outcomes (Diez Roux et al., 2002; Morenoff, House, & Hansen, 2007; Powell-Wiley et al., 2015; Powell-Wiley et al., 2014) which in turn has been associated with increased risk of obesity (Block, He, Zaslavsky, et al., 2009; Fowler-Brown, Bennett, Goodman, et al., 2009).

The perception of stress, particularly environmental, has been shown to have detrimental impacts on one's health. Like bioecological theory, Anderson (1998) states that by incorporating multiple systems, including social environmental, behavioral/psychological, organ systems, and cellular and molecular systems, researchers may be able to better understand complex disorders such as obesity, which has been echoed by other scholars (Anderson and Armstead, 1995; Matthews and Gallo, 2011; Tu & Ko, 2008). Individuals with low SES may experience greater chronic environmental stress and overall greater distress (Selye, 1975), which may lead to increased overall perceived chronic stress in life. This is particularly salient for African Americans as they are three times more likely to live in poverty than their Caucasian counterparts (National Center for Education Statistics, 2002). Powell-Wiley et al. (2014) found that those who lived in more socioeconomically disadvantaged neighborhoods over a longer period of time (>11 years) gained significantly more weight over time than those who lived in

disadvantaged neighborhoods for shorter durations (<11 years) within the Dallas Heart Study; which included a predominantly African American population. Additionally, they also found that individuals who moved to more socioeconomically deprived neighborhoods showed greater weight gain than those who remained in a neighborhood of the same socioeconomic deprivation level or moved to a lower deprivation level (Powell-Wiley, et al., 2015). This research highlights the importance of the neighborhood environment on weight-related outcomes, but also potentially how stress of individuals in these neighborhoods may impact these health outcomes overtime. This chronic stress may lead to many adverse effects, including distressed physiologic functioning, cardiovascular “wear and tear”, and eventually cardiovascular disease (CVD) and obesity (Anderson, 1998).

In line with the bioecological theory and Anderson’s stress model, the neighborhood environment has been shown to be a critical component for understanding weight-related outcomes. Socioeconomically disadvantaged individuals may experience more distress, particularly from the environment (Selye, 1975), and neighborhood deprivation (unemployment, female headed household, households in public assistance, household with a car, federal poverty line, % African American; Powell-Wiley et al., 2014, Powell-Wiley et al., 2015). African Americans living in lower socioeconomic conditions show high stress responses to many socioecological stressors such as racism, unemployment, low income, and concerns with higher crime rates (Rogers, Hummer, Nam, et al., 1996), which have been negatively associated with health outcomes (Baum, Garofalo, & Yali, 1999). Baum et al. (1999) suggested as one’s environment becomes more disadvantaged (i.e. higher crime, less perceived social control, lower SES, etc.), so

may their health, which is particularly critical as African Americans are significantly more likely to live in poverty (National Center for Education Statistics, 2002). Thus, the present study will evaluate the gene by environmental interaction and how environmental stress may increase the likelihood of increased adiposity and physiological stress responses in African Americans.

While SES has shown to influence obesity-related outcomes, another stress related environmental factor is perception of safety in one's neighborhood. Fish, Ettner, Ang, et al. (2010) found that individuals who perceived their neighborhoods as unsafe had a significantly higher BMI than those who perceived their neighborhoods as more safe, highlighting the potential importance of social neighborhood environments. Additionally, Christian, Giles-Corti, Knuiman et al. (2011) found that BMI was independently negatively associated with perceived safety from crime, while other built environment factors (i.e. graffiti and vandalism, perceived food outlets and physical activity destinations) were not. On the contrary, Grafova, Freedman, Kumar et al. (2008) found that individuals who lived in an economically advantaged neighborhood (i.e. upper quartile value of owner-occupied housing tract, % of families with income great than \$75,000, and % of adults with college degree within neighborhood tract) were significantly less likely to be obese in both men and women. Further, Putrik et al., (2015) found that individuals who perceived their environment as safe had lower BMI's. Clark et al., (2013) found that a lack of perceived safety was associated with an increase in waist circumference for women, but not men, whereas Kremers et al., (2012) found that men residing in lower SES neighborhoods reported increased crime rates which was associated with larger BMI's compared to men in higher SES neighborhoods.

Additionally, it has been shown that lower perceived safety from crime is associated with higher BMI and greater risk of obesity (Brown, et al., 2014), and the relationship between perceived safety and BMI is negative (De Bourdeaudhuij et al., 2015). In a study of mothers with young children, it was identified that obesity rates significantly increased across levels of perceived neighborhood safety from safest (37% obese), fairly safe (41% obese) to least safe (46% obese), with more than half of the sample were African American mothers. Wilson, Kirtland, Ainsworth et al. (2004) found that while those in more underserved areas perceived to have more crime, geographical information systems data did not confirm this perception. Perceived crime and destruction of property within a neighborhood (Astell-Burt, Feng, Kolt, & Jalaludin, 2015) and general perceptions of safety (Ziersch, Baum, Macdougall, & Putland, 2005) may be directly linked to feelings of stress.

Neighborhood environmental factors are important to consider when examining stress and obesity outcomes in African American adults. While environmental factors such as neighborhood SES (Matthews & Gallo, 2011) are critical, other factors such as collective efficacy, neighborhood social interaction and neighborhood satisfaction are important to consider as well (Suglia et al., 2016). One social environmental factor that has received increased attention in relation to obesity is collective efficacy. Collective efficacy is conceptualized as the overall ability of a community to instill trust and willingness to help or be helped by others within their neighborhood when help is needed. Cohen, Finch, Bower et al. (2006) found that neighborhoods of low collective efficacy were almost three times more likely to be at risk for overweight compared to neighborhoods with high levels of collective efficacy. Furthermore, based on their 12-

month follow-up longitudinal study, Brown et al. (2011) postulated that individuals with a net of support and opportunity for neighborhood social interactions had a more positive perception of their neighborhood, thus leading to more physical activity and better obesity status. Phongsavan, et al. (2006) highlighted that those who perceived higher levels of trust in their neighborhood had lower levels of stress. Bjornstrom (2011) found that higher collective efficacy was a protective factor for obesity. Specifically, Bjornstrom (2011) argued that collective efficacy is theoretically related to obesity outcomes for three different reasons, which include: 1) it is positively associated with a likelihood that individuals will partake in healthier behaviors and avoid unhealthy ones, 2) individuals with higher collective efficacy are less likely to be socially isolated, and 3) higher collective efficacy is associated with fewer crimes (Curry, Latkin, & Davey-Rothwell, 2008). With that said, the connection between collective efficacy and being less socially isolated, as well as living in neighborhoods that are associated with less crimes is especially salient for the current study.

There has been a greater number of studies that have assessed neighborhood environmental factors such as collective efficacy and SES, but fewer studies specifically on neighborhood social environmental factors like neighborhood social interaction (interacting with neighbors) and neighborhood satisfaction (perception of happiness with overall neighborhood environment) in understanding obesity-related outcomes. Interestingly, McDaniel, Wilson, Coulon, et al. (2015) found that neighborhood social interaction predicted BMI outcomes, such that more neighborhood social interaction was associated with a healthier BMI. While not specifically social interaction, Christakis and Fowler (2007) found that an individual's chances of becoming obese increase by 57% if

they had a friend who also became obese recently, and ultimately concluded that obesity seemed to “spread” via social relationships. However, to date there is limited research that utilizes neighborhood social interaction, and even less for obesity related outcomes. Additionally, there is little research investigating the impact that neighborhood satisfaction has on weight-related outcomes. To date, studies have primarily examined such factors in relation to physical activity and cardiovascular outcomes. For example, one study did find that neighborhood satisfaction was positively associated with blood pressure for individuals who believed their neighborhood was a high threat of crime (Coulon et al., 2011). In a more recent study Siceloff, Coulon and Wilson (2014) found that infrastructure for walking significantly predicted BMI, but only when mediated by moderate to vigorous physical activity (MVPA). These studies have identified that collective efficacy, neighborhood social interaction and neighborhood satisfaction as being important predictors of weight status, as well as highlighting the potential for stress to facilitate negative weight-related outcomes.

2.2 Genetic Pathways, Stress and Obesity

Body Mass Index (BMI) has been estimated to be 40-70% heritable (Day & Loos 2011; Elder, Roberts, McCrory et al., 2012; Schousboe, Visscher, Erbas et al., 2004) while waist circumference (WC) may be even more heritable for African Americans with 76% for men and 77% for women showing heritability (Nelson, Brandon, Wiggins, et al., 2002). Given that underserved ethnic minorities may be more likely to live in low SES and impoverished environments (National Center for Education Statistics, 2002), genetic pathways that link to stress may be most relevant to study in understanding obesity. An important component of the bioecological theory is individual-level factors, including the

one's biological responses. Individuals experience stress through a multitude of stressors, including environment stressors. During times of stress, one stress-response mechanism that is initiated is the sympathetic nervous system (SNS), which can engage the hypothalamic-pituitary-adrenal (HPA) axis to assist in stress regulation. The SNS has many specific roles to play in regulation, but with regards to obesity one of the most important is the regulation of energy expenditure. As energy expenditure is decreased coupled with resting metabolic rate, weight gain would occur (Ravussin, 1995; Spraul, Ravussin, Fontvieille, et al., 1993).

Taking a step back, the human genome consists of deoxyribonucleic acid (DNA). One's DNA is comprised of nucleotide codes that are the blueprint for building proteins and passing genes to one's offspring. One's mother and father each contribute 23 chromosomes, which equates to 46 chromosomes in total. Chromosomes are the structures that contain individual genes. Genes are composed of DNA, and their role is to code for the proteins that make every aspect of a person. Almost all genes come in pairs, one from the mother and one from the father, which are also referred to as alleles. Specifically, there are four chemical bases that could be coded, including Adenine (A), Guanine (G), Cytosine (C), and Thymine (T). If someone has the same alleles in both genes, it is called homozygous, and if they are carrying different alleles they are called heterozygous. Single nucleotide polymorphisms (SNPs) are polymorphisms that describe common variation in the genotype that can result in a change in the phenotype. Additionally, when individuals possess a SNP for a less common allele (also known as the minor allele), it may increase an individual's susceptibility to negative health outcomes. In order for a substitution of bases (A, T, G, C), which is a specific mutation,

to be considered a SNP it must occur in at least 1% of the population, and subsequently increases one's risk for developing an adverse health outcome. Interestingly, almost 90% of all variation in the human genome is caused by SNPs. However, even though SNPs do effect the function of protein as well as gene expression, by no means are they generally the single cause of disease development but rather generally increase the risk. Notably, SNPs represent the importance of the role that genetics play in complex chronic disease development.

There is a strong relationship physiologically between stress and obesity-related outcomes. Studies have shown that sympathetic nervous response is blunted for utilizing energy intake when individuals have metabolic syndrome and insulin resistance (Straznicky, Lambert, Masuo, et al., 2009). Additionally, several studies have shown that during weight gain there is elevated sympathetic nerve activity and increased insulin levels (Iwashita, Tanida, Terui, et al., 2002; Masuo, Katsuya, Fu, et al., 2005; Masuo, Katsuya, Hawaguchi, et al., 2005; Gentile, Orr, Davy, et al., 2007; Barnes, Lapanowski, Conley, et al., 2003). Furthermore, other studies have shown that during weight loss there is reduced sympathetic nerve activity and insulin levels (Masuo, Mikami, Ogihara, et al., 2001; Andersson, Elam, Wallin, et al., 1991; Straznicky, Lambert, Lambert, et al., 2005; Masuo, Mikami, Ogihara & Tuck, 2001; Tuck, Sowers, & Dornfeld, 1983; Grassi, Seravelle, Colombo, et al., 1998). The SNS mediated impact on energy expenditure is derived through skeletal muscle activity, with Beta-receptors and catecholamines as the catalysts (Yang & McElligott, 1989). At a molecular level, lipolysis occurs by way of B1, B2, and B3 receptors, as catecholamines bind to adrenoceptors. B-receptors couple to G-proteins which then activate adenylate cyclase which increases the production of cyclic

adenosine monophosphate (cAMP). The activation of cAMP then initiates protein kinase A (PKA) which activates the phosphorylation of hormone sensitive lipase (HSL) and increases the hydrolysis of triglycerides leading to mobilization of fatty acids, and subsequently lipolysis. Additionally, B1 adrenoceptors stimulate lipolysis of adipose tissue, B2 stimulate glycogenolysis and gluconeogenesis, and B3 adrenoceptors stimulate lipolysis of adipose tissue (Masuo & Lambert, 2011). Each of the three different B-adrenoceptors are functional in human fat cells, with B1 and B2 being the most active (Arner, 2005). Previous studies have shown that B-adrenergic stimulation from the SNS not only significantly modulates pre- and postprandial energy expenditure (Blaak, van Baak, Kempen, et al., 1993; Hagstrom-Toft, Enoksson, Moberg, et al., 1998; Enoksson, Talbot, Rife, et al., 2000), but also modulates total daily energy expenditure (Iwashita, et al., 2002; Monroe, Seals, Shapiro, et al., 2001; O'Dea, Esler, & Leonard, 1982). Additionally, the SNS works simultaneously with the HPA axis to adjust one's biological state to stressors (acute and chronic). Furthermore, catecholamine-induced lipolysis may be an important factor in understanding obesity particularly for abdominal obesity and visceral fat distribution (Gasteyger & Tremblay, 2002; Mirsa & Vikram, 2003). Specifically, there may be a redistribution of fatty acids during times of excess catecholamines, which could include times of increased psychological stress (Arner, 2005). It is important to consider how these two stress mechanisms impact weight-related outcomes.

In an effort to identify mechanisms of stress that contribute to weight-related outcomes, the SNS pathway may be promising. Recent research has pointed to SNP's within the B-adrenergic receptors that may be polymorphic, which may affect SNS

energy expenditure leading to obesity. Two SNS SNP's that this study will focus on and highlight in an effort to better understand the pathophysiology of obesity are B1- and B2-adrenergic receptors. The B1-adrenoceptor polymorphism is the Arg389Gly (rs1801253), and has been associated with obesity (Dionne, Garant, Nolan, et al., 2002; Tafel, Branscheid, Skwarna, et al., 2004; Linne, Dahlman, & Hoffstedt, 2005; Gjesing, Anderson, Albrechtsen, et al., 2007; Nonen, Yamamoto, Liu, et al., 2008). However, results are not conclusive, and thus further research on this SNP will improve our understanding of its impact on obesity. The B2-adrenoceptor is Arg16Gly (rs1042713), and has been associated with obesity, elevated blood pressure and diabetes mellitus (Meirhaeghe, Helbecque, Cotel, et al., 2000; Masuo, Katsuya, Fu, et al., 2005; Masuo, Katsuya, Kawaguchi, et al., 2006; Masuo et al., 2006; Petrone, Zavarella, Iacobellis, et al., 2006). It is believed that by changing the amino acid sequence in Beta-receptor SNP there is the likelihood that the allele mutations could be changing the function of the B-adrenoceptors (Reihnsaus, et al., 1993). With the importance that both of the SNP's have on the SNS and particularly risk factors for obesity, the current study will utilize these SNP's by utilizing a risk score (average risk of both SNPs collectively) to assess their impact on weight-related outcomes given their neighborhood social environment.

The second stress pathway, relevant to this study, which may play a critical role in understanding obesity is the HPA-axis. The initiation of the HPA-axis during a stressful event triggers a neuroendocrine stress response. Specifically, cortisol steroid hormones are released which can trigger a cascade of other neuroendocrine functioning. Cortisol hormones are a chemical messenger that communicate with bodily tissues and that is carried through the blood stream. Through its travels through the blood stream, cortisol

assists in the functioning and regulation of immune, metabolic, cardiovascular and cellular systems throughout one's body. As cortisol travels throughout the body, it binds to the intracellular glucocorticoid receptors (GR) which are in almost every cell within the human body. As it enters the cells, it translocates to the cell nucleus where it binds reversibly on their target DNA molecules (Constanti & Bartke, 1998). This highlights the influential impact that cortisol has on organs and tissues throughout the body. However, the sensitivity of GR within cells is critical for understanding the impact that cortisol has on tissues and organs; specifically, a more sensitive GR would exhibit increased binding and then impact the target tissue/organ (Constanti & Bartke, 1998). As cortisol is secreted, the neuroendocrine system is stimulated to physiologically adapt the body to internal, behavioral or environmental stressor, including acute or chronic. While cortisol is beneficial when attending to acute stress in an effort to achieve homeostasis, it is the chronic stress (i.e. neighborhood environment, job strain, low collective efficacy, low neighborhood satisfaction, low neighborhood social life, etc.) that instigates maladaptive, hyperarousal of the HPA axis and subsequent cortisol release. Given that African Americans have a high probability of experiencing environmental stress (National Center for Education Statistics, 2002), prolonged activation of the HPA-axis may lead to chronic physiological stress in this population, and it may be informative to assess the additional impact of cortisol on weight-related outcomes, ultimately.

Specifically, the HPA-axis SNPs will be the focus of this study in an effort to better understand the pathophysiology of obesity and stress reactivity are glucocorticoid receptors. Looking at glucocorticoid receptor genes are important because they could influence the body's physiological response via HPA activation. This activation can be

achieved by either increasing tissue sensitivity and/or differential regulation of the system by way of feedback mechanisms. More specifically, *Bcl1* (rs41423247) has been associated with increased abdominal obesity (van Rossum & Lamberts, 2004) as well as higher response to specifically psychosocial stress (Kumsta, et al., 2007; Stevens, et al., 2004) and higher blood pressure (Di Blaiso et al., 2003). Additionally, *FKBP5* (rs1360780) has been functionally linked to increased stress reactivity, which contributes to the development of chronic stress conditions like posttraumatic stress disorder and depression (Binder et al., 2008; Ising et al., 2008; Kirchheiner et al., 2008; Roy, Gorodetsky, Yuan, Goldman, & Enoch, 2010). These SNPs could be critical in understanding the nature of chronic stress reactivity has on obesity outcomes, thus it's important to include in this study.

As previously discussed, central adiposity disproportionately impacts African American adults (Wang & Beydoun, 2007; Bidulescu, Liu, Hickson, et al., 2013). Research has identified many factors influencing abdominal adiposity, including psychological stress which has been found to be associated with hyperarousal of the HPA axis hormone response, on increasing the amount of abdominal fat stored (Epel, McEwen, Seeman, et al, 2000; Phillips, Roseboom, Carroll, et al. 2012). While there are many psychological stressors (i.e. collective efficacy, neighborhood social life and satisfaction) that impact stress, one specific factor that increases psychological stress is neighborhood safety from crime (Fish, et al., 2010; Karb, Elliot, Dowd, et al., 2012; Stafford, Cummins, Ellaway, et al., 2007; Glass, Rasmussen, & Schwartz, 2006). Additionally, it is through stressors such as perception of lack of neighborhood safety that may lead to the chronic dysregulation of the HPA axis by way of cognitive and/or

behavioral factors which may contribute to obesity (Beenackers, Kamphuis, Burdorf, et al., 2011; Do, Diez Roux, Hajat, et al., 2011; Clark, Ommerborn, Hickson, et al., 2013; Pham, Ommerborn, Hickson, et al., 2014). Furthermore, it may be important to look at gene by environment interactions on cortisol as well because of HPA-axis dysregulation.

Given previous research, evidence suggests that adiposity may be influenced by environmental neighborhood stress factors, as well as neuroendocrine processes and genetic risk. Specifically, adiposity is thought to be partially heritable as a complex, polygenic disorder (Choquet & Meyre, 2011). Waist circumference has been estimated to be heritable, as studies have ranged between 18%-63% (Elder, Roberts, McCrory et al., 2012; Schousbe, Visscher, Erbas et al., 2004); whereas in an African American population, Nelson, et al. (2002) found that additive genetic effects in a small African American sample accounted for 77% of the variance in men, and 76% of the variance in women for waist circumference.

Psychological and physiological stress can greatly impact the body. The term “stress” has been described as a negative, adverse, or overwhelming experiences, including both psychological and physiological. Physiologically, stress occurs in reaction to an environmental stimuli that may occur regardless of whether one’s body perceives the stimuli as positive or negative (Glanz & Schwartz, 2008). However, from a psychological perspective, stress is considered any individual subjective cognitive experience that initiates stress. Important to consider though is that psychological stress not only includes the stress-related cognitions, but also the coping that occurs after, which ultimately impacts the individual’s health and well-being (Lazarus, 1991). According to Lazarus and Folkman (1984), stress is present when a person experiences a

situation/stressor that either matches or exceeds their ability to manage the situation. Initially, an individual's primary appraisal evaluates the threat to assess for significance and potential distress. Generally, the person is able to judge the events significance as stressful, challenging, controllable, benign or irrelevant (Glanz & Schwartz, 2008). Additionally, the secondary appraisal assesses their ability to control the situation including the resources that they have at their disposal (Lazarus & Folkman, 1984). In short, secondary appraisal focuses on what the person can do given the event they experienced. There are a few different key appraisals that are common, which include one's perception of their ability to change the situation, one's perception of their ability to manage their emotional reaction, and finally one's perception of their ability of their coping resources to be effective (Lazarus & Folkman, 1984).

Perceived stress has not only been linked to obesity outcomes, but chronic stress has shown to have a continual impact over time. Block, He, Zaslavsky, et al. (2009) found that for both men and women, those with high baseline BMI, weight gain measured over 9 years was associated with increasing perceived psychosocial stressors (i.e. job-related demands, lack of decision authority, perceived constraints in life, etc.), compared to those with low baseline BMI. Fowler-Brown, Bennett, Goodman, et al. (2009) found that higher baseline levels of perceived stress significantly predicted higher adjusted percentage increase in BMI for African-American females over a 13-year follow-up study, but did not find perceived stress to significantly predict BMI for African-American males. Furthermore, Epel, McEwen, Seeman, et al. (2000) concluded that stress-induced cortisol secretion may contribute to central adiposity, and may also be a link between psychological stress and obesity. Finally, Richardson, Arsenault, Cates, et al. (2015)

found that perceived stress was positively associated with severe obesity in a female population. These studies highlight that perceived stress not only influences psychological stress, but also physiological stress, as well as the interplay between psychological and physiological stress. With this in mind, it is important to consider genetic, physiological and psychological stress when trying to understand obesity, as they are all associated with increased weight status. Not only will this study look at the neighborhood social environment as potentially being stressful and impacting weight-related outcomes, but it will also examine neighborhood social environment by genetic interaction on a physiological stress indicator (i.e. cortisol).

2.3 Gene by Environment Interaction on Obesity

There is a growing literature on understanding the effects of gene by environment interactions on obesity outcomes. A gene by environment framework allows for further understanding of weight-related outcomes as the interaction of stressors, particularly neighborhood social environmental stress, and beta-adrenergic receptors and glucocorticoid receptors may increase SNS and HPA- axis arousal potentially contributing to increased adiposity over time. The bioecological theory provides a strong foundation and framework for understanding the impact that genes, neighborhood social environmental factors, and subsequently stress (including psychological and physiological processes) have on understanding obesity. Additionally, bioecological theory postulates that not only is it important to study the impact that gene by environment interactions have on health outcomes, but that studying the change over time is critical and is not to be ignored (Bronfenbrenner, 2005; Tudge et al., 2009). For the gene by environment interaction in the present study, a dual risk hypothesis is

conceptually assumed, as the impact that poorer neighborhood social environment on weight-related outcomes is expected to be worse for those with higher genetic risk, and poorer neighborhood social environment over time. Ultimately, this study aims to expand upon the limited longitudinal research on understanding how environmental stress and genetic factors interact to influence weight-related outcomes over time in African American adults.

There are conceptually several ways to test these gene by environment interactions using an additive risk framework or a susceptibility framework. More specifically, there are several ways to conceptualize gene by environment interactions. A gene by environment interaction can be defined as genotypes that only show their effect in the presence of a specific environment (van Vliet-Ostaptchouk, Sneider & Lagou, 2012). Alternatively, gene by environment interactions can be additive such that both environmental and genetic risk are predictive of worse health outcomes (e.g. obesity). Gene by environment interactions can also be defined based on the differential or susceptibility hypothesis which suggests that the combined effect of genetic and environmental factors lead to differential health outcomes depending on whether the environmental factor is negative or positive in influencing the effect of the genetic susceptibility or risk (Ahmad, Varga & Franks, 2013). With this in mind, the gene by environment framework is appropriate as it allows for genetic factors to interact with contextual, environmental factors that may influence perceived stress, physiological processes and subsequently weight-related outcomes.

There are relatively few studies that have utilized cross-sectional gene by environment interactions analyses, but even fewer studies assessing longitudinal

outcomes. While currently much of the past literature focuses on lifestyle factors such as diet (Corella et al., 2011) and physical activity (Alonso et al., 2005; Andreasen et al., 2008; Corella et al., 2011; Jacobsson et al., 2009; Kaakinen et al., 2010; Lee et al., 2010; Vimalleswaran et al., 2009 Berentzen, Dalgaard, Petersen, Pedersen, & Sorensen, 2005; Cauchi et al., 2009; Edwards et al., 2012; Fontaine-Bisson, Thorburn, Gregory, Zhang, & Sun, 2014; Kilpeläinen et al., 2011; Mitchell, Church, Rankinen, Earnest, & Blair, 2010) as environmental factors, there is little research on understanding neighborhood social environment and crime as environmental factors. However, there are a few important studies that utilize neighborhood environmental factors in understanding health outcomes. For example, Foraita, Gunther, Gwozdz, et al. (2015) found that there was an FTO (rs9939609) by socioeconomic status interaction on obesity outcomes. Additionally, they identified that children who were not carrying a risk allele (TT) and who had a more favorable environment, showed reduced obesity outcomes (i.e. BMI z-score, waist-to-hip ratio, skinfold, and % body fat) in a European population. Longitudinally, Li et al., (2010) found a significant interaction between physical activity and a genetic risk score on BMI, such that physical activity buffered the effect of genetic predisposition over time (4 years). Lagou, Liu, Zhu, et al. (2011) found similar results with socioeconomic status and a SNP in ADRB2 in a Caucasian/African-American adolescent (ages 12-19) population. Additionally, Wickrama, O'Neal and Lee (2013) utilized latent growth curve analysis to assess BMI trajectories in more than 14,000 adolescents (age range, 12-19). They found that community socioeconomic adversity (i.e. proportion of families in poverty, proportion of single-parent families, proportion of adults employed in service industry, and proportion of unemployed men) and genetic susceptibility (summed score

of variable number tandem repeats in DAT1, DRD4, 5HTTLPR, and MOAO) on BMI showed significant interactions, consistent with a dual risk hypothesis. They found that those who experienced higher socioeconomic adversity resulted in greater BMI's (main effect), and those who also experienced greater genetic susceptibility showed the greatest negative effects on BMI. Additionally, community adversity was positively associated with BMI trajectories for high and low genetic susceptibility groups, but those in the high genetic susceptibility had a steeper trajectory than those with low genetic susceptibility (Wickrama, et al. 2013).

While these studies have started to build a foundation for gene by neighborhood social environment interactions, there is still an abundance of room for growth. While these studies utilized children/adolescent populations, they provide good examples for furthering our understanding of neighborhood social environmental and genetic variables, as well as advanced statistical modeling that include longitudinal study designs. These studies are enlightening, especially as research has shown that obesity in adolescence tracks into adulthood (Singh, Mulder, Twisk, et al., 2008). However, there are gaps in the literature. This study will expand on past literature in three important ways, including placing greater importance on broader variables in the social environmental (neighborhood social factors), a stronger emphasis on identifying and testing important pathways to better understand the importance of gene by environment interactions for obesity (such as stress as a mediator), and by conducting a longitudinal analysis in an effort to attempt to identify more cause and effect relationships of gene by environment interactions (assessing baseline, 12-, 18- and 24-month time points). Ultimately, this study will attempt to narrow the literature gap for better understanding obesity through

testing gene by environment interactions with a strong focus on stress as an importance factors in understanding these relationships.

1.4 Study Aims

The current study expands on past research in a number of important ways by examining stress related gene by environment interactions on obesity outcomes in African American adults (see Figure 1). Previous studies have primarily conceptualized the environment as behavioral (physical activity, or intake of sweetened beverages). Furthermore, this study focuses specifically on an understudied population of African Americans living in a low-income area of the United States. Thus, the purpose of this study is to test the stress-related gene by environment effects on obesity outcomes in underserved African American adults over a 24 month period (including baseline, 12 month, 18month and 24 months (see Figure 1).

Aim 1. To examine how genetic risk moderates the relationship of neighborhood social environment on weight related outcomes (i.e. waist circumference). Statistically modeling the gene by environment interaction in this data will allow an understanding of weight related outcome longitudinally (i.e., over 2 years that include four corresponding time points; Figure 1).

- a. Given a dual risk hypothesis, it is hypothesized that those who experience the highest genetic risk (i.e. high genetic risk index score) and high environmental stress (i.e. low neighborhood satisfaction, low neighborhood social life, low collective efficacy or high perception of safety from crime) will exhibit the greatest waist circumferences.

Aim 2. To examine how genetic risk moderates the relationship of neighborhood social environment on physiological stress (i.e. cortisol). Statistically modeling the gene by environment interaction in this data will allow for an understanding of physiological stress.

- a. Given a dual risk hypothesis, it is hypothesized that those who experience the highest genetic risk (i.e. high genetic risk index score) and high environmental stress (i.e. low neighborhood satisfaction, low neighborhood social life, low collective efficacy or high perception of safety from crime) at 18 months will exhibit the greatest cortisol levels at 24 months (Figure 2).

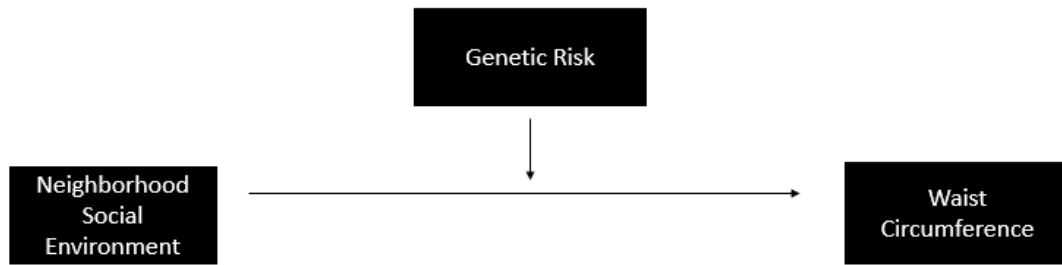


Figure 2.1. Conceptual risk model of interacting gene by environmental risk predicting waist circumference for aim 1.

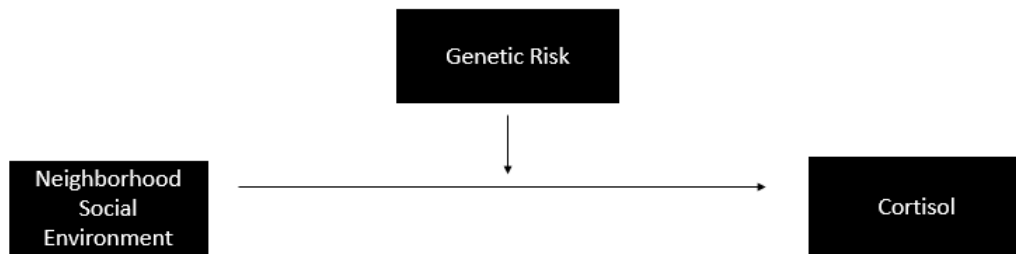


Figure 2.2. Conceptual risk model of interacting gene by environmental risk predicting cortisol for aim 2.

CHAPTER 3

METHOD SECTION

3.1 PARTICIPANTS

Study participants were all African-American adults who were recruited from the Positive Action for Today's Health (PATH) study (Wilson, et al, 2010). The PATH Trial aimed to investigate the effects of a 24-month environmental intervention to improve access and safety for walking in three matched (i.e. on crime rates, physical activity rates, prevalence of ethnic minorities, and level of annual income) low-income communities in the Southeastern United States. The three communities were randomly assigned to either 1) a police-patrolled walking program that included a social marketing component to promote physical activity, 2) a police-patrolled walking only program, or 3) control group that included general health education information. Data were collected at baseline, 12-, 18-, and 24-months. More specifically, all participants in the PATH study were given the opportunity to participate in the secondary study which assessed their genetic and cortisol data.

There were 434 participants in PATH, split among the three communities. Of the original sample, 228 participants agreed to complete additional stress scales, as well as have their cortisol and genetic samples collected. For Aim 1, there were five individuals with outlying BMI's of which they were not included in the final analysis. For Aim 2, there were only 145 participants who provided genetic data and waking cortisol samples.

There were two different types of recruiting techniques utilized for the PATH study. First, participants were recruited via a random list of households in the given

census tracts, which were provided by the University of South Carolina Survey Lab and Survey Sampling Group, and which were purchased from the Survey Sampling Incorporated. After acquiring the lists of addresses, recruitment letters were sent to the potential participants, as well as a follow-up phone call and/or a member of the community steering committee made a personal visit to their home. Out of 1216 participants reach out to, 581 declined to participate, with a total of 635 invited to participate. Of the 635 invited, a total of 231 participants enrolled and provided baseline data. A total of 54% of the study's sample came from this strategy. The second type of recruitment strategy came in the form of flyers being distributed, ads in local newspapers, posters/banners placed in local churches, schools and businesses around each of the communities. A total of 46% of the sample was recruited through these volunteer advertisements.

Inclusion criteria for PATH included: 1) African American (three of four grandparents of African heritage); 2) 18 years old or older; 3) no plans to move during the next two years; 4) no medical condition that would limit participation in moderate intensity physical activity including life-threatening illness; 5) residing in the census area of the target community; 6) availability to participate in the evaluations and intervention over the duration of the study (24 months); 7) controlled blood pressure (<180/<110) and blood sugar levels (<300 non-fasting, \leq 250 fasting).

3.2 PROCEDURES

Informed consent was conducted by either a doctoral candidate student or by a trained staff member. All staff members/doctoral students completed research and ethics trainings, and were specifically chosen based on demonstration of skills and sensitivity

for working with this underserved population. Throughout the PATH trial, and especially during the consenting process, participants were highly encouraged to ask questions about the study, as well as their role in participating. Study participants completed several psychosocial questionnaires, had anthropometric data assessed, and had a 7-day accelerometer assessment conducted at baseline, 12-, 18-, and 24-month time points. All measures were obtained by certified and trained staff.

While most of the data collected were in conjunction with the PATH study, the genetic and cortisol data were collected as a secondary study (Understanding Heredity and the Environment in African-American Risk of HyperTension; HEART; Coulon, Wilson, Van Horn, et al., 2015) that utilized PATH study as a way to recruit. Consequently, not all participants in the PATH study were willing to have their genetic and cortisol samples collected, but almost half of the participants were willing (47%). Additionally, given the sensitive nature of having participant's genetic and physiological data collected, this data was part of an additional study and not specifically part of the PATH study, researchers took extra time to ensure that participants completely understood their rights as research participants, the study design and purpose, as well as potential risks, benefits, and confidentiality of the study.

With regards to the genetic and cortisol data collection, the HEART trial had a separate protocol that employed at the 24-month PATH trial time point. More specifically, PATH trial participants that also had their genetic and cortisol data collected were informed that their participation was completely optional, and that they had the right to choose not to further participate at any point with no repercussions in the PATH trial or any future studies. Next, they were informed that they were being selected because

research has shown that African Americans are most affected by high rates of weight-related outcomes (WC and BMI) and blood pressure in the southeastern United States. The purpose of the HEART study was to increase understanding of how environmental factors and hereditary factors impacted health outcomes (including weight-related outcomes and blood pressure). Third, participants were informed they would be participating in a 45-90 minute visit, which included completing surveys, providing a saliva sample via salivettes and a genetic sample via buccal swabs. Next, participants were ensured that their genetic and cortisol samples would be confidential (and only co-investigators have access to their locked data), used for the purposes specified in the consent form, and they were given a detailed explanation of what would happen to their samples once they provided them. Finally, participants were assured that there was little risk involved in the collection process of the samples, and that while they may not personally benefit from the study participation, that it may help contribute to our understanding of how environmental and genetic factors contribute to health disparities, particularly in African American communities. After completing the study, participants were compensated for their time by either receiving a gift bag or \$10. Participants with uncontrolled blood pressure (>180 and/or >110) were referred to seek medical attention immediately.

3.3 MEASURES

Anthropometrics. Participants had their height, weight and waist circumference measured at all four time points (baseline, 12-, 18-, 24-month). Height and waist circumference was taken twice each, and if either were discrepant by more than 1cm, the trained measurement staff member would take a third measurement. Height and waist

circumference was measured with a non-tension tape measure. The same protocol occurred for weight as well, in that if the first two measurements were off by more than 1kg, the staff member would measure a third time. All measurements were averaged, either two or three measurements each, to create one final measurement for each anthropometric measure at each time point. BMI was calculated for all time points as well. More specifics provided below on data collection protocol.

Demographics. Participants completed a demographic questionnaire that inquired about age, sex, highest education level, income, and marital status (See Appendix F).

Neighborhood Satisfaction. Participants answered questions to assess their satisfaction with their neighborhood using a subscale of the NEWS (See Appendix C; Saelens, Sallis, Black, & Chen, 2003). Questions included, “How satisfied are you with highway access from your home?” and “How satisfied are you with noise from traffic in your neighborhood?” Participants answered 17 questions on a 4-point Likert scale, where higher scores indicated higher satisfaction with their neighborhood. All items were averaged to create a neighborhood satisfaction score. Previous studies have shown this scale to have high internal consistency ($\alpha = 0.86$; Morris, McAuley, & Motl, 2008), and the current study found adequate internal consistency as well ($\alpha = 0.82$). Additionally, factorial and criterion validity for this scale has been established (Cerin, Conway, Saelens, et al., 2009). The sample utilized to establish validity for this scale included 27% African Americans. Finally, this subscale has shown strong construct validity; however, the sample utilized had very few African Americans (1.9%; Saelens, et al., 2003). Neighborhood satisfaction has typically not been conceptualized within a bioecological model and weigh-related outcomes, but rather focused exclusively on health behaviors

such as physical activity (Westaway, 2007; Kruger, Reischl, & Gee, 2007; Morris, McAuley, & Motl, 2008).

Neighborhood Social Life. Participants answered questions based upon how many days they participated in a certain activity in the past month in their neighborhood (See Appendix D; Parker, Lichtenstein, Schulz, et al., 2001). Activities assessed included, “wave to a neighbor,” and “sought advice from a neighbor.” All items were averaged to create a neighborhood social life score. Neighborhood social life was assessed using a 9-item self-report measure adapted from Parker and colleagues community social interaction scale, where higher scores indicated more interactions with their neighbors (Parker, Lichtenstein, Schultz, et al., 2001). Parker et al., (2001) were able to establish construct validity for this scale, utilizing a sample 97% African-American women from communities surrounding Detroit, Michigan. The social life measure in this study demonstrated adequate internal consistency ($\alpha = 0.84$).

Collective Efficacy. While collective efficacy is typically a community level variable, this study was only able to assess it at an individual level. With that said, the collective efficacy scale utilized assessed an individual’s perceptions of trust and willingness to help others for the overall good within their neighborhood (See Appendix B; Sampson, Raudenbush & Earls, 1997). This scale has two separate subscales (informal social control & social cohesion and trust), consisting of five items each. For example, a question from the Informal Social Control subscale would be “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?” An example from the Social Cohesion and trust would be, “People around here are willing to help their neighbors?”

Previous research has reported that these scales have strong construct validity (Sampson, et al., 1997) as well as high internal consistency, which suggests that the two subscales mutually assesses collective efficacy (Cohen, et al., 2008; Sampson, et al., 1997). This study found adequate internal consistency for the informal social control subscale ($\alpha = 0.84$), and adequate internal consistency for the social cohesion and trust subscale ($\alpha = 0.68$).

Perception of Safety from Crime. There were 6 items taken from a subscale of the Neighborhood Environment Walkability Survey (NEWS) to assess participants' perceptions around neighborhood safety (See Appendix A; Saelens, Sallis, Black, & Chen, 2003). Items included, "There is a high crime rate in my neighborhood" and "My neighborhood streets have good lighting at night." Responses were given on a 4-point Likert scale. After reverse scoring some items, higher scores indicated greater perceptions of neighborhood safety. This scale showed acceptable internal consistency ($\alpha=.65$) within this sample. Additionally, Saelens, et al (2003) found this subscale to have strong construct validity; however, there were few African Americans in the sample to test for construct validity.

Waist Circumference. Trained and certified staff assessed WC on the "natural waist" line (Lean, Han & Morrison, 1995). Measurements were collected in centimeters with a non-tension tape measure. Participants stood erect with feet together, abdomen relaxed, and with arms to the side. Two measurements were taken per participant, with an additional measurement taken if values differed more than 1.0 cm. To ensure accuracy, measurement staff monitored the tape measure for horizontal alignment by working in pairs or using a mirror when working independently.

Genetic Risk. Genetic material collected via buccal swabs were delivered with and independent identification system not directly linked to PATH IDs to the biochemistry laboratory for genotyping. Extra precautions were taken to ensure the confidentiality of genetic data. Specifically, gene samples received completely different identification codes, which were distinct from all other study identification codes. These separate codes were only available to the study Principle Investigator and Laboratory Director. DNA were stored at -80°C until samples were sent for analysis.

For the analyses, this study will utilize a genetic risk score. After receiving the genotypes from the laboratory, risk was quantified in a single variable by indexing the presence of nucleotides from the targeted SNPs that are linked to increased risk of negative cardiovascular and weight-related outcomes. Each SNP was issued a score depending on whether the individual exhibited a genotype of homozygous (Table 2) for low-risk allele (score=0), heterozygous (score=1), or homozygous for high-risk allele (score=2). This study separated the 2 HPA-axis SNPs and 2 SNS SNPs into two separate genetic risk scores, and utilized them as separate predictors for each participant. This was conducted by averaging the 2 risk alleles per pathway (i.e. HPA or SNS), which created two separate risk scores for each participant. Participants were included in the analyses if they had genotype data for at least one of the two SNPs for each pathway. If a participant did not have at least one SNP for either the SNS or HPA-axis pathway model, then they were excluded from that respective analysis. Correlational analyses showed no significant correlation between the HPA-axis SNPs (rs41423247, rs1360780; $r=0.05$, $p=.21$), and the SNS SNPs (rs1801253, rs1042713; $r=0.01$; $p=0.73$).

Cortisol. Research has shown that saliva sampling offers a valid measure of basal cortisol activity (Levine, et al., 2007). This study utilized waking cortisol data via saliva samples. Salivettes were utilized to collect the saliva samples. The saliva samples were collected immediately after they woke up in the morning (waking cortisol), as participants were provided both verbal and written instructions. Participants were instructed to chew on their provided sterile cotton salivette for three minutes to appropriately collect the saliva sample. Instructions also stated to collect the sample prior to rinsing their mouths or brushing their teeth in the morning. Adherence studies have shown that individuals typically collect their cortisol samples within 6 minutes of waking, and those samples that are collected within 15 minutes of waking are stable values of cortisol concentrations (Dockray, Bhattacharyya, Molloy, & Steptoe, 2008).

The waking cortisol data was positively skewed, thus appropriate measures were taken. First, cortisol samples were removed from the analyses that were possible physiologically. Next, of samples that were possible but were still 3 SD above the mean, they were truncated at the highest value. Finally, the data were transformed via the natural log function, which has been utilized as a common transformation in other studies utilizing cortisol (Champaneri et al., 2013; Godfrey et al., 2014; Hackman, Betancourt, Brodsky, Hurt, & Farah, 2012; Vreeburg et al., 2009).

3.4 Data Analytic Plan

Aim 1 - Data Analytic Plan. A growth curve analysis approach was used to allow for the estimation of effects occurring at multiple time points within an individual. Models were developed with the R statistical software package, version 3.1.2 (R Development Core Team, Vienna, Austria), using a stepped approach. Given the

longitudinal study design, random intercepts and random slopes for time were included in each model, based upon recommendations by Raudenbush & Bryk (2002).

A growth curve analysis was used, and an extensive model building process occurred initially to determine a baseline model that would be utilized in further model building for the HPA axis and SNS models. This first model building procedure involved testing a series of model with increasing complexity to predict waist circumference. To determine which model best fit the data, a series of chi-square difference tests were conducted. When a more complex model fit the data better than a more parsimonious model, as indicated by a significant chi-square test statistic, the more complex model was retained. However, when the more complex model did not yield significantly better fit, then the more parsimonious model was retained as the final model for this phase of model building. First, the unconditional model was run, which only included a random intercept. The next model was expanded to include time as a fixed effect. The linear growth model with a random intercept and time as a fixed effect was a significantly better fitting model than the unconditional model that did not include time, $\chi^2(1) = 13.26$, $p < .001$. The next model tested included a random intercept and random slope (i.e., for time on waist circumference), and this model fit significantly better than the model in which time was modeled as a fixed covariate, $\chi^2(1) = 15.25$, $p < .001$. The fourth model tested expanded the prior model by including time² (i.e., quadratic time) as a fixed. However, this model was not a significantly better fitting model than previous model, $\chi^2(1) = 5.92$, $p = .12$. Thus, the model retained as the best fitting model, to be used as the baseline model for subsequent modeling, was a linear growth model that did not include

the quadratic time term and incorporated random intercepts and random slopes for time on the outcome.

AIM 1. For aim 1, two models were examined with waist circumference as the outcome. The first aimed to understand how the HPA axis impacts waist circumference and the second was to understand how SNS impacts waist circumference. In both instances, the best fitting model outlined above (i.e., the model with a random intercept and random effect of time) was utilized as the baseline model for a series of model comparisons which iteratively included predictors as guided by theory. In line with the method described above, the best fitting models for HPA axis and SNS were determined with a series of chi-square difference tests. Predictors of interest included neighborhood social environmental factors, genetic risk (i.e., respective to the HPA axis or SNS model) and the interaction of neighborhood social environment with genetic risk. The largest model examined included additional factors as covariates (not shown; community, baseline age, and sex) and was as follows:

Level 1: $WC_{ij} = \beta_{0i} + \beta_{1i}(\text{Time}_{ij} - 12\text{months}) + e_i$

Level 2:

$$\begin{aligned} \beta_{0i} = & \gamma_{00} + \gamma_{01}\text{GeneticRisk} + \gamma_{02}\text{NeighborhoodSatisfaction}_i + \\ & \gamma_{03}\text{NeighborhoodSocialLife}_i + \gamma_{04}\text{CollectiveEfficacy}_i + \\ & \gamma_{05}\text{SafetyFromCrime}_i + \gamma_{06}\text{GeneticRisk} * \text{NeighborhoodSatisfaction}_i + \\ & \gamma_{07}\text{GeneticRisk} * \text{NeighborhoodSocialLife}_i + \\ & \gamma_{08}\text{GeneticRisk} * \text{CollectiveEfficacy}_i + \gamma_{09}\text{GeneticRisk} * \text{SafetyFromCrime}_i + \\ & u_0 \\ \beta_{1i} = & \gamma_{10} + \gamma_{11}\text{GeneticRisk}_i + \gamma_{12}\text{NeighborhoodSatisfaction}_i + \end{aligned}$$

$$\begin{aligned}
& \gamma_{13}\text{NeighborhoodSocialLife}_i + \gamma_{14}\text{CollectiveEfficacy}_i + \\
& \gamma_{15}\text{SafetyFromCrime}_i + \gamma_{16}\text{GeneticRisk}*\text{NeighborhoodSatisfaction}_i + \\
& \gamma_{17}\text{GeneticRisk}*\text{NeighborhoodSocialLife}_i + \\
& \gamma_{18}\text{GeneticRisk}*\text{CollectiveEfficacy}_i + \gamma_{19}\text{GeneticRisk}*\text{SafetyFromCrime}_i + \\
& u_1
\end{aligned}$$

Please note that in the equations above, the genetic risk variable and terms including genetic risk are used generically to encompass both the SNS and HPA axis model, however two series of model building will occur. One will include HPA axis as the genetic variable and the other SNS. In the first equation, $\gamma_{01} - \gamma_{05}$ represent the direct effects of neighborhood social environment and genetic risk on WC at the 12 month time point, and $\gamma_{06}-\gamma_{09}$ represent the impact of the interactions of neighborhood social environment with genetic risk on the 12 month time point. The primary parameters of interest for each model will $\gamma_{06}- \gamma_{09}$, which provide evidence for the impact of the interaction of neighborhood social environmental risk by genetic risk on the overall level of waist circumference. The parameters in the subsequent equation follow in the same manner with $\gamma_{16}- \gamma_{19}$ representing the parameters of interest, that is the hypothesized interactions' influence on an individual's rate of linear change over time in waist circumference.

AIM 2 – Data Analytic Plan. A linear regression analysis approach was used. Models were developed with the R statistical software package, version 3.1.2 (R Development Core Team, Vienna, Austria). A linear regression was utilized to identify predictors at 18-months for waking cortisol at 24-months. A model different from the Aim 1 model was used because the outcome data (waking cortisol) was only collected at

the 24-month time point. Therefore, in an effort to identify any predictors of waking cortisol, predictor data from the time point before was utilized.

AIM 2. For aim 2, the following model was regressed on waking cortisol outcomes using relevant covariates, neighborhood social environmental factors, genetic risk and the interaction of neighborhood social environment with genetic risk. The model also included additional factors as covariates (not shown; community, baseline age, and sex). The linear regression model follows:

$$\begin{aligned} \text{Cortisol}_{ij} = & b_{00} + b_{01}\text{GeneticRisk} + b_{02}\text{NeighborhoodSatisfaction}_i + \\ & b_{03}\text{NeighborhoodSocialLife}_i + b_{04}\text{CollectiveEfficacy}_i + \\ & b_{05}\text{SafetyFromCrime}_i + b_{06}\text{GeneticRisk}*\text{NeighborhoodSatisfaction}_i + \\ & b_{07}\text{GeneticRisk}*\text{NeighborhoodSocialLife}_i + \\ & b_{08}\text{GeneticRisk}*\text{CollectiveEfficacy}_i + b_{09}\text{GeneticRisk}*\text{SafetyFromCrime}_i \\ & + u_0 \end{aligned}$$

In the first equation, $b_{01} - b_{05}$ represent the direct effects of neighborhood social environment and genetic risk on cortisol, and $b_{06} - b_{09}$ represents the effect of neighborhood social environment on cortisol at varying levels of genetic risk. However, the primary parameters of interest for each model will $b_{06} - b_{09}$, which provide evidence for the moderation of neighborhood social environmental risk by genetic risk on the overall level of cortisol.

Assumptions. All model assumptions and case diagnostics utilized R statistical software package, version 3.1.2 (R Development Core Team, Vienna, Austria). Tests for assessing violations of regression assumptions were completed before running the outcome analyses. Specifically, case diagnostics (DfBetas and Cooks D) were utilized to assess the presence and influence of any outliers in the data. The normality of variable distributions were examined via histograms, as well as measures of skewness and

kurtosis. Additionally, homoscedasticity was examined via scatter plots. Linearity was also assessed to ensure that the outcome variable (waist circumference) was linear in nature. Finally, multicollinearity was assessed. Each of these assumptions are discussed in the results section.

Clustering. Clustering was controlled for in the final models. Ultimately, this means that as the data were from three specific matched communities, and while the community variable was controlled for in the final models, generalization outside of these communities is not recommended given the small number of communities per intervention.

Missing Data. The current study used multiple imputations (Schafer, 1997) to address missing data in the PATH trial, consistent with previous national trials (Taljaard, Donner, & Klar, 2008). The MICE package (van Buuren & Groothuis-Oudshoorn, 2011) implemented within R (R Foundation, 2008) was used to generate 20 imputations. MVPA was coded as minutes within 4 time blocks per day (6 am-12 pm, 12 pm-4 pm, 4 pm-8 pm, and 8 pm-12 am) and imputed within time block. Imputations were conducted at the level of the individual and baseline information for each participant was included in the imputation model. Additionally, if a participant was missing data for an entire assessment period but had PA data for at least one other time point, then a summary score representing average minutes of MVPA for the entire period was imputed. All reported standard errors were adjusted for missing information. For the present study, one imputation was randomly selected for final analyses for this study, as opposed to multiple imputations.

CHAPTER 4

RESULTS

4.1 Demographics and Descriptive Data

Sample. The final sample consisted of 228 of the original 434 African-American adults whom participated in PATH for whom the genetic data was provided. Descriptives of the final sample of participants are provided in Table 1 for Aim 1, and Aim 2 as compared with the overall PATH sample. Of the total 228 participants utilized, five were removed as their weight status (both WC and BMI) was three standard deviations above the mean. For aim 1, the final sample was 223 participants. For aim 2, there were only 145 participants that provided both genetic and cortisol samples.

Statistical Assumptions. Tests for violations of regression and multilevel modeling assumptions were assessed after identifying the final primary and secondary models. Predictor variable distributions indicated adequate variability. This indicated no concerns of range restriction or skewness or kurtosis. Waist circumference data was normally distributed. However, waking cortisol was shown to have high positive estimates for skewness (2.41) and kurtosis (8.25). Thus, a natural log transformation was performed for cortisol. This transformation has been found to be appropriate for positively skewed dependent variables where the residuals increase as the dependent variable increases (Cohen, Cohen, West and Aiken, 2003). After examining scatter plots and conditional distributions of residuals, independent variables exhibited heteroscedasticity. Multicollinearity was assessed, and it was found that none of the

Table 4.1 Descriptive Data for Model Variables.

Characteristic	Aim 1	Aim 2	Total PATH Sample
Sample Size, No. (%)	223	145	417
Age (yrs)a	53.62 (15.6)	53.32 (15.78)	51.65 (15.46)
Sex, No. (%)			
Male	91 (40.8%)	55 (37.9%)	153 (36.7%)
Female	132 (59.2%)	90 (62.1%)	264 (63.3%)
Annual Income, No. (%)			
< \$10,000	68 (30.5%)	45 (31.0%)	130 (31.2%)
\$10,000 – 24,000	77 (34.5%)	40 (27.6%)	141 (33.8%)
> \$25,000	78 (35.0%)	60 (41.4%)	146 (35.0%)
Education, No. (%)			
< 12th grade	62 (27.8%)	43 (29.6%)	114 (27.3%)
GED/High School Graduate	90 (40.4%)	50 (34.5%)	172 (41.2%)
Attended College	71 (31.8%)	52 (35.9%)	131 (31.5%)
BMI (kg/m2)	31.15 (7.41)	33.05 (8.54)	31.18 (8.41)
Waist Circumference (cm)	98.91 (16.7)	99.64 (17.18)	97.01 (17.5)
MVPAb (min/day)	33.53 (42.97)	35.69 (47.55)	30.93 (39.92)
Blood Pressure			
Systolic	119.99 (27.82)	130.57 (20.52)	132.80 (17.85)
Diastolic	79.59 (11.20)	77.98 (10.87)	81.36 (10.93)
Perception of Safety	2.68 (0.61)	2.65 (0.62)	2.72 (0.62)
Neighborhood Satisfaction	3.63 (0.66)	3.59 (0.74)	3.64 (0.67)
Neighborhood Social Life	10.47 (6.82)	10.84 (7.21)	9.23 (5.82)
Collective Efficacy – Informal Social Control	3.55 (1.19)	3.63 (1.24)	3.56 (1.16)
Collective Efficacy – Social Cohesion and Trust	3.54 (0.78)	3.58 (0.79)	3.56 (0.81)

independent variables were highly correlated with each other (i.e. correlation less than 0.5), and theoretically each variable was important to have in the model. Case diagnostics identified five participants as outliers for waist circumference, and they were removed from the final dataset. Covariates that were included in the final model were age, sex, and community.

Descriptive data. Demographic, psychosocial, environmental, and biological data are depicted in detail in Table 1. Overall, the sample was predominantly female (60%), and average participant was 53 years old (SD = 15). The sample was obese on average with a BMI of 31 (SD = 7.4). Approximately two thirds of the sample (65%) made less than \$25,000 per household (US dollars), and completed less than one year of college (68.2%). All three samples (Aim 1, Aim 2 and overall PATH sample) were very similar based on descriptive data,

Genetic Data. Study genotype frequencies are provided in Table 2. This sample exhibited allele frequencies that were consistent with nationally representative data in other genetic studies (Sherry, et al., 2001). The current study's allele frequency distribution for *Bcl1* (rs41423247), Arg16Gly (rs1042713) and Arg389Gly (rs1801253) were consistent with literature cited in the National Center for Biotechnology Information SNP database (Sherry, et al., 2001), which looked at African American adult populations. However, the allele frequency for the T risk allele in FKBP5 (rs1360780) was higher for the current sample (67%) compare to those shown in the literature (39-44%) cited in the National Center for Biotechnology Information SNP database (Sherry et al., 2001).

Table 4.2 Genetic breakdown for Aim 1.

SNP	Genotypes	n (%)
<i>Bcl1</i> (rs41423247)	CC	10 (4.9%)
	CG	51 (24.7%)
	GG	145 (70.4%)
	Total	206
FKBP5 (rs1360780)	CC	67 (32.5%)
	CT	100 (48.3%)
	TT	40 (19.2%)
	Total	207
Arg16Gly (rs1042713)	GG	48 (24%)
	GA	97 (48.5%)
	AA	55 (27.5%)
	Total	200
Arg389Gly (rs1801253)	CC	64 (33.5%)
	CG	100 (52.4%)
	GG	27 (14.1%)
	Total	191

Correlations.

The correlations among model variables were calculated with alpha set at .05 for a two-tailed significance test (Table 3). Results indicated that waist circumference was positively associated with age, and inversely related HPA genetic risk score and neighborhood social life. Age was positively associated with waist circumference, safety, informal social control, social cohesion and trust, and neighborhood satisfaction, and negatively related to neighborhood social life and SNS genetic risk score. There were no significant relationship between waist circumference and waking cortisol.

4.2 Gene by Neighborhood Social Environment Interactions**Primary Aim – Gene by Neighborhood Social Environment Interaction (WC)**

HPA-axis model. The primary aim of this study was to assess how genetic risk moderated the relationship of neighborhood social environment (i.e. neighborhood satisfaction, neighborhood social life, collective efficacy, and safety from crime) on waist circumference. It was hypothesized that those who experience the highest genetic risk (i.e. high HPA-axis risk score) and who reported high environmental stress (i.e. low neighborhood satisfaction, low neighborhood social life, low collective efficacy, and high perception of crime) would exhibit the greatest waist circumferences.

Given the multilevel model building process, model comparisons were run to identify which model best fit the data. Model building was conducted by systematically adding variables of theoretical significance to determine if they improved model fit.

Based on theory, model comparisons were built. Models were as followed:

Table 4.3 Correlations between covariates, predictor, and outcome variables.

	WC	Wak Cort	HPA	SNS	Age	Safe	CE- ISC	CE- SCT	NSoc Life	NSat
Wak Cort	-0.32	1								
HPA	-0.08*	-0.09	1							
SNS	-0.05	-0.02	-0.09*	1						
Age	0.17**	0.02	0.06	-0.11**	1					
Safe	-0.02	0.01	-0.02	0.04	0.11**	1				
CEISC	0.02	-0.07	-0.04	0.05	0.11**	0.22**	1			
CESCT	0.02	0.04	-0.02	0.07	0.19**	0.34**	0.32**	1		
NSocLife	-0.14**	0.00	0.01	0.06	-0.11**	-0.09*	-0.11**	-0.12**	1	
NSat	0.03	0.08	0.05	0.09*	0.14**	0.49**	0.33**	0.39**	-0.12**	1

Note. WC, waist circumference; Wak Cort, waking cortisol, HPA, HPA-axis genetic risk; SNS, SNS genetic risk; safe, safety from crime; CE-ISC, collective efficacy-informal social control; CE-SCT, collective efficacy-social cohesion and trust; NSoc Life, neighborhood social life, NSat, neighborhood satisfaction.

1. Covariates and time
2. Covariates, time, and neighborhood variables
3. Covariates, time, neighborhood variables, and HPA GRS
4. Covariates, time, neighborhood variables, HPA GRS, and HPA
GRS*Neighborhood variables
5. Covariates, time, neighborhood variables, HPA GRS, HPA
GRS*Neighborhood variables, neighborhood variables*Time, and HPA
GRS*Time
6. Covariates, time, neighborhood variables, HPA GRS, HPA
GRS*Neighborhood variables, neighborhood variables*Time, HPA
GRS*Time, and Neighborhood variables*HPA GRS*Time

The models were additive in nature, and each one was compared to the last with five total chi-square difference tests being run (Table 4). For the HPA-axis pathway model, the best fitting model was model 5, thus only the neighborhood variables by time and HPA-axis GRS by time interaction were interpreted. Further, the model comparisons indicated the 6th model (which included three-way interactions; $\chi^2(10) = 11.15, p=0.34$) did not fit the data better, so the three way interactions will not be included in the final model).

Results from the multilevel model assessing the influence of HPA-axis pathway by neighborhood environmental interactions over time (Table 5) indicated there were no significant two-way interactions with neighborhood environment variables and time, nor was the HPA-axis GRS by time interaction. This means the model did not significantly predict change in waist circumference over time. However, on the overall model there was a main effect of time on WC, $b = 0.65, t(645) = 3.15, p < 0.01$. This finding indicated

Table 4.4 Model comparisons for HPA-axis.

Model	Df	logLikelihood	Test	Likelihood Ratio	p-value
1		-2885.66			
2	5	-2883.54	1 vs 2	4.25	0.51
3	1	-2882.49	2 vs 3	2.09	0.14
4	5	-2878.69	3 vs 4	7.61	0.17
5	1	-2881.93	4 vs 5	6.48	0.01
6	5	-2876.35	5 vs 6	11.12	0.34

Note. Model 1 included covariates and time; Model 2 included covariates, time, and neighborhood variables; Model 3 included covariates, time, neighborhood variables, and SNS GRS; Model 4 included covariates, time, neighborhood variables, SNS GRS, and SNS GRS*Neighborhood variables; Model 5 included covariates, time, neighborhood variables, SNS GRS, SNS GRS*Neighborhood variables, neighborhood variables*Time, and SNS GRS*Time; Model 6 included covariates, time, neighborhood variables, SNS GRS, SNS GRS*Neighborhood variables, neighborhood variables*Time, SNS GRS*Time, and Neighborhood variables*SNS GRS*Time.

Table 4.5 Model 1 Outcome Analyses (HPA-axis) – Waist Circumference (Aim 1)

	Estimate	SE	Est/SE	P-Value
Intercept	98.702	1.109	88.967	0.00***
Timepoint	0.652	0.207	3.149	0.00***
Tx-Walking Only	-1.380	1.565	-0.882	0.38
Tx-Full	-0.480	1.636	-0.293	0.77
Age	0.023	0.025	0.912	0.36
Sex	3.300	2.259	1.461	0.15
N Soc Life	-0.030	0.028	-1.065	0.29
CE-ISC	-0.084	0.140	-0.605	0.55
CE-SCT	0.237	0.257	0.922	0.36
Safety	0.014	0.326	0.044	0.97
NSat	0.246	0.351	0.700	0.48
HPA-GRS	-2.965	2.124	-1.396	0.16
HPA-GRS*Time	0.073	0.387	0.189	0.85
N Soc Life*HPA-GRS	0.018	0.050	0.358	0.72
N Soc Life*Time	0.004	0.031	0.137	0.89
CE-ISC*HPA-GRS	-0.301	0.263	-1.142	0.25
CE-ISC*Time	-0.134	0.186	-0.719	0.47
CE-SCT*HPA-GRS	0.080	0.488	0.165	0.87
CE-SCT*Time	0.043	0.291	-0.147	0.88
Safety*HPA-GRS	-1.432	0.657	-2.178	0.03
Safety*Time	0.394	0.383	1.029	0.30
NSat*HPA-GRS	1.125	0.692	1.627	0.10
NSat*Time	0.059	0.386	0.152	0.88

Note. Tx, treatment; N Soc Life, neighborhood social life, CE-ISC, collective efficacy-informal social control; CE-SCT, collective efficacy-social cohesion and trust; Safety, perceived safety from crime; NSat, neighborhood satisfaction; HPA-GRS, HPA-axis genetic risk score.

that on average (based upon mean centering) participants had an increase of 0.65cm in waist circumference from the 12-24 month time points.

SNS model. The primary aim of this study was to assess how genetic risk moderates the relationship of neighborhood social environment (i.e. neighborhood satisfaction, neighborhood social life, collective efficacy, and safety from crime) on waist circumference. This model was the same as the HPA-axis model, except this one utilized the SNS pathway genetic risk. It was hypothesized that those who experience the highest genetic risk (i.e. high SNS risk score) and who reported high environmental stress (i.e. low neighborhood satisfaction, low neighborhood satisfaction, low collective efficacy, and high perception of crime) would exhibit the greatest waist circumferences.

Given the multilevel model building process, model comparisons were run to identify which model best fit the data to answer the original research question. Model comparisons were built, and the degrees of freedom increased. Models were as followed:

1. Covariates and time
2. Covariates, time, and neighborhood variables
3. Covariates, time, neighborhood variables, and SNS GRS
4. Covariates, time, neighborhood variables, SNS GRS, and SNS
GRS*Neighborhood variables
5. Covariates, time, neighborhood variables, SNS GRS, SNS
GRS*Neighborhood variables, neighborhood variables*Time, and SNS
GRS*Time

6. Covariates, time, neighborhood variables, SNS GRS, SNS

GRS*Neighborhood variables, neighborhood variables*Time, SNS

GRS*Time, and Neighborhood variables*SNS GRS*Time

The models were additive in nature, and each one was compared to the last with five total test being run (Table 6). For the SNS pathway model, the best fitting model was model 5. Thus, the neighborhood by SNS GRS interactions, neighborhood variables by time interactions, and SNS by time interactions were interpreted if significant. The model comparisons indicated that the last model (which included three-way interactions; $\chi^2(10) = 15.24, p=0.12$) did not fit the data better, so the three-way interactions will not be included in the final model.

Results from the multilevel model assessing the SNS pathway by neighborhood environmental interactions over time (Table 7) indicated there were no significant two-way interactions with neighborhood environment variables and time, nor was there an SNS GRS by time interaction. This means the model did not significantly predict waist circumference change over time. However, there were three significant gene-by-environment interactions. Results indicated a significant gene by neighborhood social life interaction, $b=-0.11, t(618)=-2.02, p<0.05$. After plotting this interaction (Figure 3), as hypothesized, individuals with high genetic risk and low neighborhood social life (103.2cm) had the largest average levels of waist circumferences compared to medium (101.3cm) and low (99.5cm) risk groups for low neighborhood social life, however, those who experienced high neighborhood social life exhibited similar waist circumference measurements across genetic risk groups (low risk=98.9, medium risk=99.3, high risk=99.6).

Table 4.6 Model comparisons for SNS pathway.

Model	Df	logLikelihood	Test	Likelihood Ratio	p-value
1		-2760.70			
2	5	-2758.82	1 vs 2	3.78	0.58
3	1	-2758.67	2 vs 3	0.28	0.59
4	5	-2752.99	3 vs 4	11.35	0.04
5	1	-2758.26	4 vs 5	10.52	0.00
6	5	-2750.63	5 vs 6	15.24	0.12

Note. Model 1 included covariates and time; Model 2 included covariates, time, and neighborhood variables; Model 3 included covariates, time, neighborhood variables, and SNS GRS; Model 4 included covariates, time, neighborhood variables, SNS GRS, and SNS GRS*Neighborhood variables; Model 5 included covariates, time, neighborhood variables, SNS GRS, SNS GRS*Neighborhood variables, neighborhood variables*Time, and SNS GRS*Time; Model 6 included covariates, time, neighborhood variables, SNS GRS, SNS GRS*Neighborhood variables, neighborhood variables*Time, SNS GRS*Time, and Neighborhood variables*SNS GRS*Time.

Table 4.7 Model 2 Outcome Analyses (SNS) – Waist Circumference (Aim 1)

	Estimate	SE	Est/SE	P-Value
Intercept	99.209	1.143	86.780	0.00***
Timepoint	0.604	0.210	2.870	0.00***
Tx-Walking	-0.890	1.614	-0.551	0.58
Tx-Full	-0.471	1.700	-0.277	0.78
Age	0.031	0.025	1.233	0.22
Sex	3.568	2.327	1.533	0.13
N Soc Life	-0.039	0.029	-1.354	0.18
CE-ISC	-0.112	0.140	-0.800	0.42
CE-SCT	0.199	0.263	0.757	0.45
Safety	0.026	0.324	0.079	0.94
NSat	0.250	0.353	0.708	0.48
SNS-GRS	1.086	2.131	0.509	0.61
SNSGRS*Time	0.142	0.386	0.369	0.71
N Soc Life*SNSGRS	-0.108	0.054	-2.018	0.04*
N Soc Life*Time	0.002	0.032	0.049	0.96
CEISC*SNSGRS	-0.510	0.262	-1.950	0.05*
CE-ISC*Time	-0.050	0.189	-0.267	0.79
CE-SCT*SNSGRS	-0.339	0.450	-0.754	0.45
CE-SCT*Time	-0.026	0.296	-0.089	0.93
Safety*SNSGRS	-0.385	0.624	-0.617	0.54
Safety*Time	0.319	0.387	0.824	0.41
NSat*SNSGRS	1.482	0.664	2.233	0.02*
NSat*Time	0.043	0.392	0.110	0.91

Note. Tx, treatment; N Soc Life, neighborhood social life, CE-ISC, collective efficacy-informal social control; CE-SCT, collective efficacy-social cohesion and trust; Safety, perceived safety from crime; NSat, neighborhood satisfaction; SNS-GRS, SNS genetic risk score.

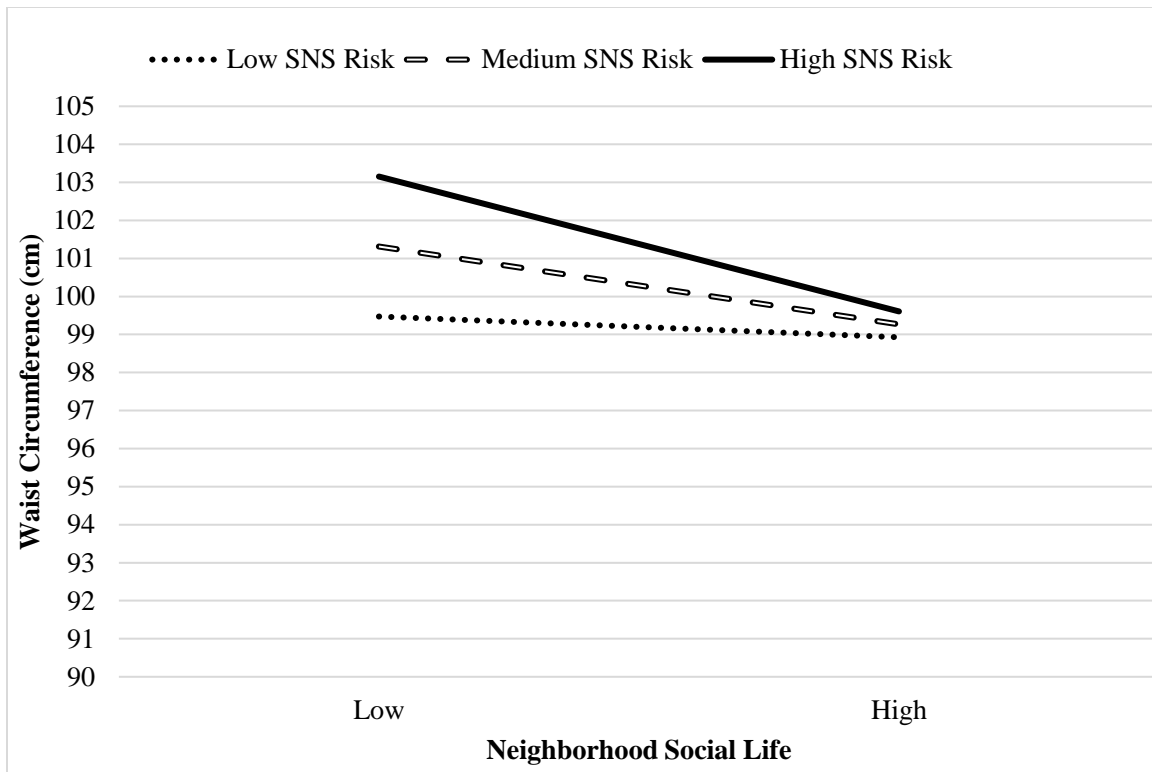


Figure 4.1. SNS genetic risk by neighborhood social life interaction predicting waist circumference.

The results also indicated a significant SNS by informal social control (collective efficacy) interaction, $b=-0.51$, $t(618)=-1.95$, $p=0.05$. After plotting this interaction (Figure 4), as hypothesized individuals with high genetic risk and low perceptions of neighborhood social control (102.7cm) had the largest average levels of waist circumferences relative to the medium (101.0cm) and low ((99.3) risk groups for low informal social control; however, with high informal social control all three risk groups exhibited similar waist circumference measurements (low risk=99.1cm, medium risk=99.5cm, high risk=100cm).

Further, the model also showed a significant SNS by neighborhood satisfaction interaction, $b=1.48$, $t(618)=2.23$, $p<0.05$. This interaction plot (Figure 5) indicated that individuals with low neighborhood satisfaction, regardless of their genetic risk (low risk=99.0cm, medium risk=99.0cm, high risk=99.1cm) exhibited nearly identical average levels of waist circumference. However, unexpectedly and counter to hypotheses it was identified that those individuals who experienced high neighborhood satisfaction and high genetic risk (103.7cm) had the largest average levels of waist circumferences compared to medium risk (101.5cm) and low risk (99.4cm) for high neighborhood satisfaction. Potential explanations for the unexpected finding are addressed in the discussion section. Finally, there was no significant gene by environment interaction for SNS genetic risk score by social cohesion and trust, nor for SNS genetic risk score by neighborhood safety.

Finally, there was a main effect of time on WC, $b = 0.60$, $t(618) = 2.87$, $p < 0.01$. This finding indicated that on average (based upon mean centering) participants had an increase of 0.60cm in waist circumference from the 12-24 month time points.

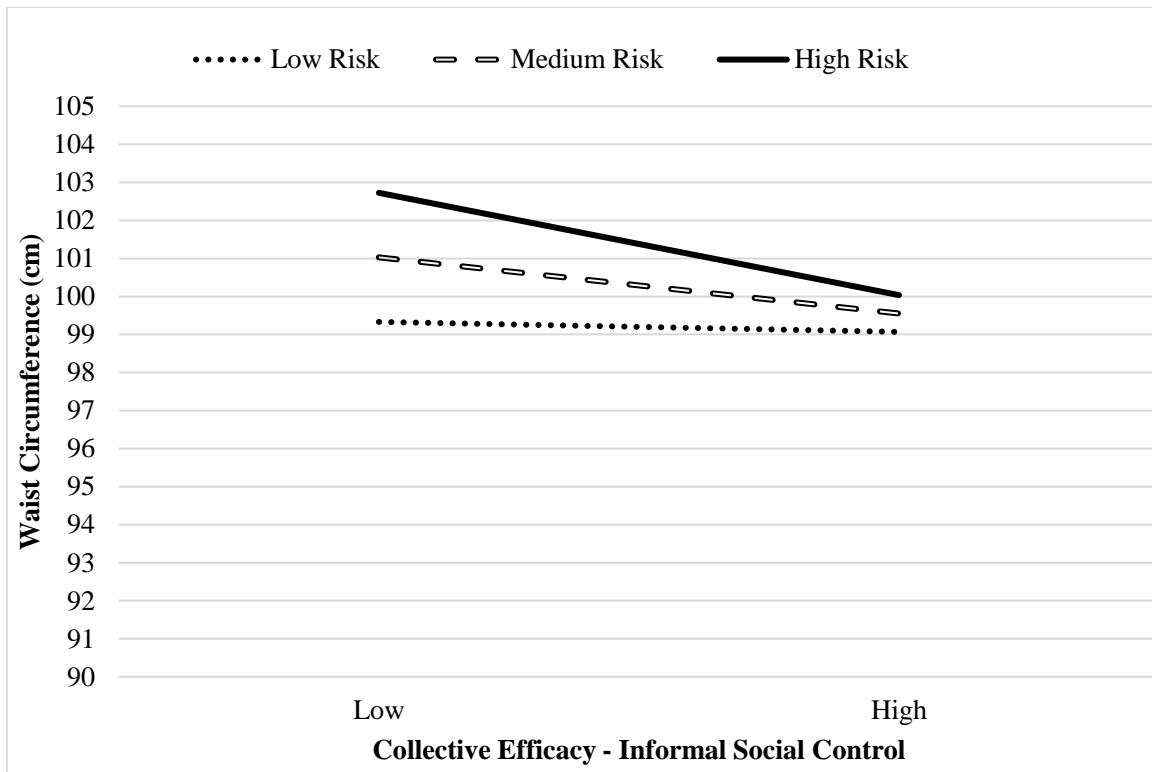


Figure 4.2 SNS genetic risk by informal social control (collective efficacy subscale) interaction predicting waist circumference.

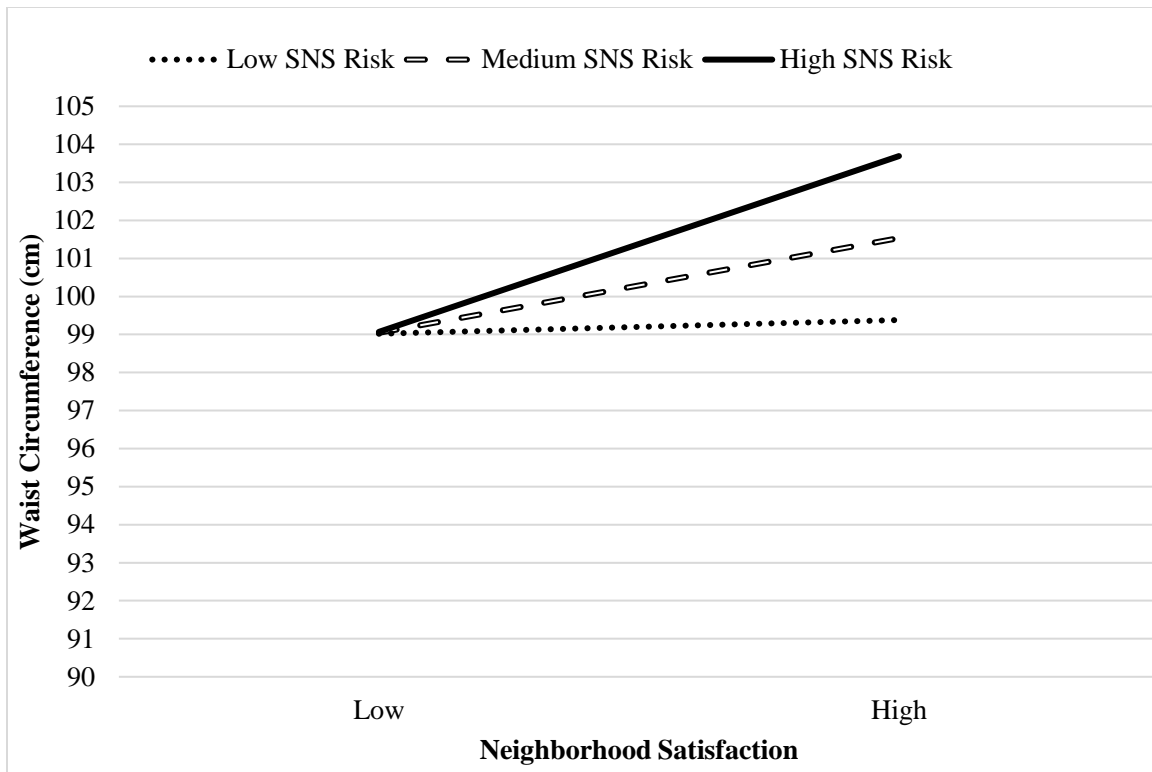


Figure 4.3 SNS genetic risk by neighborhood satisfaction interaction in predicting waist circumference.

Secondary Aim - Gene by Neighborhood Social Environment Interaction (Cortisol)

HPA-Axis model. The secondary aim of this study was to assess how genetic risk based on the HPA-Axis model to examine if it interacts with neighborhood social environment (i.e. neighborhood satisfaction, neighborhood social life, collective efficacy, and safety from crime) to predict cortisol. It was hypothesized that those who experience the highest genetic risk (i.e. high HPA-axis risk score) and who reported high environmental stress (i.e. low neighborhood satisfaction, low neighborhood satisfaction, low collective efficacy, and high perception of crime) would exhibit the greatest levels of cortisol.

Results from the linear regression are reported in Table 8. The regression model for cortisol was not significant ($F(15, 127)=0.55, p=0.90$), and only accounted for 6.2% of the variance in waking cortisol. Further, there were no significant gene-by-environment interactions in predicting waking cortisol via the HPA-axis genetic pathway.

SNS Model. The secondary aim of this study was to also assess how genetic risk based on the SNS model to examine if it moderated the relationship of neighborhood social environment (i.e. neighborhood satisfaction, neighborhood social life, collective efficacy, and safety from crime) on cortisol. It was hypothesized that those who experience the highest genetic risk (i.e. high SNS risk score) and high environmental stress (i.e. low neighborhood satisfaction, informal social control, social cohesion and trust, and high perception of crime) would exhibit the greatest levels of cortisol.

Table 4.8 Model 3 Outcome Analyses (HPA-axis) – Cortisol (Aim 2a)

	Estimate	SE	Est/SE	P-Value
Intercept	1.010	0.106	9.558	.000
Tx-Walking	0.331	0.157	2.108	0.037
Tx-Full	-0.122	0.156	-0.782	0.436
Age	0.003	0.007	0.418	0.677
Sex	-0.239	0.219	-1.088	0.279
N Soc Life	-0.011	0.016	-0.698	0.486
CE-ISC	-0.023	0.107	-0.222	0.825
CE-SCT	0.017	0.145	0.116	0.908
Safety	0.156	0.212	0.733	0.465
NSat	-0.016	0.186	-0.087	0.931
HPA-GRS	-0.163	0.201	-0.813	0.418
N Soc Life*HPA-GRS	0.035	0.032	1.068	0.288
CE-ISC*HPA-GRS	-0.127	0.193	-0.660	0.511
CE-SCT*HPA-GRS	0.136	0.306	0.443	0.658
Safety*HPA-GRS	0.249	0.411	0.605	0.546
NSat*HPA-GRS	-0.088	0.342	-0.256	0.798

Note. Tx, treatment; N Soc Life, neighborhood social life, CE-ISC, collective efficacy-informal social control; CE-SCT, collective efficacy-social cohesion and trust; Safety, perceived safety from crime; NSat, neighborhood satisfaction; HPA-GRS, HPA-axis genetic risk score.

Table 4.9 Model 4 Outcome Analyses (SNS) – Cortisol (Aim 2b)

	Estimate	SE	Est/SE	P-Value
Intercept	1.040	0.102	10.228	0.000***
Tx-Walking	0.211	0.151	1.398	0.165
Tx-Full	-0.144	0.150	-0.959	0.340
Age	0.001	0.007	0.194	0.845
Sex	-0.274	0.215	-1.275	0.205
N Soc Life	-0.020	0.015	-1.300	0.196
CE-ISC	0.024	0.010	0.250	0.803
CE-SCT	-0.063	0.141	-0.446	0.656
Safety	0.128	0.204	0.625	0.533
NSat	-0.163	0.179	-0.910	0.365
SNS-GRS	-0.015	0.182	-0.081	0.936
N Soc Life*SNS-GRS	-0.004	0.029	-0.129	0.898
CE-ISC*SNS-GRS	-0.360	0.191	-1.884	0.062
CE-SCT*SNS-GRS	0.593	0.256	2.324	0.022*
Safety*SNS-GRS	0.258	0.335	0.769	0.443
NSat*SNS-GRS	0.184	0.276	0.665	0.507

Note. Tx, treatment; N Soc Life, neighborhood social life, CE-ISC, collective efficacy-informal social control; CE-SCT, collective efficacy-social cohesion and trust; Safety, perceived safety from crime; NSat, neighborhood satisfaction; HPA-GRS, HPA-axis genetic risk score.

Results from the linear regression are reported in Table 9. The overall regression model for cortisol was not significant ($F(15, 124)=0.94, p>.05$) but accounted for 10.2% of the variance in cortisol. However, this regression analysis indicated a significant gene-by-environment interaction of social cohesion and trust (collective efficacy subscale) by SNS genetic risk score ($b=0.59, p=0.02$) on cortisol. After plotting this interaction (Figure 6), results indicated counter to hypotheses that individuals with high genetic risk and high social cohesion and trust exhibited the greatest waking cortisol, as compared to those with the low genetic risk and high social cohesion and trust. There were no other significant predictors in this model. However, there was a trend for informal social control by SNS genetic risk score ($b=-0.36, p=0.06$) on cortisol. After plotting this interaction (Figure 7), graphing it indicated that consistent with dual risk hypothesis, those individuals with high genetic risk and low informal social control exhibited the greatest waking cortisol. In addition, there was some pattern in the data that exhibited differential susceptibility, because as individuals with high genetic risk had high informal social control in their neighborhood, they exhibited the lowest waking cortisol levels.

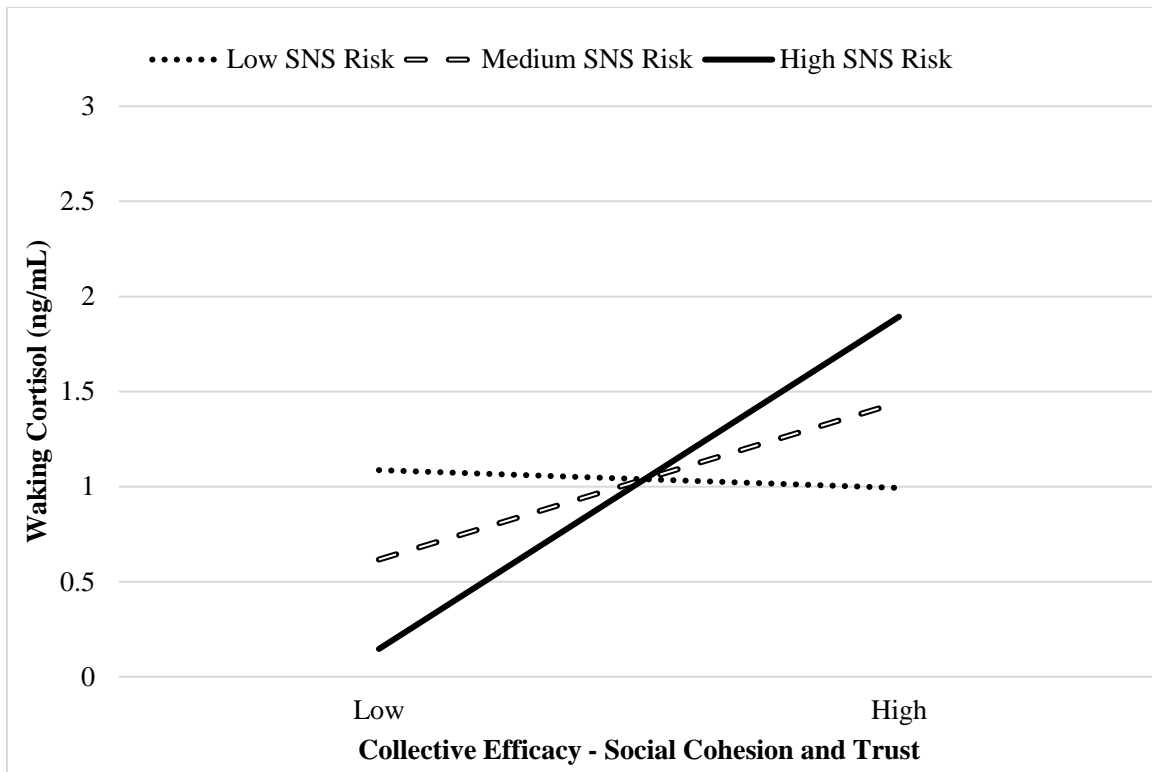


Figure 4.4 SNS genetic risk by social cohesion and trust (collective efficacy subscale) interaction predicting waking cortisol.

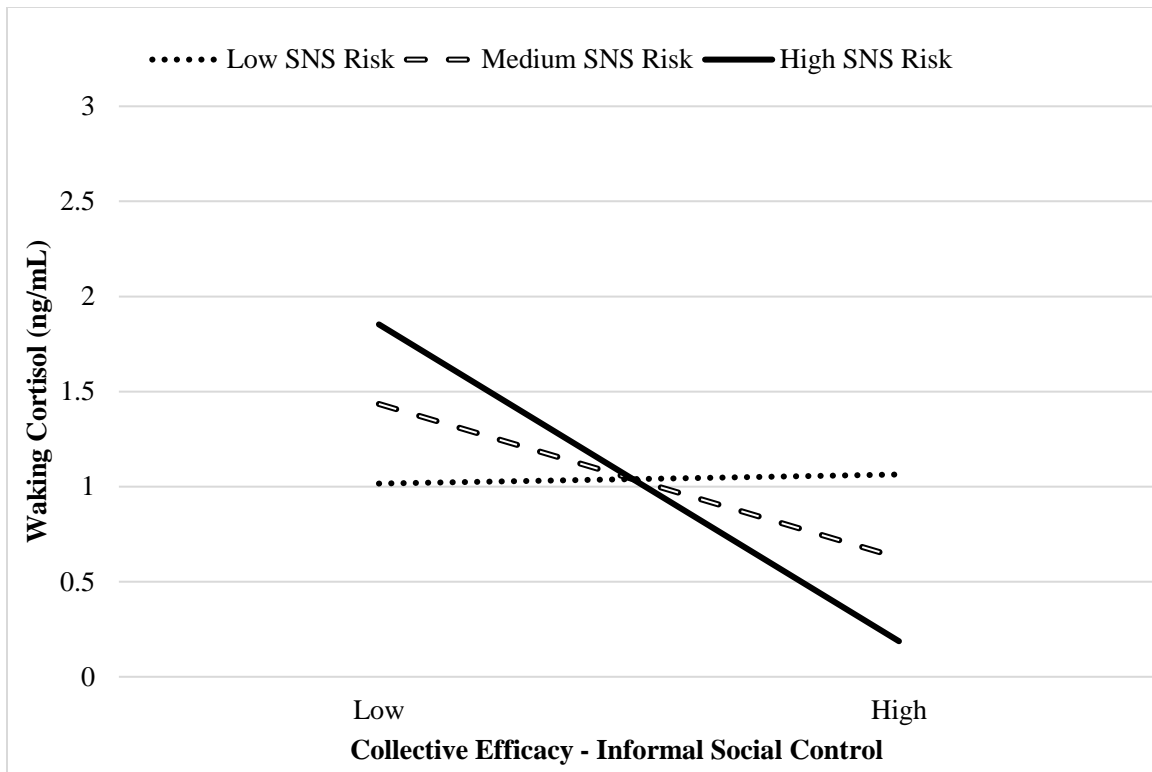


Figure 4.5 SNS genetic risk by informal social control (collective efficacy subscale) interaction predicting waking cortisol (marginally significant interaction).

CHAPTER 5

DISCUSSION

The primary aim of this study was to assess the impact of the interaction of genetic risk (i.e. HPA-axis and SNS risk score) and neighborhood social environment (i.e. neighborhood satisfaction, neighborhood social life, collective efficacy, and safety from crime) on waist circumference, with the hypothesis that those who experience the highest genetic risk and high environmental stress would exhibit the greatest waist circumferences. More specifically, two models were examined to separately understand the impact of the HPA axis and SNS, respectively, on waist circumference. In the SNS pathway model, there were three significant gene by environment interactions. These significant effects included two interactions that matched the dual risk model; the SNS genetic risk by neighborhood social life interaction, and SNS genetic risk by informal social control interaction on predicting waist circumference outcomes. However, the SNS genetic risk by neighborhood satisfaction interaction indicated that as neighborhood satisfaction increased, so did participants waist circumference, which is contrary to the dual risk hypothesis. Alternatively, there were no findings in the HPA axis model that aligned with hypotheses. In both primary aim models, there was a significant main effect of time such that, on average, an individual's waist circumference increased over time. However, contrary to hypotheses, results indicated there were no significant three-way interactions with gene by environment interactions predicting change in waist circumference over time for either stress pathway (i.e., SNS or HPA axis).

The secondary aim of this study was to assess the interaction of genetic risk (i.e. HPA-axis and SNS risk score) and neighborhood social environment (i.e. neighborhood satisfaction, neighborhood social life, collective efficacy, and safety from crime) on cortisol, with the hypothesis that those who experience the highest genetic risk and high environmental stress would exhibit the greatest levels of cortisol. Results indicated there were no significant HPA-axis genetic risk by environment interactions in predicting cortisol levels. However, the SNS genetic risk by social cohesion and SNS genetic risk by trust interaction indicated that as social cohesion and trust increased so did waking cortisol, contrary to the dual risk hypothesis.

5.1 Significant Gene by Environment Interactions in Aim 1

As mentioned, no hypothesized interactions were found when exploring the impact of HPA axis on waist circumference outcomes. Here, the significant SNS findings are discussed. As hypothesized, individuals with high genetic risk and low neighborhood social life had the largest waist circumference outcomes compared to the other two risk groups (i.e., low and medium genetic risk) at the low neighborhood social life level. This is indicative of the dual risk model as those with the highest genetic risk and in a negative environment presented the most deleterious outcome, which in this case is the largest waist circumference. However, once the environment was perceived as more supportive, then the high genetic risk group had a waist circumference similar to the other two lower risk groups. Conceptualized otherwise, individuals in the high genetic risk group are the most vulnerable for negative obesogenic outcomes, thus a more positive neighborhood social life environment is more protective for them than those individuals at less genetic risk.

This is a novel finding as there is no known research that assesses the impact of gene by environment interactions on waist circumference, especially when looking at neighborhood social life as a moderator. There is minimal research on neighborhood social environments and obesity-related outcomes, without considering the genetic component. Two recent review papers on neighborhood social environment and obesity identified there is limited research on leveraging the neighborhood social environment to promote healthy behaviors (Suglia et al., 2016; Leroux, et al., 2013). Research that has focused on the neighborhood social environment as a point of intervention has demonstrated success in promoting healthy behaviors such as fruit vegetable intake and increased physical activity (Lee, et al., 2012). However, in the aforementioned reviews, they did not find any studies that assessed obesity outcomes such BMI and waist circumference. While previous studies look at health-related behaviors (i.e. fruit and vegetable intake, physical activity, etc), this may not directly translate to a decreased rate of obesity. This study begins to connect this critical gap. There continues to be limited neighborhood social life research, however, the current finding adds further support for the importance of the interaction between neighborhood social environment and genetic risk.

When considering the dearth of existing literature pertaining to how social factors impact obesity related outcomes, there are discrepant findings. Kaplan, et al. (2003) found that when looking at perceived social support in an older Canadian adult population, social support was significantly negatively associated with obesity for women, however, there was a significant positive association for obesity for men. Kendzor, et al., (2013) researched social support and BMI in a sample which included

African Americans. Kendzor and colleagues found that social support (i.e. tangible support, belongingness, and appraisal subscales) actually exhibited a significant positive association with BMI, indicating that individuals with perceived social support demonstrated greater BMI (Kendzor, et al., 2013). Relatedly, while not specifically social interaction, Christakis and Fowler (2007) found that an individual's chances of becoming obese increase by 57% if they had a friend who also became obese recently, and ultimately concluded that obesity seemed to "spread" via social relationships. Given this literature, which is discrepant with the current findings for neighborhood social life and related factors on obesity outcomes, this brings to light that it may not just be overall social support that is important. Rather it may be that social support for positive health behaviors that is critical. The mixed results from the limited research on neighborhood social life and obesity indicate that this is an important factor to better understand, particularly when looking at obesity outcomes such as waist circumference.

Results also indicated a significant interaction between SNS and informal social control. As hypothesized, individuals with high genetic risk and low perceptions of neighborhood social control had the largest waist circumferences relative to the other two risk groups at the low informal social control level. This is indicative of a dual risk model as those with the highest genetic risk in a negative environment displayed the worse outcome, which in this case is the largest waist circumference. However, when the environment was more positive, the high genetic risk group had a similar waist circumference as the other two lower genetic risk groups. In other words, individuals with high genetic risk are the most vulnerable and having a high perception of

neighborhood informal social control was protective for genetically at-risk individuals with regards to their waist circumference.

Again, this is a novel finding as there is no known research that assesses the impact of the interaction between genetic risk and informal social control on a waist circumference outcome, even when considering literature focused on collective efficacy in general. However, while there is limited informal social control research, there is preliminary support for the importance of social control. Specifically, Cohen, Finch, Bower et al. (2006) found that individuals living in neighborhoods with low collective efficacy were almost three times more likely for being at risk for overweight compared to neighborhoods with high levels of collective efficacy. Bjornstrom (2011) also identified higher collective efficacy as a protective factor for obesity. Specifically, collective efficacy was theoretically related to obesity outcomes for different reasons, which included a positive association with a likelihood that individuals will partake in healthier behaviors and avoid unhealthy ones, and individuals with higher collective efficacy were less likely to be socially isolated (Curry, Latkin, & Davey-Rothwell, 2008). Relatedly, Mujahid, Diez Roux, Shen, et al (2008) found that overall social environment (which included components of collective efficacy) was positively associated with BMI in men. However, some findings are discrepant. For example, Burdette, et al. (2006) found that there was no significant relationship between collective efficacy and BMI in a study that assessed over 2,500 mothers (52% African American). Given these mixed findings, the current study's findings advances the research one step further by understanding how this construct interacts with genetic risk to impact an important obesity related outcome, waist circumference.

The significant SNS by neighborhood satisfaction interaction showed that under high neighborhood satisfaction conditions individuals waist circumference increased, with the increase in waist circumference was most prominent in the highest genetic risk group. This trend is unexpected, and counter to a dual risk hypothesis, as it would be expected that when individuals experience a more supportive neighborhood (i.e. high neighborhood satisfaction), their waist circumference would be lower, per the dual risk hypothesis and in line with other previous research. De Jong, Albin, Skarback, et al (2012) highlighted that neighborhood satisfaction was positively associated with perception of overall general health and Bjork, et al (2008) found that neighborhood satisfaction was negatively associated with BMI in the same population of Swedish adults. However, neighborhood satisfaction is an understudied construct in weight-related research in general, with many studies only focused on components of overall neighborhood satisfaction (e.g., access to services, walkability, green space available, etc) with respect to physical activity and cardiovascular outcomes. For example, one study which utilized the same data as the current study, did find that neighborhood satisfaction was positively related to blood pressure (Coulon et al., 2011). Much like the current study's finding, this was unexpected, as it was hypothesized that those who have higher neighborhood satisfaction would have lower blood pressure. This again underscores the notion that perhaps not all previously conceptualized positive neighborhood social environmental factors interact with genetic risk the same to impact obesity-related outcomes. Thus, more research is needed to better understand the potentially complex relationship of the interaction between genetic risk and neighborhood social environment on waist circumference.

Finally, time was a significant predictor in both stress pathway models (HPA-axis and SNS). On average, in one year, individuals in the study had an increase in waist circumference by over one-half centimeter. This was not one of the specific hypotheses, however, this finding does show that time significantly positively predicts waist circumference in the overall sample of this study. While not necessarily novel, it does corroborate previous research that suggests African-American adults continue to have an increase in waist circumference over time (Ford, 2014; Freedman & Ford, 2015; Ladabaum, et al., 2014). In addition, the general increase in waist circumference over time is consistent with other results from nationally representative samples of adults in the United States (Ford, 2014; Freedman & Ford, 2015).

5.2 Significant Gene by Environment Interactions in Aim 2

For Aim 2, results of the SNS regression analysis indicated a significant gene-by-environment interaction of social cohesion and trust by SNS genetic risk score. More specifically, results were such that individuals with high genetic risk and high social cohesion and trust exhibited the greatest waking cortisol, as compared to those with the low genetic risk and high social cohesion and trust. Interestingly, per previous research (Block, et al, 2009; Fowler-Brown, et al., 2009; Richardson, et al., 2015), it was expected that with a higher level of stress (i.e. lower feeling of informal social control), individuals would experience greater cortisol levels. However, research by Hajat, Moore, Do, et al. (2015) found a similar trend in waking cortisol and social cohesion. Specifically, they found that higher social cohesion was associated with higher waking levels of cortisol as well (Hajat, et al., 2015), in a sample of almost 1200 adults (30% African American). Further, they found that individuals with high social cohesion exhibited higher waking

cortisol, and steeper declines in early and late slopes, which may be indicative of a healthier diurnal cortisol pattern. While the current study followed a dual-risk hypothesis model which conceptualized the higher waking cortisol as indicator of increased physiological stress, the conceptualization that Hajat, et al. (2015) provided may indicate otherwise. However, the current study was only able to collect a sample immediately following awakening, and precluded the ability to graph the diurnal pattern akin to Hajat and colleagues. Thus, it is purely speculative that the current study's findings match Hajat et al. (2015) findings. Again, it is important to interpret these findings with caution as there are no other known gene by neighborhood environment interaction on waking cortisol levels. Ultimately, this finding only highlights the importance of needing further study of a gene by neighborhood environment interaction in predicting waking cortisol levels.

5.3 Relevant Genetic Findings in Current Literature

There has been increased research on HPA-axis and SNS pathways for gene by environment interactions, however, there continues to be a gap in the literature for obesity related outcomes. The SNS pathway SNPs have been associated specifically with obesity-related outcomes. Specifically, the B1-adrenoceptor stimulates the lipolysis of adipose tissue (Masuo & Lambert, 2011). One SNP used in the current study (Arg389Gly; rs1801253) has been associated with obesity-related outcomes (i.e. BMI) in some populations (Dionne, Garant, Nolan, et al., 2002; Linne, Dahlman, & Hoffstedt, 2005), while several studies did not find this SNP a significant factor in obesity related outcomes (Tafel, Branscheid, Skwarna, et al., 2004; Gjesing, Anderson, Albrechtsen, et

al., 2007; Mottagui-Tabar, Hoffstedt, Brookes, et al., 2007; Nonen, Yamamoto, Liu, et al., 2008;).

The B2-adrenoceptor stimulates glycogenolysis and gluconeogenesis (Masuo & Lambert, 2011). Similar to the B1-adrenoceptor, the B2-adrenoceptor (Arg16Gly, rs1042713) has exhibited mixed findings, as it has been significantly associated with obesity, elevated blood pressure and diabetes mellitus in some studies (Meirhaeghe, Helbecque, Cottel, et al., 2000; Masuo, Katsuya, Fu, et al., 2005; Masuo, Katsuya, Kawaguchi, et al., 2006; Masuo et al., 2006; Petrone, Zavarella, Iacobellis, et al., 2006) and not in predicting weight-related outcomes in other studies (Ruiz, Larrarte, Margareto, et al., 2011; Saliba, Reis, Brownson, et al., 2014; Zhang, Wu, & Yu, 2014). Interestingly, the current study did not have a significant direct effect of genetic risk either. But more interesting were the three significant gene by environment interactions within this stress pathway. One potential reason for the SNS genetic risk pathway to have three significant gene by environment interactions on waist circumference are the direct functional impacts that B1- and B2-adrenoceptors have on human fat cells; they significantly modulate pre- and postprandial energy expenditure and total daily energy expenditure (Hagstrom-Toft, Enoksson, Moberg, et al., 1998; Enoksson, Talbot, Rife, et al., 2000; Iwashita, et al., 2002; Monroe, Seals, Shapiro, et al., 2001).

For both of the SNS by neighborhood social environmental interaction for waist circumference that match the dual-risk model (SNS by neighborhood social life and SNS by informal social control), it follows that those with negative neighborhood social environments and high genetic risk experience the largest waist circumference, given the biologic underpinnings of B1- and B2-adrenocpetors. However, the interesting piece, and

conceivably the part that necessitates further research, is understanding how a positive neighborhood social environment moderates the impact of high genetic risk on waist circumference. To date, there are no documented gene by neighborhood social environmental interactions on waist circumference. Further, there has been limited investigation of SNS gene by environment interactions on obesity-related outcomes in general, and in those few studies there are mixed results. For example, Saliba, et al (2014) assessed an SNS SNP (Arg16Gly, rs1042713) by weight loss intervention interaction on BMI. Interestingly, they did not find a significant Arg16Gly (rs1042713) by weight loss intervention interaction on BMI, in a population of obese Brazilian women. It continues to be clear that obesity is complex, as indicated by the mixed findings in previous studies. In that vein, findings in the current study provide further support that continued research of the SNS pathway is needed to help improve our understanding of its impact on obesity. Although inconclusive, the findings in the current study do bridge the literature gap between stress pathway genetic risk by neighborhood social environment interactions and obesity-related outcomes.

Interestingly, there were null findings for both Aim 1 and Aim 2 when examining predictors related to the HPA-axis pathway (i.e., main effects and interactions). This is particularly surprising given the importance of the HPA-axis on stress regulation. While both the *Bcl1* (rs41423247; van Rossum & Lamberts, 2004; Kumsta, et al., 2007; Stevens, et al., 2004; Di Blaiso et al., 2003) and *FKBP5* (rs1360780; Binder et al., 2008; Ising et al., 2008; Kirchheiner et al., 2008; Roy, Gorodetsky, Yuan, Goldman, & Enoch, 2010) SNPs have been associated with abdominal obesity and stress outcomes, the current study highlighted mixed results when assessing a gene by environment

interaction. A potential explanation for the current study's null finding related to the HPA-axis pathway could be that the two SNPs selected to generate an HPA-axis genetic risk score may impact an older African-American adult population differently than what has been identified in previous populations. While the current study appears to be contrary to previous research, the inconclusive nature of this genetic pathway lends to further research. Keeping in mind the functional component of HPA-axis dysregulation abdominal adiposity and cortisol, understanding how the HPA-axis pathway interacts with neighborhood social environment is an important line of research to continue studying.

5.4 Limitations

There are several limitations to this study, and addressing them in future studies may improve research related to the impact of gene by environment interactions on weight-related outcomes. First, this study only utilized only two SNPs within the SNS pathway, and two SNPs within HPA-axis pathway. Future research could assess several polymorphisms per pathway to capture a better overall picture of these two stress pathways, much like the Li, et al. (2010) utilized in their study which included twelve SNPs within the genetic risk score. Second, this study did utilize the microsystem within the bioecological model by looking at several individual perceptions of neighborhood social environment and genetic risk. The impact of this self-reported perception may be different than an outside, objective rating of neighborhood attributes, which warrants investigation. While it is still important for perceptions to be assessed as well, objective census-tract data, for example, may provide a different but important perspective to understand obesity. In addition, this study did not look at multiple systems, and future

studies may benefit from examining multiple systems at once. This could allow for assessment of how multiple environments operate in concert to impact obesity-related outcomes. Third, the participants in this study were part of a larger study that only include participants without severe limitations or uncontrolled chronic disease which could impact generalizability. It may be important for future studies to enroll a broader range of study participants to expand generalizability. Next, it has previously been noted that the current study used a relatively small sample size in comparison to other gene by environment interaction studies (n=223 for Aim1, n=145 for Aim 2). However, Wong, Day, Luan, et al. (2013) stated that more precise measurement can cut down on necessity of large sample size, specifically for continuous environmental variables and a genetic factor on a continuous outcome. More specifically, Wong, et al., (2003) stated that a study with more precise measurement and repeated measures can be as powerful as a study that has a sample size that is 20 times the size. Finally, this study only looked at waist circumference and cortisol measurements, which did fill a gap in the current literature. However, continuing to assess other types of body adiposity and stress measures may be important as well.

5.5 Future Directions

The current study highlights the importance of, and necessity to, continue studying gene by social environment interactions related to weight- and stress-related outcomes. The neighborhood social life can be a great strength and buffer against negative health outcomes (SNS by neighborhood social life and SNS by informal social control on WC), or it may worsen health outcomes in an already vulnerable population (i.e. SNS by neighborhood satisfaction on waist circumference, SNS by social cohesion

and trust on cortisol). Recently Klijs, et al. (2017) found that if individuals residing in deprived neighborhoods perceived their number of personal contacts as adequate and had their social needs fulfilled, they experienced a higher health-related quality of life, in comparison to those that did not have a perceived adequate amount of personal contacts and social need fulfillment. In essence, perceived social fulfillment buffered the effect that a deprived neighborhood had on quality of life. Further, Chen et al (2011) found that individuals with at least one copy of the G allele of the oxytocin receptor gene (OXTR; rs53576) exhibited lower cortisol levels to stress after social support (compared to those with the same genotype but not social support) during a stressful activity. Again, this highlights the importance that one's social environment has not only on weight-related outcomes, but also on overall well-being and physiological stress.

However, findings from Powell, et al (2015) may warn that it is not just any social support that is helpful, but rather specific types of social support. After an extensive meta-analysis, Powell and colleagues postulated that there are three different types of social support: social contagion – network in which embedded influences their weight or weight influencing behavior; social capital – sense of belonging and social support influence weight or weight influencing behavior; and social selection – a person's network develops according to his or her weight (Powell, et al., 2015). Conceptually speaking, it might be that not all social support is created equal. As Christakis and Fowler (2007) found, individuals chance of becoming obese increased by 57% when they had a friend that was already or recently became obese may fall into social selection, such that they may be spending time with individuals that have negative health behaviors that they already exhibit. On the contrary, individuals that are in social groups that exhibit positive

health-related behaviors may fall into social capital social support, as they all encourage and promote healthy behaviors with each other. Powell, et al. (2015) do highlight the further importance of understanding the impact of an individual's environmental social support, as it may be that not all neighborhood social environments promote healthy weight- and stress-related outcomes. Future research may benefit from identifying and studying different types of social support, as the current study highlighted that not all neighborhood social environmental factors buffer genetic predisposition.

Finally, as the current study has highlighted in regards to the dual risk hypothesis, there are individuals with genetic predispositions to negative weight- and stress-related outcomes that could greatly benefit from having a positive neighborhood social environment. Gene by environment interactions have further highlighted the importance of the environment (Dominique, et al., 2014), but also magnified the complexity of obesity-related outcomes given the many discrepant findings with genetic risk. The implications of future research could aid in developing interventions to buffer genetic risk through social environmental interventions.

5.6 Conclusion

This study aimed to assess the impact of a gene by neighborhood social environment interaction on weight-related (i.e., waist circumference) and stress-related (i.e. cortisol) outcomes in underserved African-American adults. A bioecological model framework was utilized to integrate factors, including neighborhood social environmental factors (i.e. perceptions of safety from crime, neighborhood satisfaction, neighborhood social life, and collective efficacy) and genetic risk (Sympathetic Nervous System and

Hypothalamic-Pituitary-Adrenal axis genes). This study highlighted the importance of neighborhood social environment in buffering the effect of high genetic risk.

Results indicated several gene by environment interactions, including three for SNS pathway (SNS by neighborhood social life, SNS by Informal Social Control, and SNS by Neighborhood Satisfaction) on waist circumference, and one significant gene by environment interaction (SNS by neighborhood satisfaction) on cortisol. Overall, this study highlighted the potential importance of a positive neighborhood social environment, as the neighborhood social environment may buffer the individuals with high genetic risk from experiencing increased waist circumference. There is little previous research on gene by environment interactions for waist circumference and cortisol, and even less have utilized a stress pathway approach like this study, which starts filling a large literature gap that currently exists. However, Powell, et al (2015) postulate that there may be different types of social support for health-related behaviors (social contagion, social capital, and social selection), which may impact health outcomes differently; thus identifying and building up a positive neighborhood social environmental may be particularly important for those at increased genetic risk (Nam, et al., 2015). Further, utilizing a systematic, theory driven approach (Civilek & Lusi, 2014) to identify gene by environment interactions that impact obesity related outcomes may help organize and fill the gaps in the literature that currently exists. This study has highlighted the importance of continuing to research the impact of genetic risk and neighborhood stressors on obesity-related outcomes (i.e. waist circumference and cortisol), as obesity is and continues to be a complex, multifactorial disorder that increasingly impacts African-American adults. Further research will lead to a better

understanding of risk and protective factors in at-risk populations, with the intent to lead to community-based interventions for those at particularly high-risk.

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APPENDIX A

SAFETY FROM CRIME MEASURE

1. My neighborhood streets are well lit at night.
2. Walkers and bikers on the streets in my neighborhood can be easily seen by people in their homes.
3. I see and speak to other people when I am walking in my neighborhood.
4. There is a high crime rate in my neighborhood.
5. The crime rate in my neighborhood makes it unsafe to go on walks during the day.
6. The crime rate in my neighborhood makes it unsafe to go on walks at night.

Likert Response Options:

1. strongly disagree
2. somewhat disagree
3. somewhat agree
4. strongly agree

APPENDIX B

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 C

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 neighborhood?
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 D

NEIGHBORHOOD SOCIAL LIFE MEASURE

The next questions are about things that you have done in the last month.

How many days in the last month have you:

1. Waved to a neighbor? ____
2. Said hello to a neighbor? ____
3. Stopped and talked with a neighbor? ____
4. Gone to a neighbor's house to socialize? ____
5. Had a neighbor at your house to socialize? ____
6. Gone somewhere (i.e. restaurant, shopping, ball game) with a neighbor? ____
7. Asked a neighbor for help? ____
8. Sought advice from a neighbor? ____
9. Borrowed things and exchanged favors with a neighbor? ____

APPENDIX E

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"):

- | | |
|---|---|
| <input type="checkbox"/> Working | <input type="checkbox"/> Permanently Disabled |
| <input type="checkbox"/> Temporarily Laid Off | <input type="checkbox"/> Homemaker |
| <input type="checkbox"/> Unemployed | <input type="checkbox"/> Student |
| <input type="checkbox"/> Retired | <input type="checkbox"/> Other |

11. 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

12. 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: _____

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

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

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

15. 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: _____

16. 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...]