BIOBEHAVIORAL RELATIONSHIPS BETWEEN JOB STRESS AND CARDIOVASCULAR DISEASE RISK

by

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ABSTRACT

Cardiovascular disease (CVD) is the leading cause of death and disability worldwide, therefore prevention remains a leading public health concern. Job stress appears to be associated with CVD, although the mechanisms underlying the relationship are complex and not fully understood. The purpose of this study was to describe biobehavioral relationships linking job stress to cardiovascular disease CVD risk among healthcare workers in the southeastern United States (US). A predictive model of the associations between job stress, leisure-time physical activity (LTPA), hair cortisol, symptom experience of job stress, and CVD risk was developed based upon theoretical relationships found in the existing literature. It was hypothesized that increased chronic job stress would predict increased hair cortisol concentration (HCC) as well as decreased LTPA; subsequently increased HCC and decreased LTPA would predict increased CVD with the symptom experience of job stress partially mediating the relationship between HCC and CVD risk. A final sample of 106 healthcare workers (96.2% female; mean age = 42.69 years) was obtained at three healthcare facilities in the southeastern United States. No relationships were found between job stress, HCC, LTPA, symptom experience of job stress, or CVD risk. In addition, no association was evident between individual components of the psychosocial job environment (demand, control, social support) and HCC, LTPA, or CVD risk. However, a relationship was found between isostrain (high demand, low control, and low social support) and HCC. Individuals reporting isostrain...
had higher HCC \((M = 2.38, SD = 0.80)\) compared to co-workers without isostrain \((M = 1.74, SD = 0.62, t(104) = -2.59, p = .011)\). A medium effect size was seen \((\eta^2 = .061)\). This study is the first to explore the relationship between isostrain and HCC. Prior research describes an association between isostrain and CVD among men, but too little research exists to draw a conclusion among women. Therefore, additional research is needed regarding the interplay of isostrain, HCC, and CVD among women.

The form and content of this abstract are approved. I recommend its publication.

Approved: Paula Meek
DEDICATION

I dedicate this work to the memory of my grandfather, Michael L. Kostenko. He gave cardiovascular disease a face and made its heartbreak a reality. Although he cannot appreciate the life trajectory he sparked for his granddaughter, he would be proudest not of any degree earned, but rather the choice to pursue lifelong learning and service to others.

I dedicate this work to my husband, Tyson S. Hall, who knew the sacrifices required when pursuing a PhD, yet supported my aspirations and remained my unswerving encourager. Without complaining, he accepted extra home responsibilities and showed genuine interest when I needed to discuss my research. I dedicate this work to my children, Caleb, Enoch, and Victoria who have accompanied me on this journey their entire lives. Their laughter, hugs and slobbery kisses made daunting obstacles surmountable. As I watch the tenacity and fearlessness with which they face each new challenge in life, I am humbled and reminded to get up and keep learning.

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CHAPTER I
INTRODUCTION

Since the 1930s, cardiovascular disease (CVD) has remained the leading cause of death in the United States and, more recently in the world (Jones, Podolsky, & Greene, 2012). One in every three deaths in the United States is due to CVD (30.8%), accounting for 800,937 deaths in 2013 (Mozaffarian et al., 2016). Despite downward trends, psychological stress is an ongoing health concern in the United States with 22% of the adult population reporting that they are extremely stressed and a growing number of the remaining adults (39%) stating that their stress levels are increasing (American Psychological Association [APA], 2012). Sixty percent of Americans identify work as a significant source of stress (APA, 2016).

Job stress, defined as the condition occurring when job demands outweigh the capabilities, resources, or personal needs of an employee (Karasek & Theorell, 1990; National Institute for Occupational Safety and Health, 1999), increases the risk for CVD. Indeed, it directly contributes to 3.4% of all coronary heart disease (CHD) events, the most prevalent form of CVD (Kivimaki et al., 2012). Individuals with ongoing job stress have twice the risk of myocardial infarction (Rosengren et al., 2004) and a 50-65% greater risk of a recurrent CHD event (Leander et al., 2007; Li, Zhang, Loerbroks, Angerer, & Siegrist, 2014). Ischemic stroke risk is likewise increased (Ardito, d'Errico, & Leombruni, 2014). Notwithstanding the general consensus regarding stress as a CVD risk factor, the underlying mechanisms linking job stress with CVD remain poorly described (Ardito et al., 2014; Callaghan et al., 2005; Dimsdale, 2008; Kivimaki et al., 2012; Kivimaki, Virtanen, et al.,
2006; Rosengren et al., 2004; Streptoe & Kivimaki, 2012; Toren et al., 2014; Yusuf et al.,
2004). Therefore the purpose of this study was to describe biobehavioral relationships linking
job stress to CVD risk among healthcare workers in the southeastern United States.

**Rationale for the Study**

**Burden of Cardiovascular Disease**

Globally, CVD accounts for approximately 17.3 million deaths annually, or 30% of
total deaths and 48% of non-communicable disease deaths (World Health Organization
[WHO], 2011a). Within the United States, 82.6 million individuals have some form of CVD
(Roger et al., 2011). Looking ahead, the American Heart Association projects a 10% increase
in CVD over the next 20 years, assuming no change in disease prevention and treatment; thus
40.5% of the population would have some form of CVD by 2030 (Heidenreich et al., 2011).

CVD also exerts a significant financial burden. The United States exhibits the highest
healthcare expenditures in the world, with 15% of our national gross domestic product (GDP)
spent on healthcare (Heidenreich et al., 2011). Expenses from CVD account for 17% of
healthcare expenditures (Roehrig, Miller, Lake, & Bryant, 2009), costing $312.6 billion
annually (Go et al., 2013). Languishing federal programs bare a large part of this financial
burden, with 30% of Medicare spending going toward CVD treatment (Trogdon, Finkelstein,
Nwaise, Tangka, & Orenstein, 2007). In the face of these dismal reports, the cost of CVD
continues to rise. Over the last ten years, CVD cost rose 6% annually, accounting for 15% of
the escalation in medical spending (Heidenreich et al., 2011). Assuming no change in
prevention and treatment of CVD, the direct healthcare cost for CVD will reach $818.1
billion by 2030 in addition to $275.8 billion from lost productivity (Heidenreich et al., 2011).
Beyond the national healthcare burden, however, a cardiovascular diagnosis is a personal struggle. Not surprisingly, individuals with CVD suffer decreased quality of life (Schweikert et al., 2009; Soto Torres et al., 2004; Xie et al., 2006; Xie et al., 2008). The greatest decline is among females, non-Caucasians, or those < 65 years old at time of diagnosis.

CVD generates profound individual as well as societal effects. Therefore, it is imperative that we seek to better understand factors contributing to CVD morbidity and mortality. Job stress is a likely contributor with potential pathways spanning physiologic, behavioral, and symptom processes.

Figure 1. Rationale for the study. Adapted from Kaltsas, Zannas, & Chrousos. (2012).
Physiologic Pathways

Physiologic responses to stress are automatic, subconscious attempts to achieve system stability. In acute situations physiological responses are adaptive, but with chronic stimulation, they become deleterious. Several body systems are involved including the hypothalamus-pituitary-adrenal (HPA) axis and autonomic nervous system. Cortisol, the primary effector of the HPA axis, is released from the adrenal cortex in response to psychological or physiologic stress and subsequently influences many metabolic, inflammatory, and immune processes. Over-secretion or inappropriate balance with other regulatory mechanisms increases CVD risk due to the associated increased risk of adiposity, insulin resistance, dyslipidemia, hypercytokinemia, and hypertension (Figure 1) (Kaltasas, Zannas, & Chrousos, 2012). However, the exact nature of a relationship between job stress, cortisol, and CVD has remained elusive due to the complexity of the biologic stress response and conceptual and methodological limitations in stress research (Dimsdale, 2008; Steptoe, Rosengren, & Hjemdahl, 2012).

Historically, cortisol has been measured in saliva, serum, or urine. These provide single point references that may not accurately reflect changes in cortisol caused by chronic stress. Any acute stress, potentially including the testing procedure itself, may alter salivary and serum cortisol. Furthermore, time of sampling significantly alters results, as cortisol fluctuates in a marked ultradian and circadian rhythm (J. K. Gu et al., 2014). The advent of hair cortisol analysis now provides a longitudinal and retrospective assessment of cortisol activity for up to the preceding 6 months (Dettenborn, Tietze, Bruckner, & Kirschbaum, 2010), thus negating several of the major methodological limitations in job stress research to date.
Elevated hair cortisol concentration (HCC) has preliminarily been associated with CVD (Manenschijn et al., 2013; Pereg et al., 2011), increased body mass index (BMI) (Manenschijn, van Kruysbergen, de Jong, Koper, & van Rossum, 2011; Stalder et al., 2013; Stalder et al., 2012; Wester et al., 2014; Younge et al., 2015) and metabolic syndrome (Stalder et al., 2013). Perceived stress, mental burden, and forms of chronic stress including unemployment and financial strain likewise correlate with HCC although the effect of chronic job stress on HCC among a Western population has yet to be tested (Dettenborn et al., 2010; J. K. Gu et al., 2014; Kalra, Einarson, Karaskov, Van Uum, & Koren, 2007). I hypothesize that HCC may be a valuable biomarker for chronic maladaptive alterations in the HPA axis resulting from chronic job stress, offering a plausible link with CVD risk though the metabolic and inflammatory effects of long-term hypercortisolism.

**Behavioral Pathways**

The effect of job stress on behavioral CVD risk factors such as physical inactivity, smoking, diet, and excessive alcohol intake provides a complementary pathway that may further explain CVD risk among the working population. Indeed, individuals with job stress are 25-30% more likely to lead an unhealthy lifestyle and are less likely to adopt a healthy lifestyle compared to low-stressed counterparts (Heikkila et al., 2013; Kouvonnen et al., 2007).

Of lifestyle behaviors, lack of leisure-time physical activity (LTPA) has most consistently been associated with job stress. Individuals experiencing high levels of job stress are 10-60% more likely to report sedentary behavior than non-stressed colleagues (Ali & Lindstrom, 2006; Fransson et al., 2012; Kouvonnen et al., 2006; Kouvonnen et al., 2013; Nyberg et al., 2013; Wemme & Rosvall, 2005). Inversely, a low level of job stress is
predictive of LTPA (OR = 1.81, 95% CI [1.32, 2.47])(Choi et al., 2010). In prospective
analysis, participants who were physically active and also reported high job stress were more
likely to become physically inactive compared to those in a low-stress job (OR = 1.21,
95% CI [1.11, 1.32])(Fransson et al., 2012).

Interestingly, LTPA rather than sedentary behavior at work predicts the greatest
metabolic and cardiorespiratory risk during longitudinal follow-up (Saidj et al., 2016). This
risk develops along several intertwined pathways including increase adiposity and
inflammation, insulin resistance, dyslipidemia, and endothelial dysfunction. A positive
energy imbalance produced by physical inactivity or excess caloric intake leads to increased
accumulation of triglycerides in adipocytes’ lipid droplets either through adipocyte
hyperplasia or hypertrophy (Hausman, DiGirolamo, Bartness, Hausman, & Martin, 2001).
Adipose tissue, far from being a collection of inert storage cells, is a metabolically active
organ. Hypertrophied adipocytes, infiltrated by macrophages, secrete multiple hormones and
inflammatory factors that produce systemic inflammation and hypercoagulability, thus
contributing to the vascular insult and atheromatous changes central to CVD pathogenesis. In
addition, many of these inflammatory factors are implicated in the development of insulin
resistance (Hotamisligil, Shargill, & Spiegelman, 1993; Sartipy & Loskutoff, 2003) and
dyslipidemia by stimulating triglyceride synthesis in hepatic cells, encouraging cholesterol
synthesis, and promoting lipolysis in adipocytes (Jung & Choi, 2014). Lipolysis leads to fatty
acid release, stimulating insulin resistance and further potentiating dyslipidemia. Finally,
endothelial dysfunction and arterial stiffness is evident among sedentary individuals, even
when elevated inflammatory markers are not present (Nosova et al., 2014). Each of these
factors independently and synergistically increases CVD risk.
Symptom Pathways

Individuals experiencing job stress often report negative symptoms, or alterations in sensation or function leading to a realization of compromised wellbeing. Several symptoms commonly reported by individuals with chronic job stress are implicated in CVD risk, notably depression (Nicholson, Kuper, & Hemingway, 2006; Van der Kooy et al., 2007) and inadequate sleep (Covassin & Singh, 2016).

Job stress significantly increases the incidence of depressive symptoms (ORs = 2.38 - 4.84) (Blackmore et al., 2007; Clark et al., 2012b; Clays et al., 2007b; Clumeck et al., 2009). Importantly, the risk is attenuated minimally when adjusted for non-work stressors. Although the mechanisms underlying this relationship are quite complex, chronic inflammation and overstimulation of the HPA axis offer one probable explanation (Penninx, 2016).

In addition, job stress is associated with subjective poor sleep, and a dose response is likely (de Lange et al., 2009; Edme, Facq, Frimat, & Vezina, 2011; Eriksen, Bjorvatn, Bruusgaard, & Knardahl, 2008; Greubel & Kecklund, 2011; Rugulies, Norborg, Sorensen, Knudsen, & Burr, 2009). Conversely, the absence of job stress is associated with self-reported restorative sleep (Buxton et al., 2009). Stressors at home do not appear to alter findings (Burgard & Ailshire, 2009; Geiger-Brown, Trinkoff, & Rogers, 2011).

Summary

A biobehavioral framework is needed to decipher the complex relationships underlying CVD risk in individuals experiencing chronic job stress. A model of CVD risk spans physiologic, behavioral, and symptom responses to job stress. Hair cortisol analysis
presents a promising method for assessing longitudinal alterations in the HPA axis, yet requires validation as a biomarker of chronic job stress.

**Purpose**

The purpose of the study was to describe the biobehavioral mechanisms linking job stress with cardiovascular risk among healthcare workers in the southeastern United States and in particular to preliminarily test a predictive model (Figure 2) of the association between physiological and behavioral responses to stress, stress-induced symptoms, and CVD risk.

*Figure 2. Predictive model of the biobehavioral relationships between job stress and CVD risk.*
Aim 1

To test the predictive model of the relationship between chronic job stress, LTPA, HCC, symptom experience of job stress, and CVD risk. Aim 1 included the following hypotheses:

1. Increased chronic job stress will predict increased HCC.
2. Increased chronic job stress will predict decreased LTPA.
3. Increased HCC will predict increased CVD risk.
4. Decreased physical activity will predict increased CVD risk.
5. The symptom experience of job stress will partially mediate the relationship between HCC and CVD risk.

Aim 2

To determine the relationship between specific components of the psychosocial job environment and HCC. Aim 2 included the following hypotheses:

1. Increased psychological demand will predict increased HCC.
2. Decreased control will predict increased HCC.
3. Social support will moderate the effect of job stress on HCC.
4. Increased job stress will predict increased HCC.
**Design and Study Population**

A correlational design was used as the research hypotheses examine relationships and do not include manipulation of the independent variable (Wood & Ross-Kerr, 2011). Reliable measurement of the variables is available. A convenience sample was drawn from day-shift workers at three healthcare centers in the southeastern United States.

**Definitions**

**Job Stress**

Job stress occurs when job demands outweigh the control and social support of an employee. Demands are the sum psychological toll produced by completion of job requirements in a specified time or manner. Control is the autonomy held by the employee, the freedom to choose how a job is completed. Social support includes coworker and supervisors’ functional or psychological support. An employee’s personal characteristics play...
an integral role in the development of job stress as these characteristics may alter what constitutes demand, control, and support for the individual.

**Hair Cortisol**

Hair cortisol will be defined as the concentration of cortisol present in the hair shaft after washing. As hair grows approximately 1 cm per month, each additional centimeter (up to 6 cm) represents retrospective cortisol activity for an additional month (Dettenborn et al., 2010).

**Leisure-time Physical Activity**

Leisure-time physical activity is defined as any physical activity occurring outside of work that requires energy expenditure.

**Symptom Experience**

Symptom responses are alterations in sensation or function leading to a realization of compromised wellbeing. The symptom experience is composed of individual, multidimensional symptoms that synergistically interact with each other.

**Cardiovascular Disease Risk**

Cardiovascular disease risk is defined as the likelihood of a CVD diagnosis within the next 10 years. CVD includes disorders of the heart or blood vessels such as CHD, heart failure, stroke, hypertensive heart disease, peripheral vascular disease, and aortic aneurysm or dissection (WHO, 2015). Although technically forms of CVD, deep venous thrombosis, pulmonary embolism, congenital heart disease, and rheumatic heart disease have distinct pathophysiologic mechanisms not addressed by this study.
Limitations

Conceptual and methodological limitations emerge in review of the proposed study. Stress is conceptually and operationally difficult to assess (Dimsdale, 2008). Although the Demand-Control-Support (DCS) model (Karasek & Theorell, 1990) is the most widely used theoretical framework in job stress research, a conceptual limitation exists in that the DCS only accounts for environmental factors contributing to job stress. While the extent to which personal characteristics versus environmental factors contribute to stress-induced outcomes is an ongoing debate, scientists agree that job stress is a complex phenomenon formed by interaction between the person and environment (National Institute for Occupational Safety and Health, 1999). Thus research using the DCS may overlook the confounding effect of personal characteristics. Common personal and work characteristics will be evaluated for covariance with HCC and CVD risk to minimize this limitation imposed by the DCS conceptualization of job stress.

Secondly, the inability to control for all confounding factors on cortisol activity will limit the accuracy of findings. An individual’s response and adaptation to stress are a complex interaction between the HPA axis, sympathetic nervous system, inflammatory pathways, and clotting cascades. Multiple factors other than job stress affect the physiologic stress pathways such as sleep, exercise, diet, acute stress, additional forms of chronic stress, chronic disease, and epigenetics. Use of hair cortisol allows a longitudinal assessment of cortisol, thus avoiding the effect of acute fluctuations caused by some confounding factors. However, control of every potential factor in the stress response remains impossible.

Thirdly, a cross-sectional design has limitations. Although this design allows researchers to test relationships and draw conclusions regarding how one variable affects
another, the single testing time prevents the demonstration of causality as a time sequence
cannot be established. In cross-sectional studies, validity is not threatened by history, testing
effects, regression toward the mean, or attrition of subjects (Portney & Watkins, 2009).
Instead, the greatest threat to validity is cohort effect, or extraneous variables in a given
group of individuals that may not be generalizable to other generations or cohorts. Yet, the
lower cost and time commitment for participants in cross-sectional studies makes this design
ideal for preliminary research.

In addition, convenience sampling may produce a sample with critical differences
from the population of interest, especially due to the exclusion of individuals with
insufficient hair for sampling. As far as possible, the sample will be compared to the
population of interest to evaluate potential bias.

Finally, the use of self-report measures creates a limitation, although research to date
regarding the effect of job stress on behavior has almost exclusively relied on self-report
measures. These notoriously demonstrate poor concurrent validity with objective measures of
behavior; underreporting of smoking and over-reporting of physical activity are common
(Connor Gorber, Schofield-Hurwitz, Hardt, Levasseur, & Tremblay, 2009; P. H. Lee,
Macfarlane, Lam, & Stewart, 2011; Segura-Jimenez et al., 2013). Unfortunately, objective
measurement of each behavior is unrealistic in a large sample with multiple outcome
measures.

**Conclusion**

Cardiovascular disease remains extremely costly, whether in lost life, lost quality of
life, or monetary measures. Therefore prevention remains a leading public health concern. By
adding to a growing, yet new, body of literature regarding the use of hair cortisol as a
biomarker of chronic job stress this study takes a small step in clarifying biobehavioral processes underlying CVD risk in individuals experiencing chronic job stress. With its emphasis on environmental, physiologic, behavioral, and symptom responses to chronic job stress, this study emphasized a holistic approach to CVD research in line with nurses’ metaparadigm.

Nurse researchers provide a valuable contribution to CVD research through their broad understanding of pathophysiology, behavioral science, epidemiology, and quality of life issues. The knowledge gained from nursing research such as this guides nursing practice, which spans from evaluation of CVD risk in occupational health and primary care, to development of healthcare policy.
CHAPTER II

BACKGROUND

Cardiovascular disease (CVD) is recognized as the leading cause of death and disability worldwide (Jones et al., 2012). As discussed in Chapter 1, job stress is associated with CVD, although the mechanisms underlying the relationship are complex and not fully understood. The purpose of this chapter is to provide an overview of the evidence supporting the proposed predictive model of the biobehavioral relationship between job stress and cardiovascular risk. First, an overview of CVD and job stress will be provided. Secondly, the physiologic stress response, and specifically the role of cortisol, will be reviewed. Then, evidence to support each proposed relationship in the model will be presented. Finally, the chapter will conclude with a synthesis of the theoretical perspectives used to develop the proposed predictive model.

Cardiovascular Disease

Incidence and Prevalence

Although 80% of CVD deaths occur in low or middle-income countries (WHO, 2011b), one in every three deaths in the United States is due to CVD (30.8%), accounting for 800,937 deaths in 2013 (Mozaffarian et al., 2016). The highest rate of mortality from CVD is secondary to coronary heart disease (CHD) (610,000 deaths annually), with an additional 128,842 deaths attributable to ischemic stroke (Kochanek, Xu, Murphy, Minin, & Kung, 2011). Each year about 735,000 Americans have an acute myocardial infarction (AMI) of which 525,000 are first events; an additional 160,000 silent myocardial infarctions are estimated to occur annually (Mozaffarian et al., 2016).
In the southeastern state where the proposed study will occur, CVD accounted for approximately 30% of deaths in 2008 (Georgia Department of Public Health, 2012). Similar to national statistics, CHD was the leading cause of death (23%) and stroke was the third most common (5%). Men had a 1.4 times higher rate of CVD death than women; African Americans had a 1.3 times greater risk than Caucasians. Although CVD clearly increases with age, 25% of CVD deaths were in those less than 65 years of age; for African American men the percentage increased to 50%. Sadly, 33% of adults in the state were unable to identify modifiable risk factors for CVD. During 2007, the total direct and indirect cost of CVD was $7.5 billion. The cost of hospital care for CVD increased $2.1 billion between 2003 and 2010, reaching a total of $5.5 billion

**Pathophysiology**

Atherosclerosis, the underlying disorder contributing to most types of CVD, is a pathologic process beginning in the first decade of life. Indeed, fatty streaks have been noted in fetal aortas, enhanced by maternal hyperlipidemia (Napoli et al., 1997); by teenage years, one in six Americans have thickening of the coronary arteries (Tuzcu et al., 2001). Despite the insidious progression of atherosclerosis, its clinical presentation often occurs suddenly with an AMI or stroke.

Although basic elements of atherosclerosis were described by Virchow in the mid-nineteenth century, this pathologic process continues to spark debate and extensive ongoing research. Several key elements will be reviewed here including endothelial dysfunction, lipid accumulation, smooth muscle proliferation, and the over-arching role of inflammation.

**Endothelial dysfunction.** The endothelium, a single layer of cells lining each blood vessel, maintains vascular tone, regulates hemostasis and inflammation, and blocks toxic
substances from contacting potentially thrombotic material outside the vasculature. Nitric oxide (NO), the most notable factor in normal endothelial function, promotes vasodilation, angiogenesis, and endothelial proliferation. With endothelial dysfunction, NO production is reduced and consumption increased. Although multiple factors may contribute to abnormal NO consumption and production, oxidative stress and inflammation are most notable. Oxidative stress is characterized by increased reactive oxygen species (ROS), which among other factors, is promoted by dyslipidemia and hyperglycemia (Low Wang, Hess, Hiatt, & Goldfine, 2016). Inflammation will be dealt with in detail below. A dysfunctional endothelium becomes permeable to low-density lipoprotein cholesterol (LDL-C), thus ushering in the next stage of atheroma formation.

**Lipid accumulation.** Lipoprotein accumulation is a hallmark of atherogenesis. Proteoglycan in the vessel intima bind lipoprotein particles, coalescing them into aggregates and making them susceptible to modification (oxidation or glycation)(Skalen et al., 2002). Although the endothelium normally resists adhesive interaction with leukocytes, in the setting of oxidative stress, cytokines promote expression of leukocyte adhesion molecules. These adhesion molecules (including vascular cell adhesion molecule-1 [VCAM-1], intercellular adhesion molecule-1, and P-selectin) signal monocytes and T lymphocytes to adhere to the endothelium (Libby, 2012). Subsequently, chemokines direct leukocyte migration into the arterial wall. A notable chemokine, monocyte chemoattractant protein-1 (MCP-1) is released by endothelial cells in response to oxidized lipoprotein (L. Gu et al., 1998). Once in the arterial intima, monocytes absorb lipids and become foam cells, or lipid-laden macrophages. Triggered by macrophage-colony stimulating factor (M-CSF), foam cells replicate and soon produce a fatty streak (Clinton et al., 1992; Libby, 2012). This lesion lacks
key components of a more complex atheroma including fibrosis, thrombosis, and calcification (Libby, 2008).

**Smooth muscle proliferation and plaque formation.** Endothelial dysfunction and leukocyte recruitment typify early formation of atheromas. Subsequent progression to more complex plaques requires the addition of smooth muscle cells (SMCs). Activated macrophages secrete chemoattractants for SMCs, such as platelet-derived growth factor, which induce SMC migration to the arterial intima where they slowly reproduce. Here commences a struggle between SMC proliferation and cell death, either from DNA fragmentation leading to apoptosis, or in response to inflammatory cytokines and *fas* ligand expression by T lymphocytes (Geng & Libby, 2002). Apoptosis and secondary necrosis of foam cells and SMCs contributes to formation of a necrotic core in the lesion, which is subsequently extended by impaired removal of apoptotic remnants.

Small neovessels develop in the progressing lesion, their fragility contributing to intraplaque bleeding that consequentially enhances necrosis and inflammation (Bentzon, Otsuka, Virmani, & Falk, 2014). This inflammatory response is even greater among individuals with the Hp2-2 genotype, a variant particularly common among patients with diabetes mellitus, due to impaired haptoglobin function (Purushothaman et al., 2012).

Cytokines and growth factors released by activated platelets, macrophages, T leukocytes, and endothelial cells stimulate production of collagen and fibrin from SMCs, leading to growth of a dense matrix called the fibrous cap (Streptoe, 2012). Calcification may ensue. After decades of insidious progression, instability and thinning of the fibrous cap occurs due to gradual loss of SMCs or degradation of collagen-rich matrix by infiltrating macrophages (Bentzon et al., 2014). The thinned cap may rupture, exposing the highly
thrombogenic, necrotic core. This rupture may occur spontaneously, or a temporary increase in emotional or physical stress can provide the final trigger. Acute job stress may be one such trigger; compared to 25-48 hours before the coronary event, a high-pressure deadline at work within the last 24 hours markedly increases risk of AMI (OR = 6.0, 95% CI [1.8, 20.4]) (Moller, Theorell, de Faire, Ahlbom, & Hallqvist, 2005). Whatever the trigger, activation of the sympathetic nervous system or increased coagulability and platelet reactivity, leading to an accentuated thrombotic response on already ruptured plaques, promote an acute CVD event (Bentzon et al., 2014). Plaque rupture is the most common precipitating incident in an acute CVD event, however plaque erosion can be an alternative factor. Although as yet a poorly understood phenomenon, vasospasm likely contributes to endothelial erosion and thrombosis (Bentzon et al., 2014).

**Inflammation.** As was intimated throughout the above paragraphs, inflammation plays a central role in atherosclerosis. Dating back to 1858, Virchow postulated an integral role of inflammation in atherogenesis, but for almost a century his view was overshadowed by the notion of passive lipid accumulation in atheroma formation (Libby, 2012). Now chronic inflammation, induced by both an innate and adaptive immune response, is understood to be an integral part of atherosclerosis.

Innate immunity, or the body’s nonspecific and initial defense to an antigen, accompanies every stage of atherosclerosis. Endothelial cells and SMCs, rather than solely reacting to cytokines, themselves produce pro-inflammatory mediators when stimulated by products of oxidized lipoproteins or angiotensin II (Libby, 2012; Libby, Ordovas, Auger, et al., 1986; Libby, Ordovas, Birinyi, Auger, & Dinarello, 1986). Later, foam cells become small factories for pro-inflammatory mediators such as chemokines, platelet-activating
factor, and ROS. Although macrophages, functioning as foam cells, are by far the most prevalent leukocyte in atheromas, mast cells and eosinophils are present in smaller numbers. Mast cell-derived IL-6 and interferon-γ (IFN-γ) promotes atherosclerosis by augmenting the expression of matrix-degrading proteases such as chymase; these induce SMC apoptosis, leading to plaque destabilization (den Dekker et al., 2012; Sun et al., 2007). In addition, eosinophilic IgE plays a role in atherosclerosis, although its exact function has yet to be elucidated. Indeed, IgE serum levels predict CHD severity (by Gensini score) independent of CVD risk factors (Guo et al., 2016; Wang et al., 2011).

In addition, adaptive immunity participates in atherosclerotic progression. Although seen in lesser numbers than macrophages, T cells play a director’s role in plaque formation (Libby, 2012). T cells bind to endothelial cells expressing VCAM-1 and migrate into the intima in response to chemokines (Andersson, Libby, & Hansson, 2010). When activated by antigens presented by macrophages and SMCs, they potentiate the inflammatory response by producing pro-inflammatory mediators (e.g. IFN-γ) (Hansson, Holm, & Jonasson, 1989). CD4+ type 1 helper cells, regulatory T cells, and CD8+ cytolytic T cells all participate in atherosclerotic pathology (Hansson & Jonasson, 2009), although detailed examination of their presumptive roles is beyond the scope of this review. B cells are likewise present in atherosclerotic plaques. Their function continues to engender vigorous research, but in summary, B cells are divided into two basic subsets: B1 cells appear to mitigate atherosclerosis via IgM antibodies while B2 cells enhance plaque formation (Tsiantoulas, Diehl, Witztum, & Binder, 2014).
Identification of Cardiovascular Risk

Cardiovascular disease may affect individuals of any age, ethnicity, socioeconomic class, or body habitus, although certain populations are at increased risk. Yet, CVD remains largely preventable. Modifiable risk factors have a multiplicative relationship and together account for an average 61% of all CVD (Kaplan, 2016; WHO, 2009). This figure is higher among high-income countries and lower in African countries (WHO, 2009).

Because CVD has an insidious onset spanning decades, researchers often evaluate precursor risk factors when prolonged follow-up is not feasible. These include modifiable risk factors such as hypertension, smoking, obesity, dyslipidemia, physical inactivity, and hyperglycemia, as well as non-modifiable risk factors such as age, gender, ethnicity, and genetics.

Hypertension. Hypertension is the preeminent risk factor for CVD, affecting nearly 32.6% of the United States population (Mozaffarian et al., 2016). African Americans have higher prevalence, reaching 44.9% and 46.1% for men and women respectively. Hypertension directly contributes to an estimated 54% of all strokes and 47% of all CHD (Kaplan, 2016). Approximately half of all CVD deaths (Centers for Disease Control and Prevention [CDC], 2011b). Annually, an estimated 46,000 deaths could be prevented if hypertension was controlled according to current guidelines (CDC, 2011b), but unfortunately, only 54.1% of hypertensive adults in the United States reach blood pressure goals and 17.3% are undiagnosed (Mozaffarian et al., 2016).

Hypertension is easily evaluated by non-invasive means using a sphygmomanometer. Starting with readings of > 115/75 mmHg, the risk of CVD progressively increases with each incremental increase in blood pressure (BP)(Kaplan, 2016). The relative contribution of the
systolic versus diastolic BP changes with age, with systolic BP being implicated most
notably among individuals over 60 years old. The American Heart Association’s (AHA)
classifications are often used to categorize BP readings for risk stratification and treatment
decision. Table 1 presents these classifications.

Table 1
AHA Classification of Hypertension

<table>
<thead>
<tr>
<th>Classification</th>
<th>Systolic BP</th>
<th>Diastolic BP</th>
</tr>
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<tbody>
<tr>
<td>Normal</td>
<td>&lt;120</td>
<td>&lt;80</td>
</tr>
<tr>
<td>Prehypertension</td>
<td>120-139</td>
<td>80-89</td>
</tr>
<tr>
<td>Hypertension Stage 1</td>
<td>140-159</td>
<td>90-99</td>
</tr>
<tr>
<td>Hypertension Stage 2</td>
<td>160 and higher</td>
<td>100 or higher</td>
</tr>
<tr>
<td>Hypertensive Crisis</td>
<td>180 and higher</td>
<td>&gt;110</td>
</tr>
</tbody>
</table>


**Smoking.** Smoking, another prominent modifiable CVD risk factor, leads to a two- to
four-fold increased risk of CVD (CDC, 2012a). This risk is not significantly changed when
controlling for educational level, occupation, race, alcohol consumption, and dietary factors
(Thun, Apicella, & Henley, 2000). The population attributable risk (PAR) of CVD deaths for
smoking is 13.7% (95% CI [4.8, 22.3])(Go et al., 2013), and almost one-third of CHD deaths
are attributable to smoking (Mozaffarian et al., 2016).

The pathophysiology of smoking-related CVD is complex. With its 4000 different
chemical components, cigarette smoke contributes to insulin resistance and dyslipidemia,
promotes vascular thrombosis and inflammation, stimulates aberrant vascular growth and
angiogenesis, and impairs endothelial homeostatic and regenerative functions (Cooke, 2015).
These effects are partially explained in that cigarette smoke:

- impairs endothelium-dependent vasodilation, likely secondary to decreased
  availability of NO (Mayhan & Patel, 1997; Y. Ota et al., 1997).
- promotes platelet activation and adhesion by decreasing the availability of platelet-derived NO and platelet sensitivity to exogenous NO (Ichiki, Ikeda, Haramaki, Ueno, & Imaizumi, 1996; Sawada, Kishi, Numano, & Isobe, 2002).
- promotes oxidation of low-density lipoprotein (Heitzer et al., 1996).
- decreases the activity of paraoxonase, an enzyme that protects against LDL-C oxidation (Nishio & Watanabe, 1997).
- increases circulating inflammatory markers including CRP, TNF-α, and IL-6 (Bermudez, Rifai, Buring, Manson, & Ridker, 2002; Tappia, Troughton, Langley-Evans, & Grimble, 1995).

Although smoking prevalence continues to decrease in the United States, 16.9% of adults smoke (Mozaffarian et al., 2016), including slightly more men (18.8%) than women (14.8%)(CDC, 2016a). In the southeastern state where the proposed study will be conducted, 17.4% of the population smokes (CDC, 2016b), a percentage remarkably lower than any of the surrounding states. However, the specific counties where study sites are located have smoking prevalences ranging from 23.6% to 32.1% (Institute for Health Metrics and Evaluation, 2015).

**Obesity.** A third CVD risk factor, obesity, is increasingly common in the United States. Obesity is typically defined according to the World Health Organization’s International BMI Classification System, as presented in Table 2. The BMI is established from an individual’s weight in kilograms divided by the square of their height in meters and is a common, indirect measure of adiposity. Elevated BMI is associated with multiple poor health outcomes including all-cause mortality, type 2 diabetes mellitus, dyslipidemia, CVD,
poor mental health, sleep apnea and respiratory problems, gallbladder disease, osteoarthritis, and multiple cancers (Bhaskaran et al., 2014); NIH, 2012).

Table 2

*WHO International BMI Classification*

<table>
<thead>
<tr>
<th>Classification</th>
<th>BMI (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt;18.50</td>
</tr>
<tr>
<td>Severe thinness</td>
<td>&lt;16.00</td>
</tr>
<tr>
<td>Moderate thinness</td>
<td>16.00 - 16.99</td>
</tr>
<tr>
<td>Mild thinness</td>
<td>17.00 - 18.49</td>
</tr>
<tr>
<td>Normal range</td>
<td>18.50 - 24.99</td>
</tr>
<tr>
<td>Overweight</td>
<td>≥25.00</td>
</tr>
<tr>
<td>Pre-obese</td>
<td>25.00 - 29.99</td>
</tr>
<tr>
<td>Obese</td>
<td>≥30.00</td>
</tr>
<tr>
<td>Obese class I</td>
<td>30.00 - 34.99</td>
</tr>
<tr>
<td>Obese class II</td>
<td>35.00 - 39.99</td>
</tr>
<tr>
<td>Obese class III</td>
<td>≥40.00</td>
</tr>
</tbody>
</table>


In the United States, 34.9% of the adult population is obese and 69% are either obese or overweight (Ogden, Carroll, Kit, & Flegal, 2014). In the southeastern state where the proposed study will occur, 29% of the adult population self-report obesity, while the specific counties of interest have even worse rates (CDC, 2016c).

Being overweight significantly contributes to CHD (PAR 27%) and stroke (PAR 20%) (Institute of Medicine, 2010). While much of the risk from obesity is indirectly seen through the increased incidence of hyperglycemia, hypertension, and dyslipidemia, obesity itself independently increases the risk of CVD (Eckel, 1997). This is likely due to adipocyte secretion of pro-inflammatory mediators and will be discussed in detail in following sections.

**Dyslipidemia.** Dyslipidemia often accompanies other risk factors but is itself a contributor to CVD. In the United States, over 100 million adults have total cholesterol levels > 200 mg/dL (Mozaffarian et al., 2016). Unfortunately, only 48% are treated and even fewer
(33%) reach recommended goals for total and LDL-C (CDC, 2011c). The specific mechanisms driving the pathophysiologic contribution of dyslipidemia to CVD are diverse, spanning multiple types of lipid particles, each with specific risks. In brief, small LDL-C particles are especially athrogenic due to their propensity to adhere to and penetrate the endothelium, as well as their susceptibility to oxidation. Once oxidized, LDL-C acquires new properties that make it appear foreign to the immune system, thus attracting leukocytes, promoting leukocyte differentiation to foam cells, and promoting proliferation of SMCs, leukocytes, and endothelial cells (Dokken, 2008). By contrast, the cardioprotective high-density lipoprotein cholesterol (HDL-C) combats inflammation and oxidation and promotes endothelial repair. However, the most important role of HDL-C is its role in reverse cholesterol transport, or the uptake of cholesterol from arterial intima and transport to the liver for excretion in bile (Hutchins & Heinecke, 2015).

**Physical inactivity.** Physical inactivity increases CVD risk, even beyond its contribution to obesity, hypertension, dyslipidemia, and hyperglycemia (Reddigan, Ardern, Riddell, & Kuk, 2011). However, those risk factors are significant and involve several intertwined pathways. A positive energy imbalance produced by excess caloric intake or physical inactivity leads to increased accumulation of triglycerides in adipocytes’ lipid droplets either through adipocyte hyperplasia or hypertrophy (Hausman et al., 2001). Hypertrophied adipocytes, infiltrated by macrophages, secrete multiple hormones and inflammatory factors including MCP-1, TNF-α, IL-1, IL-6, IL-8, C-reactive protein (CRP), plasminogen activator inhibitor-1, angiotensinogen, platelet-activating eicosanoids, and activated platelets (Berg & Scherer, 2005; Jung & Choi, 2014; Shelton & Miller, 2010). Systemic inflammation and hypercoagulability results, contributing to the vascular insult and
atheromatous changes central to CVD pathogenesis. In addition, many of these inflammatory factors are implicated in the development of insulin resistance (Hotamisligil et al., 1993; Sartipy & Loskutoff, 2003). Indeed, a few days of extreme physical inactivity (bed-rest) leads to a 67% increase in insulin secretion following glucose loading, suggesting insulin resistance (Hamburg et al., 2007). Several of the inflammatory mediators (e.g. IL-6, TNF-α, and IL-1) stimulate triglyceride synthesis by hepatic cells, encourage cholesterol synthesis and promote lipolysis in adipocytes (Jung & Choi, 2014). Lipolysis leads to fatty acid release, stimulating insulin resistance and further potentiating dyslipidemia. Finally, endothelial dysfunction and arterial stiffness is evident among sedentary individuals, even when elevated inflammatory markers are not present (Nosova et al., 2014). Each of these factors independently and synergistically increase CVD risk.

Despite the unmistakable deleterious effects of physical inactivity, one in four American adults report no physical activity in the last month, and 79% do not meet recommendations for physical activity (CDC, 2014). These statistics are mirrored in the southeastern state where the proposed study will occur (CDC, 2016c). Yet, those who engage in moderate-intensity leisure-time physical activity (LTPA) for 150 minutes per week have 14% lower risk of CHD than those who undertake no routine physical activity (Sattelmair et al., 2011). The PAR of CVD deaths accountable to physical inactivity is 11.9% (95% CI [1.3, 22.3])(Go et al., 2013).

**Hyperglycemia.** Diabetes, defined as fasting blood sugar ≥ 126 mg/dl or A₁c ≥ 6.5%, accounts for 8.8% of CVD deaths (Go et al., 2013). Indeed, diabetics have a two- to four-fold increased risk of stroke or death from CHD over those without diabetes (CDC, 2012c). In the United States, 29.1 million adults or 9.3% of the adult population and 25.9% of those over 65
years of age were diabetic in 2012; an additional 86 million individuals had prediabetes (American Diabetes Association, 2015). In the two counties where the proposed study will occur, 10.2% and 11.4% of the adult population is diabetic (CDC, 2016c).

**Diet.** Dietary effect on hypertension, obesity, dyslipidemia, and diabetes accounts for much of the CVD risk, although other factors are implicated. Notwithstanding clear recommendations for low-fat, high-fiber, high-fruit and vegetable, whole-grain, low-sodium, energy-balanced diets, most American adults fail to comply. Between 1971 and 2004, caloric intake increased by 22% in women and 10% in men despite decreased energy expenditure through physical activity (Go et al., 2013). In 2009, only 32.5% of United States adults consumed the recommended two fruits daily and only 26.3% met the recommendations for vegetable intake (CDC, 2010). In the face of these statistics, meta-analyses demonstrate a CHD risk reduction of 4% for *each* additional daily serving of fruits or vegetables over one serving (Dauchet, Amouyel, Hercberg, & Dallongeville, 2006) and an 11% risk reduction for stroke for each serving of fruit over one serving (Dauchet, Amouyel, & Dallongeville, 2005). The PAR of CVD death for poor diet is 13.2% (95% CI [3.5, 29.2])(Go et al., 2013).

**Alcohol.** While moderate levels of alcohol intake improve CVD prevention and outcomes (Ronksley, Brien, Turner, Mukamal, & Ghali, 2011), excessive intake may contribute to heart failure, stroke, obesity, hypertension, dyslipidemia, and cardiac arrhythmias (American Heart Association, 2011). In the United States, 5% of adults drink heavily and 17% binge drink (CDC, 2012b).

**Socioeconomic status and education.** Individuals living at or below the poverty level have increased prevalence of CHD, hypertension, and stroke (CDC, 2012e). Likewise, educational level is inversely related to CVD risk (CDC, 2012e). Socioeconomic status and
education may adversely affect CVD risk through dietary choices, chronic stress, and disparate access to care (Society for Cardiovascular Angiography and Interventions, n.d.).

**Non-modifiable factors.** Several non-modifiable factors affect CVD risk including age, sex, ethnicity, and family history. Although CVD affects individuals of all ages, risk of non-congenital CVD increases with age. Men over age 45 and women over age 55 have a greater incidence of CVD, and the risk continues to rise throughout the remainder of the lifespan (Society for Cardiovascular Angiography and Interventions, n.d.).

Cardiovascular disease is the leading cause of death for both men and women, despite many Americans considering CVD a “man’s disease” (CDC, 2012d). Regrettably, only 54% of American women know that it is their greatest killer, a percentage not significantly improved in recent years (Mosca, Mochari-Greenberger, Dolor, Newby, & Robb, 2010). Gender differences do exist, however. Onset of CVD is delayed by an average 10 years in women due to the protective effect of estrogen (Jneid & Thacker, 2001). Far more women (42%) than men (24%) die within 1 year of suffering AMI (Women’s Heart Foundation, 2007).

Certain ethnic groups have greater risk of CVD, although differences are seen between types of CVD. In the United States, CHD accounts for 24.5% of African American deaths, 18% of American Indians or Alaska Natives, 23.2% of Asians or Pacific Islanders, 20.8% of Hispanics, 25.1% of Caucasian. For American Indians, Alaska Natives, and Asians or Pacific Islanders, CHD falls second to cancer as a cause of death (Heron, 2012). Among Asians, death due to stroke is more common (7.7% of all deaths) than among Caucasians (5.3%), African Americans (5.8%), or American Indians (3.5%)(Heron, 2012).
Individuals with familial history of CVD have an increased risk for CVD. Risk of CVD diagnosis is 45% higher among those who have a sibling with CVD. Stroke risk is 50% higher among those with a first-degree relative with history of a stroke, and heart failure risk is 70% higher with parental history (Mozaffarian et al., 2016). This elevated risk reflects genetic, epigenetic, and collective behavioral and environmental risk factors. Indeed, individuals with strong family history of CVD exhibit higher rates of modifiable risk factors, thus underscoring the preventable nature of considerable familial-related CVD risk. Although rare single gene mutations have been found, most genetically linked CVD is due to complex genetic disorders involving multiple genes, “each with relatively small effect, working alone or in combination with modifier genes and/or environmental factors” (Arnett et al., 2007, p. 2879).

**Job Stress**

Stress is a rampant phenomenon, yet defies definition given the highly individual and complex nature of the stress experience. Three broad variants in the understanding of stress exist, further complicating definition and research—one focusing on stress as a cause (environmental stressors), that focusing on stress as an effect (psychological experience), and finally stress as a physiologic phenomenon (Kopp et al., 2010). As will be discussed in the section on theoretical framework, the proposed study will examine job stress as a psychological experience that leads to a physiologic and behavioral response. Nevertheless, conceptualization of job stress is further hampered by the diverse knowledge that must be assimilated from disciplines stretching from sociology, psychology, epidemiology, behavioral medicine, psychoneuroimmunology, occupational health, and more (Siegrist, 1996). Finally, each occupation presents unique challenges and potential variations in job
stress. In the face of these challenges and limitations, this section aims to present prevalence data, historical background, and an overarching review of research regarding job stress as it relates to CVD risk.

**Prevalence and Cost**

Prevalence data regarding job stress is somewhat sparse in United States populations. However, the National Institute of Occupation Safety and Health (National Institute for Occupational Safety and Health, 1999) states that 26-40% of employed adults report some job stress. A study by the American Psychology Association ($N = 3068$) found that 60% of Americans report work as a significant source of stress. In the southern United States, the statistics were worse (66%)(APA, 2015). Review of the APA’s previous reports dating back to 2007 shows work as a source of stress declining from 74% to 61% between 2008 and 2009 and staying fairly constant between 60 - 70% since that time (APA, 2016).

In addition to the psychological burden, job stress directly contributes to the financial burden of healthcare. In a large, longitudinal analysis of American workers ($N = 46,026$), individuals who reported high stress at work had healthcare expenditures 46% greater than non-stressed counterparts (Goetzel et al., 1998).

**Historical Perspective**

The concept of human stress has been a subject of research and theory for decades. In fact, this area has been so copiously described, debated, and documented that it is difficult to comprehend that until the 1930’s, “stress” as a research phenomenon was virtually unknown. True, the fledgling concept may be discerned in Hippocrates’ description of disease produced not only by pathos (suffering), but also ponos (toil) in the body’s fight for normalcy (Rosch,
n.d.). But not until Hans Seyle described the stress response in 1935 did the phenomenon become a routine subject of research and, at times, heated debate (Viner, 1999).

Stress specific to work became a subject of increasing research in the 1960s when researchers at University of Michigan’s Institute for Social Research began studying stress in the industrial environment. Leading researchers in that program, Robert Kahn and John French, developed the person-environment (P-E) fit model, the first theoretical explanation of the development of job stress (Vaananen, Anttila, Turtiainen, & Varje, 2012). But by the 1980s, Karasek’s conceptual model of job strain became the dominant explanation of job stress research (Kristensen, 1996; Simmons & Swanberg, 2009). Upon recommendations by Johnson and Hall (1988), Karasek’s model was later expanded to the Demand-Control-Support (DCS) model, which recognized the integral component of supervisor and co-worker support on stress experienced at work (Karasek et al., 1998b). An alternative framework, The Model of Effort-Reward-Imbalance at Work (ERI), was introduced by Siegrist (1996) in an attempt to clarify perceived ambiguity in Karasek’s conceptualization of control although its use in research remains sparse compared to the DCS model.

**Job Stress and Cardiovascular Disease**

Extensive research has evaluated the link between job stress and CVD. Although the strongest evidence for a causal association would be experimentally manipulating job stress to evaluate the effect on CVD, a paucity of such research exists (Kivimaki & Kawachi, 2015). However, numerous prospective studies have examined the relationship between job stress and CVD.

Kivimaki et al. (2012) performed individual-level meta-analysis ($N = 197,473$) from 13 European cohort studies as part of the IPD-Work consortium to analyze the relationship...
between job stress and CHD, as defined by first non-fatal AMI or coronary death. Mean follow-up was 7.5 years ($SD = 1.7$ years) with baseline data obtained between 1985 - 2006. After adjusting for age and sex, they found increased risk of CHD among those with job stress compared to those with no job stress (HR = 1.23, 95% CI [1.10, 1.37]). This was partially attenuated after adjustment for socioeconomic status (HR = 1.17, 95% CI [1.05, 1.31]). However, additional adjustment for lifestyle factors (BMI, physical activity, smoking, and alcohol intake) or conventional risk factors (the Framingham score) did not significantly mitigate the association. The PAR for job stress was 3.4% (95% CI [1.5, 5.4]). Of note, this meta-analysis included published and unpublished studies, thus mitigating the effect of publication bias. Secondly, in order to control for an element of reverse causality, the authors examined the effect of excluding CHD events occurring within 3 years and 5 years of baseline analysis respectively; the relationship between job stress and CHD was slightly strengthened. Finally, minimal heterogeneity in effect estimates was noted between studies, suggesting reasonably consistent evidence.

In a systematic review of peer-reviewed, English-language studies from 1985 to 2014, Theorell et al. (2016) analyzed 96 studies of high or medium-high scientific quality that evaluated the relationship between job stress and CHD. Level of evidence was evaluated using the GRADE system. The authors found moderately strong evidence (grade 3 out of 4) of a relationship between job stress (as defined by job strain model) and incidence of CHD. Limited evidence (grade 2) was found for the contribution of low support at work in relation to CHD. No difference in findings existed between men and women.

Far fewer studies examine the relationship between job stress and stroke. However, Callaghan et al. (2005) undertook individual-level meta-analysis as part of the IPD-Work
consortium \( (N = 196,380) \). In all, 14 European cohort studies were included (mean follow-up 9.2 years). For ischemic stroke, the hazard ratio for job stress relative to no job stress was 1.24 (95% CI [1.05, 1.47]) after adjustment for age and sex. Further adjustment for socioeconomic status partially attenuated the risk (HR = 1.18, 95% CI [1.00, 1.39]). Hemorrhagic stroke showed no statistically significant association with job stress.

**Physiologic Stress Response**

In response to physical or psychological stimuli threatening the homeostasis of the body system, a complex and highly integrated stress response occurs involving neuroendocrine, autonomic, behavioral, and immune components. Two body systems primarily direct the physiologic stress response: the hypothalamic-pituitary-adrenal (HPA) axis and autonomic nervous system (ANS). Given the focus of the proposed study and the voluminous amount of research regarding the stress response, this review will exclusively focus on the HPA axis.

Unlike physical stress, psychological stress activates the limbic system, allowing an evaluative process to precede the physiologic stress response (Kaltasas, Zannas, & Chrousos, 2012). Complex neuro-circuitry connects the limbic forebrain structures to the hypothalamic paraventricular nucleus (PVN). With PVN innervation, the hypothalamus secretes corticotropin-releasing hormone (CRH) and arginine-vasopressin (AVP) into the hypophysial portal blood, stimulating anterior pituitary synthesis and secretion of adrenocorticotropic hormone (ACTH). The release of ACTH into systemic circulation in turn stimulates the synthesis and secretion of corticosteroids by the adrenal cortex. Cortisol is the primary corticosteroid in humans. With normal physiologic conditions, cortisol acts as a negative regulator of the synthesis and release of CRF and ACTH.
Figure 3 Central and peripheral components of the stress response system. Solid lines indicate stimulation; dashed lines indicate inhibition. ACTH = adrenocorticotropin hormone. CRH/AVP = corticotropin releasing hormone/arginine-vasopressin. DA = dopamine. IL-6 = interleukin 6. LC/NE = locus ceruleus-norepinephrine system. NE/E = norepinephrine/epinephrine. Adapted from Kaltsas, Zannas, and Chrousos (2012).

With recurrent activation of the HPA axis, as seen with chronic stress, changes may occur in neuro-circuitry responsible for the psychological stress response, prominently including pathways associated with anticipatory stress (Jankord & Herman, 2008). As a result, baseline cortisol hypersecretion, amplification of corticosteroid response to novel stressors, and down regulation of glucocorticoid receptors may results. However, in line with a biobehavioral understanding of the unique nature of each individual, considerable variation is seen in HPA axis activation with a role of epigenetic factors and early-life experiences being implicated.

Cortisol

As noted above, cortisol is the prominent corticosteroid in the human body and final effector of the HPA axis. Cortisol is secreted in a marked circadian rhythm directed by the
main circadian oscillator in the suprachiasmatic nucleus located in the hypothalamus. With normal HPA axis function, cortisol levels are lowest at midnight then slowly rise to peak 30 to 45 minutes after awaking in the morning. This is followed by a general downward tread to bedtime. Cortisol has complex regulatory mechanisms as noted above in Figure 3. In addition, cortisol undergoes tissue specific regulation via the conversion enzymes $5\alpha$- and $5\beta$-reductase and $11\beta$-hydroxysteroid dehydrogenases either by converting cortisol to its inactive form, cortisone, or vice versa. Cortisol has the ability to activate both mineralcorticoid receptors and glucocorticoid receptors.

Cortisol has long been implicated in the pathogenesis of metabolic risk due to striking similarities between Cushing’s syndrome (CS) and metabolic syndrome. This section will review the effect of cortisol on cardiovascular risk, the effect of job stress on cortisol, and current knowledge regarding hair cortisol.

**Effect on cardiovascular risk.** Hypercortisolism is associated with increased morbidity and mortality from CVD. Cushing’s syndrome, a rare disease causing excess glucocorticoid secretion, entails a four-fold increased risk of CVD mortality; excess risk may persist, even among effectively treated patients (Lambert et al., 2013). Similarly, individuals with subclinical hypercortisolism exhibit elevated rates of CHD with incremental increase risk with incremental elevation of cortisol (intermediate phenotype pattern OR = 4.1, 95% CI [1.5, 11.4], $p = .007$; florid subclinical hypercortisolism OR = 6.1, 95% CI [1.4, 26.5], $p = .016$)(Di Dalmazi et al., 2012). Recent longitudinal analyses replicated these findings (Debono et al., 2014; Di Dalmazi et al., 2014). Likewise, individuals taking exogenous glucocorticoids exhibited greater CVD risk after controlling for standard covariates (Souverein et al., 2004; Wei, MacDonald, & Walker, 2004). Lastly, elevated cortisol
predicted mortality during 8-year longitudinal follow-up of a group of elders, even after adjustment for age, gender, tobacco consumption, and waist circumference ($B = .036, p = .033$) (Mora, Serra-Prat, Palomera, & Puig-Domingo, 2014).

Specific consequences of hypercortisolism accounting for this elevated risk include hypertension; adiposity; hyperinsulinemia, hyperglycemia, and insulin resistance; dyslipidemia; and inflammation. Inhibition or activation of target genes accounts for many of these effects, although glucocorticoids also signal through membrane-associated receptors and second messengers (Kaltsas, Zannas, & Chrousos, 2012). A general overview of these effects is presented here, although more detailed review of these effects as they relate to HCC is provided in upcoming sections.

**Hypertension.** Hypertension is a prominent feature of CS, reported in 75-80% of CS patients (Magiakou, Smyrnaki, & Chrousos, 2006). Likewise, exogenous administration of glucocorticoids is known to increase both systolic and diastolic blood pressure independent of mineralocorticoid activity or alteration in plasma volume, although a dose-dependent relationship is likely (Magiakou et al., 2006; Whitworth, Gordon, Andrews, & Scoggins, 1989).

The mechanism of hypertension in hypercortisolism is multifactorial. In short, glucocorticoids tend to increase cardiac output, peripheral resistance and renovascular resistance. These effects are produced by an interplay of multiple factors including: cortisol’s intrinsic mineralocorticoid activity, activation of the renin-angiotensin-aldosterone system, enhancement of cardiovascular inotropic and pressor activity of vasoactive substances (catecholamines and or/vasopressin and angiotensin II), and suppression of vasodilation mechanisms including NO synthase, prostacyclin, and kinin–kallikrein (Magiakou et al., 2006; Whitworth, Gordon, Andrews, & Scoggins, 1989).
With normal physiologic levels of cortisol, 11β-hydroxysteroid dehydrogenase type 2 inactivates cortisol at the tissue level by converting it to cortisone, thus preventing excessive activation of mineralcorticoid receptors by cortisol (whose plasma concentration is exponentially higher than that of aldosterone). However, states of hypercortisolism may overcome the body’s ability to deactivate cortisol in tissue sensitive to aldosterone (Cicala & Mantero, 2010; Frey, Odermatt, & Frey, 2004).

Adiposity. Systemic hypercortisolism as seen in CS produces a 2- to 5-fold increase in central adiposity (M. J. Lee, Pramyothin, Karastergiou, & Fried, 2014). In non-CS individuals, alteration of normal salivary cortisol diurnal curve is likewise linked to obesity (BMI and WHR) (Rosmond, Dallman, & Bjorntorp, 1998). Frequently, serum cortisol levels fail to correlate with measures of adiposity, implicating tissue-level cortisol derangement as an important issue (Crowley et al., 2014; Pasquali, 2012). Measurement of urinary glucocorticoid metabolites allows assessment of the tissue-level cortisol activity and is more frequently associated with direct and indirect measures of adiposity. Furthermore, night-time or early morning assessments are likely optimal to detect subtle alterations in HPA axis function in obese individuals, thus potentially explaining some inconsistency in studies assessing salivary cortisol (Pasquali, 2012).

In a seminal work, Crowley et al. (2014) followed 57 obese or overweight individuals over five years with serial measures of urinary glucocorticoid and mineralocorticoid metabolites. Increasing BMI was associated with total cortisol secretion rate ($\beta = .013$, $p < .001$, 95% CI [.006, .020]). This is consistent with older studies as reviewed by Fraser et al. (1999), but adds the strength of longitudinal analysis. Dynamic studies of the HPA axis (either suppression or stimulation) in obese individuals further support the concept of a
dysfunctional HPA axis in central obesity (Vicennati et al., 2004; Vicennati & Pasquali, 2000). Hypercortisolism also induces increased appetite and a preference for sweet, fat-rich foods independent of current BMI, thus further potentiating adiposity (Dallman et al., 2004; Tataranni et al., 1996; Vicennati et al., 2011).

Cortisol’s influence on central adiposity relies on a complex interplay between increased cortisol secretion, increased receptor activation at the tissue level, and cortisol activation or inactivation in adipose tissue via 11β-hydroxysteroid dehydrogenases (Baudrand & Vaidya, 2015; Constantinopoulos et al., 2015; Morgan et al., 2014). In the presence of insulin, cortisol stimulates the differentiation of pre-adipocytes and fibroblast-like stromal vascular precursor cells into mature adipocytes (Hauner, Schmid, & Pfeiffer, 1987; M. J. Lee et al., 2014). Furthermore, cortisol and insulin act synergistically to increase activity of 11β-HSD type 1 in adipocytes, thus leading to tissue-level cortisol excess. In all, glucocorticoids affect 20% of adipose expressed genes, thus highlighting the profound affect excessive cortisol may have on adipocytes (M. J. Lee, Gong, Burkey, & Fried, 2011; Yu et al., 2010). More specific description of these complex relationships, as yet inadequately understood, is beyond the scope of this review, but has been described by M. J. Lee et al. (2014).

**Hyperinsulinemia, hyperglycemia, and insulin resistance.** Excessive or prolonged exposure to cortisol has a diabetogenic effect due to induction of peripheral insulin secretion, increased gluconeogenesis, inhibition of glucose uptake and utilization in muscles and fat, and increased hepatic glycogen deposition (Kaltsas, Zannas, & Chrousos, 2012). In longitudinal analysis, Crowley et al. (2014) found that deteriorating glucose tolerance status
was associated with total cortisol secretion during serial analysis of urinary glucocorticoid and metabolites over five years (coefficient = .074, \(p < .001\), 95% CI \([.030, .118]\)).

**Dyslipidemia.** Cortisol has a general lipogenic effect, decreasing HDL-C and increasing triglycerides and LDL-C. Although dyslipidemia among individuals with CS has been well described (Whitworth, Williamson, Mangos, & Kelly, 2005), more pertinent to this review are studies evaluating the effect of stress-induced cortisol alterations on the lipid profile. In a study \((N = 284)\) analyzing the effect of stress-induced changes in salivary cortisol, individuals showing a stress pattern in diurnal cortisol slope had worsening metabolic parameters on all measures including LDL-C, HDL-C, and triglycerides (Rosmond et al., 1998).

**Inflammation.** Glucocorticoids are, in acute situations, potent modulators of the inflammatory response. However, with chronic excessive exposure, glucocorticoids potentiate inflammation via several pathways. Most notably, prolonged glucocorticoid exposure potentiates CRP. Secondly, increased central obesity associated with hypercortisolism is a suppressor of anti-inflammatory cytokines and a potent generator of multiple proinflammatory cytokines including IL-6 (Kaltsas, Zannas, & Chrousos, 2012). In turn, IL-6 stimulates the hypothalamus to secrete CRH, thus potentiating inflammation.

**Job stress and cortisol.** Job stress shows variable relation to cortisol. Marked methodological differences between studies make comparison difficult. Steptoe, Cropley, Griffith, and Kirschbaum (2000) found that teachers \((N = 105)\) with high job demands and low control (i.e. high job strain) had salivary cortisol levels averaging 21.7% higher early in the workday, although the difference did not persist throughout the day. Alderling, Theorell, de la Torre, and Lundberg (2006) reported similar results in a much larger study \((N = 529)\),
although they found that women in high strain, passive, or active jobs all had elevated salivary cortisol early in the morning (30 minutes after awakening) compared to those with no strain; results were not significant in men. In longitudinal analysis spanning 3.5 years ($N = 77$), individuals with chronic job strain experienced elevated evening cortisol whereas morning levels were comparable to that of non-stressed individuals (Rystedt, Cropley, Devereux, & Michalianou, 2008). Cortisol area under the curve (AUC), a combination of multiple measurement points into a single score representing total daily cortisol output, was related to job stress among a small group of ambulance dispatchers and drivers ($N = 21$) (Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003; I. S. Wong, Ostry, Demers, & Davies, 2012). Finally, in a computer-simulated work environment, experimental manipulation of demand and control components of the work environment supported the DCS hypothesis that high demands in the setting of low control produces physiologic stress (salivary cortisol); this effect was negated when high control was simulated (Hausser, Mojzisch, & Schulz-Hardt, 2011).

Several studies found no relationship between the psychosocial work environment and salivary cortisol. In Thomas, Hertzman, and Power (2009), only two measurements of cortisol were obtained (45 min after awaking and 3 hours later), thus limiting the assessment of HPA axis alterations. Two studies using the ERI conceptualization of job stress failed to show a relationship with salivary cortisol (A. Ota et al., 2014; Steptoe, Siegrist, Kirschbaum, & Marmot, 2004).

Several factors may moderate the relationship between job stress and cortisol and explain some of the divergence noted above. Socioeconomic status may alter acute cortisol response to job stress, with variable effect throughout the day and with different components
of the psychosocial job environment (Kunz-Ebrecht, Kirschbaum, & Steptoe, 2004). In addition, adverse childhood experiences (ACEs) likely play a role. Westerlund, Gustafsson, Theorell, Janlert, and Hammarstrom (2012) found that individuals experiencing social adversity in adolescence subsequently reported job strain in mid-life and demonstrated allostatic load, a combined measure of the physiological consequences of chronic exposure to fluctuating or heightened neural or neuroendocrine stress responses, including dysregulation of cortisol. This is line with the concept of stress accumulation, or the additive effect of prenatal stress exposure, ACEs, and recent life stressors on physiologic consequences to stress (Hostinar, Lachman, Mroczek, Seeman, & Miller, 2015; Reynolds, 2013).

Salivary cortisol is a valuable biomarker for chronic psychosocial stress (An et al., 2016). Unfortunately research specific to job stress reveals multiple limitations including small sample sizes, inconsistent measures of salivary cortisol throughout the day, lack of covariate assessment, and different measures of job stress. Hair cortisol may diminish some of these methodological limitations while providing a measure of HPA axis activity consistent with the conceptualization of chronic job stress.

**Hair Cortisol**

Hair cortisol concentration (HCC) offers a novel mechanism to measure retrospective HPA axis activity up to the preceding 6 months much like hemoglobin A1c for serum glucose levels. As scalp hair grows an average 1 cm per month, each additional centimeter of analyzed hair represents an additional month of retrospective cortisol activity. After 6 cm, a washout effect negates effective assessment (Dettenborn et al., 2010).

**Reliability and validity.** Criterion validity of HCC has been established. In preliminary animal studies, HCC correlated strongly with salivary cortisol levels in rhesus
monkeys \( (r = 0.797, p < 0.001) \). Following stress induction by relocation, elevated salivary and hair cortisol accompanied behavioral signs of stress. Each marker returned to baseline a year later (Davenport, Tiefenbacher, Lutz, Novak, & Meyer, 2006). In human studies, HCC moderately correlated with mean salivary cortisol concentrations taken on 3 days \( (r = 0.41, p = .03) \) (van Holland, Frings-Dresen, & Sluiter, 2012) and cortisol area under the curve for 2 days \( (r_s = .398, p = .024) \) (Vanaelst et al., 2012). Also, HCC correlated significantly with cortisol metabolites in 24-hour urine \( (r = .33; p = 0.041) \) (Sauve, Koren, Walsh, Tokmakejian, & Van Uum, 2007). Serum cortisol, on the other hand, is not related to HCC (Sauve et al., 2007; Vanaelst et al., 2012). In conclusion, validity of HCC was demonstrated in a postpartum sample where retrospective HCC appropriately matched the known increase in cortisol during the third trimester (Kirschbaum, Tietze, Skoluda, & Dettenborn, 2009).

Complete consensus between serum, salivary, and urinary measures of cortisol and HCC is not required nor anticipated as different functions of the HPA axis are assessed. Each method views the HPA axis differently--the older methods assessing acute stress reactivity and diurnal variation versus the longitudinal, baseline function addressed by HCC.

**Determinants.** Hair cortisol research continues to be a rapidly developing field, thus identification of potential determinants, mediators, and moderators remains an ongoing quest and necessitates frequent review of extant literature. Wosu, Valdimarsdottir, Shields, Williams, and Williams (2013) offer an exhaustive review of extant literature. The following sections provide a summary of demographic, lifestyle, and hair characteristics and treatments as they relate to HCC in adults with the additional appraisal of recent studies not included in the previous review. Unfortunately the findings remain heterogenous for many factors.
**Demographic factors.** The effect of sex on HCC is highly inconclusive with some investigators reporting men having higher HCC than women (Dettenborn, Tietze, Kirschbaum, & Stalder, 2012; Manenschijn et al., 2013; O'Brien, Tronick, & Moore, 2012; Stalder et al., 2012) and others finding no statistical difference (Dowlati et al., 2010; Manenschijn, Koper, Lamberts, & van Rossum, 2011; Manenschijn et al., 2012; Raul, Cirimele, Ludes, & Kintz, 2004; Stalder et al., 2013; Wosu et al., 2015). Most investigators found no relationship between age and HCC (Kirschbaum et al., 2009; Manenschijn, Koper, et al., 2011; Manenschijn et al., 2012; Manenschijn et al., 2013; O'Brien et al., 2012; Raul et al., 2004; Stalder et al., 2012), although a non-linear relationship may be present with individuals under 10 years or over 50 years having elevated HCC (Dettenborn, Tietze, et al., 2012). Marital status, socioeconomic status, and educational attainment does not appear to alter HCC (O'Brien et al., 2012; Wosu et al., 2015). In terms of ethnicity and race, Wosu et al. (2015) found that African Americans and Hispanics had higher HCC independent of socioeconomic status. Alternatively, O'Brien et al. (2012) found no difference by race/ethnicity although they described an interactive effect between race and socioeconomic status on HCC. Unmeasured psychosocial stressors related to ethnicity but independent of socioeconomic status may partially explain the divergent findings (Geronimus, Hicken, Keene, & Bound, 2006).

**Lifestyle or medicinal factors.** Use of oral contraceptive does not affect HCC (Dettenborn, Tietze, et al., 2012; O'Brien et al., 2012). Findings regarding the effect of smoking on HCC are mixed (Dettenborn, Tietze, et al., 2012; Wosu et al., 2015). Alcohol consumption was associated with elevated HCC values, although the findings failed to reach statistical significance (Wosu et al., 2015).
Hair characteristics and treatments. Measurement of HCC is unaffected by natural hair color (Dettenborn, Tietze, et al., 2012; Manenschijn, Koper, et al., 2011; Raul et al., 2004; Sauve et al., 2007). Likewise, frequency or temperature of hair washing does not affect HCC in the most proximal 6 cm, although a washout effect is noted beyond 6 cm (Dettenborn, Tietze, et al., 2012; Kirschbaum et al., 2009; Manenschijn, Koper, et al., 2011; O'Brien et al., 2012; Stalder et al., 2012). Hair treatments such as hair dye likely have a modest influence on HCC (Manenschijn, Koper, et al., 2011; Sauve et al., 2007), although some investigators documented no effect (Dowlati et al., 2010; Stalder et al., 2012).

Rationale for hair cortisol assessment. Measurement of hair rather than salivary, serum, or urinary cortisol offers several benefits to this study. Hair analysis is less invasive, less easily altered by acute situational and individual factors, requires one sample rather than a time series, is not affected by work versus rest day, is stable at room temperature, and offers a retrospective and longitudinal picture of HPA axis activity consistent with the conceptualization of chronic stress.

Proposed Relationships

Job Stress and Hair Cortisol

Elevated HCC is proposed to be a physiologic marker of chronic stress, namely job stress. As systematically reviewed by An et al. (2016), salivary cortisol provides a robust reflection of chronic psychological stress. Theoretically, the same should be observed using hair cortisol with the additional benefits mentioned above. However, to date, the relationship between job stress and HCC has yet to be evaluated among a Western population.

In Bangladesh, Steinisch et al. (2014) evaluated work stress and HCC among 175 garment factory workers. Job stress was assessed with questions regarding work-related
demands, interpersonal resources, and work-related values (WRV). Only WRV was directly related to HCC ($\beta = 0.209, p = 0.021$), and specifically to the item regarding promotion prospects ($\beta = 0.230, p = 0.007$). The authors noted that, in this study setting, the prospect of promotion involves extreme pressure to perform, necessitates extraordinary loyalty to management and a willingness to penalize coworkers, and therefore, may be perceived as a chronic stressor. Occupational and cultural differences limit the generalizability of these findings to healthcare workers in the United States. Furthermore, of methodological concern, HCC was analyzed from only one to two strands of hair, thus increasing likelihood of assay error.

Other forms of chronic stress such as unemployment and financial strain positively correlate with HCC in Western populations (Dettenborn et al., 2010), and several researchers report positive correlation of HCC with reported mental burden and perceived stress (J. K. Gu et al., 2014; Kalra et al., 2007). However, the proposed study would fill a void in existing literature by examining HCC as a biomarker of the physiologic response to chronic job stress.

**Job Stress, Leisure-time Physical Activity, and Cardiovascular Risk**

In addition to physiologic outcomes of job stress, individuals experiencing job stress may exhibit negative behaviors including decreased LTPA. Indeed, individuals reporting job stress have a 10-60% increased risk of sedentary behavior when compared to non-stressed colleagues (Ali & Lindstrom, 2006; Fransson et al., 2012; Kouvonen et al., 2006; Kouvonen et al., 2013; Nyberg et al., 2013; Wemme & Rosvall, 2005). Of specific interest, Nyberg et al. (2013) pooled individual-level data from eight cross-sectional studies comprised of 47,045 participants and found that individuals experiencing job stress had elevated risk of
physical inactivity (OR = 1.34, 95% CI [1.26, 1.41]). Inversely, Choi et al. (2010) observed that low level of job stress was predictive of the presence of LTPA (OR = 1.81, 95% CI [1.32–2.47]) after controlling for multiple potential confounders including social support, obesity, depression, other chronic diseases and lifestyle behaviors.

In prospective analysis, participants who were physically active and also reported high job stress were more likely to become physically inactive compared to those in a low-stress job (OR = 1.21, 95% CI [1.11, 1.32])(Fransson et al., 2012). No association was found by job type for those inactive at baseline becoming active. Reverse causality was tested and showed slight increase risk of developing high job strain for those who were physically inactive at baseline (OR = 1.15, 95% CI [1.07, 1.24]). Yang et al. (2010) found a more profound risk among those persistently inactive during a nine year span (OR = 4.0, 95% CI [2.17, 7.39]).

Ethnic and gender differences may exist. Bennett et al. (2006) found that Caucasians experiencing job stress have an average one hour less LTPA per week compared to those without job stress ($p = .05$). Ethnic minorities, however, reported slightly higher levels of LTPA when experiencing job stress, although the difference was not statistically significant. Although most studies did not report a difference between genders, Wemme and Rosvall (2005) found a stronger effect of non-work stress factors on LTPA among women than job-related stress. Interestingly, low social participation strongly predicted LTPA (OR= 2.7, 95% CI [2.2, 3.4]), as did lack of emotional social support (OR = 1.9, 95% CI [1.6 - 2.3]). Social support at work was not assessed, but may have affected the findings, as seen with smoking (Eriksen, 2006).
Components of the psychosocial job environment specifically predict LTPA, even when job stress as a whole does not. Job control is directly related to participation in LTPA (Allard et al., 2011; Choi et al., 2010; Fransson et al., 2012; Kouvonen et al., 2005; Yang et al., 2010), but findings regarding the effect of demand are mixed (Kouvonen et al., 2005; Yang et al., 2010).

As discussed above, lack of LTPA is well established as a CVD risk factor. However, the effect of LTPA on HCC is an area of fledgling research. From extant research, intensity of activity seems to be an important determinant in HPA axis response. As noted in salivary cortisol research, endurance sports are a type of physical stress, thus activating the HPA axis and leading to an acute cortisol elevation (Collomp et al., 2016). This acute response is attenuated with chronic exercise training as the body positively adapts to the physical stress. Similarly, endurance athletes demonstrate elevated HCC (Gerber et al., 2013; Skoluda, Dettenborn, Stalder, & Kirschbaum, 2012). However, moderate LTPA does not appear to affect HCC (Gerber et al., 2013; J. K. Gu et al., 2014; Stalder et al., 2013). These findings may parallel the concept of dose-dependent protective benefits of physical activity. Like any pharmacologic treatment an upper-dose limit may be reached above which cardioprotective elements give way to increased oxidative stress and cardiac remodeling, and decreased arterial elasticity (O'Keefe et al., 2012; Paffenbarger, Hyde, Wing, & Hsieh, 1986; Schnohr, Marott, Lange, & Jensen, 2013; Williams & Thompson, 2014). Given the uncertainty of any effect LTPA may have on HCC in a sample not comprised of professional athletes, this relationship will not be included in model testing but rather be assessed as a possible confounding personal characteristic.
Hair Cortisol and Cardiovascular Risk

Increased HCC has been associated with several types of CVD including CHD, stroke, heart failure, or peripheral arterial disease (PAD). Manenschijn et al. (2013) evaluated HCC among 283 individuals. Those with elevated HCC had increased odds of CHD, stroke, or PAD (OR = 2.7; \( p = .01 \)). The researchers found no relationship between elevated HCC and non-cardiovascular diagnoses (asthma, chronic obstructive pulmonary disease, cancer, or osteoporosis).

The same year, Pereg et al. (2013) observed individuals with systolic heart failure and found that HCC positively correlated with New York Heart Association class of heart failure (\( r = .48, p = .001 \)) and negatively with treadmill stress test performance (\( r = -.37, p < .05 \)). However, no significant relationship was seen between HCC and left ventricular ejection fraction (\( r = 0.14, p = 0.37 \)) or NT-proBNP (\( r = 0.19, p = 0.22 \)).

In a case-control study, Pereg et al. (2011) found that HCC was significantly elevated in individuals hospitalized with AMI compared to controls on an internal medicine ward (\( p = .006 \), Mann–Whitney U-test). Unfortunately, the control group included individuals admitted for heart failure, which is a type of CVD and often secondary to ischemic heart disease. However, even after control of standard CVD risk factors, HCC remained the strongest predictor of AMI (OR = 17.4, 95% CI [2.15, 140.5]; \( p = .007 \)). Also of methodological concern, the researchers appear to have used unwashed hair samples. Washing may decrease total cortisol content of the sample by 5-10% (Davenport et al., 2006). As this decrease likely represents cortisol in sebum, sweat, blood, or other contaminants as opposed to cortisol incorporated into the actual hair shaft (Bechshoft et al., 2011), most hair cortisol research uses washed hair samples.
In addition to evaluating the relationship between HCC and CVD diagnoses, HCC has been assessed alongside CVD risk factors including metabolic syndrome or diabetes mellitus type 2, hypertension, and adiposity. Elevated HCC has been significantly associated with metabolic syndrome and diabetes mellitus type 2 (ORs = 1.71 - 3.2, \( p < .05 \)) (Manenschijn et al., 2013; Stalder et al., 2013). Interestingly, this was not replicated among a group of HIV-positive individuals, who demonstrated elevated risk of metabolic syndrome among those with the lowest HCC (OR = 4.23, \( p = .04 \), 95% CI [1.09, 16.47] after adjustment for age and gender) despite no difference in HCC between HIV-positive individuals and healthy controls (Langerak et al., 2015). As for hypertension, O'Brien et al. (2012) found a positive relationship between systolic blood pressure and HCC (\( r = .25, p < .001 \)), but the findings were not replicated by others (Langerak et al., 2015; Manenschijn, Koper, et al., 2011; Saleem et al., 2013). For measures of adiposity, many researchers (Langerak et al., 2015; Manenschijn, van Kruysbergen, et al., 2011; Stalder et al., 2013; Stalder et al., 2012; Wester et al., 2014; Younge et al., 2015), but not all (Manenschijn, Koper, et al., 2011; O'Brien et al., 2012) found HCC significantly associated with increased BMI. Although Manenschijn, Koper, et al. (2011) found no significant relationship between HCC and BMI, other measures of adiposity including waist circumference (\( r = .392, p = .007 \)) and waist-to-hip ratio (\( r = .425, p = .003 \)) showed significant correlation. Findings in salivary cortisol research suggest a non-linear relationship between the diurnal cortisol slope and BMI that may partially explain the mixed findings in HCC research (Kumari, Chandola, Brunner, & Kivimaki, 2010). Individuals with shallowest diurnal slopes (most adverse) in salivary cortisol had the highest (>31 kg/m\(^2\)) and lowest (<21 kg/m\(^2\)) levels of
BMI, whereas the steepest slopes were seen in those with BMI of 26 kg/m$^2$. In conclusion, HCC appears related to CVD and most strongly with the CVD risk factor of adiposity.

**Hair Cortisol, Job Stress Symptoms, and Cardiovascular Risk**

Individuals reporting job stress often experience undesirable symptoms, or alterations in sensation or function leading to a realization of compromised wellbeing. The most common symptoms of job stress have previously been described as a symptom cluster involving alterations in sleep, depression, and fatigue (Kamath, Prpich, & Jillani, 2015). A symptom cluster is defined as two or more symptoms in a stable group that are correlated with each other to a greater degree than with any other cluster, possibly with a shared etiology, leading to a common undesirable outcome (Kim, McGuire, Tulman, & Barsevick, 2005).

Symptoms from the proposed symptom cluster are implicated in CVD risk, notably depression (Van der Kooy et al., 2007) and inadequate sleep (Covassin & Singh, 2016). Job stress symptoms may partially mediate the relationship between HCC and CVD risk.

**Depression.** Job stress significantly increases the incidence of depressive symptoms (ORs = 2.38 - 4.84) (Blackmore et al., 2007; Clark et al., 2012b; Clays et al., 2007b; Clumeck et al., 2009). Importantly, the risk is attenuated minimally when adjusting for non-work stressors. Gender differences are described with significant findings noted for men rather than women, although conflicting results exist (Blackmore et al., 2007; Clays et al., 2007b; Clumeck et al., 2009; Cohidon, Santin, Chastang, Imbernon, & Niedhammer, 2012; Fandino-Losada, Forsell, & Lundberg, 2013). Psychological demands at work (ORs = 2.6 - 4.1), low social support (ORs = 1.59 - 7.5), and job insecurity (OR = 2.33) contribute to depression (Andrea, Bultmann, van Amelsvoort, & Kant, 2009a; Blackmore et al., 2007;
Boschman, van der Molen, Sluiter, & Frings-Dresen, 2013; Dagher et al., 2009), with control being less robustly implicated (Boschman et al., 2013; Clumeck et al., 2009; Dragano et al., 2008).

Two studies (Bonde, Munch-Hansen, Wieclaw, Westergaard-Nielsen, & Agerbo, 2009; Horton & Lipscomb, 2011) failed to show any significant relationship between psychosocial work environment and depression, one of which assessed depression by antidepressant medication use, the other with findings suggestive of healthy worker survivor effect. Either condition could explain the divergent results. Furthermore, the possible contribution of exposure duration and length of assessment must be considered as a possible explanation of some of the disparate results. Indeed, Ibrahim, Smith, and Muntaner (2009) found that although some element of reverse causality may occur (depression contributing to increased job stress), this is a weaker relationship and is most evident at shorter follow-up (two years) rather than longer (six years).

Elevated cortisol and increased activity of the HPA axis have been implicated in the development of depression (Swaab, Bao, & Lucassen, 2005). As previously seen with salivary and urinary cortisol, HCC appears to be elevated among individuals with depression compared to healthy controls (Dettenborn, Muhtz, et al., 2012; Rietschel et al., 2016). However, HCC failed to predict severity of depressive symptoms among a group of individuals in cardiac rehabilitation for CHD ($\beta = -0.148$, $p = .162$). As elevated HCC has been noted among individuals with CHD, these findings may represent an inability to discriminate between alterations in HCC from CHD versus depression. Indeed, in this study, average HCC in both depressed and non-depressed groups was higher than noted in healthy subjects (Sauve et al., 2007).
Finally, depression is strongly linked to CVD risk. In meta-analysis ($N = 21$), (Nicholson et al., 2006) reported an 80% increased risk of CHD among depressed individuals. Unfortunately, incomplete adjustment for conventional risk factors in most studies hampered a definite conclusion regarding depression as an independent CVD risk factor (Nicholson et al., 2006). In a more recent meta-analysis of longitudinal and case-control studies ($N = 28$), depression increased the risk of multiple forms of CVD (OR = 1.46, 95% CI 1.37, 1.55]), but results demonstrated significant heterogeneity ($I^2 = .56$) except in a few groups (Van der Kooy et al., 2007). Risk of AMI was significantly elevated among depressed individuals ($n = 8$, OR = 1.60, 95%CI [1.34, 1.92], $I^2 = .00$). Likewise, studies that evaluated individuals with clinically diagnosed major depression rather than depressive symptomology strongly predicted CVD ($n = 4$, OR = 2.54, 95%CI [2.07, 3.10], $I^2 = .00$). Women also had increased risk ($n = 9$, OR = 1.38, 95% CI [1.22, 1.55], $I^2 = .17$).

Sleep. Sleep, as it relates to job stress, has been assessed in diverse ways in the literature. Overall, fewer robust studies exist for the relationship between job stress and sleep than for depression due to the rampant use of non-validated instruments, extremely narrow occupational sampling (thus limiting generalizability), lack of appropriate covariate analysis, or ambiguous conceptualizations. Rarely are objective measures of sleep assessed (Ertel, Berkman, & Buxton, 2011; Jackowska, Dockray, Hendrickx, & Steptoe, 2011).

Despite these limitations, job stress appears to be modestly associated with subjective poor sleep, whether assessed as quantity or quality (de Lange et al., 2009; Edme et al., 2011; Eriksen et al., 2008; Greubel & Kecklund, 2011; Rugulies et al., 2009). Conversely, absence of job stress is associated with self-reported restorative sleep (Buxton et al., 2009). No evidence of reverse causality was noted by de Lange et al. (2009) although a dose response
was likely. When assessed, stressors at home did not significantly alter findings (Burgard & Ailshire, 2009; Geiger-Brown et al., 2011). However, as would be expected, an interactive effect between job stress and shift work was predictive of poor sleep (Conway, Campanini, Sartori, Dotti, & Costa, 2008).

On the other hand, job stress or a component of the psychosocial work environment failed to show any significant contribution to objective measures of sleep (Ertel et al., 2011; Jackowska et al., 2011). With weak congruence between subjective and objective assessments, some suggest different phenomena are measured (Busse et al., 2008; Jackowska, Ronaldson, Brown, & Steptoe, 2016; Mondal, Gjerve, Taylor-Gjerve, & Lim, 2013).

Specific psychosocial job characteristics showed variable and contradictory contributions to sleep, making clear conclusions impossible except in the case of high psychological demands. When assessed individually, high demands consistently had a negative influence on subjective sleep (Aasa, Brulin, Angquist, & Barnekow-Bergkvist, 2005; de Lange et al., 2009; Eriksen et al., 2008; Geiger-Brown et al., 2011).

Alterations in salivary cortisol are related to sleep disturbance and short sleep duration (Abell, Shipley, Ferrie, Kivimaki, & Kumari, 2016; Balbo, Leproult, & Van Cauter, 2010; D'Aurea et al., 2015; Kumari et al., 2009; Vgontzas et al., 1999), and this relationship is likely bidirectional (Zeiders, Doane, & Adam, 2011). Unlike job stress research, objective rather than subjective measures of sleep are most often assessed in relation to cortisol. Among the few studies that assess both subjective and objective sleep in relation to cortisol, the findings are mixed. Van Lenten and Doane (2016) found no relation between subjective sleep (Pittsburgh Sleep Quality Index [PSQI]) and waking levels of salivary cortisol, the
cortisol awakening response, or the diurnal slope among a group of 76 freshman college students, although objective sleep duration related to various parts of the physiologic stress response. The mean PSQI score was 5.76, $SD = 2.73$, indicating a sample with subjective poor sleep. On the contrary, Jackowska et al. (2016) found that subjective sleep (PSQI) was positively related to cortisol awakening response ($r = -.20$, $p < .05$) but not to AUC ($r = -.02$, $p > .05$) among a sample of 119 women (age $M = 26$ years, $SD = 4.9$). The mean PSQI score was 6.5, $SD = 2.8$. As would be expected, PSQI score was inversely related to level of optimism, life satisfaction, and positive affect while being positively related to greater negative affect and depressive symptoms. To date, HCC has not been studied directly in relation to subjective or objective sleep quality, although shift-work is known to alter HCC (Manenschijn, Koper, et al., 2011).

Cardiovascular risk has most commonly been associated with sleep duration (quantity) rather than subjective quality of sleep. In meta-analysis of prospective studies, Cappuccio, Cooper, D'Elia, Strazzullo, and Miller (2011) found that short sleep duration (subjective or objective) was associated with elevated risk of morbidity or mortality from CHD ($RR = 1.48$, 95% CI [1.22, 1.80], $P < 0.0001$) and stroke (1.15, 95% CI [1.00, 1.31], $P = 0.047$), but not total CVD (1.03, 95% CI [0.93, 1.15], $P = 0.52$).

**Summary of Background**

Cardiovascular disease remains the leading cause of mortality and morbidity worldwide (Jones et al., 2012). Despite fairly robust evidence for the contribution of chronic job stress to the incidence of CVD, the mechanisms underlying the relationship remain unclear. Alteration in the HPA axis offers a plausible link between job stress and CVD risk.
as cortisol, the primary effector of the HPA axis, is linked to hypertension; adiposity; hyperinsulinemia, hyperglycemia, and insulin resistance; dyslipidemia; and inflammation.

While abundant research detailing standard risk factors for CVD is available, a relative paucity of data exists describing the longitudinal HPA axis response to chronic job stress. Extant studies are hampered by methodological and conceptual limitations. The advent of hair cortisol offers a promising biomarker for chronic job stress which bypasses some of the limitations in prior research.

In addition to a physiologic pathway linking job stress and CVD risk, behavioral factors are strongly implicated. Most notably, individuals experiencing job stress decrease LTPA (Ali & Lindstrom, 2006; Fransson et al., 2012; Kouvonen et al., 2006; Kouvonen et al., 2013; Nyberg et al., 2013; Wemme & Rosvall, 2005), thus increasing CVD risk (Reddigan et al., 2011).

Finally, symptoms of job stress may contribute to CVD risk. Depression and sleep alterations, often described by individuals experiencing job stress and associated with elevated HPA axis response, increase cardiovascular risk.

This knowledge, together with the ongoing high prevalence of CVD among working Americans, highlights the need for additional research regarding the strength and direction of relationships underlying CVD risk in individuals experiencing chronic job stress. The purpose of the proposed study will be to address a gap in knowledge regarding the relative contribution of biobehavioral factors linking job stress with CVD risk among healthcare workers in the United States by testing a predictive model of the relationship between physiological and behavioral responses to stress, stress-induced symptoms, and CVD risk among individuals with job stress. Based upon the above evidence, I hypothesize that chronic
job stress will predict HCC and LTPA. Secondly, HCC and LTPA will predict CVD risk with symptoms partially mediating the relationship between HCC and CVD risk. This study will contribute to the knowledge necessary for detection of individuals at risk for stress-induced CVD by clarifying biobehavioral processes underlying CVD risk in individuals experiencing chronic job stress. It may also provide the knowledge needed to develop and test effective clinical interventions to decrease morbidity, mortality, and cost of care for CVD.

**Theoretical Framework**

Theoretical models allow nurses, whether in research or patient care, to connect discreet concepts, identify gaps in current knowledge, formulate research questions, and implement interventions. Unfortunately, no existing theoretical model provides an adequate framework to explore the complex relationship between job stress and CVD. Therefore, a synthesized biobehavioral model of job stress and cardiovascular risk informs the proposed study, based on the strengths of the Demand-Control-Support (DCS) model, Allostatic Load model, and the Theory of Unpleasant Symptoms (TUS).

**Demand-Control-Support Model**

The DCS model is the most widely cited and studied theoretical model regarding job stress (Kristensen, 1996; Simmons & Swanberg, 2009). In the DCS model, Karasek and Theorell (1990) propose that high psychological job demand combined with low control for workers creates “job strain.” This job strain lies along a continuum that leads to increased adverse outcomes such as CVD. Social support moderates the effect of high demand.
Concepts.

**Demands.** Psychological demands are conceptualized as the mental workload or arousal necessary to perform assigned tasks (Karasek & Theorell, 1990). This may be operationalized through concepts such as work disruption, role ambiguity, or deadlines. Physical demands (such as static loads and repetitive tasks) may create psychological demands as well (Karasek et al., 1998a). Excluded in this conceptualization of demand are hazardous environmental factors such as asbestos or coal dust, which often lead to specific injuries rather than the more generalized strain addressed by the DCS model (Karasek & Theorell, 1990).

**Control.** Karasek described control as an employee’s decision latitude, a combination of skill discretion and decision authority (Karasek & Theorell, 1990). Skill discretion is the flexibility of skills and creativity with which an employee is allowed to complete tasks. Decision authority represents the employee’s autonomy, or ability to make job-related decisions. This does not address decision authority over others (Karasek & Theorell, 1990). Skill discretion and decision authority are unique, yet mutually occurring and reinforcing components of work (Karasek et al., 1998a). The extent that one versus the other influences decision latitude may vary between occupations. This concept of control may extend beyond formal job duties into the realm of informal activities such as coffee breaks. Often, these informal activities include a social aspect (Karasek & Theorell, 1990).

**Social support.** Relationships are numerous and distinct in most work environments—interpersonal connections with customers, co-workers, and supervisors. Two types of social support may be seen in the workplace. The first, emotional support, may be operationalized as social cohesion, trust, and integration among co-workers, supervisors, and
others (Karasek & Theorell, 1990). Harassment and workplace hostility are antithetical concepts. Secondly, instrumental social support may be seen as work assistance and coordination of work.

**Limitations.** Although empirical evidence generally supports its conceptualization of job stress (Gilbert-Ouimet, Trudel, Brisson, Milot, & Vezina, 2013; Landsbergis, Dobson, Koutsouras, & Schnall, 2013), the DCS model contains several limitations for use in CVD research. Karasek & Theorell (1990) acknowledge the effect of personal characteristics on stress, but those factors are markedly absent from the DCS model. Personality is briefly discussed in terms of “personality evolution” caused by the work environment, but the primary effect of personal characteristics on development and manifestation of job stress is lacking despite evidence that characteristics such as coping style (Mauss, Li, Schmidt, Angerer, & Jarczok, 2014), gender (Li et al., 2014), and socioeconomic status (Siegrist, 2008; Theorell et al., 2014) affect job stress outcomes.

Secondly, the confounding variable of exposure duration on psychological strain and disease risk is acknowledged in passing (Karasek & Theorell, 1990) but never developed. Longitudinal studies report the increasing ill effects of chronic job stress (Slopen et al., 2012; Stansfeld, Shipley, Head, & Fuhrer, 2012), and overlooking this factor may contribute to contradictory findings in job stress research (Kivimaki, Head, et al., 2006).

Finally, Karasek and Theorell (1990) make a conceptual leap between job strain and CVD. Specific mechanisms linking high job strain to CVD are unexplained. Factors found in this unexplored territory may account for some of the contradictory findings in research using the DCS model (Eaker, Sullivan, Kelly-Hayes, D'Agostino, & Benjamin, 2004;
Kivimaki et al., 2012; Kivimaki, Virtanen, et al., 2006; Slopen et al., 2012; Streptoe & Kivimaki, 2012).

**Allostatic Load Model**

The Allostatic Load model satisfies the inadequacies observed in the DCS model by accounting for personal characteristics that contribute to stress outcomes, identifying physiologic and behavioral pathways linking stress with CVD, and acknowledging the contribution of exposure duration and/or intensity. Allostasis, first described by Sterling and Eyer in 1988, literally means stability through change. The concept was expanded into the Allostatic Load model by B. S. McEwen and Stellar (1993) and Seeman, Singer, Rowe, Horwitz, and McEwen (1997). They proposed that repeated demands for adaptation arising from internal or external stressors create a cumulative toll on the human system, or allostatic load. This results from overexposure to neurohormonal and immune mediators that protect system stability in the short-term, but in the long-term may contribute to the pathogenesis of disease, including CVD (Mattei, Demissie, Falcon, Ordovas, & Tucker, 2010; Seeman, 2001 #4; Seeman, McEwen, Rowe, & Singer, 2001). Stress may also elicit a behavioral response that may be perceived as adaptive, but in reality may either protect against or potentiate allostatic load (McEwen & Seeman, 2009).

**Concepts.**

**Allostasis.** As a primary response to internal or external threats, allostasis is the stabilization of the body system through adaptation, a process achieved by the primary mediators (cortisol, norepinephrine, epinephrine, and DHEA). Due to the influence of genetic, developmental, and experiential factors, allostasis is a highly individual process (McEwen & Seeman, 2009).
**Allostatic load.** Allostatic load, a secondary outcome, is the cumulative toll that repeated adaptation places on the body. It may develop from four distinct situations: frequent, repeated novel stressors requiring an allostatic response; the body’s failure to habituate to a similar stress, thus maintaining high levels of neurohormonal mediators; the body’s inability to terminate the stress response or abide by the normal diurnal pattern of neurohormonal mediators; or finally, an inadequate allostatic response to stressors, thus leading to an imbalance between various parts of the stress response. Like allostasis, individual differences in genetics; early childhood experiences; and behaviors such as diet, exercise, smoking, or drug abuse may influence the reactivity or efficiency of neurohormonal systems (McEwen & Seeman, 2009).

**Allostatic overload.** Allostatic overload, a tertiary outcome, is defined as systemic pathophysiology caused by ongoing or high allostatic load. Examples of allostatic overload include CVD, cognitive decline, and depression (Seeman et al., 1997).

**Behavioral responses.** When the individual perceives a stressful situation, behavioral responses parallel physiologic responses in a fight-or-flight reaction. However, behaviors may also alter the physiologic response. Even though the individual may perceive immediate adaptive effects from the behavior, behavioral responses may be protective or damaging (e.g., alcohol consumption) (Bruce S. McEwen, 1998).

**Limitations.** Empirical support for the Allostatic Load model is variable (Mauss, Li, Schmidt, Angerer, & Jarczok, 2014). Varied biomarkers and dissimilar calculation methods for allostatic load likely contribute to divergent findings.

Unfortunately, neither the DCS model nor the Allostatic Load model accounts for the symptom experience of job stress or explains how living with symptoms may contribute to
cardiovascular risk. Individuals experiencing job stress repeatedly report symptoms including feelings of depression, irritability, impatience, and anger (Ertel, Koenen, & Berkman, 2008; Simmons & Swanberg, 2009); sleep disturbance (Knudsen, Ducharme, & Roman, 2007); musculoskeletal pain (Hannan, Monteilh, Gerr, Kleinbaum, & Marcus, 2005; Rugulies & Krause, 2005, 2008; Warren, 2010); or a general loss of wellbeing (Burgard, Brand, & House, 2009).

**Theory of Unpleasant Symptoms**

The TUS provides a link between the symptom experience of job stress and cardiovascular risk. Lenz, Pugh, Milligan, Gift, and Suppe (1997) posit that physiological, psychological, or situational factors influence the symptom experience. The symptom experience is composed of individual, multidimensional symptoms that synergistically interact with each other. This leads to altered performance (physical or cognitive), which in turn affects both symptom experience and influencing factors via a reciprocal feedback loop. The relationship between influencing factors and performance outcomes may be mediated or moderated by symptom experience.

**Concepts.**

*Symptoms.* Symptoms are described as an individual’s perceived alterations in normal function, and as such, may indicate threats to wellbeing (Lenz, Pugh, Milligan, Gift, & Suppe, 1997). Symptoms often occur simultaneously, and their relationship is frequently multiplicative, rather than additive.

*Symptom experience.* Four major components comprise a symptom experience including the intensity, timing, level of distress perceived, and quality. The intensity of symptom is defined as the severity or strength of the symptom (Lenz et al., 1997). Symptom
timing includes the duration and frequency of symptoms, the interaction between frequency and duration, or a temporal association with an event. Level of distress perceived refers to the meaning the patient assigns to the symptom or to the extent to which it is bothersome. Finally, symptom quality encompasses the attributes or descriptors of the experience.

**Influencing factors.** Physiologic, psychological, and situational factors interact in a bidirectional manner prior to initiating the symptom experience (Lenz et al., 1997). Physiologic factors are readily recognized as antecedents to symptoms and may include such phenomena as trauma, altered hydration and nutritional status, severe tachycardia, or disrupted circulation. Psychological factors include the meaning assigned to an illness or the individual’s mood and mental outlook (Lenz et al., 1997). Lastly, situational factors include circumstances such as marital status, social support, lifestyle, fiscal condition, healthcare accessibility, and other environmental factors.

**Performance.** Performance, or the consequence of symptom experience, is any change in functional performance, whether physical or cognitive. Although least described by Lenz et al. (1997), performance may affect both symptom experience and influencing factors via a reciprocal feedback loop.

**Limitations.** Of the three theories included here, the TUS has the least empirical evidence and has never been applied to the symptom experience of job stress. Therefore, validity remains unknown for a population with job stress.

**Synthesized Model**

Building upon the strengths of these three models, the Cardiovascular Risk from Job Stress (CRJS) model (Figure 4) proposes that individuals who experience high levels of job demand or low levels of control and social support respond to the resulting job stress with
alterations in behavior, physiology, or symptoms. These responses are interrelated, often in a bidirectional manner and are moderated by personal characteristics. Likewise, the responses may provide positive or negative feedback to job stress. If job stress is repeated or prolonged, the body suffers oxidative, metabolic, or autonomic consequences due to the ongoing demand for adaptation. This promotes systemic pathophysiology including CVD.

**Figure 4.** The Cardiovascular Risk from Job Stress Model.

**Concepts and propositions.**

**Job stress.** Job stress occurs when job demands outweigh the control and social support of an employee. Demands are the sum psychological toll produced by completion of job requirements in a specified time or manner. Deadlines or quotas, role ambiguity, inadequate staffing, and technology may contribute to job demands. Physical factors such as poor ergonomic conditions also increase job demands. Control is the autonomy held by the
employee, the freedom to choose how a job is completed. Social support includes coworker
and supervisors’ functional or psychological support. Lack of social support, especially to the
extreme of workplace harassment or hostility, promotes job stress.

An employee’s personal characteristics play an integral role in the development of job
stress as these characteristics may alter what constitutes demand, control, and support for the
individual. Most notably, gender plays a significant role in the interplay and relative
importance of demand, control, and support (Whitworth et al., 2005). Age may also affect the
development of job stress and subsequent CVD outcomes (Chandola et al., 2008).

Responses. Responses to job stress are coordinated by the brain and may be
conscious or subconscious. They are categorized as alterations in behavior, physiology, or
symptoms.

Seeking to restore a sense of wellbeing, individuals often alter behavior in response to
job stress. These behavioral responses provide momentary reductions in the symptoms of
stress (e.g., alcohol consumption to calm anxiety or decreased physical activity to ease
musculoskeletal pain), while simultaneously creating a detrimental physiologic burden on the
body. Behaviors commonly reported include decreased physical activity (Ali & Lindstrom,
2006; Chandola et al., 2008; Choi et al., 2010; Fransson et al., 2012; Kouvonen et al., 2006;
Kouvonen et al., 2013; Nyberg et al., 2013; Wemme & Rosvall, 2005), smoking (Cunradi,
Lipton, & Banerjee, 2007; Goedhart, van der Wal, Cuijpers, & Bonsel, 2009; Heikkila et al.,
2012b; John, Riedel, Rumpf, Hapke, & Meyer, 2006; Kouvonen et al., 2009; Nyberg et al.,
2013; Rugulies, Scherzer, & Krause, 2008); alcohol use (Azagba & Sharaf, 2011; Barnes &
Zimmerman, 2013; Dawson, Grant, & Ruan, 2005; Heikkila et al., 2012a; Sterud, Hem,
Ekeberg, & Lau, 2007); and dietary changes (Chandola et al., 2008). Often, individuals
experiencing job stress exhibit three or more unhealthy behaviors (Heikkila et al., 2013; Kouvonen et al., 2007) and are less likely than those without job stress to adopt positive lifestyle behaviors (Heikkila et al., 2013).

Secondly, physiological responses are automatic, subconscious attempts to achieve stability when confronted with job stress. In acute situations physiological responses are adaptive, but with chronic stimulation, they become deleterious. Several body systems are involved including the HPA axis and autonomic nervous system (ANS). Cortisol, the primary biologic marker of the HPA axis, is released from the adrenal cortex in response to psychological or physiologic stress and subsequently influences many metabolic, inflammatory, and immune processes. Over-secretion or inappropriate balance with other regulatory mechanisms increases cardiovascular risk (Whitworth et al., 2005). Likewise, in the ANS, epinephrine and norepinephrine influence many cardiovascular processes. Dysfunction of the ANS is demonstrated by decreased heart-rate variability, increased heart rate, and hypertension among individuals with job stress (Hernandez-Gaytan et al., 2013).

Finally, symptom responses are alterations in sensation or function leading to a realization of compromised wellbeing. They often include difficulty initiating or maintaining sleep or experiencing non-restorative sleep (Dahlgren, Kecklund, & Akerstedt, 2005; Knudsen et al., 2007); fatigue; depression (Ardito et al., 2014; Siegrist, 2008; Theorell et al., 2014); anxiety (Clark et al., 2012a); or musculoskeletal pain (Hannan et al., 2005; Rugulies & Krause, 2005, 2008).

Interactions between the three types of responses are numerous, and often bidirectional. For instance, sleep disturbance alters cortisol response (Balbo et al., 2010; Rydstedt & Devereux, 2013) and contributes to poor behavior choices (Haario, Rahkonen,
Laaksonen, Lahelma, & Lallukka, 2013); inversely, unhealthy behaviors contribute to sleep disturbance (Clark et al., 2012a; Haario et al., 2013). Responses may also have a positive or negative effect on perceived job stress. For example, individuals who regularly exercise report lower levels of job stress and fatigue (Hansen, Blangsted, Hansen, Sogaard, & Sjøgaard, 2010).

**Personal characteristics.** As a whole, personal characteristics such as age, gender, socioeconomic status, developmental status, past life experience, and genetics are unique to the individual, and thus produce a distinctive response to job stress. Personal characteristics may also influence cardiovascular risk independent of job stress (National Institutes of Health, 2014).

**Allostasis to Adaptation.** The depiction of allostasis progressing to adaptation introduces the confounding variable of exposure duration by portraying the recurrent or prolonged use of the acute, adaptive stress response. For individuals with job stress, exposure duration strongly predicts the risk of systemic pathophysiology (Slopen et al., 2012; Stansfeld, Shipley, Head, & Fuhrer, 2012).

**Cardiovascular disease.** CVD includes disorders of the heart or blood vessels such as CHD, heart failure, stroke, hypertensive heart disease, peripheral vascular disease, and aortic aneurysm or dissection (World Health Organization, 2015). Although technically forms of CVD, deep venous thrombosis, pulmonary embolism, congenital heart disease, and rheumatic heart disease have distinct pathophysiologic mechanisms that fall outside the scope of this model.

**Limitations.** Although each of the models used in this synthesis have been empirically tested in diverse populations (Dimsdale, 2008; Kivimaki, Head, et al., 2006;
Kivimaki et al., 2012; Kivimaki, Virtanen, et al., 2006; Leander et al., 2007; Streptoe &
Kivimaki, 2012), the CRJS model itself requires validation and comparative analysis with
other models of job stress. Due to the numerous, complex bidirectional causal pathways
hypothesized, empirical testing of the CRJS model requires advanced statistical analyses
such as structural equation modeling. Longitudinal testing of the model would further clarify
causal pathways in CVD pathogenesis.

Secondly, the CRJS model describes only job stress, and fails to account for the
cardiovascular burden of other forms of stress. The extent or manner in which daily hassles,
marital stress, caregiver stress, or other major life stressors interact with concepts described
in the CRJS model is not addressed.

Conclusion

The CRJS model provides an enhanced framework to inform CVD research and
preventative care among workers. With its emphasis on environmental, behavioral,
physiologic, and symptom components of job stress, the CRJS model highlights the necessity
of a broad approach to CVD research and prevention, clearly aligned with nurses’ holistic
and collaborative mentality.
CHAPTER III

METHODS

Purpose

The purpose of this study was to address a gap in knowledge regarding the relative contribution of biobehavioral factors linking job stress with CVD risk among healthcare workers in the United States and in particular to test a predictive model of the relationship between physiological and behavioral responses to stress, stress-induced symptoms, and CVD risk among individuals with job stress.

Aim 1

To test the predictive model of the relationship between chronic job stress, LTPA, HCC, symptom experience of job stress, and CVD risk. Aim 1 included the following hypotheses:

1. Increased chronic job stress will predict increased HCC.
2. Increased chronic job stress will predict decreased LTPA.
3. Increased HCC will predict increased CVD risk.
4. Decreased physical activity will predict increased CVD risk.
5. The symptom experience of job stress will partially mediate the relationship between HCC and CVD risk.

Aim 2

To determine the relationship between specific components of the psychosocial job environment and HCC. Aim 2 included the following hypotheses:

1. Increased psychological demand will predict increased HCC.
2. Decreased control will predict increased HCC.
3. Social support will moderate the effect of job stress on HCC.

4. Increased job stress will predict increased HCC.

**Design**

A cross-sectional, correlational design was used as the hypotheses described relationships and did not include manipulation of the independent variable (Wood & Ross-Kerr, 2011). Reliable measurement of the variables was available. Pertinent details regarding the methods are summarized below.

**Sample**

The target population of the study was healthcare workers in the Southeastern United States. The accessible population included healthcare workers and ancillary staff at three healthcare facilities operated by the same healthcare system.

The first healthcare facility (Site 1) included hospital-operated medical practices as well as a 69-bed inpatient facility that is the sole provider of medical, surgical, and obstetric care for a town of 15,650 with a county population of approximately 55,000. The mean age of full-time employees at Site 1 ($n = 662$) is 42 years ($SD = 12$, range = 20 - 73). Average length of employment at this facility is 6.12 years ($SD = 6.38$ years, range = .21 - 39.47). Approximately 18% are non-clinical staff.

In the adjacent county, Site 2 was a 33-bed facility providing medical and surgical inpatient care to a town of 4,299 with a county population of approximately 40,000. The mean age of full-time employees at Site 2 ($n = 89$) is 43 years ($SD = 12$, range = 22 - 66). Approximately 16% are non-clinical staff. The available reported length of employment among these employees is homogenous given the recent acquisition of this facility by the
parent healthcare system on January 1, 2015. Table 3 compares demographics of Site 1 and Site 2.

Table 3

Demographics by Percentage of Population at Site 1 and Site 2

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Site 1</th>
<th>Site 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>88.4</td>
<td>95.5</td>
</tr>
<tr>
<td>African American</td>
<td>3.8</td>
<td>.2</td>
</tr>
<tr>
<td>Asian</td>
<td>1.5</td>
<td>.0</td>
</tr>
<tr>
<td>Two or More Races</td>
<td>1.2</td>
<td>.2</td>
</tr>
<tr>
<td>Hispanic or Latino origin</td>
<td>5.1</td>
<td>.3</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>22.7</td>
<td>23.6</td>
</tr>
<tr>
<td>Female</td>
<td>77.3</td>
<td>76.4</td>
</tr>
<tr>
<td>Marital status</td>
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<td></td>
</tr>
<tr>
<td>Married</td>
<td>65.7</td>
<td>65.7</td>
</tr>
<tr>
<td>Single, never married</td>
<td>27.2</td>
<td>27.2</td>
</tr>
<tr>
<td>Divorced</td>
<td>5.9</td>
<td>5.9</td>
</tr>
<tr>
<td>Separated</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>Widowed</td>
<td>0.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>

The third location (Site 3) was in an adjacent state to the other sites although run by the same healthcare system. It comprises a 64-bed inpatient facility as well as several medical practices providing medical, obstetrical, and surgical care in a town of approximately 15,000 with a county population of 68,580. Demographics for full-time employees at this location were unavailable.

Study participation rate ranged from 7.10 to 21.35% across sites. This was calculated using total full-time employees, as data by shift were unavailable. Subsequently, the actual response rate for eligible individuals would be higher.

Figure 1 summarizes progression to the final sample of 106 participants. Retention rate between initial interview and completion of online survey was 94%. Eight cases were excluded from final analysis due to missing biophysical data. Details of missing data
handling are presented in the Analysis section. With the final sample of 106, an alpha of .05, power of .80, and four predictors in linear regression analysis, an effect size of $f^2 = .12$ could be detected.

![Flowchart](image)

*Figure 1.* Participant loss flowchart.

**Recruitment**

The goal of recruitment was for a final sample size of 200 subjects in order to allow loss of follow-up and missing data. A minimum of 150 subjects were required to test the hypothesized mediation model using structural equation modeling at a power of .80 if a medium effect size was present in the proposed relationships {Fritz, 2007 #444}. This number was not attained therefore alternative methods of analysis were employed as outlined in the Analysis section. Employees were recruited during an annual benefits fair at Site 2 and via employer-generated electronic mail at Site 1 and 3. At each site, information flyers were distributed to all employees via employee intranet. Interested individuals were screened for inclusion criteria prior to informed consent being obtained.

**Inclusion and Exclusion Criteria**

Inclusion criteria were holding a full-time, day-shift job of at least 30 hours per week at one of the study locations. Day-shift, non-pregnant workers were purposely studied to
control for the known alteration in cortisol secretion among shift workers and pregnant women (Manenschijn, van Kruysbergen, et al., 2011; Matthews, Schwartz, Cohen, & Seeman, 2006). Given the retrospective nature of hair cortisol measurement, only individuals employed in their current job for the prior 6 months were included. Age inclusion was 18-60 years, as alterations in hair cortisol levels may occur with greater age (Dettenborn, Tietze, et al., 2012).

Individuals were excluded from this study if they fell outside the appropriate age range, were bald at the posterior vertex of the scalp, had hair too short to trim in a non-disfiguring manner, or failed to provide informed consent. Individuals currently employed in more than one job (not including volunteer positions or housecleaning < 4 hours/week) were excluded to avoid confounding measurement of job stress from more than one work environment. Individuals who took systemic glucocorticoid medications within the last 3 months or reported endocrine disorders affecting the HPA axis were excluded as well. The inability to read and write English excluded individuals as informed consent could not be obtained. Inclusion and exclusion data were obtained by self-report.

**Procedures**

Interested individuals were screened for inclusion and exclusion criteria prior to informed consent being obtained. Following informed consent, individuals completed a brief intake form including email address and inclusion and exclusion screening.

A nurse then obtained blood pressure and weight measurements in a private, screened area. Participants were seated with both feet flat on the floor while blood pressure measurement was obtained. While still seated, a hair sample was obtained from the posterior vertex of the scalp as described below. Participants were requested to remove any outer-wear
such as lab jackets prior to standing on scales for weight. Further details of measurement are described below.

Participants were given instruction to complete online questionnaires via the HIPAA-compliant, web-based application Research Electronic Data Capture (REDCap) system. Individuals who did not complete the questionnaires within one week’s time were sent a reminder email at one, two, and four weeks after hair collection. The principal investigator provided a $20 gift card electronically to each participant when they completed the online portion of the study. Following completion of data analysis, participants were given their hair cortisol and job stress results via electronic mail as well as general conclusions of the study.

**Measures**

Chapter II provided detailed background and rationale for the inclusion of each variable of interest in this study. Table 4 summarizes each of these variables. The following sections describe the operationalization of each variable.

**Table 4**  
*Primary Variables of Interest*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychosocial Job Environment</td>
<td>Job Content Questionnaire (JCQ)</td>
</tr>
<tr>
<td>Demand</td>
<td>JCQ - Demand scale</td>
</tr>
<tr>
<td>Control</td>
<td>JCQ - Decision Latitude scale</td>
</tr>
<tr>
<td>Social Support</td>
<td>JCQ - Social Support scale</td>
</tr>
<tr>
<td>Job Stress</td>
<td>JCQ Demand and Control scale</td>
</tr>
<tr>
<td>Leisure-time Physical Activity</td>
<td>Stanford Leisure-Time Activity Categorical Item</td>
</tr>
<tr>
<td>Cortisol</td>
<td>Hair cortisol concentration by enzyme immunoassay</td>
</tr>
<tr>
<td>Depression</td>
<td>PROMIS-D</td>
</tr>
<tr>
<td>Fatigue</td>
<td>PROMIS-F</td>
</tr>
<tr>
<td>Sleep Disruption</td>
<td>PROMIS-SD</td>
</tr>
<tr>
<td>Sleep-related Impairment</td>
<td>PROMIS-SRI</td>
</tr>
<tr>
<td>CVD Risk</td>
<td>Framingham Heart Study General CVD 10-year Risk score</td>
</tr>
</tbody>
</table>
**Personal and Work Characteristics**

Demographic data including age; gender; marital status; tobacco, alcohol, and illicit drug use; educational level; socioeconomic status; and current medical diagnoses were assessed with a basic demographic questionnaire. A single question was asked regarding the current or past diagnosis of any form of CVD, diabetes, obstructive sleep apnea, major depressive disorder or bipolar disease, or endocrine disorders affecting the HPA axis.

Screening for obstructive sleep apnea (OSA) among those undiagnosed was obtained with the Berlin Questionnaire (BQ)(Netzer, Stoohs, Netzer, Clark, & Strohl, 1999). The 10 items from the BQ are categorized into three sections, with positive scores in two of the three sections indicating a high risk of OSA. In the general population, the BQ demonstrates sensitivity and specificity of 37% and 84% respectively and has a positive predictive value of 61.3%, negative predictive value 66.2% (Hrubos-Strom et al., 2011). Finally, screening for adverse childhood experiences (ACEs), a known risk factor for CVD and depression (Su, Jimenez, Roberts, & Loucks, 2015), was obtained with the Kaiser-CDC Adverse Childhood Experiences questionnaire (Felitti et al., 1998). This instrument uses questions from other published surveys to assess eight categories of ACEs. It has shown excellent predictive value for multiple adverse outcomes during adulthood including lifestyle behaviors, psychiatric conditions, and CVD in a dose-dependent manner (Anda et al., 1999; Felitti et al., 1998; Schussler-Fiorenza Rose, Xie, & Stineman, 2014).

Various work characteristics were also assessed to confirm eligibility for inclusion in study and to allow assessment of non-psychosocial elements of employment that could affect outcomes. These included number of jobs, hours worked per week, length of time in current job, and job title.
Psychosocial Job Environment

The Job Content Questionnaire (JCQ) remains the preeminent tool measuring components of the psychosocial job environment with translation into 23 languages (Job Content Questionnaire Center, n.d.). Based on the theoretical formulations of the Demand-Control-Support (DCS) model (Karasek & Theorrell, 1990), the JCQ contains 49 items, each using a four-level Likert-scale. For the purpose of this study, only the subscales of psychological demands (5 items), decision latitude (9 items), and social support (11 items) will be utilized.

Throughout its 30-year history, the JCQ has undergone extensive psychometric testing showing moderate to good reliability and validity. Among US populations, Cronbach alphas for psychological demands .63 - .71, decision latitude .83 - .84, supervisor support .80 -.85, coworker support .72 - .80 (Karasek et al., 1998a). Test-retest reliability has been established among US populations with re-testing ranging from 5-57 days. ICCs were moderate to good, ranging from .44 to .62 on four subscales of the JCQ, the lowest being co-worker support and highest supervisor support (Thakkar, Sharma, & Sahota, 2014).

Criterion validity is established by comparing the instrument to a “gold standard.” However, the idea that the psychosocial environment at work alters health outcomes was a new concept in the mid-to-late-1900s. As the conceptualizations of job stress shifted from a focus on the individual to that of the environment, the JCQ was developed to fill the void of instruments. Although it has been repeatedly evaluated next to similar instruments such as the Effort-Reward-Imbalance measure (Siegrist, 1996), it remains the most prominent and widely used tool in the area of job stress research and is often cited as the criterion against which new instruments are evaluated.
The JCQ demonstrates predictive ability for poor health outcomes including depression (Chandola et al., 2008; Steinisch et al., 2014), worsening cognitive health (Rivera-Torres, Araque-Padilla, & Montero-Simo, 2013), CVD (Qi et al., 2015), and diabetes (Heraclides, Chandola, Witte, & Brunner, 2012; Schneider, Pankow, Heiss, & Selvin, 2012). In addition, the JCQ exhibits responsiveness to change within the work environment, whether negative or positive (Clays et al., 2007a; Hellerstedt & Jeffery, 1997; Herane Vives et al., 2015; Stalder et al., 2017).

Job stress was calculated from the demand and decision latitude scales using two different JCQ scoring methodologies—the recommended quadrant method with job stress defined as those above the sample median for psychological demands and below the median for decision latitude and secondly as a continuous ratio between psychological demands and decision latitude (C. A. Wong & Spence Laschinger, 2015). Given the unequal number of items between the two subscales, scores were normalized prior to ratio calculation. This double scoring for job stress has several strengths. First, it aids in comparison of my findings to previous studies using different scoring methods (Landsbergis, Schnall, Warren, Pickering, & Schwartz, 1994). Secondly, it follows the recommended scoring method while also applying a method more closely aligned to the theoretical proposition of a job stress continuum described by Karasek and Theorell (1990). Finally, the double scoring allows partial assessment of the extent to which JCQ scoring methods alters conclusions.

Social support was assessed for a moderating effect between job stress and hair cortisol. Gender differences were unable to be assessed given the small male sub-sample, although women often demonstrate greater adverse outcomes in a non-supportive or socially
hostile work environment compared to their male counterparts (Ho, Rohan, Parent, Tager, & McKinley, 2015; Liu et al., 2009).

Job stress is a phenomenon based both on the perception and ability of self to withstand and flourish within the pressures presented at work (Kopp et al., 2010). Therefore, a self-report is an appropriate measurement method.

**Hair Cortisol**

Hair cortisol samples were obtained by close clipping of 25 to 50 strands of hair at the posterior vertex of the scalp, as lower intra-individual variation has been found in this area (Sauve et al., 2007). A part was made from left to right along the posterior vertex. A thin layer of hair was separated along this part and twisted prior to cutting as close to scalp as possible. Hair was affixed to foil using painters tape at least 3 cm below the scalp end. The scalp end was indicated using permanent marker, and a label with participant’s study identification number was affixed inside the foil. The foil was folded to enclose all hair, and then placed in an envelope labeled with the participant’s identification number. For individuals with hair length less than 3 cm, a part was attempted at the posterior vertex. An assistant held hair up against the part while hairs were clipped as close to the scalp as possible just below the posterior vertex. These were allowed to fall into an envelope. Once sufficient hair sample was obtained, hair was transferred from the envelope to foil with the participant’s identification number. The foil was securely folded and placed in the envelope with participant’s identification number again placed on the outside.

Once obtained, the hair sample was analyzed by hair cortisol concentration (HCC) using up to the proximal 3 cm of hair representing 3 months of retrospective cortisol activity (Dettenborn et al., 2010). In one sample, 6 cm were used to obtain required hair weight.
Cortisol was extracted from hair following the method outlined extensively by Hoffman, D'Anna-Hernandez, Benitez, Ross, and Laudenslager (2017). In brief, this method includes washing hair samples in 99% isopropyl alcohol then allowing them to dry completely prior to grinding with a ball mill. Washing may decrease total cortisol content of the sample by 5-10% (Davenport et al., 2006), but this likely represents cortisol in sebum, sweat, blood, or other contaminants as opposed to internal cortisol incorporated into the actual hair shaft (Bechshoft et al., 2011). Samples were then extracted for 24 hours in methanol and dried using nitrogen steam. Hair cortisol concentration was determined using a commercial high sensitivity enzyme immunoassy kit (Salimetrics LLC, State College, PA) per manufacturer's instructions. The inter-assay coefficient of variation (CV) reported by the lab was 9.2% and intra-assay CV was 2.8%. Results were reported in pg/mg of hair and treated as a continuous variable.

**Stanford Leisure-Time Activity Categorical Item**

The Stanford Leisure-Time Activity Categorical Item (L-Cat) is a self-administered, single-item measure of LTPA during the prior month (Kiernan et al., 2013). Six possible categorical responses include descriptions of representative activities based upon the Metabolic Equivalent of Task (MET) for each category.

During psychometric testing, the L-Cat showed good test-retest reliability (Spearman’s $r = .80; P < .001$)(Kiernan et al., 2013). Concurrent criterion validity was acceptable when compared to baseline BMI, pedometer steps, and weight loss. Each subsequent increase in L-Cat category was reflected by lower baseline BMI of 0.5 BMI unit ($\beta = -0.4; 95\% \text{ CI} [-0.8, -0.1]; \beta = -0.14; P = .02$). For pedometer steps, each subsequent increase in L-Cat category corresponded to an additional 1059 steps ($\beta = 0.38; 95\% \text{ CI} [712,
When comparing weight loss at six months to reported physical activity, each subsequent increase in L-Cat category paralleled an increase in the percent of initial weight lost at 6 months of $-1.9\%$ ($\beta = -0.38; 95\%$ CI $[-2.4, -1.3]; P < .001$). In addition, the L-Cat demonstrated sensitivity to change at six-month follow-up; for women who did not meet physical activity recommendation at baseline, those who increased activity by $\geq 1$ L-Cat category lost more weight than those who stayed in the same category or dropped to a lower category ($M = -4.6\%, 95\%$ CI $[-6.7, -2.5]; P < .001$).

This tool was evaluated for reliability and validity among multi-ethnic, middle-aged women. Although this is a relatively new instrument and psychometric testing has yet to be performed in a male population, use of this measure is justified for several reasons. First, the target population for the proposed study is predominantly middle-aged women. Secondly, men routinely have higher correlation between self-report and direct measures of physical activity than do women (Prince et al., 2008); thus arguably this tool should perform in concurrent validity testing for a male sample at least as well as for women. In the current study, the L-Cat score was treated as interval level data and also dichotomized into active (score $\geq 4$) and inactive (score $\leq 3$).

**Symptom Experience**

The variable of symptom experience was derived using the theory-driven, data reduction technique of principle component analysis among four symptom (depression, fatigue, sleep disruption, and sleep-related impairment). These symptoms were operationalized with the Patient Reported Outcomes Measurement Information System (PROMIS) tools. The National Institutes of Health developed these highly reliable and precise tools using Item Response Theory (graded response model). Using a T-scale metric, a
mean score on any PROMIS instrument is 50 with $SD = 10$. Thus, an individual scoring 60 would be one standard deviation above the general population. During development, a scale-setting subsample ($n = 5,239$) was taken from the total wave 1 sample ($N = 21,133$) to align the testing sample with the U.S. Census data from 2000 (Cella et al., 2010).

For each PROMIS tool, individual items use a five-level response scale and assess self-reported health outcomes from the prior seven days. The use of computerized adaptive testing (CAT) allowed for real-time scoring, while being extremely brief (4-7 items routinely) and precise. The total T-score and standard deviation were reported and entered into principle component analysis.

**Depression.** The PROMIS Bank v1.0 - Depression (PROMIS-D) is a 28-item scale evaluating negative mood, decreased positive affect, information-processing deficits, negative views of self, and negative social cognition. This instrument shows excellent reliability ($a \geq .92$ for most of the score distribution). Construct validity has been demonstrated by acceptable correlation to several legacy measures including the Center for Epidemiologic Studies Depression Scale (CES-D)($r = .83$) and Mood and Anxiety Symptom Questionnaire (MASQ)($r = .72$).

**Fatigue.** PROMIS Bank v1.0 - Fatigue (PROMIS - F) is a 95-item bank evaluating fatigue as defined as “an overwhelming, debilitating, and sustained sense of exhaustion that decreases one's ability to carry out daily activities, including the ability to work effectively and to function at one's usual level in family or social roles” (Cella et al., 2010, p. 1180). This instrument shows good reliability ($a \geq .91$ for scores ranging from $2 SD$ less than the mean to $4 SD$ greater than the mean). Construct validity was demonstrated by acceptable
correlation to several legacy measures including the Functional Assessment of Chronic Illness Therapy fatigue scale \( r = .96 \) and SF-36 vitality scale \( r = .89 \).

**Sleep disturbance.** The PROMIS Bank v1.0 - Sleep Disturbance (PROMIS - SD) is a 27-item bank focusing on the individual’s perceptions of sleep quality and depth, restoration associated with sleep, difficulty getting to sleep or maintaining sleep state, and overall perception of adequacy or satisfaction with sleep (Cella et al., 2010). Specifically not included are questions regarding sleep quantity or symptoms of specific sleep disorders. This instrument shows excellent reliability \( \alpha > .88 \) across most of the distribution. Construct validity has been demonstrated by acceptable correlation with the Pittsburg Sleep Quality Index \( r = .85 \).

**Sleep-related impairment.** PROMIS Bank v1.0 - Sleep-related Impairment (PROMIS - SRI) is a 16-item bank focusing on perceived wake-time functional impairments related to poor sleep. This instrument shows good reliability \( \alpha \geq .84 \) across most of the distribution. Construct validity has been demonstrated by acceptable correlation with the Pittsburg Sleep Quality Index \( r = .70 \). As expected, the PROMIS - SRI is highly correlated with the PROMIS - SD \( r = .75 \).

**Framingham Heart Study CVD Risk Score**

The 10-year CVD risk was assessed with the Framingham Heart Study General Cardiovascular Disease 10-year Risk score. This calculates the 10-year risk of coronary death, myocardial infarction, coronary insufficiency, angina, ischemic stroke, hemorrhagic stroke, transient ischemic attack, peripheral artery disease, and heart failure among individuals 30 to 74 years of age (Framingham Heart Study, 2013). Predictors of risk
included age, diabetes, smoking, treated and untreated systolic blood pressure, and BMI (Framingham Heart Study, 2013).

**Diabetes.** Diabetes was assessed by a single yes/no question regarding past and current diagnoses. Glycemic control was not assessed.

**Smoking.** Participants were asked whether they smoke currently (yes/no) or any in the last 12 months (yes/no). Pack years were not assessed.

**Hypertension.** Hypertension was assessed by a single question regarding current diagnosis. The participants were also asked if they took antihypertensive medication. A blood pressure reading was obtained on all participants as described above. This did not provide hypertension diagnosis, but rather was used to document systolic blood pressure for computation of the CVD risk score.

**Body mass index.** The body mass index (BMI) was established from individual participant’s weight in kilograms divided by the square of his or her height in meters. BMI is a common, indirect measure of adiposity due to its ease of measurement, and elevated BMI is associated with multiple poor health outcomes including all-cause mortality, Type 2 Diabetes, dyslipidemia, CVD, poor mental health, sleep apnea and respiratory problems, gallbladder disease, osteoarthritis, and multiple cancers (Bhaskaran et al., 2014)(NIH, 2013). Individuals are typically categorized according to the World Health Organization’s International BMI Classification System, as presented in Table 5.
Table 5

**WHO International BMI Classification**

<table>
<thead>
<tr>
<th>Classification</th>
<th>BMI (kg/m^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt;18.50</td>
</tr>
<tr>
<td>Severe thinness</td>
<td>&lt;16.00</td>
</tr>
<tr>
<td>Moderate thinness</td>
<td>16.00 - 16.99</td>
</tr>
<tr>
<td>Mild thinness</td>
<td>17.00 - 18.49</td>
</tr>
<tr>
<td>Normal range</td>
<td>18.50 - 24.99</td>
</tr>
<tr>
<td>Overweight</td>
<td>≥25.00</td>
</tr>
<tr>
<td>Pre-obese</td>
<td>25.00 - 29.99</td>
</tr>
<tr>
<td>Obese</td>
<td>≥30.00</td>
</tr>
<tr>
<td>Obese class I</td>
<td>30.00 - 34.99</td>
</tr>
<tr>
<td>Obese class II</td>
<td>35.00 - 39.99</td>
</tr>
<tr>
<td>Obese class III</td>
<td>≥40.00</td>
</tr>
</tbody>
</table>


Despite its universal use in healthcare and research, assessment of BMI has limitations. According to a recent meta-analysis (N = 31,968 individuals from 32 different studies), BMI has a sensitivity to identify excess adiposity of only 50% (95% CI [43%, 57%]) despite a specificity of 90% (95% CI [86%, 94%])(Okorodudu et al., 2010). This indicates a missed diagnosis in half of individuals if using the BMI to identify excess body fat. Unfortunately, more direct, and thus more accurate, measures of body composition such as dual energy X-ray absorptiometry, hydrostatic weighing, air-displacement plethysmography, isotope dilution are impractical for both clinical use and most research due to cost, equipment requirements, and time commitment. Although it is common to categorize BMI, for the purpose of the proposed study, BMI will be treated as a continuous variable as is consistent with the Framingham Heart Study CVD Risk Score. Furthermore, this minimizes loss of information and variance in the sample.

**Analysis**

The hypothesized biobehavioral relationships between chronic job stress, LTPA, HCC, symptom experience, and CVD risk are complex and multidimensional. Thus, data
analysis sought to describe the strength and direction of these relationships. Bivariate relationships between variables were tested using correlation and regression analysis as the final sample size did not support the use of structural equation modeling.

**Missing Data**

Missing data for biophysical measures (blood pressure, height, and HCC) were handled using listwise deletion. Listwise deletion may introduce bias and a significant loss of power, especially as these variables were unlikely missing at random. Blood pressure readings were missing on individuals unable to be properly fitted with a sphygmomanometer due to excessive arm adiposity and short humeral shaft. Excessive adipose tissue in these individuals could be associated with elevated blood pressure, but this is unknown. Likely, the non-detectable levels of HCC were due to sampling error, as the two cases were on lighter samples than ideal for analysis (4.76 & 5.89 mg respectively). Hair cortisol is still an experimental laboratory measure with unclear distribution in the population at large. Therefore utilizing methods of handling missing data that are based on estimation of the mean may create misleading results and introduce bias into the study.

Overall, the online questionnaire had less than 1% missing data. Only one variable had >1% missing data; the final question regarding co-worker support (“People I work with are helpful in getting the job done”) had 5.7% missing data. No association was found with job title or site, or with other items within the JCQ. Data was not missing completely at random (Little’s MCAR p > .05), but the assumption was that data was missing at random. Graphing patterns of missing data showed no clear association between missing items.

To preserve sample size and power, multiple imputation was used for missing data in questionnaire data. At this time, multiple imputation is considered the most reputable method
of handling missing data and has the advantage of not requiring MCAR. It is appropriate for any form of general linear modeling (Tabachnick & Fidell, 2013). All items of the JCQ measuring demand, control, support, and job satisfaction as well as PROMIS tools were entered into the imputation model. Five iterations were requested using fully conditional specification (MCMC). The fourth imputed model was chosen as it consistently used plausible values and approached the mean scores for each item. Repeated analyses showed no change in results with and without the imputed data.

**Exploratory Data Analysis**

Preceding hypothesis testing, exploratory data analysis (EDA) was performed to better understand the data (Portney & Watkins, 2009). This served several purposes. EDA provided a summary of study participants and thus informed the extent of generalizability of study conclusions. Secondly, EDA evaluated whether the data met the underlying assumptions for each statistical analysis. Thirdly, EDA informed proper method to deal with missing data (Tabachnick & Fidell, 2013).

**Hypothesis Testing**

Job stress, HCC, and CVD risk were analyzed with demographic and work-related variables using Pearson correlational analyses for continuous variables or Spearman’s rho for categorical variables. Variables with medium effect size ($r = .3 - .5$, $p \leq .05$)(Cohen, 1992) were considered to have a significant effect, and thus could alter conclusions from the predictive model and would be considered for inclusion in future model testing.

Following EDA and missing data handling, correlational analysis was pursued to address Aim 2, hypotheses 1, 2, and 4. Correlations describe the strength and direction of the relationship between two variables (Portney & Watkins, 2009). The Pearson product moment
correlation coefficient will be used for this analysis. An alternative, categorical formulation for job stress (presence or absence of job stress) for Aim 2, hypothesis 4 was then tested using logistic regression. Individuals above the sample median for demand and below the sample median for control were said to have job stress. Aim 2, hypothesis 3 was to assess a moderator relationship as outlined by Frazier, Tix, and Barron (2004), however previous findings in the correlational analysis made this unfeasible. Subsequently, linear regression was performed to address each of the hypotheses in Aim 1.

**Conclusion**

Cardiovascular risk is a complex, multidimensional phenomenon incorporating physiologic and behavioral factors. This study was guided by a theoretical framework, as described in Chapter II, allowing exploration of the complex relationships influencing CVD risk from a holistic framework. With its emphasis on behavioral, physiologic, and symptom outcomes of job stress, the study takes a broad approach to CVD research, clearly aligned with nurses’ holistic and collaborative mentality. Use of structural equation modeling for model testing was unwise due to final sample size, therefore correlation and regression analysis was undertaken to test the relationships in the predictive model.
CHAPTER IV

RESULTS

The purpose of this study was to describe biobehavioral relationships linking job stress to cardiovascular disease (CVD) risk among healthcare workers in the United States. A predictive model of the associations between job stress, leisure-time physical activity (LTPA), hair cortisol, symptom experience of job stress, and CVD risk was tested in the current study. Data analysis was conducted using IBM SPSS 24. The results of this analysis are presented in this chapter.

Descriptive Statistics

Descriptive statistics are provided for sites and overall participants. In addition, coding and transformation of variables in preparation for hypothesis testing is described in this section.

Sites

The study utilized three sites in two Southeastern states. Participation rate ranged from 7.10 to 21.35% across sites. This was calculated using total full-time employees, as data by shift were unavailable. Therefore, the actual response rate for eligible individuals would be higher. Table 1 summarizes these samples.

Table 1
Participants by Site

<table>
<thead>
<tr>
<th>Site</th>
<th>Number of Participants</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>44</td>
<td>41.5</td>
</tr>
<tr>
<td>2</td>
<td>17</td>
<td>16.0</td>
</tr>
<tr>
<td>3</td>
<td>45</td>
<td>42.5</td>
</tr>
</tbody>
</table>
No significant differences existed between sites for age, body mass index (BMI), systolic blood pressure, hair cortisol, any component of the Job Content Questionnaire (JCQ), job satisfaction, or symptom scores (all \( p \)'s > .05). A significant difference existed for diastolic blood pressure between Site 1 and 2 \( (F(2, 103) = 5.421, p = .006) \), and a borderline significant difference in 10-year CVD risk appeared between Site 1 and 2 \( (F(2, 103) = 3.091, p = .050) \).

**Participants**

A final sample of 106 was obtained as outlined in Chapter III. In brief, retention rate between initial interview and completion of online survey was 94%. Eight cases were excluded due to missing biophysical data. Characteristics of the participants are summarized in Table 2, 3, and 4. The sample was predominantly female (96.2%), white (100%), and married (77.4%). The mean age of participants was \( 42.69 \pm 10.69 \) years.

**Table 2**

*Demographic Characteristics*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (SD)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years):</td>
<td>42.69 (10.69)</td>
<td>23 - 60</td>
</tr>
<tr>
<td>Gender:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>102</td>
<td>96.2</td>
</tr>
<tr>
<td>Male</td>
<td>4</td>
<td>3.8</td>
</tr>
<tr>
<td>Marital status:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>82</td>
<td>77.4</td>
</tr>
<tr>
<td>Widowed</td>
<td>1</td>
<td>.9</td>
</tr>
<tr>
<td>Divorced/Separated</td>
<td>15</td>
<td>14.2</td>
</tr>
<tr>
<td>Never married</td>
<td>8</td>
<td>7.5</td>
</tr>
<tr>
<td>Highest level of education:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H.S. degree/GED</td>
<td>8</td>
<td>7.5</td>
</tr>
<tr>
<td>Some college</td>
<td>33</td>
<td>31.1</td>
</tr>
<tr>
<td>Associate degree</td>
<td>35</td>
<td>33.0</td>
</tr>
<tr>
<td>Bachelor’s degree</td>
<td>22</td>
<td>20.8</td>
</tr>
<tr>
<td>Graduate degree</td>
<td>8</td>
<td>7.5</td>
</tr>
<tr>
<td>Household income:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;$20,000</td>
<td>4</td>
<td>3.8</td>
</tr>
<tr>
<td>$20,000 - 49,999</td>
<td>27</td>
<td>25.5</td>
</tr>
<tr>
<td>$50,000 - 74,999</td>
<td>34</td>
<td>32.1</td>
</tr>
<tr>
<td>$75,000 - 99,999</td>
<td>24</td>
<td>22.6</td>
</tr>
<tr>
<td>≥$100,000</td>
<td>17</td>
<td>16.0</td>
</tr>
</tbody>
</table>
Table 3
*Health-related Characteristics of the Sample*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (SD)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>29.82 (7.37)</td>
<td>17.60 - 57.60</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>127.14 (12.99)</td>
<td>97 - 165</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>78.87 (8.10)</td>
<td>59 - 101</td>
</tr>
<tr>
<td>10-year CVD Risk (%)</td>
<td>5.77 (6.16)</td>
<td>0.5 - 34.9</td>
</tr>
<tr>
<td>Adverse Childhood Experience Score</td>
<td>1.34 (1.70)</td>
<td>0 - 8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>History of:</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAD/MI</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cushing’s syndrome/Addison’s disease</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Depression/Bipolar</td>
<td>20</td>
<td>18.9</td>
</tr>
<tr>
<td>Diabetes</td>
<td>11</td>
<td>10.4</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>1</td>
<td>.9</td>
</tr>
<tr>
<td>Hypertension</td>
<td>24</td>
<td>22.6</td>
</tr>
<tr>
<td>Obstructive sleep apnea</td>
<td>2</td>
<td>1.9</td>
</tr>
<tr>
<td>PAD</td>
<td>1</td>
<td>.9</td>
</tr>
<tr>
<td>Stroke</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Currently taking medication:

<table>
<thead>
<tr>
<th>medication</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihypertensive</td>
<td>21</td>
<td>19.8</td>
</tr>
<tr>
<td>Antihyperlipidemic</td>
<td>6</td>
<td>5.7</td>
</tr>
<tr>
<td>Non-insulin antidiabetic</td>
<td>11</td>
<td>10.4</td>
</tr>
<tr>
<td>Insulin</td>
<td>2</td>
<td>1.9</td>
</tr>
<tr>
<td>Antidepressant</td>
<td>16</td>
<td>15.1</td>
</tr>
<tr>
<td>Anxiolytic</td>
<td>17</td>
<td>16.0</td>
</tr>
<tr>
<td>Oral steroid</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Oral contraceptive</td>
<td>8</td>
<td>7.5</td>
</tr>
<tr>
<td>Hormone replacement therapy</td>
<td>6</td>
<td>5.7</td>
</tr>
<tr>
<td>Anti-insomnia</td>
<td>4</td>
<td>3.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Berlin Questionnaire</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>81</td>
<td>76.4</td>
</tr>
<tr>
<td>High risk</td>
<td>25</td>
<td>23.6</td>
</tr>
</tbody>
</table>
Table 4
*Job Characteristics of Sample*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Job Type:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical</td>
<td>74</td>
<td>70.5</td>
</tr>
<tr>
<td>Non-clinical</td>
<td>31</td>
<td>29.5</td>
</tr>
<tr>
<td>Coded Job Title:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direct patient care providers</td>
<td>33</td>
<td>31.4</td>
</tr>
<tr>
<td>Supervisory staff</td>
<td>14</td>
<td>13.3</td>
</tr>
<tr>
<td>Paramedical staff</td>
<td>24</td>
<td>22.9</td>
</tr>
<tr>
<td>Other</td>
<td>34</td>
<td>32.4</td>
</tr>
<tr>
<td>Hours worked per week:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 30</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>30 - 40</td>
<td>72</td>
<td>67.9</td>
</tr>
<tr>
<td>Greater than 40</td>
<td>34</td>
<td>32.1</td>
</tr>
<tr>
<td>Job satisfaction:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not at all</td>
<td>1</td>
<td>0.9</td>
</tr>
<tr>
<td>Not too</td>
<td>2</td>
<td>1.9</td>
</tr>
<tr>
<td>Somewhat</td>
<td>35</td>
<td>33.3</td>
</tr>
<tr>
<td>Very</td>
<td>69</td>
<td>63.8</td>
</tr>
</tbody>
</table>

**Coding and Transformation of Variables**

The variables of demand, control, and support were calculated as per standard scoring of the Job Content Questionnaire (JCQ). Job stress was calculated using the quadrant method recommended by JCQ authors. This categorizes individuals as having job stress if they fall above the sample median for demand and below the sample median for control. Therefore, in this study participants were identified as having job stress if their score for demand was > 32 and control < 66. In addition, a continuous job stress ratio between psychological demands and control (decision latitude) was formed after normalization of the subscales (C. A. Wong & Spence Laschinger, 2015).

For analyses evaluating physical inactivity rather than total LTPA, the LTPA variable was dichotomized into physically active (score ≥4 on Stanford Leisure-Time Activity Categorical Item) and physically inactive (score ≤3 on Stanford Leisure-Time Activity...
Categorical Item). This dichotomization aligned with meeting or failing to meet the current recommendations for aerobic exercise (National Institutes of Health [NIH], 2016).

Job title was coded to include four groups. These were: (a) direct patient care providers including nursing staff, nurse practitioners, physician assistants, and medical doctors; (b) supervisory staff including administrators, directors, and supervisors; (c) paramedical staff including respiratory, physical, and occupational therapists, dieticians, radiology and laboratory personnel; and (d) other support staff including certified nursing assistants, medical office assistants, receptionists and billing personnel.

The 10-year CVD risk was calculated using the online Framingham Heart Study General CVD 10-year Risk calculator. Individuals taking anti-hypertensive medication without reporting a diagnosis of hypertension were not coded as being on hypertensive treatment in the Framingham Risk calculation as multiple other conditions may be treated with anti-hypertensive medication.

Descriptive statistics are provided for major study variables in Table 5. Normality was assessed using skew and kurtosis. Conventionally, a variable is considered to have normal or near normal distribution when skew is between plus two and minus two. The same applies to kurtosis, although some authors offer more stringent guidelines of plus one to minus one while others liberalize guidelines to plus three to minus three (Garson, 2012).

To address the severe skew of hair cortisol concentration (HCC), this variable was transformed using natural logarithmic transformation, resulting in vast improvement in the distribution ($M = 1.78$, $SD = 0.65$, skew = 1.35, kurtosis = 3.94). The 10-year CVD Risk score was not transformed to allow interpretation of a well-known and meaningful scale (Tabachnik & Fidell, 2007).
Table 5
Descriptive Statistics for Raw Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>SD</th>
<th>Range</th>
<th>Skew</th>
<th>Kurtosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>29.82</td>
<td>7.37</td>
<td>17.61 - 57.61</td>
<td>1.01</td>
<td>1.491</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>127.14</td>
<td>12.99</td>
<td>97 - 165</td>
<td>0.13</td>
<td>0.269</td>
</tr>
<tr>
<td>Hair cortisol</td>
<td>7.45</td>
<td>8.76</td>
<td>1.2 - 77.5</td>
<td>5.72</td>
<td>40.54</td>
</tr>
<tr>
<td>Demand</td>
<td>32.63</td>
<td>5.74</td>
<td>18 - 48</td>
<td>0.33</td>
<td>0.64</td>
</tr>
<tr>
<td>Control (decision latitude)</td>
<td>67.57</td>
<td>11.21</td>
<td>40 - 92</td>
<td>0.29</td>
<td>-0.33</td>
</tr>
<tr>
<td>Skill discretion</td>
<td>35.53</td>
<td>4.50</td>
<td>24 - 46</td>
<td>0.17</td>
<td>-0.41</td>
</tr>
<tr>
<td>Decision authority</td>
<td>32.04</td>
<td>7.80</td>
<td>12 - 48</td>
<td>0.14</td>
<td>-0.01</td>
</tr>
<tr>
<td>Job stress ratio</td>
<td>0.99</td>
<td>0.26</td>
<td>0.40 - 1.92</td>
<td>1.01</td>
<td>1.98</td>
</tr>
<tr>
<td>Support</td>
<td>25.65</td>
<td>3.67</td>
<td>16 - 32</td>
<td>0.18</td>
<td>0.00</td>
</tr>
<tr>
<td>Co-worker</td>
<td>13.17</td>
<td>1.78</td>
<td>10 - 16</td>
<td>0.54</td>
<td>-1.13</td>
</tr>
<tr>
<td>Supervisor</td>
<td>12.48</td>
<td>2.39</td>
<td>4 - 16</td>
<td>-0.49</td>
<td>1.88</td>
</tr>
<tr>
<td>Job satisfaction</td>
<td>3.6</td>
<td>.582</td>
<td>1 - 4</td>
<td>-1.446</td>
<td>2.696</td>
</tr>
<tr>
<td>10-year CVD Risk</td>
<td>5.77</td>
<td>6.16</td>
<td>0.5 - 34.9</td>
<td>2.34</td>
<td>6.352</td>
</tr>
</tbody>
</table>

Assessment of Potential Confounding Variables. After logarithmic transformation, HCC was evaluated for any potential confounding effects from hair treatment or personal characteristics. These statistics are available in Appendix A. In short, no difference in HCC was seen with any hair treatment, demographic factor, or health status except diastolic blood pressure, which was weakly correlated ($r = .191, p = .050$). Individuals were excluded from the study if they used systemic steroid medications within the last 3 months. However, participants were asked about any type of steroid use (e.g. intranasal, inhaler) within the last 6 months to evaluate any potential effect. Interestingly, mean HCC for those receiving a steroid injection (either intra-articular or intramuscular) within the last 6 months was significantly lower than those not reporting injection ($M = 1.26, SD = .51$ versus $M = 1.81, SD = .64; t(104) = 2.072, p = .041$).

Description of Job Stress Group. After coding for the quadrant model of job stress, participants identified as having job stress comprised 18.9% ($n = 20$) of the total sample. Individuals reporting job stress were no different than their non-stressed co-workers in regard
to study location, basic demographic factors, BMI, risk of sleep-disordered breathing, Adverse Childhood Experience (ACE) score, past medical history, or current medication use (all \( p \)'s > .05). Only having a diagnosis of diabetes approached significance (\( \chi(1) = 2.85, p = .091 \)); no participants with job stress reported a history of diabetes. More individuals with job stress smoked (\( n = 2 \) versus not (\( n = 1 \))(\( \chi(1) = 4.61, p = .032 \)). And the one individual reporting illegal drug use within the past 12 months also reported job stress.

Individuals with job stress held a variety of jobs with no statistical difference by coded job title, length of time in current job, or hours worked per week. However, only full-time employees were included in this study, so this comparison was limited to that of a 30 to 40-hour work week versus >40-hour work week.

**Aim 1**

Aim 1 was to test the predictive model of the relationship between chronic job stress, LTPA, HCC, symptom experience of job stress, and CVD risk. Aim 1 included the following hypotheses:

1. Increased chronic job stress will predict increased HCC.
2. Increased chronic job stress will predict decreased LTPA.
3. Increased HCC will predict increased CVD risk.
4. Decreased physical activity will predict increased CVD risk.
5. The symptom experience of job stress will partially mediate the relationship between HCC and CVD risk.

No significant correlations were found in the main study variables with the exception of LTPA and symptom experience as outlined in Table 6. The effect size for this relationship
was small \( (r^2 = .043) \). Regression analysis was run as per the hypotheses and no significant relationships were found.

Table 6

*Correlations between Main Study Variables*

<table>
<thead>
<tr>
<th>Independent Variable</th>
<th>Dependent Variable</th>
<th>Pearson Product-Moment Correlation</th>
<th>( p ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Job Stress</td>
<td>HCC</td>
<td>.059</td>
<td>.551</td>
</tr>
<tr>
<td>Job Stress</td>
<td>LTPA</td>
<td>-.115</td>
<td>.241</td>
</tr>
<tr>
<td>HCC</td>
<td>CVD Risk</td>
<td>-.033</td>
<td>.738</td>
</tr>
<tr>
<td>LTPA</td>
<td>CVD Risk</td>
<td>-.154</td>
<td>.115</td>
</tr>
<tr>
<td>LTPA</td>
<td>Symptom Experience</td>
<td>-.207</td>
<td>.033</td>
</tr>
<tr>
<td>Symptom Experience</td>
<td>CVD Risk</td>
<td>.085</td>
<td>.389</td>
</tr>
</tbody>
</table>

To address Aim 1, hypothesis 5, principal component analysis (PCA) was conducted to extract a data-derived principal component from variables that were hypothesized to be related. Indeed, the symptom variables were highly correlated as illustrated in Table 7. The sample was adequate for PCA as demonstrated by Kaiser-Meyer-Olkin (KMO) of 0.739 and Bartlett’s test of sphericity \( (\chi^2 (6) = 193.63, p < .001) \).

Table 7

*Correlation of Symptoms*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Fatigue</th>
<th>Sleep Disturbance</th>
<th>Sleep-related Impairment</th>
<th>Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>.532</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep-related impairment</td>
<td>.753</td>
<td>.719</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>.500</td>
<td>.408</td>
<td>.497</td>
<td>1</td>
</tr>
</tbody>
</table>

*Note.* All correlations significant at < .001 level (2-tailed).

These four variables (fatigue, sleep disturbance, sleep-related impairment, and depression) were thought to theoretically represent the symptom experience of job stress.

This single component explained 68% of the variance. Factor loadings are noted in Table 8. Despite the principle component formation, the mediation model proposed in Aim 1,
hypothesis 5 was not tested as no significant correlation was found between HCC and CVD risk ($r = -0.033$, $p = 0.738$).

Table 8
*Principle Component Analysis of Variables Representing Symptom Experience*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Component Score</th>
<th>Standardized Coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>.851</td>
<td>.314</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>.814</td>
<td>.301</td>
</tr>
<tr>
<td>Sleep-related impairment</td>
<td>.909</td>
<td>.336</td>
</tr>
<tr>
<td>Depression</td>
<td>.704</td>
<td>.260</td>
</tr>
</tbody>
</table>

*Note. KMO = 0.739; Bartlett’s Test of Sphericity = 193.63; $p < 0.001$*

In addition, individuals with job stress had no statistical difference in any symptom or total symptom experience. The depression scale neared significance ($t(104) = -1.81$, $p = 0.073$) with the job stress group reporting greater symptoms of depression ($M = 49.97$, $SD = 6.62$) compared to their co-workers ($M = 46.83$, $SD = 7.06$), but both groups remained below the US population norm ($M = 50.00$).

**Aim 2**

Aim 2 was to determine the relationship between specific components of the psychosocial job environment and HCC. Aim 2 included the following hypotheses:

1. Increased psychological demand will predict increased HCC.
2. Decreased control will predict increased HCC.
3. Social support will moderate the effect of job stress on HCC.
4. Increased job stress will predict increased HCC.

No significant correlations were found in these study variables as outlined in Table 9. Regression analysis was run and no significant relationships were found. Aim 2, hypothesis 3 was unable to be tested given the non-significant relationship between job stress and HCC.
Given the null results from hypothesis testing, further statistical analyses of the data were undertaken. Specifically, the measurement tools were appraised for performance and the data were re-visited from a theoretical standpoint using the Demand-Control-Support (DCS) model (Karasek & Theorell, 1990).

**Measurement Tools**

**Job Content Questionnaire.** First, the performance of the Job Content Questionnaire was evaluated. This questionnaire includes several scales: psychological demand; control (decision latitude); and total support, which is divided into supervisor support and co-worker support. Basic reliability measures are presented in Table 10. A Cronbach’s alpha of >.70 is generally viewed as acceptable although reports range from .70 - .95 (Tavakol & Dennick, 2011). However, Cronbach alpha >.90 likely indicates redundancy of items.

<table>
<thead>
<tr>
<th>Scale</th>
<th>Cronbach’s alpha</th>
<th>Inter-Item Correlations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychological demands</td>
<td>.75</td>
<td>.38</td>
</tr>
<tr>
<td>Control (decision latitude)</td>
<td>.72</td>
<td>.24</td>
</tr>
<tr>
<td>Total support</td>
<td>.91</td>
<td>.55</td>
</tr>
<tr>
<td>Supervisor support</td>
<td>.93</td>
<td>.77</td>
</tr>
<tr>
<td>Co-worker support</td>
<td>.88</td>
<td>.65</td>
</tr>
</tbody>
</table>

Table 9

**Correlations of Components of Psychosocial Job Environment and HCC**

<table>
<thead>
<tr>
<th>Independent Variable</th>
<th>Dependent Variable</th>
<th>Pearson Product-Moment Correlation</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Job stress ratio</td>
<td>HCC</td>
<td>.059</td>
<td>.551</td>
</tr>
<tr>
<td>Psychological demand</td>
<td>HCC</td>
<td>.114</td>
<td>.141</td>
</tr>
<tr>
<td>Control (decision latitude)</td>
<td>HCC</td>
<td>.051</td>
<td>.602</td>
</tr>
<tr>
<td>Social support</td>
<td>HCC</td>
<td>-.088</td>
<td>.370</td>
</tr>
</tbody>
</table>
In prior psychometric evaluation of the JCQ among US populations, Cronbach’s alphas were reported for psychological demands (.63 - .71), decision latitude (.83 - .84), supervisor support (.80 - .85), and coworker support (.72 - .80)(Karasek et al., 1998a).

**Stanford Leisure-Time Activity Categorical Item.** The measure for LTPA, Stanford Leisure-Time Activity Categorical Item, was likewise assessed for performance in the current study. As would be expected, the measure of physical activity was negatively correlated with weight ($r = -.262, p = .007$) and BMI ($r = -.251, p = .009$), albeit weakly. Surprisingly, the item was not correlated with systolic or diastolic blood pressure or CVD risk.

**Theoretical Reconsideration of the Data**

Although outside the scope of testing the original model proposed in this study, all job types identified in the Demand-Control model were described during follow-up data analysis. Individuals were deemed to have a (a) passive job if they scored lower than sample median for control and demand; (b) high strain job if scored lower than sample median for control but higher than median for demand; (c) active job if above sample median for control and demand; (d) low strain job if above sample median for control but below for demand; and finally (e) indeterminate if their scores landed on a median score, not clearly placing them in a single quadrant. Table 11 outlines the frequency of these job types in this sample.

<table>
<thead>
<tr>
<th>Job Type</th>
<th>Cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Passive</td>
<td>21</td>
<td>19.8</td>
</tr>
<tr>
<td>High strain</td>
<td>20</td>
<td>18.9</td>
</tr>
<tr>
<td>Active</td>
<td>22</td>
<td>20.8</td>
</tr>
<tr>
<td>Low strain</td>
<td>25</td>
<td>23.6</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>18</td>
<td>17.0</td>
</tr>
</tbody>
</table>
No differences in age, BMI, LTPA, HCC, symptoms, symptom experience, or job satisfaction were seen among different job types. A statistically significant difference was noted between groups for total support ($F(4,101) = 3.323, p = .013$) and supervisor support ($F(4, 101) = 4.676, p = .002$). Due to a significant Levene statistic, a Kruskal-Wallis test was performed using pairwise comparison instead of ANOVA for 10-year CVD risk score; this showed a significant difference between groups ($\chi(4) = 9.94, p = .041$). Contrary to the original hypothesis of the DCS model, individuals in high strain (job stress) positions had the lowest CVD risk ($M = 4.17, SD = 3.12$) while those in indeterminate jobs had the highest risk ($M = 9.17, SD = 8.42$). For supervisor support, participants in active jobs had the highest supervisor support ($M = 13.36, SD = 2.04$) while those with job stress had the lowest ($M = 10.75, SD = 3.14$).

In an update to the original model, Karasek and Theorell (1990) hypothesized that those at greatest risk for adverse outcomes had high job strain combined with low social support. They labeled this highest-risk group as those with “isolated strain” as isostrain. In this sample, seven participants (6.6%) were categorized as having isostrain based upon a score > 32 for demand, < 66 for control, and < 24 for total support.

Individuals reporting isostrain had higher HCC ($M = 2.38, SD = 0.80$) compared to co-workers without isostrain ($M = 1.74, SD = 0.62, t(104) = -2.59, p = .011$). They also reported greater symptoms of depression ($M = 52.49, SD = 5.32$) compared to those without isostrain ($M = 47.07, SD = 7.05, t(104) = -1.99, p = .049$). A medium effect size was seen with HCC ($\eta^2 = .061$) and small effect size with depression symptoms ($\eta^2 = .037$). Depression symptoms and HCC were unrelated ($r = -.038, p = .702$). No difference in CVD
risk between those with isostrain and those without was found ($t(104) = 1.126, p = .263$). A conservative, non-parametric test (Mann-Whitney U) confirmed these findings.

In conclusion, the data failed to support the predictive model regarding biobehavioral relationships between job stress and CVD risk. Additional analysis was undertaken and demonstrated several findings of interest including the potential relationship between isostrain and HCC and between isostrain and depression. These will be discussed in Chapter V along with implications for nursing practice and future research.
CHAPTER V
DISCUSSION

The purpose of this study was to describe biobehavioral relationships linking job stress to cardiovascular disease (CVD) risk among healthcare workers in the southeastern United States (US). A predictive model of the associations between job stress, leisure-time physical activity (LTPA), hair cortisol, symptom experience of job stress, and CVD risk was developed based upon theoretical relationships in the existing literature and then was tested.

As was discussed in Chapter I, CVD remains a global concern as the leading cause of death. In the US, it accounts for one in every three deaths (Mozaffarian et al., 2016). Notwithstanding the general consensus regarding stress as a CVD risk factor, the underlying mechanisms linking job stress with CVD remain poorly described (Ardito et al., 2014; Callaghan et al., 2005; Dimsdale, 2008; Kivimaki et al., 2012; Kivimaki, Virtanen, et al., 2006; Rosengren et al., 2004; Streptoe & Kivimaki, 2012; Toren et al., 2014; Yusuf et al., 2004). The rationale for this study was based upon an understanding that job stress creates physiologic, behavioral, and symptom changes that form a complex milieu conducive to development of CVD. As part of the physiologic response to stress, the adrenal glands release cortisol, which subsequently influences many metabolic, inflammatory, and immune processes. Hair cortisol analysis presents a promising method for assessing longitudinal alterations in this hormone, yet requires validation as a biomarker of chronic job stress.

Data from this study did not support the proposed model in which job stress predicted increased hair cortisol concentration (HCC) and decreased LTPA, both subsequently increasing CVD risk with symptom experience mediating the relationship between HCC and
CVD risk. However, several interesting findings were noted that suggest a need for further exploration. This chapter will discuss the findings, limitations, and implications for nursing practice and future research.

**Job Stress and Cardiovascular Disease Risk**

In the current study, no association was found between job stress and CVD risk. This is contrary to the preponderance of previous reports (Kivimaki et al., 2012). However, several key points are noted which may partially account for the divergence including differences in samples, use of self-report, and assessment method for CVD.

The greatest volume of research regarding job stress and CVD has utilized European samples. While Western cultures are similar in many ways, healthcare, transportation, and job market differences may limit generalizability to the US. Furthermore, while many of the European samples included healthcare workers, healthcare is largely socialized in Europe; this difference may have contributed to variability in job stress and its outcomes.

When evaluating the findings of this study compared to prior studies performed in the US, the outcomes are slightly less divergent. In longitudinal analysis, both the Nurses’ Health Study (NHS; n = 35,086 female registered nurses) and the Framingham Offspring Study (FOS; n = 3039, 44% female) failed to demonstrate increased incidence of CVD among individuals with job stress (Eaker et al., 2004; S. Lee, Colditz, Berkman, & Kawachi, 2002). However, the short period between enrollment and follow-up (4 years) as well as failure to assess for possible dose effect of job stress may have contributed to null findings in the NHS. In contrast, researchers for the Women’s Health Study (WHS; n = 22,086) found a 38% increased risk of incident CVD among women with job stress compared to their counterparts who reported low job stress (RR=1.38, 95% CI [1.08, 1.77]).
Additionally, the use of self-report may explain some of the divergence in findings. The WHS relied on medical record confirmation to identify incident CVD over the 10-year follow-up rather than self-report measures, unlike the current study, NHS, and FOS. Given the younger sample and correlational study design, the current study used the Framingham Heart Study General CVD 10-year Risk score rather than incident CVD disease, thus partially relying upon self-report (smoking status, diabetes diagnosis, and height) and partially upon objective measures (systolic blood pressure and weight). Given the Centers for Disease Control and Prevention’s (CDC) estimate that 27.8% of American diabetics are undiagnosed (CDC, 2014), the reliance on self-reported diabetes diagnosis may have contributed to underestimation of CVD risk. Also, Schneider et al. (2012) found specificity for self-reported diabetes of 84%–97% and sensitivity of 55%–80% depending upon definition and method of assessing diabetes. Theoretically, this sample should have had fewer undiagnosed diabetics than the general population, as they predominantly had employer-provided health insurance and wellness programs; however this cannot be ascertained. Additional underestimation of CVD risk may have arisen from self-reported smoking status. Smokers tend to underreport smoking (Connor Gorber et al., 2009), and the current sample may have been further influenced toward underreporting by employment at healthcare facilities that do not hire smokers and maintain tobacco-free campuses.

Regardless of the amount of bias introduced from self-report, measurement of 10-year CVD risk rather than incident CVD would lead to some expected variation in findings. Atherosclerosis, the pathologic process underlying most types of CVD, is an insidious disease beginning in the earliest decades of life (Tuzcu et al., 2001). Vascular insult is clinically undetected for decades. Indeed, with the average age of first cardiac event being
72.2 years among women, the comparatively young age of this sample ($M = 42.69$, $SD = 10.69$, range 23-60 years) put them at low risk for CVD within the next 10 years. Only individuals up to 60 years of age were included due to potential alteration of HCC with greater age. The restricted heterogeneity of CVD risk scores limited the ability to identify an effect.

However, a positive feature in the assessment of job stress must be noted in the current study. Job stress was calculated from the demand and control (decision latitude) scales using two different Job Content Questionnaire (JCQ) scoring methodologies—the recommended quadrant method with job stress defined as those above the sample median for psychological demands and below the median for decision latitude and secondly as a continuous ratio between psychological demands and decision latitude (C. A. Wong & Spence Laschinger, 2015). This double scoring aided in comparison of current findings to those of previous studies using different scoring methods (Landsbergis et al., 1994). Also, this follows the recommended scoring method while also applying a method more closely aligned to the theoretical proposition of a job stress continuum described by Karasek and Theorell (1990). Finally, the double scoring allowed partial assessment of the extent to which methods of JCQ scoring alter conclusions.

**Job Stress and Hair Cortisol**

Chapter II outlined potential mechanisms linking job stress and CVD. Although these mechanisms remain unclear, cortisol continues to be suspect with its influence over many metabolic, inflammatory, and immune processes. Over-secretion or inappropriate balance with other regulatory mechanisms increases CVD risk due to the associated increased risk of adiposity, insulin resistance, dyslipidemia, hypercytokinemia, and hypertension (Kaltasas,
Zannas, & Chrousos, 2012). The advent of hair cortisol analysis now provides a longitudinal and retrospective assessment of cortisol activity for up to the preceding 6 months (Dettenborn et al., 2010), thus negating several of the major methodological limitations in job stress research to date. However, it requires validation as a biomarker of job stress.

The data failed to support a correlation between job stress and HCC \( r = .059, \ p = .551 \). Given the novel nature of HCC, limited research to date offers comparison of these findings. Of the three studies that have been published to date, the null results are consistent. Since the current study was designed and executed, Janssens et al. (2017) reported no association between HCC and job stress measures using the JCQ among 102 Belgium production company employees (mean age = 43.4 years, \( SD = 10.4 \); 40\% female). As with the current study, these researchers found limited variability in job stress exposure with few participants reporting high levels of stress and with insufficient power to distinguish significant differences. Similarly, Qi et al. (2015) found no relationship between job demands, control and HCC among a small sample of female Kindergarten teachers in China \( n = 43; \ \text{mean age} = 28 \ \text{years}, \ SD = 6 \), although a significant association appeared between HCC and need for recovery after work \( r = -.41, \ p = .006 \). Finally, Steinisch et al. (2014) found little relationship between the psychosocial job environment and HCC among 175 garment factory workers in Bangladesh. However, the study has limited comparison to the current due to occupational and cultural differences, assessment of job stress with singular questions rather than the JCQ, and of significant methodological concern, analysis of HCC from only one to two strands of hair.

The findings of the current study regarding job stress differ from recent meta-analysis of individual-level data that considered the effect of general chronic stress on HCC.
Stalder et al. (2017) described a 22% increase in HCC among chronic stress-exposed groups, including those exposed to caregiving stress, unemployment, work-related stress, or natural disasters. When data were coded for present/ongoing stress as opposed to absent/past stress, individuals with ongoing stress at the time of study had a 43% increase in HCC. No significant difference existed for those with past stress.

Of note, various working populations show remarkable variation in mean HCC with reports ranging from 3.27 pg/mg among young Bangladeshi workers (Steinisch et al., 2014), to a median of 12.5 pg/mg among Chinese kindergarten teachers, and even up to mean of 47.3 pg/mg for older shift workers in the Netherlands (Manenschijn, van Kruysbergen, et al., 2011). However, of the studies regarding job stress mentioned above, all were performed using liquid chromatography-tandem mass spectrometry (LC-MS/MS), as opposed to the enzyme immunoassay (EIA) used in the current study. This limits comparison of raw HCC values, as EIA has been shown to over-estimate HCC in a linear manner, possibly due to cross-reactivity with other steroids (Kirschbaum et al., 2009; Russell et al., 2015). Nonetheless, the accuracy of relative HCC has recently been demonstrated by the first International Round Robin exchange between the primary laboratories responsible for hair cortisol analysis, including the one used in this study (Russell et al., 2015). After analyzing the same hair samples per their standard procedure, four laboratories using EIA were highly inter-correlated ($r^2 = .92 - .97, p \text{ 's } < 0.0001$) and each of the laboratories using EIA were strongly correlated with the two laboratories using LC-MS/MS methods ($r^2 = .88 - .98; p \text{ 's } < 0.0001$). Immunoassay results from the laboratory at the University of Colorado, used in the current study, strongly correlated with the LC–MS/MS measurements in European laboratories ($r^2 = 0.98, p < 0.0001$). Thus, while raw scores cannot be compared between
EIA and LC-MS/MS, each laboratory may use a corrective factor to allow comparison with other raw data as was demonstrated by Stalder et al. (2017).

While the current study failed to show an association between job stress and HCC, as the first study among a US population, it substantively adds to current knowledge regarding this biomarker. However, the current study came with limitations that will be discussed in a future section.

**Isostrain and Hair Cortisol**

Given the null findings regarding job stress and HCC, further exploratory data analyses were performed to better understand any relationship HCC may have with the psychosocial work environment, including evaluation of Karasek and Theorell’s isostrain hypothesis. In an update to the Demand-Control model, Karasek and Theorell (1990) hypothesized that individuals who are at highest risk for adverse outcomes related to the psychosocial work environment are those with high demand, low control, and low social support (isolated job strain or isostrain). While this has had less study than the job strain hypothesis, an association between isostrain and CVD appears consistent among men, but has had too little study among women to draw a conclusion (Eller et al., 2009).

In this study, individuals with isostrain had significantly higher HCC compared to those without isostrain. These findings are consistent with prior research using salivary cortisol (Rystedt et al., 2008). Unfortunately, the current study identified only seven individuals with isostrain. Given the small group size, additional non-parametric testing was performed, adding some credence to the findings. However, this association must be viewed cautiously due to the overall sample size and limited cases of isostrain.
In addition, the study was not powered sufficiently to statistically control for depression during analysis of isostrain. Although a link between HCC and depression was described in prior work (Herane Vives et al., 2015; Wosu et al., 2013), a recent meta-analysis surprisingly found no association (Stalder et al., 2017). Nonetheless, evaluation of depression would be an important feature of future research exploring a link between isostrain and HCC to control for potential influence of depression on reporting of isostrain.

**Job Stress and Leisure-time Physical Activity**

Job stress was unrelated to LTPA in this sample. This differs from the majority of reports in the literature (Ali & Lindstrom, 2006; Fransson et al., 2012; Kouvonen et al., 2006; Kouvonen et al., 2013; Nyberg et al., 2013; Wemme & Rosvall, 2005) including a meta-analysis of prospective studies that demonstrated physically active participants reporting high job stress are more likely to become physically inactive during follow-up compared to those in a low-stress job (OR = 1.21, 95% CI [1.11, 1.32])(Fransson et al., 2012). In two US studies, control rather than job stress was identified as the primary predictive factor of LTPA (Choi et al., 2010; Hellerstedt & Jeffery, 1997). While the current study found control neared significance as a weak predictor of active LTPA (OR = 1.04, 95% CI [.99, 1.09], p = .09), this became clearly non-significant with control of age, gender, level of education, and combined family income (OR = 1.03, 95% CI [.97, 1.10], p = .281).

Several factors may partially explain the divergent results found in the current study including confounding factors and self-report measurement. Several potential confounding factors were not assessed. Although gender differences regarding job stress effects on LTPA are unclear in the literature (Kirk & Rhodes, 2011), Wemme and Rosvall (2005) found a stronger effect of non-work stress factors on LTPA among women than job-related stress.
Interestingly, low social participation strongly predicted LTPA (OR= 2.7, 95% CI [2.2, 3.4]), as did lack of emotional social support (OR = 1.9, 95% CI [1.6 - 2.3]). Non-work stressors and social participation were not assessed in the current study.

In addition, the use of a subjective measure of LTPA likely introduced bias. To date, studies examining the relationship between job stress and LTPA have used a variety of tools, but objective measures are lacking (Kirk & Rhodes, 2011). Unfortunately, self-report demonstrates poor concurrent validity with objective measures of LTPA with over-reporting of physical activity common (Connor Gorber et al., 2009; P. H. Lee et al., 2011; Segura-Jimenez et al., 2013). The cost and logistics of including accelerometer data in the current study made it unfeasible, however this is a needed focus of future research.

**Symptom Experience of Job Stress**

It was hypothesized that the symptom experience of job stress would partially mediate the relationship between HCC and CVD risk. The data did not support this proposition since no relationship was found between HCC and CVD risk ($r = -.033$, $p = .738$). However, the data did support formation of a principle component theoretically thought to represent the symptom experience of job stress. This was composed of four individual symptoms (fatigue, sleep disturbance, sleep-related impairment, and depression) and explained 68% of the variance. These symptoms have previously been described as a symptom cluster among breast cancer patients (Ho et al., 2015; Kamath et al., 2015; Liu et al., 2009), but to date, a symptom cluster of job stress has not been described in the literature. However, the current study failed to support any relationship between job stress and the symptom experience component.
The lack of an association between job stress and depression seen in this study may partially be explained by the predominantly female sample. In previous literature, a significant relationship between job stress and depression was most commonly noted for men rather than women (Blackmore et al., 2007; Clays et al., 2007b; Clumeck et al., 2009; Cohidon et al., 2012; Fandino-Losada et al., 2013), although conflicting findings exist (Clays et al., 2007a). The data also failed to support a relationship between HCC and depression. This is consistent with the findings of a recent meta-analysis (Stalder et al., 2017).

As would be expected, individuals at high risk for sleep-disordered breathing as assessed by the Berlin Questionnaire (but not diagnosed as having obstructive sleep apnea) reported more symptoms of fatigue, sleep disturbance, sleep-related impairment, and depression (see Appendix A for data). This highlighted the necessity of controlling for obstructive sleep apnea in future research involving job stress symptoms.

In summary, the data failed to support the proposed model regarding job stress and CVD risk. However, given the investigational use of hair cortisol as a biomarker for chronic job stress, the null findings significantly contribute to the literature. In addition, several other important findings were discussed including the possible relationship between isostrain and HCC and the confounding potential for undiagnosed obstructive sleep apnea in job stress research. Together, these findings add to the existing body of knowledge and indicate the need for ongoing investigation.

**Evaluation of Sample**

In order to understand how the findings may be generalized and compared to results from other studies, the sample was evaluated for similarity to the population of interest and to samples from prior studies.
Representation of Population of Interest

The population of interest was healthcare workers in the southeastern US. Unfortunately, most health measures are not available for that subset of the total population. Therefore study statistics were compared to health status of the general population in the two states where study sites were located (Table 1)(CDC, 2015). In general, the sample had a greater rate of obesity and physical inactivity compared to the general population, but lower rate of smoking and hypertension. Site 1 and 2 has not hired smokers for the past 8 years, although current smokers were retained at that time, and individuals choosing to commence tobacco use during employment are not terminated. Site 3 was the only location with self-reported smokers, although even the number of employees who smoke at that location is drastically lower than the reported state level (n = 3 or 6.7% of participants at Site 3).

Table 1
Comparison of Study Sample Health Status to State Populations

<table>
<thead>
<tr>
<th>Variable</th>
<th>Study Sample %</th>
<th>State 1 %</th>
<th>State 2 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obese (BMI ≥ 30)</td>
<td>42.5</td>
<td>30.7</td>
<td>33.8</td>
</tr>
<tr>
<td>Diabetes</td>
<td>10.4</td>
<td>11.3</td>
<td>12.7</td>
</tr>
<tr>
<td>Hypertension</td>
<td>22.6</td>
<td>36.2</td>
<td>38.5</td>
</tr>
<tr>
<td>Smoking</td>
<td>2.8</td>
<td>17.7</td>
<td>21.9</td>
</tr>
<tr>
<td>Physical inactivity*</td>
<td>84.9</td>
<td>52.0</td>
<td>54.6</td>
</tr>
</tbody>
</table>

* Defined as participation in <150 min. of aerobic activity per week.

Similarity to Samples in Prior Studies

The preponderance of research regarding job stress and cardiovascular risk has been conducted among European samples in large studies such as Belstress, JACE, Whitehall II, and the IPD-Work Consortium. Many of these samples include healthcare workers, although healthcare in Europe is predominantly socialized. In addition, previous studies demonstrate a
significantly greater number of male participants. A recent meta-analysis included only 15% female participants (Kivimaki et al., 2012).

Robust studies among US populations are, by comparison, sparse. The NHS (S. Lee et al., 2002), FOS (Eaker et al., 2004), and WHS (Slopen et al., 2012) are the predominant studies evaluating job stress as it relates to CVD in the US. The samples in each comprised, on average, older and less obese individuals than the current sample. Pertinent variables are compared in Table 2.

Table 2
Sample Characteristics Compared to Prior United States Studies

<table>
<thead>
<tr>
<th>Variable</th>
<th>Study Sample</th>
<th>NHS</th>
<th>FOS*</th>
<th>WHS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean)</td>
<td>42.7</td>
<td>55.0</td>
<td>48.2</td>
<td>57.2</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>96.2</td>
<td>100</td>
<td>44</td>
<td>100</td>
</tr>
<tr>
<td>Currently married</td>
<td>77.4</td>
<td>81.6</td>
<td>60.7</td>
<td>74.2</td>
</tr>
<tr>
<td>Combined family income ≥ $50,000</td>
<td>70.7</td>
<td>-----</td>
<td>2.2</td>
<td>59.7</td>
</tr>
<tr>
<td>Education ≤ 12 years</td>
<td>7.5</td>
<td>0</td>
<td>46.1</td>
<td></td>
</tr>
<tr>
<td>Graduate degree</td>
<td>7.5</td>
<td>20.8</td>
<td>-----</td>
<td>22.7</td>
</tr>
<tr>
<td>Obese (BMI ≥ 30)</td>
<td>42.5</td>
<td></td>
<td></td>
<td>24.5</td>
</tr>
<tr>
<td>BMI (mean)</td>
<td>29.8</td>
<td>26.1</td>
<td>25.0</td>
<td>27.0</td>
</tr>
<tr>
<td>Diabetes</td>
<td>10.4</td>
<td>3.5 - 3.9</td>
<td>0.4 - 3.9</td>
<td>4</td>
</tr>
<tr>
<td>Hypertension</td>
<td>22.6</td>
<td>26.2 - 27.5</td>
<td>-----</td>
<td>37.8</td>
</tr>
<tr>
<td>Smoking</td>
<td>2.8</td>
<td>13.4 - 16.4</td>
<td>23.3 - 33.4</td>
<td>10.8</td>
</tr>
<tr>
<td>Physical inactivity**</td>
<td>84.9</td>
<td>-----</td>
<td>-----</td>
<td>89.6</td>
</tr>
</tbody>
</table>

*Note. Data are percentages unless noted otherwise. *FOS data for subsample of women only. **Defined as participation in <150 min of aerobic activity per week except in the WHS number of days of physical activity being ≤ 3 (no report of intensity or time given).

The WHS was similar to the current sample in regard to inclusion of multiple healthcare occupations (75% registered nurses, 15% licensed practical/visiting nurses, 2.5% medical doctors, 8% other health professionals), and the NHS was entirely composed of registered nurses of various educational levels. Ethnicity was not reported, although authors of the WHS noted it was predominantly white. In general, the FOS included lower income
individuals with only 2.2% of participants reporting income ≥ $50,000 although combined family income was not reported. Education was stratified too differently for table comparison, however in general participants in the FOS had significantly less schooling (46.1% had high school degree or less compared to 7.5% in current sample).

Differences in combined family income are largely explained by inflation with the average wage having increased approximately $16,000 since 2000 (Social Security Administration, 2017). Similarly, the higher prevalence of obesity in this sample is at least in part a reflection of trends in the general population, as overall prevalence of obesity has increased 4.1% since 2004, and up to 6.3% among various healthcare occupations (J. K. Gu et al., 2014). As with obesity, the greater prevalence of diabetes among the current study sample may be explained by an increase rate of diabetes in the general population since prior research. It is also plausible that easy and cost effective access to healthcare among the current sample would lead to earlier diagnosis than samples with less education, lower income, and limited access to care (e.g. FOS). In addition, the current sample was drawn entirely from the southeastern United States, which is known to have higher prevalence of diabetes than other areas of the country. In terms of smoking, the increasing number of healthcare facilities hiring only non-smokers is likely reflected in the current sample’s markedly lower rate of smokers.

In general, the current sample was most closely aligned to the WHS except for significantly older age of the WHS’s participants. As this is the most recent study, many of the commonalities between samples likely reflect a change in the national population since the NHS and FOS collected data in the 1980-1990s. The similarity of the current sample to that of the WHS is worthy of notice as it was the only one of the three compared studies to
find a positive relationship between job stress and incident CVD. Therefore the divergent findings are not entirely explained by sampling differences alone except to re-emphasize the contribution of age in the assessment of job stress as it related to CVD. Unfortunately, the exclusion of individuals >60 years of age limited sampling among older healthcare workers in the current sample.

**Comparison of Job Content Questionnaire Scores**

In Table 3, the JCQ results obtained in this sample were compared to population norms generated by the US Department of Labor Quality of Employment Survey (Job Content Questionnaire User Guide, 2015) and the FOS (Eaker et al., 2004). Median JCQ scores were not reported in the WHS or NHS. As the current study sample was predominantly women (96.2%), the national norms and FOS scores for women were analyzed. This showed significant difference between the current study sample and national norms for demand, but not for control. JCQ scores for women in the FOS were not statistically different. Thus the null findings in the current study are not explained by marked differences in JCQ scores as compared to prior studies.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Current Study Mean (SD)</th>
<th>QES Mean (SD)</th>
<th>p</th>
<th>FOS Mean (SD)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demand</td>
<td>32.63 (5.74)</td>
<td>30.26 (7.17)</td>
<td>.000</td>
<td>31.9 (6.0)</td>
<td>.192</td>
</tr>
<tr>
<td>Women</td>
<td>30.76 (7.07)</td>
<td></td>
<td>.001</td>
<td>69.0 (12.6)</td>
<td>.191</td>
</tr>
<tr>
<td>Control</td>
<td>67.57 (11.21)</td>
<td>70.20 (15.87)</td>
<td>.000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>65.69 (15.80)</td>
<td></td>
<td>.088</td>
<td>69.0 (12.6)</td>
<td>.191</td>
</tr>
</tbody>
</table>

*Note.* FOS = Framingham Offspring Study (Eaker et al., 2004)

**Limitations**

In Chapter I several limitations were discussed. These included inability to control for all confounding factors, correlational design, sampling technique, and use of self-report
measures. This section will reconsider these limitations as they applied to the current study.

**Confounding Factors**

Cortisol has complex regulatory mechanisms even including tissue specific regulation. Thus the number of factors potentially affecting cortisol assessment is staggering. Although some of the most common confounding factors were included in this study, others were not addressed.

The present study did not account for the potential effect of alternative forms of stress. Perceived stress, marital stress, daily hassles, or major life events may have contributed to some variability in HCC and CVD risk. Unfortunately, the effect of perceived stress on HCC remains unclear. In recent meta-analysis, Stalder et al. (2017) found no clear correlation between HCC and perceived stress, social support, and depressiveness, mirroring the same inconclusive findings from traditional forms of cortisol assessment. This may be due to variation in quality of self-report data that arises from awareness of the affective state, social desirability or retrospection bias. Less subjective forms of stress assessment such as a stressful life events index have found greater concordance with HCC (Grassi-Oliveira et al., 2012; Karlen et al., 2011; Staufenbiel et al., 2014). Therefore, future research may benefit from inclusion of a general stressful life events index to decrease potential confounding effect from alternative forms of stress while decreasing entirely subjective stress measures.

Stressors such as childcare, household responsibilities balanced with full-time work, and gender inequality in the workplace are of additional concern for the current study sample as these traditionally affect women predominantly. Also, healthcare providers may experience compassion fatigue, a form of chronic stress arising from caring roles. The
relative contribution of compassion fatigue and childcare stress on HCC and CVD risk is unknown.

Finally, anxiety disorders likely affect HCC. In recent meta-analysis, Stalder et al. (2017) described a 16.7% decrease in median HCC among individuals with anxiety disorders. Additionally, anxiety has been described as an outcome of job stress (Andrea, Bultmann, van Amelsvoort, & Kant, 2009b; Godin, Kittel, Coppieters, & Siegrist, 2005; Griffin, Greiner, Stansfeld, & Marmot, 2007). Anxiety was not directly measured in the current study, although no difference in HCC was seen among individuals taking anti-anxiety medication ($t(104) = 0.281, p = .778$).

While multiple potential confounding variables were assessed in the current study, the ability to control for each variable was severely limited by statistical power. Some variables were evident in a very small subsample (e.g. male sex) limiting ability to detect an effect in that subgroup.

With a sample of 106, an alpha of .05, power of .80, and four predictors in linear regression analysis, an effect size of $\hat{f}^2 = .12$ could be detected. A larger sample size would have increased the ability to detect an effect in the predictive model as well as control for potential confounding variables. Furthermore, larger samples are more likely to accurately represent the population of interest. Therefore, replication of this study using a larger sample may yield different results.

**Cross-sectional Design**

Although a cross-sectional design allows researchers to test relationships and draw conclusions regarding how one variable affects another, causality cannot be demonstrated as a time sequence cannot be established. While validity of a cross-sectional study is not
threatened by history, testing effects, regression toward the mean, or attrition of subjects (Portney & Watkins, 2009), the greatest threat arises from cohort effect, or extraneous variables in a given group of individuals that may not be generalizable to other generations or cohorts. Yet, the lower cost and time commitment for participants in cross-sectional studies makes this design ideal for preliminary research such as this.

Prospective analysis would allow better understanding of the progression of CVD risk. Cardiovascular risk factors may initiate or potentiate the insidious pathologic process of atherosclerosis while the clinically detectible effects remain hidden for years. Use of the Framingham 10-year CVD Risk Score attempted to truncate that time lapse by identifying intermediate “pre-CVD” indicators. However, this predictive measure does not perfectly reflect incident CVD nor make any projection beyond 10 years. This is especially concerning among a sample of younger females (31% were < 35 years of age) as women routinely have later onset of clinical CVD due to a protective estrogen effect (Rosano, Spoletini, & Vitale, 2017). Even if job stress creates inflammatory and metabolic changes conducive to atherosclerotic progression, the effects may take decades to create a notable consequence.

**Sampling**

Convenience sampling may produce a sample with critical differences from the population of interest. For example, except at Site 2, individuals solely participated during work hours. Therefore, it is plausible that individuals with the highest job demand were unable to leave their responsibilities in order to participate in the research study.

Also, inclusion and exclusion criteria likely introduced bias into the study. For instance, individuals were excluded if they were bald or had hair too short to clip in a non-disfiguring manner. As a result, more male participants were excluded than female. In
addition, individuals over 60 years of age were excluded. This excluded individuals with longer exposure to job stress and greater likelihood of a CVD event within the next decade. Only three individuals were at high risk (≥ 25%) for a CVD within the next 10 years, and this lack of heterogeneity limited the ability to distinguish any effect of job stress on CVD risk.

Measurement Methods

This study heavily relied upon self-report measures with the exception of systolic blood pressure and weight. Although research to date regarding the effect of job stress on health behaviors has almost exclusively relied on self-report measures, these notoriously demonstrate poor concurrent validity with objective measures (Connor Gorber et al., 2009; P. H. Lee et al., 2011; Segura-Jimenez et al., 2013). Indeed, the lack of association between LTPA and CVD risk raises concern regarding the performance of these instruments in this sample as this relationship is repeatedly and strongly represented in the literature (Reddigan et al., 2011). Indeed, the use of the Framingham 10-year General CVD Risk Score may have incorrectly portrayed risk among this sample. This tool was validated for individuals 30 - 74 years of age and calculation of risk scores required a minimum age of 30 to be entered. Per instructions with the tool, if a score was less than the minimum, the minimum value was entered. This may have led to slight inflation of CVD risk among the youngest members of this sample. However, as has already been discussed in prior sections, inaccurate self-report of diabetes, hypertension, and height may have under-represented CVD risk among other participants.

Implications for Future Research

This study failed to demonstrate an association between job stress and CVD risk. This is in contrast to multiple large-scale studies (Ardito et al., 2014; Callaghan et al., 2005;
Dimsdale, 2008; Kivimaki et al., 2012; Kivimaki, Virtanen, et al., 2006; Rosengren et al., 2004; Streptoe & Kivimaki, 2012; Toren et al., 2014; Yusuf et al., 2004). The relationship has been less clear among US populations, although the most robust of three similar studies found a relationship between job stress and incident CVD (Slopen et al., 2012). Replication of the current study using a larger sample may produce results more closely aligned to previously published investigations. As mentioned above, power to detect an effect and control for confounding factors is directly related to the sample size. A larger sample size would also make structural equation modeling possible. This method alone allows complete and simultaneous testing of multiple relationships between complex and multidimensional phenomena (Tabachnick & Fidell, 2013).

Replication of the current study using prospective analysis and incident CVD rather than CVD risk is also an important direction for future research. Longitudinal analysis aids in establishing causality, and assessment of HCC and job stress at different junctures would allow understanding of dose effect as it relates to incident CVD. The use of incident CVD as the outcome measure would decrease the threat to validity arising from an indirect measure such as was used in this study.

Even if prospective analysis and measurement of incident CVD proved unfeasible, decreased use of self-report measures would bolster study validity. Specifically, assessing height, lipid and glycemic status instead of relying on self-report would decrease potential bias arising from reporting error. While this would increase the invasiveness of study procedures, these measures are fairly routine as part of work-place wellness programs and could be assessed in conjunction with that.
Another benefit to replicating this study in conjunction with a work-place wellness program would be the ability for workers to participate in hair sampling while not responsible for work duties. Potential bias arose from sampling during the workday when those with the highest levels of job stress may have been unable to leave their duties.

Finally, recent data has emerged in hair cortisol research that suggests the need for assessment of additional confounding factors. Measurement of anxiety and non-work stress using a stressful life events index would make a replication study more robust.

**Implications for Nursing Practice**

The purpose of this study was to elucidate the biobehavioral relationships between job stress and CVD risk. A predictive model of job stress was presented. Given the findings and preliminary nature of this study, direct application to clinical nursing practice is limited at this time. However, the null findings emphasize the need for ongoing nursing research and theory testing.

Theoretical models allow nurses, whether in research or clinical practice, to connect discreet concepts, identify gaps in current knowledge, formulate research questions, assess risks, and implement interventions. As prevention of CVD remains a leading public health concern, development of a theoretical model regarding biobehavioral processes underlying CVD risk in individuals experiencing chronic job stress remains an important venture. Nurse researchers are uniquely prepared to contribute to research in this area through their broad understanding of pathophysiology, behavioral science, epidemiology, and quality of life issues.
Conclusion

In conclusion, CVD is the leading cause of death and disability worldwide, therefore prevention remains a foremost public health concern. Job stress appears to be associated with CVD, although the mechanisms underlying the relationship are complex and not fully understood. The purpose of this study was to test a predictive model regarding the biobehavioral relationships between job stress and CVD risk. The data failed to support any portion of the model. The lack of corroboration for even established relationships (e.g. LTPA and CVD risk) emphasizes the need for additional model testing with a larger sample, objective measures, and additional control for confounding factors.

This study added to the fledgling body of literature regarding the use of hair cortisol as a biomarker for chronic job stress. The lack of an association between HCC and job stress was consistent with the singular prior study in a Western populations. However, this study is the first to explore the relationship between isostrain and HCC. Isostrain also appears to be related to CVD among men, but too little research exists to draw a conclusion among women. Additional research is needed regarding the interplay of isostrain, HCC, and CVD among women.
REFERENCES


APPENDIX A

SUPPLEMENTAL DATA ANALYSIS

Table 1
Potential Confounding Factors of Hair Cortisol

<table>
<thead>
<tr>
<th>Variable</th>
<th>t(df)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>.161 (104)</td>
<td>.872</td>
</tr>
<tr>
<td>Chemically straighten hair (yes/no)</td>
<td>.428 (103)</td>
<td>.669</td>
</tr>
<tr>
<td>Color/bleach hair (yes/no)</td>
<td>-.804 (104)</td>
<td>.423</td>
</tr>
<tr>
<td>High risk of sleep-disordered breathing</td>
<td>1.426 (104)</td>
<td>.157</td>
</tr>
<tr>
<td>Medication use (yes/no)</td>
<td>.189 (104)</td>
<td>.851</td>
</tr>
<tr>
<td>Steroid medication use in last 6 months</td>
<td>1.350 (104)</td>
<td>.076</td>
</tr>
<tr>
<td>Injected (joint or intramuscular)*</td>
<td>2.072 (104)</td>
<td>.041</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>F(df)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marriage status</td>
<td>1.428(4, 101)</td>
<td>.230</td>
</tr>
<tr>
<td>Household income</td>
<td>.849</td>
<td>.498</td>
</tr>
<tr>
<td>Educational status</td>
<td>1.165(4, 101)</td>
<td>.331</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pearson Product-Moment Correlation</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>.092</td>
<td>.347</td>
</tr>
<tr>
<td>BMI</td>
<td>.069</td>
<td>.479</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>.040</td>
<td>.684</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>.191</td>
<td>.050</td>
</tr>
<tr>
<td>Depression symptoms</td>
<td>-.038</td>
<td>.702</td>
</tr>
<tr>
<td>Sleep-related impairment</td>
<td>.140</td>
<td>.155</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>.101</td>
<td>.304</td>
</tr>
<tr>
<td>Fatigue</td>
<td>.085</td>
<td>.387</td>
</tr>
<tr>
<td>Adverse childhood experience score</td>
<td>.030</td>
<td>.757</td>
</tr>
<tr>
<td>Weight of hair sample</td>
<td>-.079</td>
<td>.423</td>
</tr>
<tr>
<td>Frequency of hair washing</td>
<td>-.166</td>
<td>.102</td>
</tr>
</tbody>
</table>

Note. Mean HCC for those having steroid injection within the last 6 months were statistically significantly lower than those not reporting steroid injection (\(M = 1.26, SD = .51\) versus \(M = 1.81, SD = .64\)).
<table>
<thead>
<tr>
<th>Variable</th>
<th>M(SD)</th>
<th>M(SD)</th>
<th>t(df)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High Risk</td>
<td>No Risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Depression</strong></td>
<td>52.16 (6.29)</td>
<td>45.97 (6.66)</td>
<td>-4.11 (104)</td>
<td>.000</td>
</tr>
<tr>
<td><strong>Fatigue</strong></td>
<td>54.73 (6.10)</td>
<td>49.12 (6.93)</td>
<td>-3.63 (104)</td>
<td>.000</td>
</tr>
<tr>
<td><strong>Sleep-related impairment</strong></td>
<td>52.22 (6.18)</td>
<td>46.73 (8.61)</td>
<td>-3.468 (52)</td>
<td>.005</td>
</tr>
<tr>
<td><strong>Sleep disturbance</strong></td>
<td>53.62 (6.05)</td>
<td>47.90 (8.10)</td>
<td>-3.79 (53)</td>
<td>.000</td>
</tr>
<tr>
<td><strong>Symptom experience factor</strong></td>
<td>.686 (.713)</td>
<td>-.203 (.985)</td>
<td>-4.12 (104)</td>
<td>.000</td>
</tr>
</tbody>
</table>
APPENDIX B
MEASUREMENT TOOLS

Demographic info

Thank you for completing the survey below. You will be sent a $20 gift card via email after completing this survey. If you have any questions or concerns regarding this research study, please do not hesitate to contact the researcher at kieston@southern.edu or 423-443-9498.

COMIRE Protocol # 16-1931

1) Are you:
   ○ Male
   ○ Female

2) What is your age?
   ○ 18
   ○ 19
   ○ 20
   ○ 21
   ○ 22
   ○ 23
   ○ 24
   ○ 25
   ○ 26
   ○ 27
   ○ 28
   ○ 29
   ○ 30
   ○ 31
   ○ 32
   ○ 33
   ○ 34
   ○ 35
   ○ 36
   ○ 37
   ○ 38
   ○ 39
   ○ 40
   ○ 41
   ○ 42
   ○ 43
   ○ 44
   ○ 45
   ○ 46
   ○ 47
   ○ 48
   ○ 49
   ○ 50
   ○ 51
   ○ 52
   ○ 53
   ○ 54
   ○ 55
   ○ 56
   ○ 57
   ○ 58
   ○ 59
   ○ 60
   ○ Other
3) What is your height?
   - 3 ft 10 in
   - 3 ft 11 in
   - 4 ft
   - 4 ft 1 in
   - 4 ft 2 in
   - 4 ft 3 in
   - 4 ft 4 in
   - 4 ft 5 in
   - 4 ft 6 in
   - 4 ft 7 in
   - 4 ft 8 in
   - 4 ft 9 in
   - 4 ft 10 in
   - 4 ft 11 in
   - 5 ft
   - 5 ft 1 in
   - 5 ft 2 in
   - 5 ft 3 in
   - 5 ft 4 in
   - 5 ft 5 in
   - 5 ft 6 in
   - 5 ft 7 in
   - 5 ft 8 in
   - 5 ft 9 in
   - 5 ft 10 in
   - 5 ft 11 in
   - 6 ft
   - 6 ft 1 in
   - 6 ft 2 in
   - 6 ft 3 in
   - 6 ft 4 in
   - 6 ft 5 in
   - 6 ft 6 in
   - 6 ft 7 in
   - 6 ft 8 in

4) Are you currently:
   - Married
   - Widowed
   - Divorced
   - Separated
   - Never married

5) What is the highest level of school you have completed or the highest degree you have received?
   - Less than high school degree
   - High school degree or equivalent (e.g., GED)
   - Some college but no degree
   - Associate degree
   - Bachelor degree
   - Graduate degree

6) What category best describes your combined family income (wages, salaries, Social Security or retirement benefits, dividends, etc.) before taxes?
   - Less than $20,000
   - $20,000 - $29,999
   - $30,000 - $49,999
   - $50,000 - $74,999
   - $75,000 - $99,999
   - More than $100,000
Past Medical History

Has a healthcare provider ever told you that you have or had (check all that apply):

- [ ] Coronary heart disease/myocardial infarction (heart attack or a blockage in the heart)
- [ ] Cushing's syndrome or Addison's disease
- [ ] Depression or bipolar disorder
- [ ] Diabetes
- [ ] Heart failure
- [ ] Hypertension (high blood pressure)
- [ ] Obstructive sleep apnea
- [ ] Peripheral artery disease (blockages in blood vessels other than in the heart or brain)
- [ ] Stroke

Do you currently take any medication?

- [ ] Yes
- [ ] No

Do you take any of the following medications?

- [ ] Blood pressure medicine (antihypertensives)
- [ ] Cholesterol medicine
- [ ] Diabetes medicine (pills or injections other than insulin)
- [ ] Insulin
- [ ] Oral steroids (such as prednisone or cortisone)
- [ ] Antidepressant
- [ ] Anti-anxiety medicine
- [ ] Oral contraceptives
- [ ] Hormone replacement (such as estrogen)
- [ ] Sleeping medicine

During the last 6 months, have you taken steroids at any time:

- [ ] By mouth (such as prednisone, cortisone, dexamethasone)
- [ ] By injection
- [ ] Topical (including creams, lotions, ointments)
- [ ] Eye drops
- [ ] Inhaled (such as Advair, Symbicort, Flomvent, Pulmicort, etc.)
- [ ] Nasal spray (such as Flonase, Nasacort, Nasonex, etc.)
Sleep Questionnaire

Do you snore?  
☐ Yes  
☐ No

Your snoring is:  
☐ Slightly louder than breathing  
☐ As loud as talking  
☐ Louder than talking

How often do you snore?  
☐ Almost every day  
☐ 3-4 times per week  
☐ 1-2 times per week  
☐ Rarely or never

Has your snoring ever bothered other people?  
☐ Yes  
☐ No  
☐ Don’t know

Has anyone noticed that you stop breathing during your sleep?  
☐ Almost every day  
☐ 3-4 times per week  
☐ 1-2 times per week  
☐ Rarely or never

How often do you feel tired or fatigued after you sleep?  
☐ Almost every day  
☐ 3-4 times per week  
☐ 1-2 times per week  
☐ Rarely or never

During your waking time, do you feel tired, fatigued, or not up to par?  
☐ Almost every day  
☐ 3-4 times per week  
☐ 1-2 times per week  
☐ Rarely or never

Have you ever nodded off or fallen asleep while driving a vehicle?  
☐ Yes  
☐ No

How often does this occur?  
☐ Almost every day  
☐ 3-4 times per week  
☐ 1-2 times per week  
☐ Rarely or never
Hair Care History

How many times per week do you wash your hair on average?

- [ ] 1
- [ ] 2
- [ ] 3
- [ ] 4
- [ ] 5
- [ ] 6
- [ ] 7 or more

Do you chemically straighten your hair?

- [ ] Yes
- [ ] No

Do you color or bleach your hair?

- [ ] Yes
- [ ] No

When was the last time that you colored or bleached your hair?

__________________________

Do you use any over-the-counter or prescription medications for any scalp conditions (i.e. Rogaine, fungal treatments, parasites, etc.)?

- [ ] Yes
- [ ] No

Please list any medications you apply to your scalp.

__________________________
Lifestyle History

Do you currently smoke?
☐ Yes
☐ No

Have you smoked within the last 12 months?
☐ Yes
☐ No

During the last 12 months, how often did you usually have any kind of drink containing alcohol?
☐ Every day
☒ 3 to 6 times a week
☐ 1 to 2 times a week
☐ Once a month
☐ 1 or 2 times in the past year
☐ Never

When you drink alcohol, how many drinks do you usually drink at any one time? By a drink we mean half an ounce of absolute alcohol (e.g., a 12 ounce can or glass of beer or cooler, a 5 ounce glass of wine, or a drink containing 1 shot of liquor).

☐ Over 6 drinks
☐ 5 or 6 drinks
☐ 3 or 4 drinks
☐ 1 or 2 drinks
☐ Less than 1 drink

During the last 12 months, did you ever consume illegal drugs?
☐ Yes
☐ No
During the past month, which statement best describes the kinds of physical activity you usually did? Do not include the time you spent working at a job. Please read all six statements before selecting one.

- I did not do much physical activity. I mostly did things like watching television, reading, playing cards, or playing computer games. Only occasionally, no more than once or twice a month, did I do anything more active such as going for a walk or playing tennis.
- Once or twice a week, I did light activities such as getting outdoors on the weekends for an easy walk or stroll. Or once or twice a week, I did chores around the house such as sweeping floors or vacuuming.
- About three times a week, I did moderate activities such as brisk walking, swimming, or riding a bike for about 15-20 minutes each time. Or about once a week, I did moderately difficult chores such as raking or mowing the lawn for about 45-60 minutes. Or about once a week, I played sports such as softball, basketball, or soccer for about 45-60 minutes.
- Almost daily, that is five or more times a week, I did moderate activities such as brisk walking, swimming, or riding a bike for 30 minutes or more each time. Or about once a week, I did moderately difficult chores or played sports for 2 hours or more.
- About three times a week, I did vigorous activities such as running or riding hard on a bike for 30 minutes or more each time.
- Almost daily, that is, five or more times a week, I did vigorous activities such as running or riding hard on a bike for 30 minutes or more each time.
### Adverse Childhood Experience

While you were growing up, during your first 18 years of life:

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>32) Did a parent or other adult in the household often or very often...</td>
<td></td>
<td></td>
</tr>
<tr>
<td>swear at you, insult you, put you down, or humiliate you? or Act in a way</td>
<td></td>
<td></td>
</tr>
<tr>
<td>that made you afraid that you might be physically hurt?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>33) Did a parent or other adult in the household often or very often...</td>
<td></td>
<td></td>
</tr>
<tr>
<td>push, grab, slap, or throw something at you? or Ever hit you so hard that</td>
<td></td>
<td></td>
</tr>
<tr>
<td>you had marks or were injured?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>34) Did an adult person at least 5 years older than you ever...</td>
<td></td>
<td></td>
</tr>
<tr>
<td>touch or fondle you or have you touch their body in a sexual way? or</td>
<td></td>
<td></td>
</tr>
<tr>
<td>attempt or actually have oral, anal, or vaginal intercourse with you?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>35) Did you often or very often feel that no one in your family loved</td>
<td></td>
<td></td>
</tr>
<tr>
<td>you or thought you were important or special? or Your family didn't look</td>
<td></td>
<td></td>
</tr>
<tr>
<td>out for each other, feel close to each other, or support each other?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>36) Did you often or very often feel that you didn't have enough to eat,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>had to wear dirty clothes, and had no one to protect you? Your parents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>were too drunk or high to take care of you or take you to the doctor if</td>
<td></td>
<td></td>
</tr>
<tr>
<td>you needed it?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>37) Were your parents ever separated or divorced?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>38) Was your mother or stepmother often or very often pushed, grabbed,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>slapped, or had something thrown at her? or Sometimes, often, or very</td>
<td></td>
<td></td>
</tr>
<tr>
<td>often kicked, bitten, hit with a fist, or hit with something hard? or</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever repeatedly hit at least a few minutes or threatened with a gun or</td>
<td></td>
<td></td>
</tr>
<tr>
<td>knife?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>39) Did you live with anyone who was a problem drinker or alcoholic or</td>
<td></td>
<td></td>
</tr>
<tr>
<td>who used street drugs?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40) Was a household member depressed or mentally ill, or did a household</td>
<td></td>
<td></td>
</tr>
<tr>
<td>member attempt suicide?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>41) Did a household member go to prison?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Note. The Patient-Reported Outcomes Measurement Information System (PROMIS) short-form questionnaires were included as examples only. Exact questions may have differed as the computer-adaptive testing option was used in the current study.

### Sleep Related Impairment – Short Form 8a

Please respond to each item by marking one box per row.

<table>
<thead>
<tr>
<th>Step</th>
<th>Item</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step10</td>
<td>I had a hard time getting things done because I was sleepy ...........................................</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Step19</td>
<td>I felt alert when I woke up .................................</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Step28</td>
<td>I felt tired ................................................................</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Step25</td>
<td>I had problems during the day because of poor sleep .........................................................</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Step27</td>
<td>I had a hard time concentrating because of poor sleep ......................................................</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Step20</td>
<td>I felt irritable because of poor sleep. ...............</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Step8</td>
<td>I was sleepy during the daytime .......................</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Step7</td>
<td>I had trouble staying awake during the day. ........................................................................</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>
**Sleep Disturbance – Short Form 4a**

Please respond to each question or statement by marking one box per row.

<table>
<thead>
<tr>
<th>Sleep104</th>
<th>My sleep quality was..................</th>
<th>Very poor</th>
<th>Poor</th>
<th>Fair</th>
<th>Good</th>
<th>Very good</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sleep111</th>
<th>My sleep was refreshing................</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sleep120</th>
<th>I had a problem with my sleep...........</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sleep144</th>
<th>I had difficulty falling asleep..........</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>
Fatigue – Short Form 4a

Please respond to each question or statement by marking one box per row.

<table>
<thead>
<tr>
<th>During the past 7 days...</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>FT07</td>
<td></td>
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<tr>
<td>I feel fatigued</td>
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<td>FT08</td>
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<tr>
<td>I have trouble starting things because I am tired</td>
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<tr>
<td>In the past 7 days...</td>
<td></td>
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<tr>
<td>FTA020</td>
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<tr>
<td>How run-down did you feel on average? ...</td>
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<tr>
<td>FTA020</td>
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<tr>
<td>How fatigued were you on average?........</td>
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</table>
PROMIS Item Bank v1.0 – Emotional Distress-Depression – Short Form 4a

**Emotional Distress-Depression – Short Form 4a**

Please respond to each question or statement by marking one box per row.

<table>
<thead>
<tr>
<th>In the past 7 days...</th>
<th>Never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Often</th>
<th>Always</th>
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</table>

*Note.* The Job Content Questionnaire was not included here as reproduction of this tool was expressly forbidden as part of the user’s agreement.