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Although rates of morbidity and mortality from cardiovascular disease have improved over the past decades, racial disparities in cardiovascular disease risk have persisted for ethnic and racial minorities. Research seeking to explain these disparities has largely focused on traditional risk factors such as obesity, hypertension, diet, and physical activity. However, a large body of literature has evidenced the psychological and social implications of race on cardiovascular risk.

The weathering hypothesis posits that stress associated with racial inequities, racism, and discrimination may cause physiological deterioration among African Americans as early as young adulthood, thus contributing to cardiovascular disease disparities. Allostatic load is widely accepted as a quantitative metric used to study the consequences of weathering. This metric provides researchers with the ability to measure both the acute and long-term outcomes of the stress response. Measurement of allostatic load is based on a set of biomarkers that represent the current status of each physiological system that responds to stress (e.g. hypothalamic-pituitary-adrenal (HPA) axis, cardiovascular system, metabolic processes and the immune system). An algorithm is then used to compute allostatic load by demarcating clinical cut points to dichotomize continuous biological measurement into binary high risk variables (0 = low, 1 = high). This value is then summed to yield an allostatic load score which determines the presence of allostatic load. There are three important limitations to this approach. First, clinical

cut points may not capture the full extent of biological risk. Second, categorizing otherwise continuous data results in loss of valuable information captured by the variables used to calculate allostatic load. Third, it is improbable that each biomarker equally contributes to the calculation of an allostatic score.

The purpose of this study was to expand the weathering hypothesis by developing cardiovascular risk profiles using latent profile analyses on biomarkers commonly used in allostatic load calculations as an alternative to the traditional algorithm.. In addition, this study examined the relationship between demographic variables (race, age, sex, SES), psychosocial factors (depression, social support) and membership in cardiovascular disease risk profiles. Initial analysis using a national sample of a population age 3 to 85 identified four profile groups; low overall risk, kidney risk, vascular risk, and inflammation risk. Compared to Whites, Hispanics were more likely to exhibit an inflammation risk profile while African Americans were more likely to exhibit both inflammatory and vascular risk profiles. In addition, age, sex, and poverty to income ratio were significant predictors of all risk profiles. When focusing on depression and social support in a sample of individuals 40 years and older, analysis identified two profile groups; a low overall risk profile and an inflammation risk profile. Compared to Whites, African Americans were more likely to be members of the inflammatory risk profile. Further, an increase in depression score significantly increased the odds of an inflammatory risk profile membership. Moreover, the relationship between inflammation risk profile membership and social support (emotional, financial, social network) was examined in which no significant relationship was found. However, analysis revealed that

the relationship between depression and inflammatory risk was moderated by emotional support, such that having received emotional support significantly decreased the association between depression and inflammatory risk.

Findings from this study suggests that examining cardiovascular risk profiles that account for age, race, sex, and socioeconomic status may be useful for extending the weathering hypothesis and identifying different patterns of risk among those who experience allostatic load. Further understanding of the racial differences in depression and inflammatory risk may be beneficial in eliminating disparities in cardiovascular disease. Results from this project indicate that a higher level of emotional support may be promising strategy to reduce cardiovascular risk.

THE ASSOCIATIONS AMONG DEPRESSION, SOCIAL SUPPORT AND

RACIAL/ETHNIC DISPARITIES IN CARDIOVASCULAR RISK

PROFILE MEMBERSHIP IN THE NATIONAL HEALTH

AND NUTRITIONAL EXAMINATION SURVEY:

A LATENT PROFILE ANALYSIS

by

Amber Jamill Johnson

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Approved by

_____
Committee Chair

To my friends and family. I could not have come this far without the strength of my

support system. Your support is the only reason why I am able to accomplish the goals I

once believed were unobtainable. To my father. With this dissertation, I hope to continue

your legacy. To my daughter "Abri". You have been there with me every step of the

way. It is my hope that I will serve as an example of strength, perseverance, and

dedication.

This dissertation written by Amber Jamill Johnson has been approved by the following committee of the Faculty of The Graduate School at The University of North Carolina at Greensboro.

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CHAPTER I

INTRODUCTION

Statement of Problem

Of all racial and ethnic groups, African American have the highest mortality rates in coronary artery disease, hypertension, stroke, and congestive heart failure (Go et al., 2014). Though overall rates of cardiovascular disease (CVD) have decreased in the United States, CVD disparities among African Americans have remained. Understanding differential cardiovascular risk factors between African Americans and their counterparts may provide insights into persistent CVD disparities. Current research suggests broadening risk identification from traditional risk factors (i.e. lifestyle, and genetics) to risk factors associated with stress.

The weathering hypothesis which has to date focused solely on race related stress may also be employed to explain how disproportional rates of depression among minorities account for some CVD disparities. This hypothesis proposes that chronic stress over the lifespan accelerates biological weathering among minorities (Geronimus, 2000; Geronimus & Thompson, 2004). The weathering hypothesis posits that stress associated with racial inequities may cause health deterioration among African Americans as early as young adulthood, leading to racial disparities in health outcomes over the life span. African Americans often report stress associated with perceived racism and

discrimination which has been shown to contribute to depressive symptomology (Banks & Kohn-Wood, 2007; Flores et al., 2008).

African Americans can experience racism and discrimination on multiple levels, including interpersonal (discriminatory interactions between individuals), institutional (discrimination in employment, housing, or health care), and cultural (widespread acceptance of stereotypes) (Harrell, 2000; Jones, 2000; Krieger, 1999).   Racism also increases the likelihood of objective stress from stressors such as job insecurity and financial strain that can promote depressive symptomology (Arrow, 1998; Pager & Shepherd, 2008; Mezuk, Rafferty, et al., 2010). Sellers and colleagues (2006) found the racial discrimination reduced psychological well-being, while increasing depressive symptoms and perceived stress (Sellers, Copeland-Linder, Martin, & Lewis, 2006). Further, racism has been shown to facilitate depressive symptoms by threatening self-esteem, invoking sense of hopelessness, and normalizing failure (Clark, Anderson, Clark, & Williams, 1999).

Evidence suggests there is a complex and bidirectional relationship between cardiovascular disease and depression (Lippi, Montagnana, Favaloro, & Franchini, 2009). Cardiovascular disease has been shown to contribute to the onset of depressive symptoms.   One out of every five patients with cardiovascular disease will report a major depressive disorder (Thombs et al., 2006). Moreover, a growing body of literature provides evidence that depression increases the risk of cardiovascular disease. Researchers have found that an increase a depressive symptomology predicts incidence of coronary artery disease, coronary heart disease, myocardial infarction (Barefoot &

Schroll, 1996; Charlson, Stapelberg, Baxter, & Whiteford, 2011; Ferketich, Schwartzbaum, Frid, & Moeschberger, 2000; Keyes, 2004; Van der Kooy et al., 2007). Further, depression has also been shown to worsen cardiovascular disease prognosis and increase overall mortality from cardiovascular disease (Barth, Schumacher, & Herrmann-Lingen, 2004; Ferketich et al., 2000; Frasure-Smith et al., 2000, 2000; Lett et al., 2004; Van Melle et al., 2004). Thus, the nature of the relationship between depression and cardiovascular disease is unclear and the mechanism for the complex interplay between depression and cardiovascular diseases remains unexplained.

Depression, particularly chronic depression, represents a persistent stress state which may erode the physiological systems that adapt to stress (McEwen, 1998; McEwen, 2003; Juster et al., 2011; Kobrosly, van Wijngaarden, Seplaki, Cory-Slechta, & Moynihan, 2014). Allostasis, the process of stress adaptation, activates the sympathetic nervous, hypothalamic-pituitary-adrenal axis (HPA) and the immune systems. Allostatic load is the consequence of chronic allostasis activation. In an allostatic load state, the physiological stress response becomes impaired, reducing the ability to functionally adapt to future stressors (Seplaki, Goldman, Weinstein, & Lin, 2004).

Research has documented a relationship between allostatic load and CVD (Geronimus, 1996; B. McEwen, 1998; Merkin, Karlamangla, Diez Roux, Shrager, & Seeman, 2014; Merkin et al., 2014; Seeman, Singer, Rowe, Horwitz, & McEwen, 1997; M. G. Taylor, 2008). Moreover, depression has been shown to alter a number of biological mechanisms, including autonomic nervous system function, HPA axis function, inflammations and insulin resistance (Joynt, Whellan, & O'Connor, 2003;

Kiecolt-Glaser & Glaser, 2002; Lett et al., 2004; B. S. McEwen, 2003; Miller, Stetler, Carney, Freedland, & Banks, 2002; C. B. Taylor, 2010; Thayer, Yamamoto, & Brosschot, 2010; Vrany, Berntson, Khambaty, & Stewart, 2015). Therefore, depression may increase cardiovascular disease risk in racial/ethnic minorities by accelerating the development of allostatic load.

The presence of social support has been shown to decrease cardiovascular disease risk and mortality (Berkman, Leo-Summers, & Horwitz, 1992; Cohen & Wills, 1985; Frasure-Smith et al., 2000; Treiber et al., 2003). Two main hypothesis that have sought to explain this relationship. First, it is hypothesized that social support may exhibit independent effects on cardiovascular risk (House, Umberson, & Landis, 1988). For example, social support may decrease cardiovascular risk by facilitating healthy behaviors such as exercise, healthy eating, and adherence to medical treatment (DiMatteo, 2004; Franks, Campbell, & Shields, 1992; Lewis & Rook, 1999; Uebelacker et al., 2013) Secondly, social support may buffer the relationship between depression and cardiovascular risk (Cohen & Wills, 1985; George, Blazer, Hughes, & Fowler, 1989). Higher family support has also been shown to lower the association between depression symptoms and stressors such as racial discrimination (Brody et al., 2006; Noh & Kaspar, 2003; Uebelacker et al., 2013; Wei, Heppner, Ku, & Liao, 2010). Moreover, the absence of support has been associated with the onset of depression both independently and through modifying perceptions of negative life events (Paykel, 1994).

Allostatic load is widely accepted as a quantitative metric used to study the consequences of weathering, giving researchers the ability to measure both the acute and

long-term outcomes of the stress response. Measurement of allostatic load is based on a set of biomarkers that represent the current status of each physiological system that responds to stress (e.g. hypothalamic-pituitary-adrenal (HPA) axis, cardiovascular system, metabolic processes and the immune system). An algorithm then computes allostatic load by demarcating clinical cut points to dichotomize continuous biological measurement into binary variables (0 = low risk, 1 = high risk). These values are then summed to yield an allostatic load score which determines the presence/absence of allostatic load. There are three important limitations to this approach. First, clinical cut points may not capture the full extent biological risk. Secondly, categorizing otherwise continuous data results in loss of valuable information captured by the variables used to calculate allostatic load. Third, it is improbable that each biomarker equally contributes to the calculation of an allostatic score. Therefore this study sought to achieve the following aims and address the subsequent hypotheses.

Specific Aims and Hypotheses

Aim #1

Apply Latent Profile Analyses (LPA) to continuous level biomarkers in the National Health and Nutritional Examination Survey (NHANES) data to segment the participants into a set of qualitatively distinct biological risk profile subgroups.

Hypothesis 1a

Prior research using two-step cluster analysis on similar biomarkers in NHANES data yielded four biological risk profiles for Vascular Risk, Kidney Risk, Inflammatory

Risk, Cholesterol Risk, and Low Overall Risk (Johnson et. al., 2005). It is hypothesized that LPA will identify at least five profiles associated with cardiovascular risk.

Hypothesis 1b

According to the weathering hypothesis, African Americans experience symptoms of biological weathering beginning in their 20s. However, there is no work to date which has looked at the impact of age on cardiovascular risk profiles. Thus in this exploratory hypothesis we anticipate that an increase in age will be associated with membership in higher risk profiles.

Hypothesis 1c

Cardiovascular risk has been shown to differ by sex. For example, African American men have been shown to have higher risk of kidney failure whereas African American women display higher risk of hypertension. Therefore it is hypothesized that males will more likely have membership in kidney risk profiles while females will hold membership in vascular risk profiles.

Aim #2

Expand upon the model in Aim 1 to examine the association between depression, social support and risk profile membership.

Hypothesis 2a

Evidence suggests a positive association exists between the severity of depressive symptomology and risk of cardiovascular disease, such that those with higher depression

scores are more likely to experience a cardiovascular event. Therefore, it is hypothesized that increased depression scores will be associated with membership in high risk profiles.

Hypothesis 2b

Prior research finds that social support may independently lower the risk cardiovascular disease. Social support has been shown to reduce cardiovascular reactivity to stress. As such, it is hypothesized that social support will increase the probability of membership in a low risk profile.

Hypothesis 2c

Social support has been shown to buffer the effects of stress, resulting in reduced cardiovascular risk. This suggest that social support may moderate the relationship between stress and cardiovascular disease risk. Therefore, it is hypothesized that social support will moderate the relationship between depression and cardiovascular risk by reducing the odds of higher risk profiles.

Figure 1. Overall Study Conceptual Framework
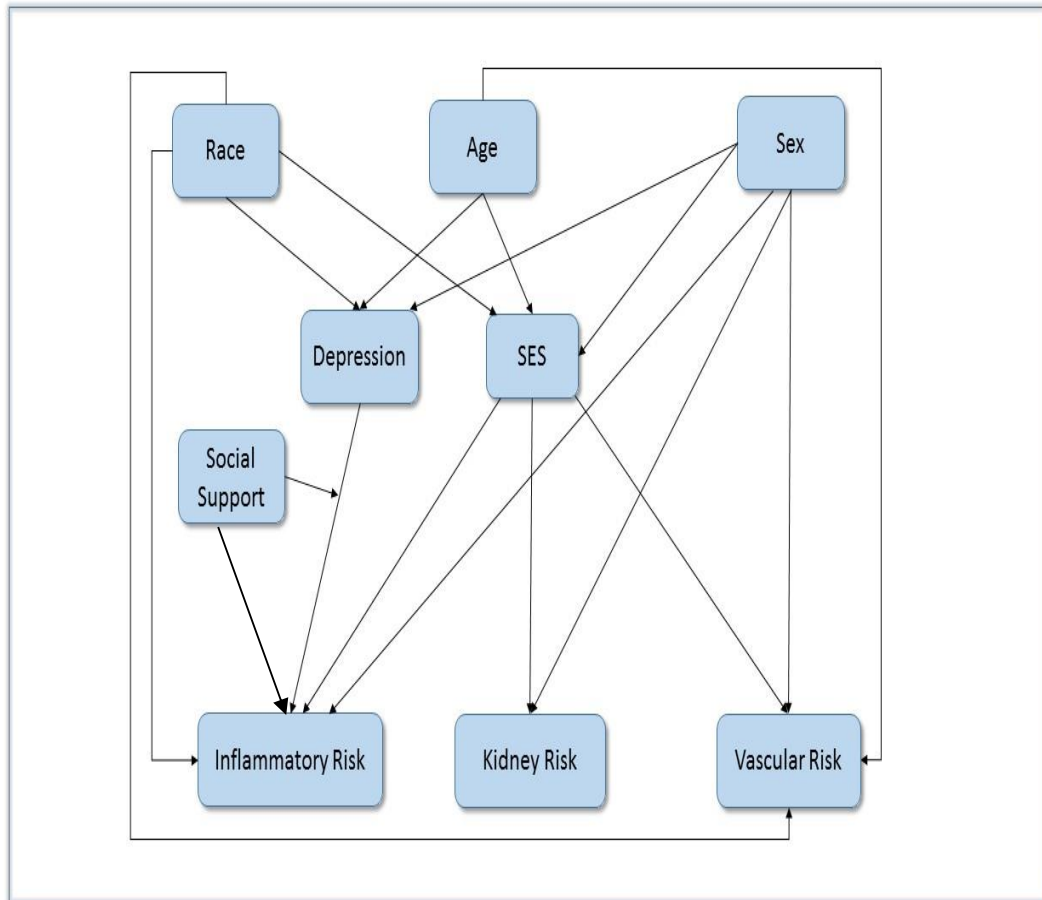
CHAPTER II

REVIEW OF THE LITERATURE

Introduction to Cardiovascular Disease Epidemiology

Cardiovascular Disease (CVD) is the leading cause of death in the United States (CDC, 2013). Though cardiovascular diseases encompasses more specific diagnoses, there are 5 major diagnoses that are discussed. Myocardial infarction, heart failure, coronary artery disease, stroke, and high blood pressure are prominent measures of CVD outcomes. Therefore, this literature review focuses on these five diagnoses as the frame for my discussion on racial/ethnic disparities in cardiovascular disease. Further, this review discusses racial/ethnic differences in traditional cardiovascular risk factors (e.g., lifestyle and genetics) as well as cardiovascular risk associated with endocrine and metabolic disorders. Lastly, I will provide a rationale for the use of the weathering hypothesis in accounting for the impact of psychosocial factors such as depression and social support on cardiovascular risk.

Epidemiologic data in my discussion has been collected from numerous state and national databases in addition to epidemiologic research studies. The data presented focus primarily on racial ethnic differences in incidence, prevalence, all-cause mortality, age-specific mortality, and age adjusted mortality. I chose these measures of racial/ethnic difference in health indicators and outcomes based on the data available from these data sources. However, there is a need to discuss the methodological limitations of data

collected for analysis as these sources may not accurately depict the extent of CVD disparities.

One important limitation is revealed when epidemiologic data does not account for the various age distributions within the different racial and ethnic groups. Age-adjusted rates are the weighted average of age-specific rates in which the weights are determined by an age standard. In most cases, the age standard is the population distribution identified by United States Census.   However, racial/ethnic populations differ by age structure with Whites having an older median age than all racial and ethnic minorities. Therefore, age-adjusted rates are indices for comparison but cannot be risk measures (NCHS, 2004). Use of age-specific data, as compared to age-adjusted, represents different patterning of death rates. For example, the all-cause age-adjusted death rate for African Americans is about 30% higher than that of Whites. However, age-specific rates show that all-cause mortality for African Americans are about 75% higher than Whites (Thomson, Mitchell & Williams, 2006).

Further, issues of external validity may arise when data does not account for intraethnic variation among subgroups. Certain ethnic minorities such as Hispanics and Asian/Pacific Islanders may be grouped into large ethnic categories. For example, Hispanics report higher incidence rates of CVD risk factors but exhibit lower rates of overall CVD (Mensah, 2005; Mitchell et. al., 1990; Liao et. al., 1997). Highest prevalence of hypertension and hypertension-related death rates were seen among Puerto Rican Americans compared to all Hispanic subgroups. Hypertension-related death rates were lowest among Cuban Americans. Mexican Americans exhibited a higher

prevalence of hypertension and prehypertension compared to Whites. Analysis of

Hispanic subgroups is needed to understand the CVD risk factors among Hispanics and

other ethnic groups. Ignoring intraethnic variation among subgroups misses the

opportunity to distinguish CVD risk within racial/ethnic groups.

Frequently, mortality data is presented as all-cause versus cause-specific. Racial

differences may go unrecognized based on presentation of epidemiologic data as all-

cause or cause-specific. One example of this is demonstrated by data that shows

Hispanics as having a lower all-cause mortality rate than Whites but a higher cause

specific mortality rates (Thomson, Mitchell, & Williams, 2006). Many CVD

epidemiologic studies, many which are used in this paper, do not differentiate between

all-cause mortality and cause-specific mortality rates. This c to incorrect inferences about

CVD disparities among certain study populations. Research suggest that, when available,

use of age-specific and cause-specific rates provides a more accurate depiction of

differential health statuses between groups (NCHS).

Cardiovascular Disease and Outcomes

Myocardial Infarction

Each year 735,000 people experience a myocardial infarction (MI) in the United

States.   Of these cases, 525,000 will suffer their first MI while 210,000 will be diagnosed

with a recurrent MI.   (Mozaffarian et al., 2015). In 2013, MI was the cause of death for

6,456 African American males compared to 6,004 African American females. Among

women age 20 and older 1.8% of Whites have had an MI which is comparable to the

Hispanic rate (1.7%). However, this rate is elevated among African American women at

2.2%. MI incidence rates among African American (3.4%) and Hispanic men (3.5%) were comparable to one another but higher than rates of women.

Coronary Heart Disease

Coronary Heart Disease (CHD) is the leading underlying cause of MI. Approximately 370,000 people die each year from CHD (Mozaffarian et. al, 2015). In 2011, CHD affected 15.5 million people over the age of 20 accounting for 6.2% of the population. Overall CHD prevalence differs by gender. CHD prevalence among men was 7.6% compared to 5.0% for women (Newman et. al., 2013). Prevalence is highest among White men (7.8%) but slightly lower for African American men (7.2%). CHD prevalence among Hispanic men is 6.7%. Among females, CHD prevalence was highest among African American women (7.0%). CHD prevalence lowers to 5.9% for Hispanic women and 4.6% for White women (Newman et. al., 2013)

CHD has an overall death rate of 109.2 per 100,000 causing 1 in 7 of all deaths in 2011 (NHLBI, 2014). African American men had the highest CHD death rate. The death rate per 100,000 for African American males was 161.5 compared to 146.5 for White males. The death rate per 100,000 was higher for African American women (99.7) compared to White females (80.1) (NHLBI, 2014). Incidence of fatal CHD has decreased between 1987 and 2011. Fatal CHD decreased the most for White men (5%). CHD deaths decreased similarly for White (3.9%) and African American women (3.4). However, fatal CHD was reduced by only 2.2% for African American men.

Though White men have a slightly higher prevalence of CHD than African Americans as a racial group, there are stark differences in CHD mortality. A study

conducted by Gebreab and Diez Roux (2012) sought to explain disparities in CHD

mortality rates by examining spatial heterogeneity of African American and White

differences in CHD mortality and the contributions of poverty and segregation. The

authors found that African American and White differences in CHD was significantly

related to spatial heterogeneity when controlling for poverty and segregation. However,

when accounting for race-specific poverty and segregation, heterogeneity no longer

predicted differential mortality rates. This suggest that though African American and

White men may be similarly affected by CHD, issues associated with high density

poverty areas for African Americans (i.e. lack of resources, quality of care) could be

driving CHD mortality disparities.

Heart Failure

There were approximately 870,000 new cases of Heart failure each year from

2005-2011 (Mozaffarian, 2015). Heart failure is more frequently seen in women and the

elderly (Goldberg, Spencer, Farmer, Meyer, & Pezzella, 2005). After age 40, 1 in 5 men

and women will developed Heart failure (Lloyd-Jones et al., 2010). Research conducted

by the Coronary Artery Risk Study in Young Adults (CARDIA) found that heart failure

before age 50 years is more common among African Americans (Ovbiagele et al., 2013)

According to Atherosclerosis Risk in Communities (ARIC) study, the age-adjusted

incidence rate per 1000 person-years was highest among African American men (9.1).

This was followed by African American women (8.1), White men (6.0) and White

women (3.4).

In 2011, heart failure was the underlying cause of 58,309 deaths with an overall any-mention death rate for Heart Failure of 83.0 (NCHS, 2011). In the Multi-Ethnic Study of Atherosclerosis (MESA) study, African Americans held the greatest risk of heart failure of 4.6 per 1000 person-years. This was followed by Hispanic (3.5), White (2.4) and American Indian/Alaska Native (1.0) (Bahrami, 2008). Any mention death rates were similar among White and African American men with 98.5 and 98.6 respectively. The death rate per 100,000 was smaller for American Indians or Alaska natives (73.2) and Asians or Pacific Islanders (44.1). The death rate per 100,000 was similar for African American women (77.4) and White women (73.6). Among American Indians/Alaska Natives women, the death rate was 61.9 per 100,000 compared to 33.9 per 100, 000 Asian/Pacific Islanders women (Mozaffarian et al., 2015).

Stroke

Approximately, 795,000 people in the US suffer from a new or recurrent stroke. Approximately, 610,000 are first onset strokes while 185, 000 are recurrent strokes (NHLBI, 2011). In 2010, 2.7% of men and 2.7% of women aged 18 or older have a history of stroke. This number is almost doubled for African Americans (4%). This is followed by non-Hispanic Whites of 2.5%, 2.3% of Hispanics, and 1.3% of Asian/Pacific Islander (Kleindorfer, 2010).

By 2030, 3.4 million people over 18 years of age or older will have a stroke increasing the prevalence to 20.5% from the year 2012. The highest projected increase in stroke prevalence is expected to increase by 29% among Hispanic men (Ovbiagele, 2013). Compared to data in 1990, stroke incidence in 2005 decreased for Whites but not

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for African Americans. Stroke incidence among Whites was primarily driven by decline in ischemic strokes in this population. There were no changes in ischemic stroke or hemorrhagic strokes for African Americans (Kleindorfer, 2010).

Non-traditional risk factors may play a role in excess stroke risk leading to the largest projected increase in stroke prevalence among Hispanic men. For example, Hispanics have lower health literacy, concerns for side effect medication, burden of filling prescriptions, a perceived racial bias from healthcare system which may influence receipt and compliant of treatment for traditional risk factors (Cruz-Flores et al., 2011). Cruz-Flores and colleagues (2011) also noted lower socioeconomic status (SES), limited healthcare access and use, and inadequate community resources among Hispanics may help to explain Hispanics increasing risk of stroke.

Hypertension

Approximately 33% of US adults age 20 and older have been diagnosed with hypertension from 2009-2012. African American adults have the highest prevalence of hypertension. Age-adjusted prevalence of hypertension among African American men and women during this time period was 44.9% and 46.1% respectively. Prevalence was lowest among those 18 to 39 years of age (7.3%) followed by those 40 to 59 years of age (32.4%). The highest prevalence was seen in people over 60 (32.4%) (Nwankwo, Yoon, Burt, & Gu, 2013). More men than women have hypertension before age 45. However, among those aged 45-64, the percentage of men and women with hypertension is comparable. However, for those age 65 and older, the percentage of women with hypertension are higher than men (Nwankwo et al., 2013).

Overall the hypertension mortality rate was 110.0 per 100,000. From 2001-2011 the mortality rate attributed to hypertension increased 13.2% (NCHS, 2011). African American males had the highest mortality rate of 212.8 per 100,000 compared to 114.5 per 100,000 for White males. Among African American females, rates were 157.9 per 100,000 compares to rates of 92.00 per 100,000 for White females (Murphy, Xu, Kochanek, & others, 2013). The age-standardized mortality rate per 100,000 among Hispanic females was 118.3 compared to Hispanic men (135.9) (CDC, 2013).

Among all CVD's, hypertension seems to be a major precursor of other CVDs. The highest prevalence in risk factors for African Americans seem to by hypertension and diabetes (Gillum, 1999; Kittner, White, Losonczy, Wolf, & Hebel, 1990; Kleindorfer et al., 2009). For example, among those who experience their first stroke, blood pressure was found to be above 140/90 while 75% of heart failure patients have hypertension (Kissela et al., 2012). African American adults have the highest incidence of hypertension in the US (Mensah, Mokdad, Ford, Greenlund, & Croft, 2005). Higher systolic blood pressure accounts for approximately 50% of the excess risk for African Americans compared to Whites (Kleindorfer et al., 2009). There are racial differences in levels of systolic blood pressure. For every 10 mm Hg increase in systolic blood pressure, stroke risk increased among White approximately 8%. However, African Americans experience, a 24% increased risk of stroke with each increase of 10 mm Hg (Howard et al., 2013). African Americans and Mexican Americans have higher blood pressure but have been shown to have lower blood pressure control in the US (Redmond, Baer, & Hicks, 2011).

Cardiovascular Disease Risk Factors

Lifestyle Factors

Evidence points towards racial differences in life style risk factors as potential contributor to CVD disparities. Risk factors for CVD seem to have a larger impact on minorities than for Whites (Howard et al., 2013). Poor diet quality has been attributed to 678,000 annual deaths of all- causes in US. Fruit and vegetable consumption is lowest among African Americans with an average range of 2%-6% meeting the 2 cup requirement for both fruits and vegetables. Among Whites this range was 9-12% and among Hispanics 4%-11%.

In the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, participants who reported physical activity less than 4 times a week demonstrated a 20% increase risk of stroke compared to those who exercised over 4 times a week (McDonnell et. al, 2013). According to the 2013 National Health Interview Survey, women were less likely to meet the guidelines of at least 150 minutes of moderate physical activity or 75 minutes of vigorous physical activity per week. African Americans and Hispanics were also less likely to be physical active. 41.4% of African Americans and 42.9% of Hispanics met the aerobic activity guidelines, compared to 53.4% of Whites (NCHS, 2013). Lowest fitness (physical activity and nutrition) levels have been seen among African Americans (Kurian & Cardarelli, 2007; Carnethon, Gulati, & Greenland, 2005).

Overweight and Obesity

Low fitness levels have been associated with overweight and obesity (Blair & Church, 2004). Overweight and obesity was a risk factor for CVD for all ages, sexes, and racial and ethnic groups (Kurian & Cardarelli, 2007; Roger et. al., 2011). Overall, 69% of US adults were overweight or obese. For men, Hispanics (80%) and Whites (73%) were more likely to be overweight or obese compared to African American men (69%). For women, African Americans (82%) and Hispanics (76%) were more likely to be overweight or obese compared to Whites (61%) (Mozaffarian, 2015). Further, data from the Framingham Heart study indicates that obesity (BMI greater than 30 kg/m) has been driving rapid increases of diabetes diagnoses within the last 30 years (Fox et. al, 2006).

Diabetes

Diabetes increases the incidence of stroke for all ages. Patients diagnosed with stroke and diabetes are more likely to be African American. However, the risk of stroke is the most prominent before age 65 among both African American and White patients (Khoury et. al., 2013). The prevalence of total diabetes in 2013 among African Americans (15.4%) is twice that of Whites (8.6%) but only slightly higher than Mexican Americans (15.2%) (Selvin, 2014). The prevalence of diabetes is expected to increase by 127% among Hispanics, 107% among African Americans, and 99% among Whites. The largest increase is projected among African Americans over 75 years old (606%) (Narayan, 2006).

Metabolic Syndrome

Metabolic syndrome is a group of lifestyle related cardiometabolic risk factors associated with obesity and insulin resistance.   Metabolic syndrome has been linked to left ventricular dysfunction, even when controlling for blood pressure (Ingelsson, et. al., 2006). Metabolic syndrome is diagnosed when individuals exhibit 3 of 5 risk factors: Fasting plasma glucose over 100 mg/dL or prescription for elevated glucose; HDL cholesterol less than 40 mg/dL for men and less than 50 mg/dL in women, waist circumference over 102 cm for men and more than 88 cm for women, and blood pressure over 130/85 mmHg diastolic or on medication for elevated blood pressure (Alberti et. al., 2009).

Overall, the age-adjusted prevalence of metabolic syndrome has decreased for women but remained stable for men. In 2000, age-adjusted prevalence was 27.50% of women and 23.35% of men. In 2010, the age adjusted prevalence was 23.69 for men and 21.80% for women (Beltrán-Sánchez, 2013). Reduced metabolic syndrome has been observed primarily among Whites but has remained stable for both African Americans and Mexican Americans. The age adjusted prevalence for metabolic syndrome in 2010 was highest among Hispanic men (34.76) compared to White men (21.77) and African American men (18.99). Research shows that metabolic syndrome and insulin resistance are significant risk factors for heart failure among Hispanics in US. Compared to all other racial/ethnic groups, Mexican Americans have the highest age-adjusted prevalence of metabolic syndrome (Ford, Giles, & Dietz, 2002).

Genetics

Genetic factors associated with heart disease are complex. The link between specific genetic pathways are not well of established past that of establishing family history (Holmes et. al., 2011). Among adults over 20 years of age, approximately 12% have reported a parent or sibling diagnosed with angina or a myocardial infarction before age 50 from 2009-2012 (Mozaffarian, 2015). Stratified by race and ethnicity, 11.5% of White men and 14.6 of White women reported having a parent or sibling diagnosed with angina or myocardial infarction. This was followed by 9.1% of African American men and 12.3% of African American women as well as 7.6% of Hispanic men and 10.1% for Hispanic women (10.1%). Paternal history of myocardial infarction before age 50 has been found to increase risk approximately 50% among women and 70% among men (Lloyd-Jones, 2004). Sibling history of CVD was found to increase the odds of CVD approximately 45% when controlling for other CVD risk factors (Murabito, 2005).

Depression

Depression and cardiovascular disease are the two of the most common causes of disability across the world (Murray & Lopez, 2013). Evidence suggests there is a complex and bidirectional relationship between cardiovascular disease and depression (Lippi et al., 2009). One out of every five patients with cardiovascular disease will experience a major depressive disorder (Thombs et al., 2006). Depression not only worsens cardiovascular disease prognosis but it increases overall mortality from cardiovascular disease (Barth et al., 2004; Ferketich et al., 2000; Frasure-Smith et al.,

2000, 2000; Lett et al., 2004; Van Melle et al., 2004). Yet, the pathway for the complex interplay between depression and cardiovascular disease remains unexplained.

Increasing evidence suggests that depression may serve as an antecedent for a number of cardiovascular diseases including coronary artery disease, coronary heart disease, myocardial infarction (Barefoot & Schroll, 1996; Charlson et al., 2011; Ferketich et al., 2000; Keyes, 2004; Van der Kooy et al., 2007). Psychosocial factors have been shown to increase the risk of cardiovascular disease more so than traditional risk factors (e.g. hypertension, diet, exercise) (Joynt et al., 2003; Kim & Setias, 2016; Lett et al., 2004). A study conducted by Yusuf and colleagues (2004) found that psychosocial factors such as perceived stress, negative life events, and depression were stronger risk factors for cardiovascular disease than diabetes, smoking, hypertension, and obesity. On the premise of this study and other studies examining the global burden of cardiovascular disease, the 2010 Global Burden of Disease study recognized depression as a recognized risk factor for coronary heart disease (Charlson et al., 2011). A positive association has been observed between the severity of depressive symptomology and the odds of cardiovascular disease (Barefoot & Schroll, 1996; Charlson et al., 2011). This relationship may be additive in nature as existing literature finds that traditional cardiovascular risk factors may strengthen the association between depression and cardiovascular disease risk (Rugulies, 2002).

National data suggests that the rate of depression diagnosis is increasing across all races and ethnicities. A study examining data from the National Ambulatory Medical Care Survey from 1992-1993 to 2003-2004 found depression diagnoses rose from 4.8 to

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7.0 per 100 for Hispanics, 4.2 to 7.6 for African Americans and 10.9 to 15.4 for whites (Sclar, Robison, & Skaer, 2008). Although Whites exhibit higher depression diagnosis, the burden of depression is higher among minorities. In a national epidemiological study of mental health and service usage, 63.7% of Latinos and 58.8% of African Americans lacked access to mental health treatment compared to 40.2% of Whites (Alegría et al., 2015; Williams et al., 2007). Further, African-Americans have been shown to have the highest rate of severe depressive symptoms and suffer with depression over a longer period of time (Pratt & Brody, 2014; Williams et al., 2007). These findings suggests minorities often have an increased burden of severe depressive symptoms disability even though Whites have a higher prevalence of depression.

Disparities in depression diagnoses are apparent early in the lifespan as evidence suggests that racial/ethnic minority adolescents have higher rates of depressive symptoms and limited access to treatment. In a study comparing white and Hispanic youth, Whites (36%) were significantly more likely than Hispanics (27%) to receive adequate mental health (Alexandre, Martins, & Richard, 2009). Further, Cummings and colleagues used data from the National Survey on Drug Use and Health to examine racial/ethnic differences in mental health services for White, African American, Hispanic, and Asian adolescents. Results of the study showed that when accounting for family income and insurance status, African American, Hispanic, and Asian adolescents were significantly less likely than Whites to receive prescription medication for depression, receive treatment from a health care provider, or receive outpatient mental health treatment (Cummings & Druss, 2011).

Social Support

The presence of social support has been shown to decrease cardiovascular disease risk and mortality (Berkman et al., 1992; S. Cohen & Wills, 1985; Frasure-Smith et al., 2000; Treiber et al., 2003). Two main hypothesis have sought to explain this relationship. First, it is hypothesized that social support may exhibit independent effects on cardiovascular risk (House et al., 1988). For example, social support may decrease cardiovascular risk by facilitating healthy behaviors such as exercise, healthy eating, and adherence to medical treatment (DiMatteo, 2004; Franks et al., 1992; Lewis & Rook, 1999; Uebelacker et al., 2013)   Secondly, social support may buffer the relationship between of depression and cardiovascular risk (S. Cohen & Wills, 1985; George et al., 1989). Higher family support has also been shown to lower the association between depression symptoms and stressors such as racial discrimination (Brody et al., 2006; Noh & Kaspar, 2003; Uebelacker et al., 2013; Wei et al., 2010).   Moreover, the absence of support has been associated with the onset of depression both independently and through modifying perceptions of negative life events (Paykel, 1994).

Weathering Hypothesis

Though the risk factors discussed above contribute to CVD disparities, they do not fully account for racial disparities in CVD outcomes. Over the past twenty years, research has been conducted on the impact of race based stressors on health (Krieger, 1990; Geronimus et. al., 2006; Mwendwa et al., 2011). Though this is not a new area of research, the need for further inquiry lies in the continual need to understand health outcomes beyond individual level factors (i.e., physical activity, nutrition).   This is

particularly true when attempting to understand the development and persistence in CVD disparities among minorities, particularly African Americans.

The weathering hypothesis, developed by Geronimus (2000), posits that stress associated with racial inequities may cause health deterioration among African Americans as early as young adulthood. The weathering hypotheses was developed in response to observed racial differences in health outcomes among young women that were exacerbated across age. More specifically, in a study of hypertension prevalence among women of childbearing age, African American and White differences in hypertension prevalence were unobserved among teenagers. However, by their mid-20's, African American women were twice as likely as White women to be hypertensive (Geronimus, 1991). Geronimus asserts that differential age pattern of health disadvantages among African Americans may represent the process of biological weathering (Geronimus, 1991; Geronimus, 2001).

The impact of broad economic, social, and structural inequities based on race have been shown to impact the health of Africans Americans more so than their White counterparts (Geronimus, 2004). The weathering hypothesis theorizes that minorities experience repeated exposure to subjective (discrimination) and objective stressors (job security, financial strain), resulting in increased engagement of chronic active coping. Active coping is defined as taking a problem focused action toward reducing stressful conditions (Carver & Scheier, 1994, James, 1994)). Geronimus asserts that chronic active coping with stressors such as discrimination can lead to physiological deterioration.

Allostatic Load

Active coping has been shown to have deleterious effects on health (James et. al., 1992; McEwen, 1998).Though there has not been a direct measure of weathering, researchers have used indices such as infant mortality, disability, and mortality that reveal an aging pattern among African Americans that is consistent with the premise of the weathering hypothesis (Geronimus, 2000; Geronimus et. al., 2001, Astone, Ensminger, & Juon, 2002). For example, Geronimus and colleagues examined telomere length among women in the Women's Health across the Nation (Swan). Telomeres are stabilizing caps on chromosomes that shorten during cell division resulting in cell aging or death. An inverse relationship between telomere length and age has been found (Benetos et al., 2001). The authors found that between the ages of 49-55, African American women were 7.5 years biologically older than White women (Geronimus et. al., 2010).

Though different indices have been used to examine the process of weathering, the most commonly used indicator of weathering is allostatic load (AL). When individuals experience acute and chronic stressors, physiological consequences occur from neglecting internal need (McEwen & Stellar, 1993). During the stress response, internal physiological needs are suppressed to combat external stressors. The major physiological systems that adapt to stress are the sympathetic nervous system, hypothalamic-pituitary-adrenal axis (HPA), metabolic system, and the immune system. These physiological systems are responsible for adapting to external stressors such as danger, hunger, or infection (McEwen, 1998). When individuals experiences acute and chronic stressors, physiological consequences occur resulting from neglected internal

need (McEwen & Stellar, 1993). This physiological consequence is considered allostatic load. As a result, physiological systems lose the ability to adapt to future stressors (Seplaki, Goldman, Weinstein, & Lin, 2004).

Measuring allostatic load requires assessment of biomarkers associated with each physiological system. There are four primary hormones that are released in response to stress; cortisol, noradrenalin, epinephrine, and dehydroepiandrosterone-sulfate (DHEA-S). These hormonal mediators influence the release of other physiological hormones in the body. For example, cortisol is a glucocorticoid that provides various effects on the body from energy metabolism to transporting immune cells (McEwen & Seeman, 1999). Most allostatic load calculations measure secondary outcomes associated with the effects of primary mediators. For example, waist to hip ratio and glycated hemoglobin reflects sustained levels of glucose and insulin resistance which portrays sustained levels of cortisol and sympathetic nervous system activity. Other indicators such as blood pressure and heart rate are indicators of overall cardiovascular activity. Allostatic load has been associated with increased risk of cardiovascular disease (Geronimus et al., 2006; McEwen & Seeman, 1999; Seeman et al., 1997). Compared to Whites, African American experience higher allostatic load scores earlier in life. Further evidence suggests that African American women experience allostatic load earlier in life. Chyu and Upchurch () found that African American women age 40-49 years of age had allostatic load scores 1.14 times higher than White women 50-59 years of age scores (Chyu & Upchurch, 2011). Higher allostatic load scores have been associated with a decline in physical and

cognitive functioning, cardiovascular disease incidence, and mortality (Geronimus et al., 2006; McEwen & Seeman, 1999; Seeman et al., 1997).

Weathering Hypothesis Examined

Geronimus used data available from the 2003-2006 National Health and Nutritional Examination Survey (NHANES) to conduct a population based study of weathering among African American and white women. She selected 10 biomarkers to include in her calculation of allostatic load; Systolic and diastolic blood pressures, body mass index (BMI), Glycated hemoglobin, albumin, creatinine clearance, triglycerides, C-reactive protein, homocysteine, and total cholesterol. Each biomarker was given a high risk threshold based on the distribution of the biomarker within the NHANES sample. For albumin and creatinine clearance, the high risk threshold was set at the measurement that represented the 25th percentile. For other biomarkers, measurements were set at the 75th percentile. Each biomarker with measurements beyond each threshold received a point with a maximum score of 10. Participants who were taking medication for diabetes, hypertension, and cholesterol was given a point for glycated hemoglobin, blood pressure, or total cholesterol if their respective biomarkers did not meet the high risk threshold. The high risk value for allostatic load score was 4. To test the weathering hypothesis, mean scores were calculated based on age categories (18–24, 25–34, 35–44, 45–54, and 55–64 years). Geronimus also subdivided African American and White samples by measures of socioeconomic status. Geronimus and colleagues found that allostatic scores for African Americans were significantly higher than Whites for each age category. African Americans had a higher probability of a high score (≥ 4) than

Whites at all ages. Also African American women had the greatest probability of a high allostatic load score.

Secondly, the estimated odds of African Americans 18-24 years old having a high allostatic score was 1.49 times higher than Whites.   For those aged 55-64, the odds of African Americans having an allostatic load score increased to 2.31 times that of Whites. By the time African American women were 45 years old, 50% of African American women had a high allostatic score. However, by 64 years old, more than 80% of African American women exhibited an allostatic high score. Fifty percent of white men and women reached allostatic load around 60 years old. Whites were not seen to reach levels much above 60%. For African American and white women, the odds were more pronounced. The estimated African American-White odds per age category was as followed: 35–44 years (2.24); 45–54 years (2.23), and 55–64 years (2.73). The relative odds of African American women between the ages of 55-64 having a high allostatic score was twice that of African American men.

Limitations of Approach

Geronimus' calculation of allostatic load requires dichotomizing continuous biological measurements into low and high risk categories. There are several limitations of categorizing continuous variables. Two major drawbacks are the use of clinical cut points that are not universally applicable (across sex, race and time) and loss of information (Altman et al., 1994, Royston et al., 2006). Geronimus' work suggests that African American women experience physiological deterioration earlier in life compared to White women. Therefore, a clinical cut point of 4 may be appropriate for White

populations but may not be the best indication of physiological breakdown among African American women. There may also be need for the age appropriate clinical cut points for African American women as the weathering hypothesis suggest African American woman age earlier than other populations.

Preliminary Cluster Analysis

Using data from the 2013-2014 National Health and Nutrition Examination Survey (NHANES), a cluster analysis was conducted using the following 8 biomarkers similar to the ones utilized in Geronimus' article: Triglyceride; C-reactive protein; Albumin, homocysteine; total cholesterol; HDL; LDL and Creatinine clearance (Johnson, 2015). A two-step cluster analysis was employed using the standardized Z-scores of each biomarker in order to provide standardization of biomarkers with various units of measure. Results of this 2-step cluster analysis yielded 5 distinct risk profiles (see Figure 2).

Cluster 1: Vascular Risk Profile

Cluster 1 exhibited elevated levels of homocysteine and albumin. Homocysteine is an amino acid within blood plasma. Albumin is a plasma protein, formed in the liver. Albumin constitutes approximately 6-8% of the protein concentration in the plasma. There is a relationship between homocysteine and albumin. Jagger and colleagues (2001) found that increases in homocysteine levels was associated with increase in albumin levels. Further, increases in albumin levels and homocysteine levels were associated with increase arteriosclerotic risk (Lee, et. al., 2006).

Figure 2. Preliminary Cluster Analysis
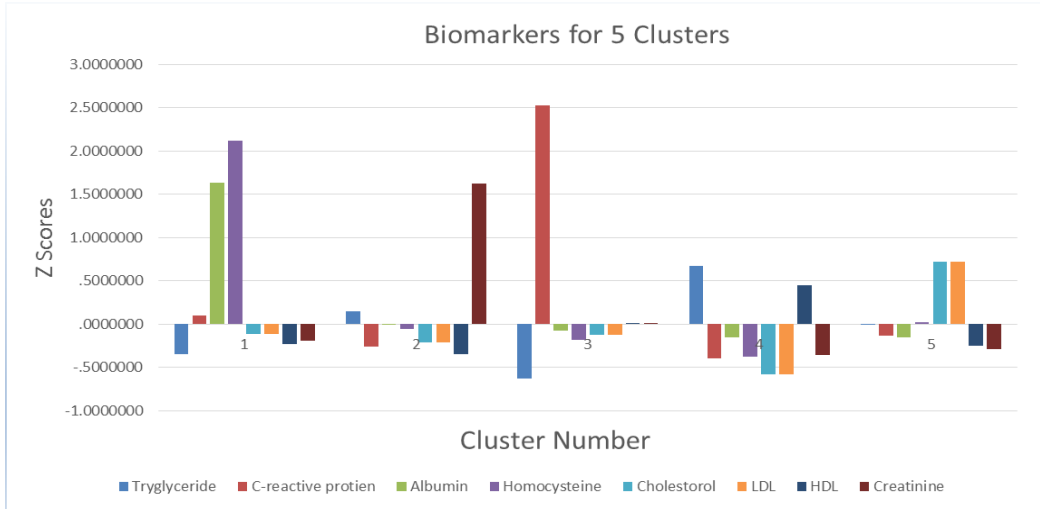
Cluster 2: Kidney Risk Profile

This profile consists of elevated levels of creatinine which is a key indicator of kidney functioning. Chronic kidney function is a major risk factor for all-cause mortality and cardiovascular disease. Chronic kidney disease in more pronounced in African American populations (Wiener et. al, 2004). Kidney disease also increases risk for hypertension and dyslipidemia. Further, hypertension and dyslipidemia can increase the progress of renal failure (Han et. al., 2007).

Cluster 3: Inflammatory Risk Profile

This profile consist of elevated levels of C-reactive protein which indicates the presence of inflammation and associated with progression of atherosclerosis (Ridker et.al, 2000). It has been shown to be an independent indicator of cardiovascular events even when LDL levels are not elevated (Mendell, 1996).

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Cluster 4: Low Overall Risk Profile

In this profile, no biomarker shows any distinguished difference and the levels are relatively low on all biomarkers. This profile group consisted of our reference group in which I compared the other risk profiles when conducting multinomial regression.

Cluster 5: Cholesterol Risk Profile

In this profile, LDL and triglycerides are elevated suggesting cholesterol risk. Research has been conducted on the joint effect of triglycerides and LDL cholesterol levels on cardiovascular risk outcomes (Manninen et. al., 1992). For example, the Helsinki Heart Study examined dyslipidemic middle aged men. In this study, the relative risk of a cardiac event with a ratio of LDL to HDL greater than 2.4 mmol/l compared to those with ratio less than 2.3 mmol/l was 3.8. This suggests that increases of LDL cholesterol is related to cardiovascular disease risk outcomes.

Study Significance

The goal of this project is to expand upon Geronimus' weathering hypothesis in several ways. First, current measurement of the variable allostatic load requires dichotomizing continuous biological measurements into low and high risk categories (yes/no) to construct a composite allostatic load score. Categorizing otherwise continuous-level data results in loss of information and independent effects otherwise captured by the variables used to calculate allostatic load (Altman et. al. 1994; Cohen, 1983). Further, calculation of an allostatic load score requires the use of clinical cut points for clinical biomarkers to determine high and low allostatic load risk. Clinical cut

points may not be universally applicable to all subjects and do not account for clinical

values that may fall into either high or low risk categories (Royston et. al, 2006).

In addition, examining allostatic load as composite score for dichotomization

(yes/no) presents challenges in determining if a specific biomarker is driving allostatic load

scores. That is to say, in this scoring process, cases may be categorized as having AL for

very different profiles of biomarkers which could indicate very different metabolic profiles.

As noted above, preliminary cluster analysis of NHANES data set yielded five qualitatively

distinct biological profiles. Specific psychobiological response patterns are necessary to

adapt to specific threats which may require different outcomes (McEwen & Stellar, 1993).

Research suggests that the HPA axis is not universally activated in response to all negative

stressors. Increased HPA activity is linked to specific stressors (Blascovich & Mendes,

2000; Dickerson & Kemeny, 2004). Preliminary cluster analysis revealed an inflammatory

risk profile that consisted of elevated levels of C- reactive protein. Activation of the HPA

axis in response to stress has been shown to increase inflammatory activity similar to that

seen when a foreign pathogen enters the body (Watkins, Nguyen, Lee, & Maier, 1999).

Dickerson and colleagues (2004) conducted a study to examine the relationship between

psychological stress and inflammatory activity. Participants were randomly assigned to a

self-blame condition or a neutral control group. Those in the self-blame condition reported

increased shame and guilt compared to any other emotion but also exhibited increased

proinflammatory cytokine activity. No changes in proinflammatory cytokine activity were

seen in the control condition. This suggest that specific psychosocial stressors may increase

proinflammatory cytokine activity and subsequent inflammation (Dickerson, Kemeny,

Aziz, Kim, & Fahey, 2004). These study findings also suggest the importance of

identifying particular drivers of allostatic load.

CHAPTER III

METHODS

Participants

We utilized data from the 2005-2006 National Health and Nutritional Examination Survey (NHANES) collected by the National Center for Health Statistics. NHANES collects national data from both interviews and examinations. The interview portion also collects data on demographics, socioeconomic status, diet, and health outcomes.   The examination portion collects medical, dental, physiological measurements, and laboratory data.   NHANES employs a stratified multistage probability sample that represents the United States population for civilian, noninstitutionalized individuals. Thus, in addition to the breadth of data collected, the nation probability sample was also a major advantage to this study.

Respondents who self-identified as Mexican, Other Hispanic, Non-Hispanic African American, Non-Hispanic White, and other race including Multi-Racial were recruited for participation in NHANES. Oversampling of individuals aged 60 and older, African Americans, and Hispanics allowed for an increase in the reliability of statistical analysis. NHANES provided a weighting variable to compensate for oversampling.

Procedure

Given that this study was designed to provide an alternative approach to the traditional allostatic load algorithm, we conducted a latent profile to develop cardiovascular disease risk profiles. On the premise of existing research examining biomarkers of stress and the data availability, 7 biomarkers were selected for inclusion in a latent profile analysis; C-reactive protein, total cholesterol, glycohemoglobin, homocysteine, albumin, creatinine clearance, and triglycerides were collected via participant blood samples. Latent profile analysis (LPA) was used to develop risk profile categories. LPA is conceptually similar to cluster analysis as this analysis assigns individuals to mutually exclusive subgroups (classes) based on a set of "indicator" variables.(Masyn, 2013; B. Muthén, 2006) LPA is a special case of Latent Class Analysis (LCA) in which the indicators are continuous as opposed to categorical. Unlike LCA, LPA does not assume local independence which limits the possibility of covariance among indicator variables used in latent profile models.   Thus, use of LPA allows for flexibility in the structure of the classes in regards to the means, variances and covariances of the indicator variables. The default in LPA is that the means of the indicator variables are free to vary across classes (thus resulting in different profiles across classes).   In addition, one may allow the variances and covariances of the indicator variables to be either invariant or unrestricted across classes. The specification of the means structure can have a significant impact on the number and characteristics of the classes.

Statistical Approach

A conservative approach was adopted in the development of the model class structure. First, each biomarker was transformed into standardized Z-scores based on raw data to account for different units of measurements among each biomarker. Many of the biomarkers exhibited a highly positive skew. To our knowledge, there are no strong recommendations regarding the impact of skewness on latent profile analysis. Therefore we adopted a systematic approach for trimming the raw data. We established three levels of trimming at the 99th percentile, 97th percentile and the 95th percentile. Using the raw data and the three levels of trimming we estimated a series of LPA models ranging from 2 – 7 classes. Models with untrimmed data often did not converge thus creating rationale for utilizing trimmed data. We also allowed variable correlation within classes during model development. Identification of an ideal number of classes was determined through a series of steps.

First, we adopted the assumption that the pattern of means held unrestricted variance across classes (this is the default assumption in LPA). Second, because the formula for computing total cholesterol incorporates some portion of the triglycerides value, we allowed total cholesterol and triglycerides to covary across all classes with the restriction that this covariance was invariant across classes. Third, we allowed the variances and the pattern of variance among the indicator variables to vary across classes.

Using Mplus version 7, (Muthén & Muthén, 2012) changes across the number of classes were examined in respect to the following fit indices; Akaike Information

Criterion (AIC), Bayesian Information Criterion (BIC), and the Sample Size Adjusted Bayesian Information Criterion (SS-BIC). Secondly, we employed the Lo-Mendell-Rubin (LMR) test to determine the appropriateness of K versus K+1 number class. We were unable to employ the bootstrapped LMR as NHANES utilizes sample weights. Lastly, we examined the distribution of cases across each class to identify symmetry within the latent profile model (Masyn, 2013). Determining case distribution across the classes are important to determine whether the distribution of cases follow a normal distribution. Multinomial logistic regression analysis was used to determine odds of risk profile membership for race (African American, White, Hispanic), sex, age and family income to poverty ratio.

Variables and Measures

C-reactive Protein (CRP)

CRP is a protein released in an acute response during an inflammatory event. Increased levels of CRP detect the presence of disease and support differential diagnoses (Rosalki, 2001). Moreover, raised levels of CRP are also indicative of a poor prognosis among patients who present with symptoms related to a cardiovascular event. There have been a wide range of prospective epidemiological studies that suggest that CRP is a robust indicator of cardiovascular events among patients with no prior cardiovascular disease (Hackam & Anand, 2003; Harris et al., 1999; Ridker, 2003; Ridker, Buring, Shih, Matias, & Hennekens, 1998; Ridker, Hennekens, Buring, & Rifai, 2000). Further, CRP levels have a long-term predictive value of a cardiovascular event such that increased

cardiovascular risk is present 20 years after an initial CRP recording was obtained (Sakkinen et al., 2002). Values of CRP are reported as mg/dL in NHANES 2005-2006.

Albumin

Albumin is a protein produced by the liver that is essential to tissue growth and repair. Low albumin levels have been associated with poor health outcomes and increased risk of mortality (Corti, Guralnik, Salive, & Sorkin, 1994; Reuben et al., 2000; Sahyoun, Jacques, Dallal, & Russell, 1996). Further, low concentrations of albumin have increased risk of cardiovascular disease (Gillum & Makuc, 1992; Horwich, Kalantar-Zadeh, MacLellan, & Fonarow, 2008). Albumin has been shown to have an inverse relationship with CRP as Albumin is a negative acute phase protein that decreases in response to inflammation (Iwata, Kuzuya, Kitagawa, & Iguchi, 2006). Values of albumin are reported as g/dL in NHANES 2005-6.

Homocysteine

The link between homocysteine and cardiovascular diseases was first revealed in patients who were born with dysfunction in homocysteine metabolism and subsequent hyperhomocysteinaemia (Wald, Law, & Morris, 2002). Hyperhomocysteinaemia has been shown to increase the risk of stroke, heart disease, stroke, and atherosclerosis (Arnesen et al., 1995, 1995; Nygard et al., 1995). Further, artery wall thickening, a common precursor to cardiovascular disease, has been associated with increased levels of homocysteine (Hankey & Eikelboom, 1999). Values of homocysteine are reported as mg/dL in NHANES 2005-6.

Triglycerides

Triglycerides are a form of excess energy or fats that exist within the body. Excess plasma triglycerides have been associated with cardiovascular disease, particularly coronary artery disease. Elevated levels of plasma triglycerides have been shown in those who are obese or overweight and consume a diet high in carbohydrates. Further, triglycerides have been associated with all-cause cardiovascular risk and mortality (Nordestgaard & Varbo, 2014). Values of triglycerides are reported as mg/dL in NHANES 2005-6.

Total Cholesterol

Total cholesterol is measured by adding values for high density lipoprotein (HDL), low density lipoprotein (LDL) and 20% of the triglyceride level. HDL is considered the "good" cholesterol because research reveals that cardiovascular disease such as atherosclerosis are inversely related to level of HDL. Further, LDL has been coined the "bad" cholesterol. LDL has been shown to contribute to plaque buildup and subsequent cardiovascular disease. Individual with high triglycerides usually exhibit high overall total cholesterol. Elevated levels of total cholesterol has been shown to be a strong predictor of CHD, particularly among men (Carroll, Kit, Lacher, & Yoon, 2013; Peters, Singhateh, Mackay, Huxley, & Woodward, 2016). Values of total cholesterol are reported as mg/dL in NHANES 2005-6

Glycohemoglobin

Glycohemoglobin, estimated by a percentage of hemoglobin A1c, reflects the level of glucose in the blood. Glycohemoglobin has been linked to vascular

complications which contributes to subsequent cardiovascular disease events. Further, glycohemoglobin has also been useful in detecting risk for incident cardiovascular events (Khaw et al., 2004; Meigs, Nathan, D'Agostino, & Wilson, 2002; Park, Barrett-Connor, Wingard, Shan, & Edelstein, 1996). Values of glycohemoglobin are reported as ' % of Hemoglobin A1C' in NHANES 2005-6.

Creatinine

Creatinine serves as a measure of glomerular filtration. Elevated levels of creatinine indicate the presence of acute and chronic renal insufficiency and/or urinary obstruction. Further chronic kidney disease has been shown to significantly increase the risk of cardiovascular disease. However, there has been evidence that suggest that this increase could be a result of pre-existing subclinical vascular disease (Weiner et al., 2004). Values of Creatinine are reported as mg/dL in NHANES 2005-6.

Risk Profile Membership

The independent variable for this study is risk profile membership. Risk profile membership will be developed through Latent Profile Analysis (LPA) of the variables commonly used to examine allostatic load (discussed in more detail in analysis). Examining allostatic load requires measurements that represent the major physiological systems that are activated during a stress response. These systems include the sympathetic nervous system, hypothalamic-pituitary-adrenal axis (HPA), metabolic, and immune system. Therefore the following biomarkers at baseline will be used to determine risk profile membership.

Depression

The PHQ-9 (α =0.89) is a 9 item depression scale that establishes criteria for depression diagnosis and rates the severity of depressive symptoms (Kroenke & Spitzer, 2002). This scale consist of 9 questions that measure the frequency of depressive symptoms (e.g. little interest in doing things, feeling down depresses, or hopeless; difficulty these problems have caused) within the past 2 weeks. Frequency was assessed on a scale of 0-3 with 0 indicating rarely experienced and 3 indicating a symptom was experienced most to all of the time. Higher PHQ-9 scores indicated a higher frequency and severity of symptoms. The PHQ-9 is a shortened version of the primary care evaluation of mental disorders (PRIME-MD®) used for assisting health providers in determining criteria based diagnoses (e.g. mood, anxiety, alcoholism) commonly faced among medical patients (Spitzer et al., 1994). The PHQ-9 is a self-administered three page version of the PRIME-MD® with a comparable sensitivity (65%-95%) and specificity (85%-95%) of lengthier depression scales (Kroencke, Spitzer, & Williams, 2001).

Social Support

Emotional support, financial support, and social network were assessed using social support questions collected in NHANES. Emotional support was measured by participants' response to the question, "Can you count on anyone to provide you with emotional support such as talking over problems or helping you make a difficult decision?" Financial support was measured by participants' responses to, "If you need some extra help financially, could you count on anyone to help you; for example, by

paying any bills, housing costs, hospital visits, or providing you with food or clothes?"

Emotional and financial support were coded into a binary variables in which participants

either received a "1" when answering "yes" or a "0" when answering "no". Social

network was measured by participants' responses to the question "how many close friend

do you have". Close friends were defined as relatives or non-relatives that participants

felt at ease with, could talk to about private matters, and who they believed they could

call on for help. Participants' responses could range from 0-50 friends

Family Income Poverty Ratio

The family income poverty ratio is calculated by dividing family income, specific

to family size, by the poverty guidelines set forth by the Department of Health and

Human Services (HHS). These guidelines are used to determine eligibility for federal

assistance programs such as the Supplemental Nutrition Assistance Program (SNAP),

Special Supplemental Nutrition Program for Women, Infants, and Children (WIC), and

the National School Lunch Program. Sampling weights as provided by NHANES were

also employed.

Body Mass Index (BMI)

BMI is a measure by an individual's weight in kilograms divided by the height in

meters squared. Though BMI does not directly measure body fat, a high BMI score is an

indicator of body fatness.

Smoking

Smoking was assessed by participants' response to the question "have you smoked at least 100 cigarettes in life. Responses were coded into a binary variables in which participants either received a "1" when answering "yes" or a "0" when answering "no".

Data Analysis

LPA is also a person-centered approach that accounts for intra-individual variation in different biomarkers use to better represent multiple biological pattern of biological risk (Marsh, Lüdtke, Trautwein, & Morin, 2009). Using this analysis approach to determine biological risk groups as an outcome variable is novel and somewhat exploratory. Therefore, final determination of the outcome variable (biological risk profile) can only be obtained after the completion of AIM 1. Each hypothesis and directionality between predictor and outcome variables have been derived from the weathering hypothesis, preliminary cluster analysis, and cardiovascular epidemiological data. Note that preliminary work indicated that we may identify groups of individuals who fall into low risk profiles such as profile number four seen in Figure 1. I anticipate that a similar profile will emerge in the data and this profile will serve as the referent group for our analyses.

Latent profile analysis (LPA) offers a probability based clustering or classification that allows for probability testing. Latent profile analysis draws on the assumption that a population, in which the sample is derived, follows a statistical model of probability (Vermunt & Madigson, 2002). Under this assumption, classification of individuals

based on their observed scores should follow the same probability distribution. In the context of my research interest, a latent profile class that determines a cardiovascular risk profile is assumed to follow the same probability of that of the population in which it was derived. The use of a probability distribution, allows one to test a hypothesis on class membership against a p-value.   A latent profile model represents the distribution of biomarkers and other indicator variables as a function of probability of latent class membership. A latent profile model, as a function of probability, also allows for maximum likelihood estimation which provides estimated probabilities of class membership. Therefore selected fit criteria can be utilized to determine the latent profile model that best represents the estimated probability distributions for each latent profile class (Nylund, Asparouhov, & Muthén, 2007; Vermunt & Magidson, 2002).

LPA will be utilized to develop risk profiles. Selected biomarkers will be log transformed so that standardized Z-scores for each biomarker will be used in the latent profile model.   LPA, conceptually similar to cluster analysis, will be used to assign individuals to mutually exclusive subgroups based on distinct patterns of z-scores for each biomarkers (Muthen, 2006). Using Mplus version 7 several LPA models will be conducted to determine the best model fit. Beginning with a one class model, the number of classes will be increased until fit indices suggest the most accurate model. The following fit indices will be considered: Bayesian Information Criterion (BIC), Akaike Information Criterion (AIC), and the Lo Mendel Rubin (LMR) which provides a p-value in which a value less .05 suggests the model with one less class should be rejected in support of the model in question. Using full information maximum likelihood (FIML)

estimation, LPA will allow for missing data in the development of risk profiles. After the risk profile groups are identified, multinomial logistic regression modeling will be used to determine the role of age and sex on membership in biological risk profile. The output from this analysis will provide profile membership which will be the primary dependent variable for the following analyses. This is similar to running a Confirmatory Factor Analysis as the first step in a Structural Equation Model. It is a crucial step because it sets the stage for all further analyses which will employ multinomial logistic regression to examine predictors of profile membership.

Multinomial logistic regression has been used to determine the probability of a dependent variables membership in category membership as a result of multiple independent variables.   The probability of categorical membership is evaluated by use of maximum likelihood estimation. Multinomial regression is an ideal analysis as it does not require consideration of sample size and identification of outliers.   Further, multinomial logistic regression analysis is not influenced by issues of normality, linearity, or homoscedasticity.

Multinomial logistic regression assumes several assumptions. Multinomial regression assumes that the membership in one category is not related to the membership in another variable. In addition, multinomial regression assumes non-separation. Therefore, predictors with perfect separation will result in inaccurate coefficients that are greatly overestimated.

Multinomial logistic regression modeling will be used to test the relationship between depression, social support and risk profile membership.   Several logistic models will be created to examine these relationships while understanding the moderating role off social support and cardiovascular risk.

Study Limitations

Though this study is novel in approach, there are several limitations. First, the study approach consists of a cross-sectional design. One aspect of the weathering hypothesis hinges on physiological deterioration over time. Though we examine age as a major variable, the study can be strengthened by the use of longitudinal study design. Though this goes beyond the scope of this dissertation study, future studies could employ longitudinal study methods to account for allostatic load over time. Future studies should seek to examine this relationship.   Further, NHANES is a rich national dataset that allows for examination of racial differences in biological risk across the lifespan. However, this data set did not include measures of primary mediators (e.g., cortisol, norepinephrine, epinephrine). Though examining secondary mediators of stress is informative, investigation of primary mediators of stress is important for linking biological risk due to stress to clinical outcomes. Future research should consider using primary mediators of stress to further validate and strengthen the biological risk patterns found in this study.

CHAPTER IV

CARDIOVASCULAR RISK PROFILE MEMBERSHIP IN THE NATIONAL HEALTH AND NUTRITIONAL EXAMINATION SURVEY: A LATENT PROFILE ANALYSIS

Additional Authors: Dudley, William, PhD, Morrison, Sharon, PhD, Schulz, Mark, PhD, Wideman, Laurie, PhD

Introduction

Although rates of morbidity and mortality from cardiovascular disease have improved over the past decades, racial disparities in cardiovascular disease risk have persisted for ethnic and racial minorities (Berry et al., 2012; Go et al., 2014; Romero, Romero, Shlay, Ogden, & Dabelea, 2012). Research seeking to explain these disparities has largely focused on traditional risk factors such as obesity, hypertension, diet, and physical activity (Daviglus, Pirzada, & Talavera, 2014; Mathieu et al., 2012; Romero et al., 2012). However, a large body of literature has evidenced the psychological and social implications of race on cardiovascular risk (Jackson, McGibbon, & Waldron, 2013; Krieger et al., 2013; Sims et al., 2012). The weathering hypothesis, posits that stress associated with racial inequities may cause health deterioration among African Americans as early as young adulthood, leading to racial disparities in health outcomes over the life span. Further, African Americans often report stress associated with

perceived racism and discrimination. African Americans can experience racism and discrimination on multiple levels, including interpersonal (discriminatory interactions between individuals), institutional (discrimination in employment, housing, or health care), and cultural (widespread acceptance of stereotypes) (Harrell, 2000; Jones, 2000; Krieger, 1999). Racism and discrimination also increases the likelihood of objective stressors such as job insecurity and financial strain (Arrow, 1998; Pager & Shepherd, 2008) Stress associated with economic, social, and structural inequities accelerates physiological erosion or "weathering" particularly among African American women (Geronimus, 2000; Geronimus & Thompson, 2004). Weathering is believed to create age patterns of morbidity and mortality among younger African Americans that are similar to older Whites thus creating differences in racial and age patterns in health outcomes of cardiovascular disease, infant mortality, death, and disability (Geronimus, 1996; Geronimus, Hicken, Keene, & Bound, 2006; Warren-Findlow, 2006; Geronimus et al., 2010).

Allostatic load is widely accepted as a quantitative metric used to study the consequences of weathering, thus giving researchers the ability to measure both the acute and long-term outcomes of the stress response. These efforts have been driven by literature linking social factors such as neighborhood quality, poverty, and occupation to physiological measures such as cortisol, blood pressure and levels of glycohemoglobin (Seeman, Singer, Wilkinson, & McEwen, 2001; Schnorpfeil et al., 2003; Barrington et al., 2014). Allostasis is the process that activates the sympathetic nervous system, hypothalamic-pituitary-adrenal axis (HPA) and the immune systems to adapt to external

stressors. Prolonged allostasis results in allostatic load, a state of impaired ability to adapt to future stressors (Seplaki et al., 2004). The measurement of allostatic load is based on a set of biomarkers which represent the current state of each physiological system activated during stress exposure. Previous studies have employed an algorithm that includes measures of the hypothalamic-pituitary-adrenal (HPA) axis (e.g., cortisol), cardiovascular system (e.g., blood pressure), metabolic processes (e.g., glycohemoglobin) and the immune system (e.g. C-reactive protein)(Seeman et al., 1997; Geronimus et al., 2006; Chyu & Upchurch, 2011; Brody et al., 2013). This algorithm computes allostatic load by demarcating clinical cut points to dichotomize continuous biological measurement into binary high risk variables (0 = low, 1 = high). These binary variables (one for each biomarker) are then summed to yield an allostatic load score which determines the presence of allostatic load. Higher allostatic load in general have been associated with a decline in physical and cognitive functioning, cardiovascular disease incidence, and mortality (McEwen & Seeman, 1999). Moreover, evidence suggests that African Americans have a greater probability than Whites of a high allostatic load with racial differences growing more pronounced with increasing age (Geronimus et al., 2006).

Although this method of examining physiological weathering has been foundational (Seeman et al., 1997; Geronimus et al., 2006), there are three important limitations to this approach. First, clinical cut points may not capture the full extent of biological risk (Royston, Altman, & Sauerbrei, 2006). For example, low values for albumin in the presence of other elevated biomarkers has shown specific clinical significance (Kuller et al., 1991; Lee et al., 2010). Secondly, categorizing otherwise

continuous data results in loss of valuable information captured by the variables used to calculate allostatic load (Altman, Lausen, Sauerbrei, & Schumacher, 1994; J. Cohen, 1983). This could be problematic when determining risk stratification for those who are near but do not meet the clinical thresholds of risk. Third, it is improbable that each biomarker equally contributes to the calculation of an allostatic load score. A dichotomized composite score presents challenges when determining the extent in which a specific biomarker drives an allostatic load score. Further, cases may exhibit high allostatic load scores but exhibit different patterns of elevated biomarkers. For instance, an individual may exhibit elevated C-reactive protein, triglycerides, cholesterol and homocysteine while another individual may exhibit elevated of homocysteine, albumin, and creatinine and C-reactive protein. Therefore, dichotomizing allostatic load scores may mask the physiological nature of allostatic load.

This standard practice of computing allostatic load has supported fundamental research of the nature of racial/ethnic disparities in chronic diseases. We propose an alternative approach, which is believed to improve data sensitivity and reduce information loss. Therefore the purpose of this study was to expand upon the weathering hypothesis by addressing the limitations of utilizing a traditional algorithm for computing allostatic load. In this process we conducted a latent profile analysis (Masyn, 2013; B. Muthén, 2006) using continuous level biomarkers commonly used to assess allostatic load. In addition to addressing the limitations of the traditional methodology, we broadened the scope of the study to include a sample of Hispanics. Evidence of weathering has been consistent for African Americans but mixed among studies

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examining weathering among Hispanic populations (Collins, Rankin, & Hedstrom, 2012; Wildsmith, 2002). Therefore our study sought to examine racial differences in memberships in cardiovascular risk profile among Whites, African Americans, and Hispanics. We also examined age and sex differences in risk profiles memberships.

Methods

Participants and Measures

We utilized data from the 2005-2006 National Health and Nutritional Examination Survey (NHANES) collected by the National Center for Health Statistics. NHANES collects national data from both interviews and examinations. The interview portion collects data on demographics, socioeconomic status, diet, and health outcomes while the examination portion collects medical, dental, physiological measurements, and laboratory data. NHANES employs a stratified multistage probability sample that represents the United States population for civilian, noninstitutionalized individuals. Thus, in addition to the breadth of data collected, a national probability sample was also a major advantage to this study.

Respondents who self-identified as Mexican, Other Hispanic, Non-Hispanic Black, Non-Hispanic White, and other race including Multi-Racial were recruited for participation in NHANES. Oversampling of individuals aged 60 and older, Blacks, and Hispanics allowed for an increase in the reliability of statistical analysis. NHANES provided a weighting variable to compensate for oversampling.

Procedure

Given that this study was designed to provide an alternative approach to the traditional allostatic load algorithm, we conducted a latent profile analysis to develop cardiovascular disease risk profiles. On the premise of existing research examining biomarkers of stress and the data availability, 7 biomarkers were selected for inclusion in a latent profile analysis; C-reactive protein, total cholesterol, glycohemoglobin, homocysteine albumin, creatinine clearance, and triglycerides were collected via participant blood samples. Latent profile analysis (LPA) was used to develop risk profile categories. LPA is conceptually similar to cluster analysis as this analysis assigns individuals to mutually exclusive subgroups (classes) based on a set of "indicator" variables.(Masyn, 2013; B. Muthén, 2006) LPA is a special case of Latent Class Analysis (LCA) in which the indicators are continuous as opposed to categorical. Unlike LCA, LPA does not assume local independence which limits the possibility of covariance among indicator variables used in latent profile models. Thus, use of LPA allows for flexibility in the structure of the classes in regards to the means, variances and covariances of the indicator variables. The default in LPA is that the means of the indicator variables are free to vary across classes (thus resulting in different profiles across classes). In addition, one may allow the variances and covariances of the indicator variables to be either invariant or unrestricted across classes. The specification of the means structure can have a significant impact on the number and characteristics of classes.

Statistical Approach

A conservative approach was adopted in the development of the model class structure. First, each biomarker was transformed into standardized Z-scores based on raw data to account for different units of measurements among each biomarker. Many of the biomarkers exhibited a highly positive skew. To our knowledge, there are no strong recommendations regarding the impact of skewness on latent profile analysis. Therefore we adopted a systematic approach for trimming the raw data. We established three levels of trimming at the 99th percentile, 97th percentile and the 95th percentile. Using the raw data and the three levels of trimming we estimated a series of LPA models ranging from 2 – 7 classes. Models with untrimmed data often did not converge thus creating rationale for utilizing trimmed data. We also allowed variable correlation within classes during model development. Identification of an ideal number of classes was determined through a series of steps.

First, we adopted the assumption that the pattern of means held unrestricted variance across classes (this is the default assumption in LPA). Second, because the formula for computing total cholesterol incorporates some portion of the triglycerides value, we allowed total cholesterol and triglycerides to covary across all classes with the restriction that this covariance was invariant across classes. Third, we allowed the variances and the pattern of variance among the indicator variables to vary across classes.

Using Mplus version 7, (Muthén & Muthén, 2012) changes across the number of classes were examined in respect to the following fit indices; Akaike Information

Criterion (AIC), Bayesian Information Criterion (BIC), and the Sample Size Adjusted

Bayesian Information Criterion (SS-BIC). Secondly, we employed the Lo-Mendell-

Rubin (LMR) test to determine the appropriateness of K versus K+1 number class. We

were unable to employ the bootstrapped LMR as NHANES utilizes sample weights.

Lastly, we examined the distribution of cases across each class to identify symmetry

within the latent profile model. (Masyn, 2013)

Multinomial logistic regression analysis was used to determine odds of risk

profile membership for race (African American, White, Hispanic), sex, age and family

income to poverty ratio. Age for this study ranged from 3-85 years. The family income

poverty ratio is calculated by dividing family income, specific to family size, by the

poverty guidelines set forth by the Department of Health and Human Services (HHS).

These guidelines are used to determine eligibility for federal assistance programs such as

the Supplemental Nutrition Assistance Program (SNAP), Special Supplemental Nutrition

Program for Women, Infants, and Children (WIC), and the National School Lunch

Program. Sampling weights as provided by NHANES were also employed.

Results

Latent Profile Model

A series of models were run on each of level of trimming which revealed that

trimming at the 97th percentile resulted in the best fit. This level of trimming resulted in a

total sample size of 7436. LPA revealed a 4-class solution. See Table 1.

Table 1. Fit Indices for 4 Profile Solution.

	AIC	BIC	SSABIC	LMR
Class 2	65709.04	66089.31	65914.53	0.0052
Class 3	62094.39	62612.95	62374.61	0.0306
Class 4	59364.94	60021.78	59719.89	0.0096

Figure 3. Cardiovascular Risk Profiles for 4 Profile Solution.
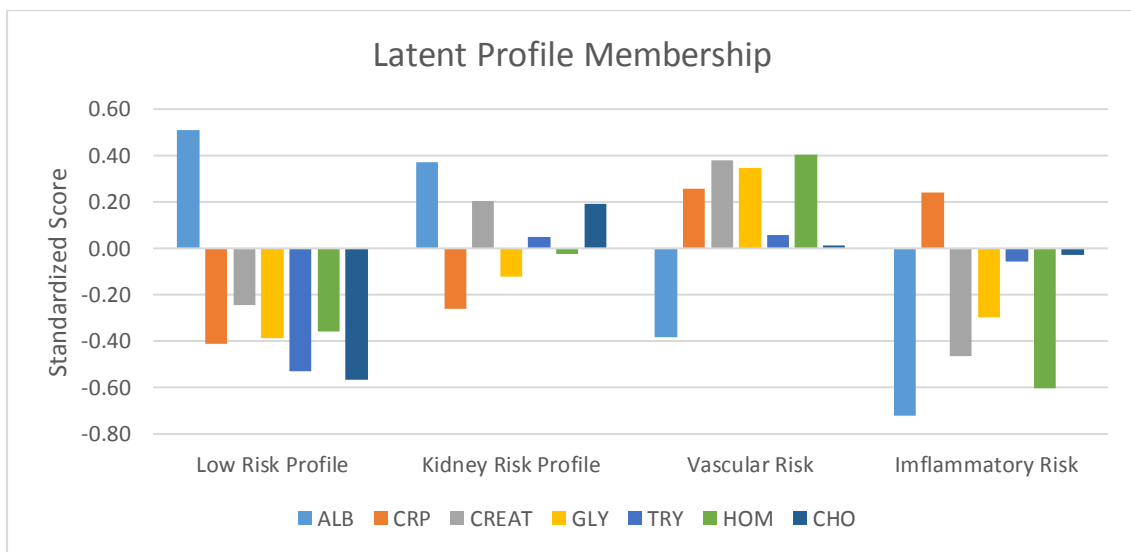
The standardized means for each biomarker including in the 4 profiles are

depicted in Figure 2. These means and the results of the one way analysis of variance

(ANOVA) for each profile are presented in Table 2. The one-way analysis of variance

produced an F statistics that indicated the presence of significant variation among each

biomarker across the profiles. The first profile revealed the youngest participants with a

mean age of 20 years (n= 2206, 29.6%). This profile revealed patterns of increased levels

of Albumin while exhibiting lower levels of C-reactive protein, glycohemoglobin,

triglyceride, homocysteine and cholesterol levels. Minimal variation was observed for

creatinine levels among members of this profile. On the basis of scientific literature, this

profile was classified as the *low risk profile* (Mueller & Caudill, 1999). The second

profile yielded a mean age of 46.   This profile held the largest number of participants

(n=2,473, 33.2%) and revealed elevated levels albumin, creatinine, and cholesterol.

Elevated levels of both albumin and creatinine indicate some degree of kidney

risk(Peralta et al., 2011), thus we categorized this profile as a *kidney risk profile*.   The

third profile (n=12211, 16.5%) revealed elevated levels of C-reactive protein but

exhibited low levels of albumin, creatinine, glycosylated hemoglobin, and homocysteine.

Triglycerides and total cholesterol demonstrated minimal to no variation within this

profile. The mean age for this profile was 33 years. Research indicates that low albumin

levels in the presence of elevated C-reactive protein may represent an inflammatory risk,

particularly among those with chronic disease (Menon et al., 2005). Therefore, we

labeled this profile *inflammatory risk*. The fourth profile (n= 1146, 20.7%) yielded the

highest overall risk as this profile was characterized by increased levels of creatinine,

glycohemoglobin, and homocysteine with moderate levels of C-reactive protein.   Based

on the clinical literature, this profile was classified as an *overall vascular risk profile*

(Hackam & Anand, 2003). The mean age for the vascular risk profile was 61 years.

Table 2. Mean Scores and ANOVA for Risk Profiles

Variables	Low Profile N= 2,200 (29.6%) Mean Age = 20		Kidney Profile N= 2,473 (33.2%) Mean Age= 46		Vascular Profile N= 1,221 (16.5%) Mean Age= 61		Inflammatory Profile N= 1,541 (20.7%) Mean Age = 33		
	Mean Z-Score	*SD*	*Mean Z-Score*	*SD*	*Mean Z-Score*	*SD*	*Mean Z-Score*	*SD*	*F*
Albumin	0.51	0.69	0.37	0.63	-0.38	0.81	-0.72	1.19	730.69**
C-reactive Protein	-0.41	0.04	-0.26	0.13	0.26	0.54	0.24	0.52	1954.37**
Creatinine	-0.24	0.41	0.20	0.42	0.38	0.63	-0.46	0.34	1009.23**
Glycohemoglobin	-0.39	0.34	-0.12	0.39	0.35	0.63	-0.30	0.43	668.34**
Triglyceride	-0.39	0.31	0.05	0.66	0.06	0.63	-0.06	0.61	382.33**
Homocysteine	-0.36	0.37	-0.02	0.39	0.40	0.60	-0.60	0.32	984.25**
Cholesterol	-0.56	0.66	0.19	0.80	0.01	0.83	-0.03	0.84	280.61**

Multinomial Regression

We conducted a multinomial logistic regression using the low risk profile as the referent group. This analyses were designed to determine which predictive variables (age, race, and poverty income ratio) were related to profile membership in the 3 focal profiles compared to low risk profile. All of the predictive variables were entered simultaneously into each model. Table 3 displays the results of our multinomial regression with the low risk profile as the referent group. Negative coefficients were indicative of greater odds of membership in the reference profile while a positive coefficient indicated greater odds of membership in the focal profile.

Compared to Whites, Hispanics had a significantly greater odds of membership in the inflammatory risk profile only (OR= 1.94) while African American participants held significant greater odds of membership in both the inflammatory risk profile (OR= 4.29) and the vascular risk profile (OR= 1.35). Age was also found to be a significant predictor risk profile membership. Compared to low risk profile, older participants have greatest odds of membership in the vascular risk profile (OR= 1.23). This was followed by odds of membership in the kidney risk (OR= 1.23) and inflammatory risk profiles (OR= 1.6). Females were significantly less likely to be in the kidney risk profiles and vascular risk profiles but much more significantly likely to be in the inflammatory risk profile (OR= 4.11). Poverty to income ratio (PIR) was also a significant predictor of risk profile membership. Those with higher PIR scores were the least likely to be in the Inflammatory Risk Profile (OR= .19). Higher PIR scores were also less likely to be in the hypertension risk (OR = .88) and Vascular Risk (OR= .71).

Table 3. Results of Multinomial
Regression for 4 Profiles.

Kidney Risk Profile	Logit	SE	OR	*p*-value
Hispanic	-0.14	0.199	0.87	0.483
African American	0.238	0.216	1.27	0.27
Age	0.147	0.014	1.16	0.001*
Female	-2.966	0.367	0.05	0.001*
PIR	-0.128	0.054	0.88	0.017*
Vascular Risk Profile				
Hispanic	-0.216	0.267	0.81	0.418
African American	1.456	0.245	4.29	<.001*
Age	0.205	0.015	1.23	<.001*
Female	-2.904	0.384	0.05	<.001*
PIR	-0.34	0.063	0.71	<.001*
Inflammatory Risk Profile				
Hispanic	0.665	0.131	1.94	<.001*
African American	0.301	0.13	1.35	.021*
Age	0.054	0.007	1.06	<.001*
Female	1.413	0.215	4.11	<.001*
PIR	-1.65	0.038	0.19	<.001*

SE=Standard Error

OR= Odds Ratio

PIR Poverty Income Ratio

*Indicates Significance

White & Male used for reference for race and gender predictor variables

Protective Profile use for reference profile

Discussion

Using a cross-sectional design, we aimed to advance the weathering hypothesis by investigating potential pathways that may present various patterns of cardiovascular disease risk stratification among a national sample. Using continuous level variables rather than dichotomized variables revealed different patterns of biomarkers. This suggests there may be different stratifications of cardiovascular disease risk contributing to overall allostatic load. The LPA yielded three distinct patterns of risk (kidney, vascular, and inflammatory) with one profile identified as a low risk profile. Members of the low risk profile exhibited increased levels of albumin and lower levels of all other biomarkers. Previous research conducted with NHANES found a higher prevalence of albumin excretion in children than adults (Mueller & Caudill, 1999). The average age in the low risk profile was 20 years, representing a large number of participants under 18 years old. Evidence suggests that elevated levels of albumin are a normal part of development in children (Bangstad, Dahl-Jørgensen, Kjaexsgaard, Mevold, & Hanssen, 1993). However, there is a need to investigate the role of elevated albumin in the susceptibility to chronic diseases over the lifespan.

We also observed the starkest racial disparities among members of the overall vascular risk profile. Compared to Whites, African Americans were about four times more likely to be members in the vascular risk profile versus the low risk profile. This risk was heightened if participants were male. The overall vascular risk profile exhibited the most likely risk of cardiovascular disease. Particularly, the combined effects of C-reactive protein and glycohemoglobin has been associated with the progression of

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advanced early atherosclerosis and increases the risk of a vascular event for both diabetics and non-diabetics (Sander et al., 2006). Further, the presence of homocysteine, which is believed to irritate the lining of the blood vessel, has been associated with heart disease, stroke, and increased the overall risk of cardiovascular disease (Wald et al., 2002). We also observed that lower PIR predicted risk for all risk profiles. . However, the lowest PIR was associated with overall vascular risk.

Consistent with weathering hypothesis, these findings provide evidence that age alone does not contribute to overall cardiovascular risk. The impact of chronic stress from limited financial resources may contribute to increasing cardiovascular risk among African Americans. Further, the weathering hypothesis juxtaposes that living in a race-conscious society contributes to both limited access to financial resources and exposure to subjective racial stress leading to early health deterioration of health than Whites. We found that African Americans and Hispanic were more likely to have an inflammatory risk. Patterns of C-reactive protein and albumin in the inflammatory risk profile were similar to systematic inflammatory responses in chronic diseases such as cancers and cardiovascular diseases while increasing the likelihood of all-cause mortality (Kuller et al., 1991; Menon et al., 2005). We found that Hispanic and African American participants held greater odds of membership of the inflammatory risk profile. Further, females were over four times more likely than males to be in this profile. In our study, we found the mean age for the inflammatory risk profile was 33 years. Geronimus and colleagues (2006) found the largest racial differences in physiological breakdown among those between the ages of 35-64 with lower PIR. This profile may portray the initial

biological patterning of physiological breakdown among minorities who are experiencing allostatic load. This pattern may be more pronounced among females with lower socioeconomic statuses.

The kidney risk profile yielded a different risk stratification that was evidenced by increases in albumin, creatinine, and cholesterol. Elevation of these biomarkers has predicted hypertension, atherosclerosis, and renal injury (Lee et al., 2010). The presence of kidney disease has been a strong predictor of cardiovascular disease (Strippoli et al., 2008). There is a high prevalence of kidney disease among African Americans, particularly among those 65 years and up. Therefore, we expected to find that African Americans had the greatest odd of membership in the kidney risk profile. However, we did not observe any significant racial differences in membership in the kidney risk profile versus the low risk profile for Hispanics. We did find that membership in the profile was significantly predicted by increase in age, lower PIR, and being male. We speculate that there may be limited racial differences in kidney risk between the ages of 40-50. However, racial differences may be revealed as age increases, particularly among those with limited financial resources. Also consistent with literature, this increase kidney risk may be exacerbated for African American males (Jacobs et al., 2002).

We have identified different cardiovascular risk stratifications by age, race, and sex demonstrating that the physiological stress response may differ across specific populations. Future investigative efforts should examine the relationship between psychosocial stressors (e.g. racism, discrimination, life stress) and various patterns of cardiovascular risk. A large body of research examining the weathering hypothesis finds

that minority women, particularly African American women hold the highest biological

risk. However, we found that males were more likely to exhibit kidney and overall

vascular risk, indicating the physiological drivers of allostatic load may differ by sex.

Our findings also provide several opportunities to enhance treatment options and

tailored preventative interventions across the lifespan. For example, clinical

interventions may consist of screening for inflammatory biomarkers for African

American and Hispanic women beginning at the age of 30. This may be useful in

identifying women who have sub-clinical cardiovascular risk.   Moreover, enhancing

cultural and age specific coping efforts with other resources such as social support may

be important in reducing biological risk for African American and Hispanic women who

exhibit similar inflammatory biomarker patterns. The biological pattern exhibited in the

kidney risk profile may also indicate early cardiovascular risk via kidney susceptibility

before racial disparities are revealed. This provides the opportunity to examine

psychosocial factors that contribute to increasing racial disparities among participants

who exhibit kidney susceptibility, particularly those who are over 40 years old.

The present study held several limitations. Assignment of latent profile groups is

probabilistic in nature and does not yield conclusive subgroups in the population. Profile

grouping is determined by the indicator variables included in the latent profile model.

Further, NHANES is a rich national dataset that allows for examination of racial

differences in biological risk across the lifespan. However, this data set did not include

measures of primary mediators (e.g., cortisol, norepinephrine, epinephrine). Though

examining secondary mediators of stress is informative, investigation of primary

mediators of stress is important for linking biological risk due to stress to clinical

outcomes. Future research should consider using primary mediators of stress to further

validate and strengthen the biological risk patterns found in this study. Moreover, we

included acute phase biomarkers, such as C-reactive protein in this study. Acute phase

biomarkers may not be completely indicative of the cumulative physiological burden of

the stress. Though this study accounted for outliers for each biomarker, this study cannot

fully determine the degree in which the results are influenced by current physiological

states, such as the presence of an active infection.

CHAPTER V

THE ASSOCIATIONS BETWEEN DEPRESSION, SOCIAL SUPPORT AND CARDIOVASCULAR RISK PROFILE MEMBERSHIP

Additional Authors: **Dudley, William, PhD, Morrison, Sharon, PhD, Schulz, Mark, PhD, Wideman, Laurie, PhD**

Introduction

Depression and cardiovascular disease are two of the most common causes of disability across the world (Murray & Lopez, 2013). Evidence suggests there is a complex and bidirectional relationship between cardiovascular disease and depression (Lippi et al., 2009). There is evidence that cardiovascular disease contributes to the onset of depressive symptoms. One out of every five patients with cardiovascular disease will report a major depressive disorder (Thombs et al., 2006). Moreover, depression has also been shown to worsen cardiovascular disease prognosis and increase overall mortality from cardiovascular disease (Barth et al., 2004; Ferketich et al., 2000; Frasure-Smith et al., 2000, 2000; Lett et al., 2004; Van Melle et al., 2004). Thus, the nature of the relationship between depression and cardiovascular disease is unclear and the mechanism or mechanisms for the complex interplay between depression and cardiovascular diseases remain unexplained.

A growing body of literature provides evidence that depression increases the risk of cardiovascular disease. Researchers have found that an increase a depressive

symptomology predicts incidence of coronary artery disease, coronary heart disease, and myocardial infarction (Barefoot & Schroll, 1996; Charlson et al., 2011; Ferketich et al., 2000; Keyes, 2004; Van der Kooy et al., 2007). Psychosocial factors have been shown to increase the risk of cardiovascular disease more so than traditional risk factors (e.g. hypertension, diet, exercise) (Joynt et al., 2003; Kim & Setias, 2016; Lett et al., 2004). A study conducted by Yusuf and colleagues (2004) found that psychosocial factors such as perceived stress, negative life events, and depression were stronger risk factors for cardiovascular disease than diabetes, smoking, hypertension, and obesity (Yusuf et al., 2004). Further, a positive relationship has been observed between the severity of depressive symptomology and risk of cardiovascular disease (Barefoot & Schroll, 1996; Charlson et al., 2011). On the premise of this study and other studies examining the global burden of cardiovascular disease, the 2010 Global Burden of Disease study recognized depression as a recognized risk factor for coronary heart disease (Charlson et al., 2011). There also may be a positive interaction between depression and traditional CVD risk factors as existing literature finds that traditional cardiovascular risk factors may strengthen the association between depression and cardiovascular disease risk (Rugulies, 2002).

National data suggests that rates of depression diagnosis are increasing across all races and ethnicities. A study examining data from the National Ambulatory Medical Care Survey from 1992-1993 to 2003-2004 found that depression diagnoses rose from 4.8 to 7.0 per 100 for Hispanics, 4.2 to 7.6 for African Americans and 10.9 to 15.4 for whites (Sclar et al., 2008). Although Whites exhibit higher depression diagnosis, the

burden of depression is higher among minorities. In a national epidemiological study of mental health and service usage, 63.7% of Latinos and 58.8% of African Americans lacked access to mental health treatment compared to 40.2% of Whites (Alegría et al., 2015; Williams et al., 2007). Further, African Americans have been shown to have the highest rate of severe depressive symptoms over the longest length of time (Pratt & Brody, 2014; Williams et al., 2007). These findings suggests minorities often have an increased burden of severe depressive symptoms disability even though Whites have a higher prevalence of depression.

Disparities in depression diagnoses are apparent early in the lifespan as evidence suggests that racial/ethnic minority adolescents have higher rates of depressive symptoms and limited access to treatment (Alexandre et al., 2009; Cummings & Druss, 2011). For example, In a study comparing White and Hispanic youth, Whites (36%) were significantly more likely than Hispanics (27%) to receive adequate mental health (Alexandre et al., 2009). Further, Cummings and colleagues used data from the National Survey on Drug Use and Health to examine racial/ethnic differences in mental health services for White, African American, Hispanic, and Asian adolescents. Results of the study showed that when accounting for family income and insurance status, African American, Hispanic, and Asian adolescents were significantly less likely than Whites to receive prescription medication for depression, receive treatment from a health care provider, or receive outpatient mental health treatment (Cummings & Druss, 2011).

Depression has been shown to alter a number of biological mechanisms, including autonomic nervous system function, HPA axis function, inflammation and insulin

resistance (Joynt et al., 2003; Kiecolt-Glaser & Glaser, 2002; Lett et al., 2004; B. S. McEwen, 2003; Miller et al., 2002; Taylor, 2010; Thayer et al., 2010; Vrany et al., 2015). Depression, particularly chronic depression represents a persistent stress state which may erode the physiological stress response systems (Juster et al., 2011; Kobrosly et al., 2014; McEwen, 1998; McEwen, 2003). Depression is believed to activate the allostatic processes that adapt to external stress. Allostasis activates the sympathetic nervous, hypothalamic-pituitary-adrenal axis (HPA) and the immune systems in response to external stress. Moreover, chronic activation of allostasis leads to biological wear and tear or "weathering", increasing the probability of allostatic load. In an allostatic load state, the physiological stress response becomes impaired, reducing the ability to functionally adapt to future stressors (Seplaki et al., 2004). Allostatic load has been associated with a decline in physical and cognitive functioning, cardiovascular disease incidence, and mortality (Geronimus et al., 2006; McEwen & Seeman, 1999; Seeman et al., 1997).

The weathering hypothesis may explain how disproportional rates of depression among minorities account for some cardiovascular disease disparities. This hypothesis proposes that chronic stress over the lifespan accelerates biological weathering among minorities (Geronimus, 2000; Geronimus & Thompson, 2004). Evidence suggests that minorities are prone to economic and social stressors that increase the likelihood of depressive symptomology (Mezuk, Rafferty, et al., 2010). Further, minorities often report exposure to racism and discrimination, which can contribute to depressive symptomology (Banks & Kohn-Wood, 2007; Flores et al., 2008). Sellers and colleagues

(2006) found the racial discrimination reduced psychological well-being, while increasing depressive symptoms, and perceived stress (Sellers et al., 2006). Further, racism has been shown to facilitate depressive symptoms by threatening self-esteem, invoking sense of hopelessness, and normalizing failure (Clark et al., 1999).

The presence of social support has been shown to decrease cardiovascular disease risk and mortality (Berkman et al., 1992; S. Cohen & Wills, 1985; Frasure-Smith et al., 2000; Treiber et al., 2003). Two main hypothesis that have sought to explain this relationship. First, it is hypothesized that social support may exhibit independent effects on cardiovascular risk (House et al., 1988). For example, social support may decrease cardiovascular risk by facilitating healthy behaviors such as exercise, healthy eating, and adherence to medical treatment (DiMatteo, 2004; Franks et al., 1992; Lewis & Rook, 1999; Uebelacker et al., 2013)   Secondly, social support may buffer the relationship between of depression and cardiovascular risk (Cohen & Wills, 1985; George et al., 1989). Higher family support has also been shown to lower the association between depression symptoms and stressors such as racial discrimination (Brody et al., 2006; Noh & Kaspar, 2003; Uebelacker et al., 2013; Wei et al., 2010).   Moreover, the absence of support has been associated with the onset of depression both independently and through modifying perceptions of negative life events (Paykel, 1994).

Thus, the purpose of the study was to examine the mechanisms in which depression may increase the risk of cardiovascular disease. Further, we sought to understand whether previous literature suggesting that social support reduces cardiovascular disease risk holds true in a study that examines the relationship between

depression and cardiovascular disease risk. This study, guided by the weathering

hypothesis, assumes that depression contributes to the development of allostatic load.

Traditionally, allostatic load is determined by an algorithm that demarcates clinical cut

points to dichotomize continuous biological measurement into binary high risk variables

(0 = low, 1 = high). Biomarkers included in these calculation represent the state of the

physiological systems activated in the stress response (e.g., C-reactive protein,

glycohemoglobin, albumin). This value is then summed to yield an allostatic load score

which determines the presence of allostatic load. Previous work conducted by Johnson et.

al., suggests that cardiovascular risk is variant across race/ethnicity, age and

socioeconomic statuses. Johnson and colleagues examined allostatic load biomarkers

used to assess allostatic load and found that 4 distinct cardiovascular risk profiles; low

risk profile, kidney risk profile, inflammatory risk profile, and vascular risk profile.

Therefore, we sought to extend this method of examining cardiovascular risk by

incorporating the psychosocial variables depression and social support.

Methods

Participants

The 2005-2006 National Health and Nutritional Examination Survey (NHANES)

was used for the study analysis. NHANES employs a stratified multistage probability

sample of the United States population for civilian, non-institutionalized individuals.

Participants who self-reported race ethnicity as Mexican, Other Hispanic, Non-Hispanic

Black, Non-Hispanic White, other race including Multi-Racial were recruited for the

NHANES study. In our study, we focused on Hispanic (Mexican and Other Hispanic), African American, and White.

Measures

The PHQ-9 (α =0.89) is a 9 item depression scale that establishes criteria for depression diagnosis and rates the severity of depressive symptoms (Kroenke & Spitzer, 2002). This scale consist of 9 questions that measure the frequency of depressive symptoms (e.g. little interest in doing things, feeling down depressed, or hopeless; difficulty these problems have caused) within the past 2 weeks. Frequency was assessed on a scale of 0-3 with 0 indicating rarely experienced and 3 indicating a symptom was experienced most to all of the time. Higher mean PHQ-9 scores indicated a higher frequency and severity of symptoms. The PHQ-9 is a shortened version of the primary care evaluation of mental disorders (PRIME-MD®) used for assisting health providers in determining criteria based diagnoses (e.g. mood, anxiety, alcoholism) commonly faced among medical patients (Spitzer et al., 1994). The PHQ-9 is a self-administered three page version of the PRIME-MD® with a comparable sensitivity (65%-95%) and specificity (85%-95%) of lengthier depression scales (Kroencke et al., 2001).

Emotional support, financial support, and social network were assessed using social support questions collected in NHANES. Emotional support was measured by participants' response to the question, "Can you count on anyone to provide you with emotional support such as talking over problems or helping you make a difficult decision?" Financial support was measured by participants' responses to, "If you need some extra help financially, could you count on anyone to help you; for example, by

paying any bills, housing costs, hospital visits, or providing you with food or clothes?"
Emotional and financial support was coded into a binary variables in which participants
either received a "1" when answering "yes" or a "0" when answering "no". Social
network was measured by participants' responses to the question "how many close friend
do you have". Close friends were defined as relatives or non-relatives that participants
felt at ease with, could talk to about private matters, and who they believed they could
call on for help. Participants' responses could range from 0-50 friends.

Statistical Analysis

Seven biomarkers were selected for inclusion in a latent profile analysis; C-
reactive protein, total cholesterol, glycohemoglobin, homocysteine albumin, creatinine
clearance, and triglycerides. These biomarkers were collected via participant blood
samples. Risk profile categories were developed by latent profile analysis.   A
conservative approach was adopted in the development of the model class structure. First,
each biomarker was transformed into standardized Z-scores based on raw data to account
for different units of measurements among each biomarker. Second, because many of the
biomarkers exhibited a highly positive skew. We followed trimming analysis similar to
Johnson et. al. and trimmed at the 97th percentile. Using Mplus version 7(L. K. Muthén &
Muthén, 2012), we estimated a series of latent profile models ranging from 2-4 classes
changes and examined the following fit indices; Akaike Information Criterion (AIC),
Bayesian Information Criterion (BIC), and the Sample Size Adjusted Bayesian
Information Criterion (SS-BIC). We also employed the Lo-Mendell-Rubin (LMR) test to
determine the appropriateness of K versus K+1 number class. Although symmetry in

class size was not a requirement for our models, we were most interested in solutions with relative frequency. Thus, case distribution across each class was examined to identify symmetry within the latent profile model (Masyn, 2013).

We used multinomial logistic regression analysis to determine odds of risk profile membership for race (African American, White, Hispanic), depression score and social support (emotional, financial, network). Evidence suggests that social support may moderate the relationship between depression and cardiovascular risk. Thus, interaction terms were created to examine whether moderation relationships might exist between depression and social support. We included the following covariates in the regression model; sex, age, family income to poverty ratio, BMI (kg/m**2), and smoking status (yes/no). Age for this study ranged from 40-85 years. The family income poverty ratio is calculated by dividing family income, specific to family size, by the poverty guidelines set by Department of Health and Human Services (HHS). All of the predictive variables and covariates were entered simultaneously into each model.

Results

Trimming analysis found that models with raw data did not converge and the trimming at the 97th percentile resulted in the best fitting model (see Johnson et. al. for procedure). This resulted in a sample size of 2,341. LPA revealed a 2-class solution. The fit indices are reported in Table 4.

The standardized means for each biomarker are including in Figure 3. Table 5 represents the standardize means and results of one-way analysis of variance for each profile. The one-way analysis of variance produced an F statistics indicating the presence

of significant variation across the profiles. The first profile (n=1384, 59%) revealed a

low risk profile similar to the profile found in work by Johnson and colleagues, thus we

labeled this profile *low risk*. This profile exhibited patterns of high levels of Albumin

and lower levels of C-reactive protein, triglyceride, cholesterol levels, homocysteine and

glycohemoglobin,. The second profile (n= 957, 41%) revealed elevated levels of C-

reactive protein with slightly elevated levels of homocysteine. Low levels of Albumin,

triglycerides, total cholesterol were observed in this profile while creatinine and

glycohemoglobin yielded minimal to no variation. Low albumin levels in the presence of

elevated C-reactive protein has been characteristic an inflammatory risk (Menon et al.,

2005). Therefore, we labeled this profile *inflammatory risk*.

Table 4. Fit Indices for 2 Cluster
Solution

	AIC	BIC	SSABIC	LMR
Class 2	23773.60	24142.12	23932.77	<.001*
Class 3	22337.18	23290.64	22995.16	.76
Class 4	21944.93	22647.41	22259.83	.78

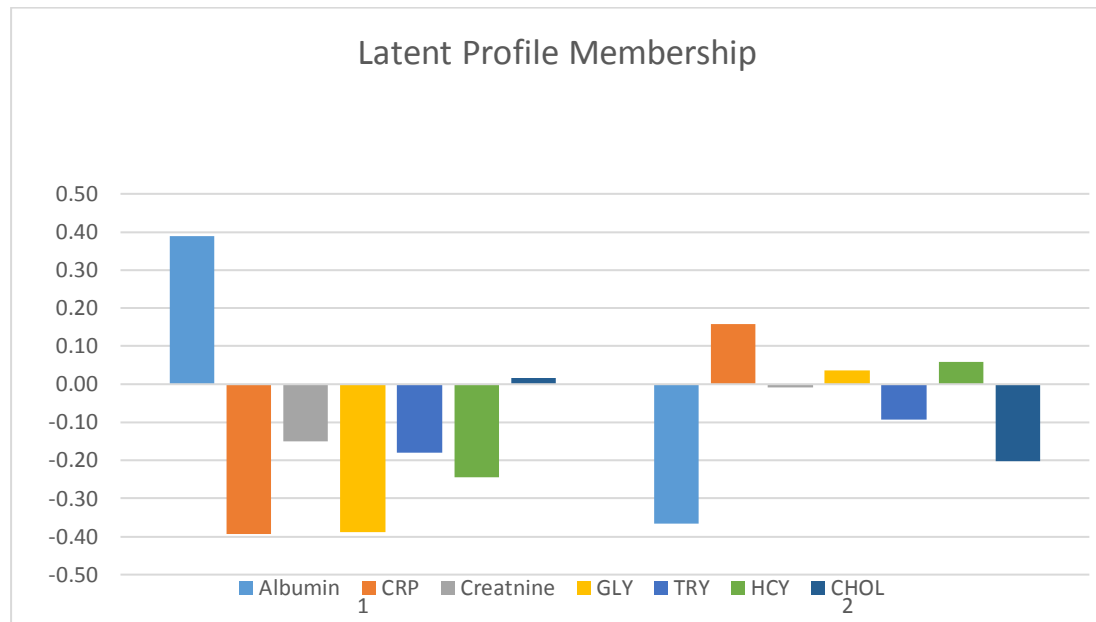Figure 4. Risk Profile Membership for Low Risk and Inflammatory Risk Profiles.

Table 5. Mean Scores and ANOVA for Risk Profiles

	Low Risk Profile		Inflammatory Risk Profile		
Variables	*Mean Z-Score*	*SD*	*Mean Z-Score*	*SD*	*F*
Albumin	0.38	0.79	-0.36	1.00	395.55**
C-reactive Protein	-0.40	0.14	0.16	0.56	1109.48**
Creatinine	-0.15	0.34	-0.01	0.55	50.65**
Glycohemoglobin	-0.39	0.30	0.03	0.63	415.51**
Triglyceride	-0.19	0.60	-0.09	0.60	15.32**
Homocysteine	-0.25	0.39	0.06	0.65	195.60**
Cholesterol	0.01	0.80	-0.19	0.90	30.05**

We conducted a multinomial logistic regression using the low risk profile as the referent group. Table 6 displays the profile descriptive for each profile group. Table 7 displays the results of our multinomial regression with the low risk profile as the referent

group. Negative coefficients were indicative of greater odds of membership in the low

risk profile while a positive coefficient indicated greater odds of membership in the

inflammatory risk profile We found that increasing depression score significantly

increased the odds of membership in the inflammatory risk profile (OR= 1.36). We did

not find a significant association between risk profile membership and social network,

financial support, or emotional support. However, analysis revealed a moderating

relationship between depression and emotional support. The association between

depression and inflammatory risk profile membership was significantly reduced with an

increase in emotional support (OR = .15). Compared to Whites, African Americans had a

significantly greater odds of membership in the inflammatory risk profile (OR= 2.83).

We did not find that evidence that being Hispanic predicted membership is a risk profile.

Age was also found to be a significant predictor risk profile membership. We found that

the mean age in the low risk profile (54 years) was slightly lower than that of the

inflammatory risk profile (59 years). Subsequently, an increase in age significantly

heightened the odds of inflammatory risk membership (OR= 1.6). Poverty to income

ratio was also a significant predictor of risk profile membership. Those with higher PIR

scores were the less likely to be in the inflammatory Risk Profile (OR= .82). Lastly, an

increase in BMI increased the odds of membership in the inflammatory risk profile

(OR=1.19).

Table 6. 2 Profile Descriptives

	Low Risk Profile		Inflammatory Risk Profile	
Variables	Mean	SE	Mean	SE
Age	54	.297	59	.419
Depression Score	.22	.009	.37	.016
Social Network	7.38	.201	7	.28
Financial Support	1.7	.011	1.76	.014
Emotional Support	1.9	.006	1.94	.007
BMI	26.99	.129	32.59	.258
PIR	3.58	.040	2.83	.050

Table 7. Results of Multinomial Regression for
Inflammatory Risk Profile.

Inflammatory Risk Profile	Logit	SE	OR	p-value
Hispanic	0.307	0.244	1.35	0.209
Black	1.04	0.221	2.82	<.001*
Age	0.05	0.009	1.05	<.001*
Female	0.197	2.42	1.21	0.415
BMI	0.178	0.023	1.19	<.001*
Poverty Income Ratio	-0.199	0.051	0.81	<.001*
Smoking Status	-0.189	0.154	0.82	0.22
Depression	0.789	0.219	2.20	<.001*
Social Network	0.005	0.009	1.00	0.554
Financial Support	0.112	0.179	1.11	0.531
Emotional Support	-0.074	0.324	0.92	0.82
Depression*Social Network	-0.036	0.033	0.96	0.272
Depression*Financial Support	0.31	0.478	1.36	0.568
Depression*Emotional Support	-1.874	0.009	0.15	.004*

SE=Standard Error
OR= Odds Ratio
PIR Poverty Income Ratio
*Indicates Significance
White & Male used for reference for race and gender predictor variables
Protective Profile use for reference profile

Discussion

We sought to extend work conducted by Johnson and colleagues by examining the relationship between depression, social support and risk profile memberships. The latent profile analysis revealed a low risk profile and an inflammatory risk profile. Consistent with Johnson and colleagues, members of the low risk profile exhibited increased levels of albumin and lower levels of all other biomarkers. A relationship has been found between increased levels of albumin and reduced cardiovascular risk and mortality. For example, a cohort study examining albumin levels in elderly adults found that all-cause mortality rates decreased with increasing albumin levels (Horwich et al., 2008). Therefore, replication of a "low risk profile" may validate the presence of an overall physiological low risk profile. Also consistent with previous findings, was the manifestation of an inflammatory risk profile. Inflammatory risk, particularly with elevated levels of glycohemoglobin and homocysteine, has been shown to advance atherosclerosis and increase the risk of a vascular event (Hackam & Anand, 2003; Sander et al., 2006). Patterns of C-reactive protein and albumin in the inflammatory risk profile were similar to systematic inflammatory responses in chronic diseases such as cancers and cardiovascular diseases while increasing the likelihood of all-cause mortality.(Kuller et al., 1991; Menon et al., 2005)

We found that depression was significantly associated with membership in the inflammation risk profile. Prior research examining the relationship depression and inflammation has been mixed (Vogelzangs et al., 2012; Whooley et al., 2007) Yet growing evidence suggests that depression may augment production of C-reactive protein

as suggested by our findings. The effects of depression on inflammation can been seen as early as childhood. Miller & Cole (2012) found that depressed individuals with a history of childhood adversity showed increased in C-reactive protein. Further, the authors found that participants who experienced depression and childhood adversity experienced a heightened immune response over a 6 month period. (Miller & Cole, 2012). This suggests that the association between effects of depression on the immune response may be persistent across the lifespan. (Alesci et al., 2005; Bouhuys, Flentge, Oldehinkel, & van den Berg, 2004; Kahl et al., 2005).

Two main theories of social support, independent effects and buffering effects, portray how social support could reduce the inflammatory risk associated with depression (S. Cohen & Wills, 1985; House et al., 1988). Prior research has found that the size of the social network, emotional and financial support predicted increased immune reactivity (Loucks et al., 2006; Mezuk, Roux, & Seeman, 2010). However, we did not find any evidence of that social support yielded independent effects on inflammatory risk. Alternatively, the buffering hypothesis suggests that social support is advantageous to health when stressors, such as depression, threaten health. Thus social support has been shown to buffer the harmful effects associated with these stress (Bell, Thorpe, & LaVeist, 2010; Loucks et al., 2006; Mezuk, Roux, et al., 2010). We did find that emotional support moderated the relationship between depression and inflammatory risk membership such that an increase in emotional support significantly decreased the association between depression and inflammatory risk. This was consistent with evidence that high social support buffers the relationship between stress and inflammatory risk

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(Mezuk, Roux, & Seeman, 2010). Therefore, the results of our study strengthens the assertion that social support may buffer against the deleterious health effects of depression. Our findings suggests that the mechanism in which this occurs may be attributed to a reduced inflammatory response.

In regards to the weathering hypothesis, these findings are consistent with evidence that suggests age alone does not fully contribute to inflammatory risk (Johnson, nd). Being African American, older in age, and low socioeconomic status was associated with inflammatory risk. The impact of depression with access to little financial resources may increase inflammatory risk among African Americans, though we did not find the financial support would impact the relationship between depression and inflammatory risk. Depression may serve as a chronic stressor and accelerate biological weathering over the lifespan beginning in an early adulthood (Geronimus, 2000; Geronimus & Thompson, 2004). This is possibly bolstered by evidence that African Americans are more susceptible to economic and social stressors that increase the likelihood of depressive symptomology (Mezuk, Rafferty, et al., 2010). In addition, the weathering hypothesis suggests that minorities more frequently report racism and discrimination which has been found to increase perceived stress and depressive symptomology (Banks & Kohn-Wood, 2007; Brody et al., 2006; Clark et al., 1999; Flores et al., 2008; Sellers et al., 2006). Thus, future research should examine depressive symptoms as a potential mediator between experiences of racism and discrimination and physiological outcomes.

The present study held several limitations. NHANES is a rich national dataset that allows for examination of racial differences in biological risk across the lifespan.

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However, in order to examine the relationship between depression, social support, and risk profile membership, we were limited to a sample age 40 and older. This limited our ability to fully assess the relationship of the variables across the lifespan. Further, this data set did not include measures of primary mediators (e.g., cortisol, norepinephrine, epinephrine). Though examining secondary mediators of stress is informative, investigation of primary mediators of stress is important for linking biological risk due to stress to clinical outcomes. Further we only studied emotional support, financial support, the size of the social network. It is possible there are other mechanism of support such as informational support may influence the relationship between depression and inflammatory risk.

Our findings suggest that different stressors may drive specific physiological responses more so than others, enhancing how researcher conceptualize cumulative physiological burden or allostatic load. This provides several opportunities to enhance treatment options and tailored preventative interventions to reduce cardiovascular risk among those who experience depression. For example, clinical interventions may consist of screening for inflammatory biomarkers for African Americans who report depressive symptomology. Johnson and colleagues found that inflammatory risk group that consisted of a primarily African American women with an average age of 33. Therefore, screening of inflammatory markers should be recommended for African Americans, particularly those who report depressive symptomology. Moreover, enhancing cultural specific coping efforts with other resources such as emotional support

may be important in reducing biological risk for African Americans, particularly those who experience depression.

CHAPTER VI

CONCLUSION

This dissertation sought to achieve two aims: (1) Apply Latent Profile Analyses (LPA) to continuous level biomarkers in the National Health and Nutritional Examination Survey (NHANES) data to segment the participants into a set of qualitatively distinct biological risk profile subgroups and (2) expand upon the model in Aim 1 to examine the association between depression, social support and risk profile membership. To address Aim 1, I tested the hypothesis that latent profile analysis would identify at least five profiles associated with cardiovascular risk (Hypothesis 1a.). However, latent profile analysis only identified four cardiovascular risk profiles (i.e. vascular risk, kidney risk, inflammatory risk, and low risk). It is possible this could have occurred as a result of the use of different biomarkers used in the latent profile analysis. Preliminary work using cluster analysis to develop cardiovascular risk profile groups used LDL and HDL to develop the profiles. Upon further research, total cholesterol was identified as a more favorable measure as it incorporated both HDL and LDL. However, this may have influenced the presence of a cholesterol risk profile.

It was also hypothesized that an increase in age will predict membership in higher risk profiles (Hypothesis 1b). We found evidence that this hypothesis was correct. Increase in age was associated with vascular, kidney, and inflammatory risk. We also

found that inflammatory risk was observed in group where the mean age is 33. This group were more likely to be African American and female. These findings well align with the weathering hypothesis which suggests African American women may experience symptoms of biological weathering beginning in their 20s. These findings also support the hypothesis that risk profile membership will differ by sex. The working hypothesis for this dissertation asserted that the males will more likely have membership in the kidney risk while females will more likely hold membership in vascular risk profiles (Hypothesis 1c). Our results indicate that males were at least 20 times more likely to be in the kidney in profile and the vascular risk profile. However, females were much more likely to be in the inflammatory risk profile. This may give credence to the notion that the driving biological mechanisms of allostatic load may differ by sex.

A sample of participants 40 and over were required to address Aim 2 based on the availability of the variables of interest. In this sample, latent profile analysis identified two risk profiles; low risk and inflammatory risk. It was hypothesized that an increase in depression scores would result in membership in risk profiles (Hypothesis 2a). We found evidence that this hypothesis was true as an increase in depression scores significantly increased odds of membership in the inflammatory risk profile. These results are consistent with literature that suggests that depression increases cardiovascular risk. Further, these findings may provide evidence that the mechanism in which this occurs is through an inflammatory response.

We also examined the hypothesis that social support would increase the probability of membership in a low risk profile. We examined three aspects of social

support; financial, emotional, and social network. We did not find evidence that social support was significantly related to inflammatory risk. However, we find evidence that social support moderates the relationship between depression and inflammatory risk (Hypothesis 2c). Emotional support was shown to significantly reduce the positive association between depression and inflammatory risk. However, financial support and social network showed no moderating effect.

Future Study

This dissertation project finds evidence that there are varying biological drivers of allostatic load. This adds to the literature that suggests that physiological responses to different stressors are not identical. Therefore, a specific stressor may elicit a specific physiological response that may differ from other stressors. For example, those who may suffer from chronic depression may have inflammatory risk compared to those who may experience a lifetime of financial hardship. Future studies should investigate whether this premise holds true across different stressors in the development of cardiovascular risk profiles. In addition, the weathering hypothesis suggests that minorities frequently report racism and discrimination. Future study should examine the impact of reported experiences of racism and discrimination among minorities as these experiences may have specific "drivers" of allostatic load, particularly in the context of cardiovascular disease disparities. Lastly, depression and cardiovascular disease risk has been shown to have a bidirectional relationship. Future research should examine the effect on cardiovascular risk profile on the subsequent diagnosis of depression or having depressive symptoms.

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