CARDIOVASCULAR RISK AND PSYCHOSOCIAL FACTORS IN BLACKS: A META-ANALYSIS OF INDIVIDUAL PARTICIPANT DATA

by

Amanda J. Onwuka

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Doctoral Committee:

Professor Ana V. Diez Roux, Co-Chair, Drexel University
Professor Carlos F. Mendes de Leon, Co-Chair
Professor Lynda D. Lisabeth
Associate Professor Brisa N. Sánchez

Amanda J. Onwuka

richaj@umich.edu

ORCID iD: 0000-0001-6662-8560

Acknowledgments

I was 10 years old when my mother and I relocated to Charlottesville, Virginia so she could pursue her doctoral studies. I read with her in the library as she studied for classes, I sat outside the room when she defended, and I more than filled her plate with troublesome antics in the meantime. I am the 5th generation of women in my family to be college educated and the 3rd generation of women to gain a Doctorate of Philosophy. I am grateful for the women in my family who have paved the way for me to pursue this degree, and I am certain that Jeanita Richardson, Jean White, and Anita Anderson are dancing today.

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List of Abbreviations

BMI: Body Mass Index

CARDIA: Coronary Artery Risk Development in Young Adults Study

CES-D: Center for Epidemiologic Studies Depression Scale

CDC: Centers for Disease Control and Prevention

CI: 95% Confidence Interval

CRP: C-Reactive Protein

CVD: Cardiovascular Disease

DBP: Diastolic Blood Pressure

EOD: Experiences of Discrimination Scale

HPA: Hypothalamic-Pituitary-Adrenal

HR: Hazard Ratio

JHS: Jackson Heart Study

MESA: Multi-Ethnic Study of Atherosclerosis

MI: Myocardial Infarction

SBP: Systolic blood pressure

SD: Standard Deviation

SEP: Socioeconomic Position

SES: Socioeconomic status

SNS: Sympathetic Nervous System

Abstract

Background. Blacks have higher age-adjusted mortality rates than any other ethnic groups; however, the reasons for these disparities are still largely unknown. Many have theorized that psychosocial risk factors, such as depressive symptoms, hostility, discrimination and job strain, may contribute to CVD risk; however, few studies have had a large enough sample size to investigate to what extent psychosocial factors predict cardiovascular risk in Blacks or whether other factors like age or sex modify these effects.

Methods. This study pooled individual-level data from three population-based cohort studies (the Coronary Artery Risk Development in Young Adults, the Multi-Ethnic Study of Atherosclerosis, and Jackson Heart Study) to investigate the effect of psychosocial factors on hypertension (Aim 1), diabetes (Aim 2), and incident cardiovascular disease (Aim 3) in Blacks. We estimated the cross-sectional and longitudinal relationship between psychosocial risk factors and cardiovascular risk using Poisson and Cox regression, and we tested for heterogeneity of effect using interaction terms.

Results. One standard deviation increase in depressive symptoms were associated with a 14% increase in the rate of hypertension (CI: 1.08, 1.20), an 8% increase in the rate of diabetes (CI: 1.00, 1.16), and a 13% increase in the rate of CVD (CI: 1.03, 1.25). One standard deviation increase in hostility was associated with 15% increase in incident hypertension in the pooled sample (CI: 1.09, 1.21), and effects of hostility on diabetes and CVD were noted within specific cohorts and age groups. Discrimination is associated with a 9% increase in incident hypertension in Black men (CI: 1.00, 1.18), but not in Black women, and the effects of

discrimination tended to be strongest in the MESA cohort. Finally, we observed that job strain is associated with a 27% increase in the rate of hypertension in the pooled sample (CI: 1.07, 1.50), and effects of job strain on diabetes and CVD were noted within specific cohorts and geographic regions.

Conclusions: Depression poses a threat to cardiovascular health in Blacks, and the integration of mental health services is a promising strategy to reduce the incidence of CVD in Blacks. Given the variability of effects among other psychosocial characteristics, though, it does not appear that these risk factors explain systematic differences in the CVD risk profiles in Blacks. Particular attention to macrosocial constraints on mental health and healthy lifestyles will enable researchers to intervene on the broader social and environmental context which perpetuate racial disparities in cardiovascular disease.

CHAPTER 1. INTRODUCTION

1.1 Overview

Cardiovascular diseases are consistently the leading cause of death in the U.S., and Blacks have the highest age-adjusted mortality rates due to cardiovascular disease than any other ethnic group. These disparities are due in part to established behavioral and biomedical risk factors for cardiovascular disease (CVD), although other reasons for the strong racial patterning of established CVD risk factors are not well known. Many have theorized that specific psychosocial risk factors, such as depressive symptoms, hostility, discrimination and job strain, may affect the distribution of established CVD risk factors and may also contribute to CVD risk independent of these risk factors. Blacks tend to have a higher prevalence of these adverse psychosocial characteristics, and may be more vulnerable to the deleterious effects of these risk factors.

The overall goal of this dissertation was to conduct a systematic evaluation of the role of psychosocial risk factors in the etiology of cardiovascular disease (CVD) in Blacks. In prior research, few studies have had a large enough sample sizes to investigate to what extent these psychosocial factors predict cardiovascular risk in Blacks, or whether other factors like age or sex modify these effects. This study pooled individual-level data from three large, population-based cohort studies (the Coronary Artery Risk Development in Young Adults, the Multi-Ethnic Study of Atherosclerosis, and the Jackson Heart Study) to enable the investigation of

psychosocial effects on cardiovascular health in a large sample of Black study participants heterogeneous in age, sex, geographic region and socioeconomic position.

1.2 Cardiovascular Disease and Health Disparities

Cardiovascular diseases (CVD) are a persistent threat to public health in the U.S. Roughly 1 in every 3 deaths is due to CVD in the U.S., and CVD has been the leading cause of death annually since 1918[1]. Though the majority of these deaths occur late in life, one third of deaths due to CVD occur prior to age 75, well before the average life expectancy of 77.9 years[2]. Recent decades have seen marked decreases in CVD mortality largely due to medical therapies and the changing distribution of CVD risk factors[2]. However, cardiovascular diseases continue to be major sources of morbidity and disability in the U.S., where we observe roughly 1.5 million heart attacks and strokes each year[3].

It is well established that African Americans are at a higher risk for CVD than Whites. Black-White disparities in cardiovascular disease are apparent as early as ages 25-34, where Blacks have 4.0 times the rate of mortality from hypertensive diseases[4]. Disparities in stroke mortality become apparent between the ages of 35-44, where Blacks are twice as likely to die from cerebrovascular diseases[4]. Mortality disparities are preceded by disparities in CVD incidence. The Multi-Ethnic Study of Atherosclerosis (MESA) found that the risk of developing congestive heart failure over a four-year period was higher among Black compared with White participants (HR: 1.8, CI: 1.1-3.1)[5]. The Reasons for Geographic and Racial in Stroke (REGARDS) study found that Blacks were 4 times as likely to experience a stroke during ages 45–54 years compared to Whites (CI: 1.23–13.11)[6]. Black-White disparities in CVD incidence

and mortality remain relatively stable over the life course until ages 65 and over where we see reductions in disparities, likely due to survival bias[3].

Hypertension and Type 2 Diabetes Mellitus are consistently identified as key biomedical risk factors for cardiovascular diseases. The National Heart, Lung, and Blood Institute suggests that "approximately 69% of people who have a first heart attack, 77% of those who have a first stroke, and 74% of those who have [congestive heart failure] have blood pressure >140/90 mm Hg"[1]. Diabetes has become a more salient risk factor for CVD as the population ages and the prevalence of obesity and sedentary life habits increase[7]. In a matched case-control study, researchers found 3-fold increases in the odds of mortality from stroke among adults with diabetes compared to those without[8].

Disparities in hypertension and diabetes precede disparities seen in cardiovascular diseases. The Behavioral Risk Factor Surveillance System found that 38% of Blacks report high blood pressure compared to 29% in Whites, and 13% of Blacks report being diagnosed with diabetes compared to 8% of Whites in 2014[9]. Hypertension and diabetes share a range of social and behavioral risk factors including, socioeconomic position, physical activity, diet, and tobacco use. The distribution of these characteristics partially explains different CVD risk profiles, but even after their adjustment, researchers find persistent racial differences in cardiovascular risk[10,11]. This suggests that other risk factors may be at play, making Blacks in the U.S. more susceptible to hypertension, diabetes, and eventually CVD.

1.3 The Role of Psychosocial Factors

Many have theorized that psychosocial factors may help to explain excess cardiovascular risk in Blacks through two key mechanisms. The first pathway suggests that psychosocial stress and negative affect may alter one's behavior, namely increasing smoking, decreasing physical activity and compromising diet. These behaviors, then, increase susceptibility to cardiovascular risk factors and disease. There is fairly strong evidence that individuals who experience stress or negative affect are at increased risk to initiate smoking[12] and sedentary leisure habits[13]. Further, many have documented the relationship between obesity and depressive symptoms[14], job strain[15], hostility[16], to suggest that one mediator may also be diet. In sum, individuals with negative affect or psychosocial stress may engage in risk behaviors as coping mechanisms, increasing their vulnerability to cardiovascular disease.

The second potential pathway is that chronic stress has a direct effect on physiological processes. Chronic stress can cause the excessive activation of the sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenal (HPA) axis. Increased cortisol, a product of HPA activation, can restrict alter the body's sensitivity to insulin[17]. Catecholamine release, a function of the SNS, increases the heart rate, blood pressure and respiratory rate. Also, inflammation, a product to SNS activation, can cause arterial plaque and thrombus formation[18]. The cumulative effects of the hyperactivity of the HPA axis and SNS include insulin resistance, hypertension and atherosclerosis, substantiating the link between psychosocial stress and cardiovascular disease. Indeed, psychosocial stressors have been found to have a direct effect on coronary artery calcification [19–22], inflammation [23–26] , and metabolic syndrome [16,27,28].

There is a growing body of evidence establishing a relationship between specific psychosocial factors, such as depressive symptoms, hostility, racial discrimination and job strain, and cardiovascular risk. Depressive symptoms and hostility are indicators of negative affect, and discrimination and job strain are indicators of psychosocial stress. These four risk factors are of particular interest because their prevalence is often higher among Blacks than other populations groups, they are measured reliably and with high internal consistency, and because they are thought to have the greatest influence on cardiovascular disease. Findings of previous research are discussed below.

1.3.1 Depressive Symptoms

Depression is a state of sadness and pessimistic ideation, and symptoms generally include loss of pleasure in normally enjoyable activities, feelings of worthlessness, diminished ability to think or concentrate, or recurrent thoughts of death or suicide[29]. Depressive symptoms are often the subject of cardiovascular research. A meta-analysis of nine prospective studies in 2012 found that depressive symptoms were significantly associated with hypertension incidence [Rate Ratio: 1.42, CI: 1.09 to 1.86][30]. Another meta-analysis of 13 prospective studies demonstrated that depressive symptoms are associated with a 60% increase in the risk of diabetes (RR: 1.60, CI: 1.37–1.88)[31]. Finally, another meta-analysis of 17 studies demonstrated a significant positive association between depressive symptoms and risk of stroke (RR: 1.34, CI: 1.17–1.54)[32]. There are also a range of studies that investigate the relationships between depressive symptomatology and other forms of cardiovascular disease[33–35]. Evidence for this relationship in diverse populations suggests that the relationship between depressive symptoms and cardiovascular risk

is often stronger in Blacks than Whites[36–39].Although there is some evidence of heterogeneity of effect by other sociodemographic characteristics, that research is less consistent [40,41].

Depressive symptoms were assessed using a 20-item Center for Epidemiologic Studies Depression Scale (CES-D) in all three cohort studies[42]. CES-D was assessed in exam 1 of MESA and JHS and in exam 3 of CARDIA. CES-D evaluates multiple symptom clusters, including depressed affect, lack of hope, feelings of guilt and shame, and somatic symptoms (e.g., disrupted sleep or appetite). Participants are asked to identify their experience with various symptoms over the past week. Sample items include "I thought my life had been a failure", "I felt that I could not shake off the blues even with help from my family or friends," and "I felt that everything I did was an effort". Each item is measured on a frequency scale (0 = Rarely or None of the Time, 1 = Some or a Little of the Time, 2 = Occasionally or a Moderate Amount of Time, 3 = Most or All of the Time). Four items are framed positively and reverse coded. Total scores can range from 0 to 60, and higher scores represent more depressive symptoms. The validity of the CES-D scale has been confirmed across age, sex and racial groups[43,44], and we consider CES-D to be appropriate for the study of depressive symptoms in Blacks.

1.3.2 Hostility

Hostility is a stable personality trait characterized by "cynicism, or the belief that others are motivated by selfish concerns, and mistrust, or the belief that others are likely to be provoking and hurtful" [45,46]. It is distinct from anger and aggression, which are dynamic behaviors and emotions. Most of the research conducted on hostility took place in the 1980s and 1990s, and these studies show mixed results. One investigation using the CARDIA study found that the highest quartile of hostility was associated with 84% higher odds of hypertension

compared to the lowest quartile, after adjusting for known confounders[47]. But, only half of the studies on hostility and coronary heart disease, for example, report positive associations; the other half report null associations[48–51]. As a result, there is a lack of understanding on the role of hostility in cardiovascular disease, particularly among racial and ethnic minorities. A key limitation of this research is that it was conducted in the psychology discipline where researchers relied on self-reported measures of heart disease and could not adequately adjust for potential confounders of this association. Further, the study of hostility in Blacks is also limited, but some evidence from CARDIA suggests that the effects of hostility are similar for Blacks and Whites[47,52].

Hostility was assessed using the Cook-Medley Hostility Scale [53]. The Cook-Medley Hostility Scale is a 50-item questionnaire derived from the Minnesota Multiphasic Personality Inventory and the key construct assessed by the scale is cynicism [54]. Sample items include "I think most people would lie to get ahead" and "Most people make friends because friends are likely to be useful to them". Each item is rated on a binary scale (0 = Probably False, 1 = Probably True). The Cook-Medley scale has been validated, and hostility scores tend to be positively correlated with negative life events and negatively correlated with social support[55]. Hostility was assessed in exam 3 of CARDIA, exam 1 of JHS and in exam 2 of MESA. There are seven common items across the studies that were used in the primary analysis and these items were summed to create the hostility score. Scores range from 0 to 7, and higher scores indicate higher cynicism and hostility.

1.3.3 Discrimination

Discrimination is described as the unfair treatment of a person or group based on race, sex, or other physical or social characteristics[29]. The relationship between racial discrimination and cardiovascular risk factors and disease is difficult to characterize. There is a great deal of research assessing the effect of discrimination on hypertension, but very little on discrimination and other cardiovascular outcomes. Of the more than 20 peer-reviewed studies on the relationship between racial discrimination and hypertension, the evidence is mixed with 8 studies showing inverse or null associations.

This inconsistency may be the result poor assessment of discrimination or limitations in study design. Researchers have operationalized discrimination using a various different scales making it difficult to compare across studies[56]. Further, much of this research has been conducted in community settings using self-reported measures of health[56]. These studies do not reliably assess health outcomes, and they often lack variability across demographic groups, limiting researchers' ability to adjust for confounders of the associations and generalize their results. Discrimination research has also relied heavily on cross-sectional data, which prevents researchers from making causal inference concerning the role of psychosocial characteristics and CVD [56]. There is much to be discovered about the impact of racial discrimination on cardiovascular health using studies with rigorous and comparable measurement.

Discrimination was assessed with the Major Experiences of Discrimination Scale [57,58]. This scale, also described as the Lifetime Discrimination Scale, assesses interpersonal experiences of unfair treatment that are attributed to one's group rather than one's own individual characteristics. Sample items include "Have you ever been unfairly fired" and "Have

you ever been unfairly discouraged by a teacher or advisor from continuing your education". Each item is rated on a binary scale (0: No, 1: Yes). We considered discrimination attributed to any cause cumulatively, not merely racial discrimination. The rationale for this decision was that unfair treatment, regardless of the cause, likely has similar effects on physical health. Discrimination was assessed in exam 1 of MESA and JHS and in exam 4 of CARDIA. There were four common items collected in all three studies and these items composed the discrimination score – a sum of the domains (e.g. work, school, community, etc.) where an individual has experienced discrimination. Scores range from 0 to 4, and higher scores indicate an experience of discrimination in more domains.

1.3.4 Job Strain

Job strain refers to the experience of high psychological demands and low decision latitude with one's employer[59]. The literature on job strain is ample, but also inconsistent. There are mixed results related to hypertension; however, the majority of the evidence supports the finding that individuals with job strain have a higher prevalence of hypertension[60–62]. The literature linking job strain to cardiovascular events, though, is both rich and consistent suggesting job strain increases risk of incident CVD and stroke[63–65]. One study found that job strain was strongly associated with incident coronary events even in models adjusted models for CHD risk factors (HR: 2.35, CI: 1.003-5.49)[23]. In sum, there appears to be a relationship between job strain and cardiovascular events that is independent of known behavioral risk factors, though the effect of job strain among Blacks is largely unknown[66,60,67]. More research in diverse populations is necessary better understand the relationship between job strain and CVD risk and the potential contributions of job strain to racial disparities in CVD.

Job strain was assessed using Karasek Job Content Questionnaire [59]. The scale evaluates two key domains: psychological demands and decision latitude. Psychological demands are an appraisal of stressors in the workplace and sample items include, "My job requires that I work fast" and "I have enough time to get the job done". Decision latitude assesses the extent of an individual's control over his/her tasks and sample items include, "I get to do a variety of different things on my job" and "I have very little freedom to decide how I do my work". Each item is rated on a frequency scale (0 = Rarely or None of the Time, 1 = Some or a Little of the Time, 2 = Occasionally or a Moderate Amount of Time, 3 = Most or All of the Time). The application of this scale in racial minorities has been limited, but the scale has been validated in other populations[59]. Job strain was assessed in exam 2 of MESA and CARDIA and in the second-year annual follow up call in JHS. The cohort studies had four common items, half of which were worded positively and reverse coded. Using median cutoffs for decision latitude and psychological demands, we constructed quadrants of job strain which included (1) low demand and high decision latitude (low strain), (2) high demand and high decision latitude (active jobs), (3) low demand and low decision latitude (passive jobs), and (4) high demand and low decision latitude (high strain).

1.4 Within-Group Study of Psychosocial Risk Factors

There is a strong rationale for the study of psychosocial stress within specific population groups. Various studies have demonstrated that psychosocial factors may have heterogeneous effects by race. A study by Lewis and colleagues found that elevated depressive symptoms were associated with CVD mortality in older Blacks but not in Whites[37]. Other research conducted by Thomas and colleagues suggests that less control at work is associated with larger increases in

diastolic blood pressure in Blacks than in Whites[68]. Others, too, have also found effect modification by race[38,39,69]. These findings signal that Blacks may be more susceptible to psychosocial stress, and though, potential explanations have not been tested in the literature, below are several hypotheses for the observed heterogeneity of effect.

First, evidence suggests that the prevalence of psychosocial risk factors relevant to CVD is substantially higher among Blacks compared with Whites[36,55,70,71]; however, differences in the chronicity of these psychosocial factors has not been tested. The substantially higher frequency of these psychosocial risk factors in Blacks may signal prolonged negative affect or stress. For example, the experience of job strain among someone with high employability may have different physiologic effects compared to the chronic and prolonged exposure to job strain in those with fewer employment opportunities. If Blacks are more likely to experience discrimination in hiring, have fewer jobs over their lifecourse, or otherwise stay in their jobs for considerably longer, this may explain a stronger effect of job strain in Blacks. In short, the chronicity of stress, undetected in current psychosocial scales, may be associated with stronger health effects than acute stressors.

Second, stronger psychosocial effects in Blacks may signal a higher severity of stress or negative affect in Blacks compared to Whites. There is a great deal of research in the education literature on the unfair treatment of Black boys in schools. Black boys are more likely to be suspended, expelled and referred to remedial education compared to White students with comparable behavior[72]. As a result, the experience of unfair treatment in school may more severe or carry different consequences in Blacks than in Whites. In short, psychosocial questionnaires

may be inadequate to assess differences in the severity of psychosocial factors, and this may result in heterogeneous effects of psychosocial factors as seen in the literature.

This trend may also indicate different clustering of stressors in Blacks compared to other racial and ethnic groups. For example, the trait of hostility may co-occur with race-related vigilance in Blacks, which independently associated with obesity, sleep quality, and other cardiovascular risk factors[73,74]. Further, psychosocial stressors may co-occur with macro-stressors, such as highly publicized examples of discrimination or historical trauma, which are also independently associated with poor health[75,76]. For example, the experience of being unfairly treated by police in a context of frequent and highly publicized police killings may induce a stress-response in Blacks that is unique to that of Whites. There are many potential explanations for heterogeneity of psychosocial effects by race that arise from the sociopolitical history of Blacks in the U.S., and as a result, the study of psychosocial stress both between and within populations is an asset to psychosocial research.

1.5 Heterogeneity in the Effect of Psychosocial Factors

In the same way that the effect of psychosocial stress is modified by race, psychosocial characteristics may also have differential effects by other demographic and contextual factors, such as age, sex, geographic location and socioeconomic position. Preliminary findings suggest that psychosocial characteristics may be particularly relevant in contexts where individuals have fewer resources to cope with stress.

1.5.1 Age

Psychosocial factors are also patterned by age, and the way that individuals cope or react to psychosocial stress may change throughout the life course. Several studies have found that stress response was heightened in older versus younger participants[77–79], one in particular showing that older participants had increased salivary alpha-amylase, cortisol and heart rates in response to a stress test[80]. This result is consistent with a "weathering" approach that would suggest that the additive effect of chronic stressors over the life course increases susceptibility to disease[81]. Also, older individuals may experience more isolation or financial strain which could magnifies the effect of negative affect and psychosocial stress in older populations. As a result, an informed hypothesis might suggest that older individuals have an increased vulnerability to psychosocial stress than younger individuals; however, this hypothesis has yet to be tested systematically in a population of racial and ethnic minorities.

1.5.2 Sex

There is a great deal of research related to effect modification of psychosocial stressors by sex. One study of job strain indicates that women with job strain have 4.2 times the odds of diabetes (OR: 4.2, CI: 2.0-8.7) compared to women without job strain, while men with job strain that show a protective effect against diabetes (OR: 0.4, CI: 0.2, 0.9)[82]. Another study conducted in JHS found that depressive symptoms are associated with metabolic syndrome in women, but not men[83]. These differences may be attributable to differing coping behaviors among men and women[84]; however, this hypothesis has not been thoroughly tested, nor has this trend been confirmed in ethnic minority groups. A systematic investigation of the interaction between

psychosocial stress and sex in Blacks would further elucidate if these growing trends are relevant across population groups.

1.5.3 Geographic Region

Few studies have investigated the potential role that geographic region of the U.S. might have on moderating the effect of psychosocial stress on CVD risk. This interaction, though, is reasonable given geographical region is not merely an indication of one's physical residence, but also, regions of the U.S. are characterized by different values, behaviors and political and social histories. That context, unique to each region, might have implications for the frequency of psychosocial stress, the physiologic effect of that stress, as well as potential resources to cope with or manage the stressor. Particularly given the prominence of the Stroke belt across the southern U.S.[85], the investigation of the role of psychosocial stress by geographic region may help to elucidate excess risk in the region.

1.6 Data Sources

The Coronary Artery Risk Development in Young Adults (CARDIA) Study is intended to examine the development and determinants of clinical and subclinical cardiovascular disease and their risk factors. It began in 1985 with a group of 5115 Black and White participants aged 18-30 years. The participants were free of chronic illness and disability and selected so that there would be approximately the same number of people in subgroups of race (52% Black), sex (46% male), education (40% high school diploma or less) and age (45% between 18-24 years) at baseline. All participants resided in one of four centers: Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA. Each site established its own recruitment strategies that were most appropriate for their populations. Most of the sites identified community-based target

populations to achieve desired diversity, though the Oakland site recruited from a Kaiser Permanente health plan. Participants were recruited through random digit-dialing, mailings and door-to-door outreach. These same participants were asked to participate in follow-up examinations in 1987-1988 (Exam 2, Year 2), 1990-1991 (Exam 3, Year 5), 1992-1993 (Exam 4, Year 7), 1995-1996 (Exam 5, Year 10), 2000-2001 (Exam 6, Year 15), 2005-2006 (Exam 7, Year 20), and 2010-2011 (Exam 8, Year 25). The study has maintained high retention levels at each follow-up exam (90%, 86%, 81%, 79%, 74%, 72%, and 72%, respectively). [86]

The Multi-Ethnic Study of Atherosclerosis (MESA) is a study of the characteristics of subclinical cardiovascular disease and the risk factors that predict progression to cardiovascular disease. The MESA sample consists of 6,814 asymptomatic men and women aged 45-84 at baseline. Approximately 38% of the recruited participants are White, 28% are African-American, 22% are Hispanic, and 12% are Asian. Participants were recruited from six centers across the United States, including Forsyth County, NC, Chicago, IL, New York, NY, Baltimore, MD, St. Paul, MN and Los Angeles, CA. Center-specific recruitment strategies were employed, but generally they included random-digit dialing, targeted mailings for racial and ethnic minorities, and referral for elderly minority populations. The participants were 47% male at baseline. The first examination took place over two years, from July 2000-July 2002, and was followed by four subsequent examinations: 2002-2004, 2004-2005, 2005-2007, and 2010-2012. Retention rates were high for all follow-up visits (94%, 89%, 86%, and 69% respectively). [87]

The Jackson Heart Study (JHS) study is the largest investigation of causes of CVD in an African-American population. JHS consists of 5,301 participants recruited from the Jackson, Mississippi, metropolitan area (Hinds, Madison, and Rankin counties). Roughly 17% of the

sample was recruited through random digit dialing; 30% of the cohort volunteered to be a part of the study; 22% of the participants were recruited as a part of the ARIC study, and the remaining 31% of participants were family of an index participant and referred to the study. Participants were 20-95 years of age when they enrolled in the study. At baseline, the mean age was 55, 37% were male, 39% had a high school diploma or less and 10% had a history of cardiovascular disease. Exam 1 took place between 2000-2004, exam 2 between 2005-2008, and exam 3 between 2009- 2012. Retention rates for exam 2 were 79% and 71% for exam 3[88].

The total sample of Blacks from all three studies aggregated to 9787 participants at baseline. CARDIA contributed 2644 Black participants to this study enrolled from all sites; MESA contributed 1892 Black participants to this study from five sites, as St. Paul, MN did not enroll Black participants, and JHS contributed 5301 participants from Jackson, Mississippi. The sample was limited to MESA, CARDIA, and JHS participants who have completed data for exposures and outcomes of interest and have no history of a cardiovascular event at baseline. History of cardiovascular disease included a physician-diagnosed heart attack, angina, stroke or transient ischemic attack, heart failure, current atrial fibrillation, or having undergone procedures related to cardiovascular disease (e.g. angioplasty, valve replacement, pacemaker or any surgery on the heart or arteries). These studies each have comparable measurement of the exposures and outcomes of interests, although the timing of this assessment varies quite a bit across studies (Appendix A). Detailed information on inclusion criteria and loss to follow up can be found in the Appendix B.

1.7 Rationale for This Study

The goal of this dissertation was to conduct a systematic investigation of the importance of several key psychosocial factors suspected in the etiology of CVD in Blacks – depressive symptoms, hostility, discrimination and job strain. Black-White disparities are not explained by socioeconomic, behavioral and biomedical risk factors, and psychosocial factors may account for elevated CVD risk in Blacks. Notable inconsistencies and methodological limitations in prior psychosocial research have prevented a better understanding of the true relationship between psychosocial factors and CVD outcomes, particularly in Blacks. Further, few studies have considered either the demographic or geographic contexts that may modify the influence of key psychosocial risk factors in contributing to CVD risk.

This research is novel in that it will provide the most rigorous and systematic study thus far of the role of psychosocial characteristics in the etiology of CVD, with a focus on negative affect and stressors that have particular relevance to the Black population. By pooling three cohort studies, we take advantage of available data with common conceptualization and measurement of psychosocial variables and cardiovascular outcomes. We also improve the power to detect an association between psychosocial characteristics and CVD and identify sources of heterogeneity within Blacks. A better understanding of how these psychosocial characteristics contribute to CVD risk in this population will have important implications for the prevention of cardiovascular disease, and the elimination of racial disparities in CVD.

1.8 Specific Aims and Hypotheses

Specific Aim 1: To investigate the association between psychosocial characteristics (depressive symptoms, hostility, discrimination and job strain) and both prevalent and incident hypertension among Blacks, and to determine if this relationship is modified by age, sex or geographic region.

Hypothesis 1a: Increased levels of depressive symptoms, hostility, discrimination and job strain will be positively associated with prevalent hypertension.

Hypothesis 1b: Increased levels of depressive symptoms, hostility, discrimination and job strain will be positively associated with incident hypertension.

Hypothesis 1c: The relationship between psychosocial factors and hypertension will be modified by social characteristics, such that the association is greater in participants who are older, females, and living in the South.

Specific Aim 2: To investigate the association between psychosocial characteristics (depressive symptoms, hostility, discrimination and job strain) and both prevalent and incident diabetes among Blacks and to determine if this relationship is modified by age, sex or geographic region.

Hypothesis 2a: Increased levels of depressive symptoms, hostility, discrimination and job strain will be positively associated with prevalent diabetes.

Hypothesis 2b: Increased levels of depressive symptoms, hostility, discrimination and job strain will be positively associated with incident diabetes.

Hypothesis 2c: The relationship between psychosocial factors and diabetes will be modified by social characteristics, such that the association is greater in participants who are older, females, and living in the South.

Specific Aim 3: To investigate the association between psychosocial characteristics (depressive symptoms, hostility, discrimination and job strain) and incident cardiovascular events (including but not limited to myocardial infarction, stroke, and heart failure) among Blacks and to determine if this relationship is modified by age, sex or geographic region.

Hypothesis 3a: Increased levels of depressive symptoms, hostility, discrimination and job strain will be associated with incident cardiovascular disease.

Hypothesis 3b: The relationship between psychosocial factors and cardiovascular events will be modified by social characteristics, such that the association is greater in participants who are older, females, and living in the South.

CHAPTER 2. PSYCHOSOCIAL FACTORS AND HYPERTENSION IN BLACKS

2.1 Abstract

Objectives. Examine the influence of depressive symptoms, hostility, discrimination and job strain on both prevalent and incident hypertension, as well as heterogeneity of effect by age, sex, and geographic region, in a diverse sample of Blacks.

Methods. We pooled individual-level data from 3 cohort studies comprising 8146 Black men and women who were free of cardiovascular disease at baseline. We used multivariate Poisson regression models to estimate prevalence ratios for prevalent hypertension at baseline, and we used Cox regression to estimate hazard ratios for incident hypertension. We tested for heterogeneity of effect using interaction terms.

Results. There were 1544 incident cases of hypertension in 54,628 person-years. One standard deviation increase in depressive symptoms was associated with a 14% increase in incident hypertension (CI: 1.08, 1.20), and one standard deviation increase in hostility was associated with a 15% increase in incident hypertension (CI: 1.09, 1.21). Job strain was associated with a 27% increase in the rate of hypertension (CI: 1.07, 1.50), but this effect was attenuated after adjustment for health behaviors in the pooled sample. Discrimination was associated with a 9% increase in incident hypertension but only among men (CI: 1.00, 1.18).

Conclusions. This study provided longitudinal evidence that depressive symptoms and hostility are independently risk factors for incident hypertension in a diverse sample of Blacks in the U.S. The use of an abbreviated job strain scale likely caused us to underestimate the effect of job strain on hypertension. Discrimination may also be a risk factor for hypertension among Black men. Efforts to minimize the prevalence and impact of psychosocial factors may be promising strategies to reduce hypertension incidence in Blacks.

2.2 Introduction

Hypertension presents a disproportionate threat to Blacks, compared to Whites, and the reasons for this disparity remain poorly understood. Between 2011 and 2014, the age-adjusted prevalence of hypertension among Blacks was 41%, while the prevalence among Whites was 28% [89]. While many have attributed this disparity to health behaviors or economic inequality, evidence suggests that these factors do not explain all of the disparity[90,91]. Mujahid and colleagues found that adjustment for neighborhood, and individual, socioeconomic status attenuated the association of race with hypertension, but race remained a significant predictor of hypertension [92]. Similarly, adjustment for health behaviors attenuates the association of race with hypertension, but race remains a significant predictor of hypertension [93].

Psychosocial stress and negative affect are well-established risk factors for hypertension. Depressive symptoms, for example, were associated with an increase in the risk of incident hypertension in a meta-analysis of nine prospective studies [30]. Hostility is also associated with higher odds of hypertension [47]. Sims and colleagues found a higher risk of prevalent hypertension among individuals reporting lifetime discrimination compared to participants who had not reported discrimination [94]. Still others have found that job strain is associated with higher risk of

elevated blood pressure [95]. There has also been evidence to the contrary, suggesting that each of these psychosocial characteristics are not, in fact, associated with hypertension [96–99]. A great limitation of prior research is the administration of studies in cross-sectional, community samples with little participation of racial and ethnic minorities, and as a result, much can be learned from the rigorous investigation of these factors within racial groups.

Negative affect and psychosocial stress may cause hypertension through a variety of mechanisms. Directly, psychosocial characteristics can cause sustained activation of the sympathetic nervous system and hypothalamic-pituitary-adrenal axis which can result in hypertension and atherosclerosis [17,18]. Indirectly, psychosocial characteristics may affect an individual's behavior, increasing smoking or yielding poor eating habits, which are known to increase blood pressure [12,13]. These behaviors may be motivated by physiologic responses to stress as one study found that chronic stress leads to increases in cortisol, which may drive individuals to consume hedonic, energy-dense foods[100]. One study of 12,000 participants found that high stress was associated with a higher fat diet, less frequent exercise and cigarette smoking[101].

Psychosocial risk factors are more prevalent in Blacks than Whites, but also, they may have stronger effects on the health of Blacks [36,55,70,71]. For example, the duration, severity or co-occurrence of stressors may vary by race, as well as the resources necessary to resolve or alleviate that condition [91,102]. Davidson found a stronger effect of depressive symptoms on hypertension in Blacks than in Whites in CARDIA[36]. Other research conducted by Thomas and colleagues suggests that less control at work is associated with larger increases in diastolic blood pressure in Blacks than in Whites [68]. These findings suggest that Blacks may be more susceptible

to psychosocial stress. As such, it is informative to study the effects of psychosocial stress not only across populations, but also within the Black population.

Preliminary findings suggest that psychosocial characteristics may also be particularly relevant in contexts where individuals have fewer resources to cope with stress [78,103,104]. One study in the Baltimore Longitudinal Study of Aging found that depressive symptoms were more strongly associated with blood pressure in older adults compared to young adults, and in women compared to men [40]. The investigation of heterogeneity of effect is still quite novel and particularly relevant within the Black population given age, sex and geographic region of the country are associated with different sociocultural experiences than in Whites [102].

To better understand these relationships, we designed a study to investigate the effects of selected psychosocial characteristics on hypertension in a diverse population of Blacks.

2.3 Methods

We pooled individual-level data from three prospective cohort studies: Coronary Artery Risk Development in Young Adults (CARDIA), Jackson Heart Study (JHS), and Multi-Ethnic Study of Atherosclerosis (MESA). The Coronary Artery Risk Development in Young Adults study began in 1985 with 2644 Black participants aged 18-35 at baseline. Participants were recruited from 4 study sites (Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA) and attended 8 examinations, the most recent ending in 2011 [86]. The Multi-Ethnic Study of Atherosclerosis began in 2000 with 1892 Black participants aged 45-84 years at baseline. Participants were recruited from 6 study sites (Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles, CA; New York, NY; and St. Paul, MN), attended 5 examinations, the most recent ending in 2012, and were asymptomatic of cardiovascular disease at baseline [87]. The

Jackson Heart Study began in 2000 with 5301 Black participants aged 20-95 at baseline. Participants were recruited from three counties in Jackson, MS and attended 3 examinations, the most recent ending in 2012 [88].

2.3.1 Inclusion Criteria

To maximize comparability, cross-sectional analyses were based on data from exam 1 (calendar years 2000-2002) from MESA, exam 1 (calendar years 2000-2004) for JHS and exam 6 (calendar years 2000-2001) from CARDIA. For our analysis, we included participants who self-identified as Black, who were free of cardiovascular disease at the corresponding exam and for whom complete data on psychosocial risk factors and hypertension were available. Cardiovascular disease was defined as physician-diagnosed heart attack, angina, stroke or transient ischemic attack, heart failure, current atrial fibrillation, peripheral vascular disease, deep vein thrombosis, or having undergone angioplasty, coronary bypass, catheterization, carotid endarterectomy, or other arterial revascularization (MESA=0, JHS=741, CARDIA=32). After these exclusions, there were 8146 participants included in the cross-sectional analysis.

For the survival analysis, we included data from the start of all cohort studies (2000 for JHS and MESA, 1985 for CARDIA). Prevalent cases of hypertension at the start of follow up were excluded (MESA=1126, JHS=2559, CARDIA=136), leaving 5186 participants in the incident hypertension analysis. Participants participated up to 3 exams in JHS, up to 5 exams in MESA and up to 8 exams in CARDIA. See the appendix for additional information on inclusion criteria and loss to follow up (Appendix B).

2.3.2 Exposure Measures

There are four psychosocial exposures that had been measured comparably across the three studies. Depressive symptoms were assessed using a 20-item Center for Epidemiologic Studies Depression Scale (CES-D) in all three cohort studies [42]. CES-D was assessed in exam 1 of MESA and JHS and in exam 3 of CARDIA. CES-D evaluates multiple symptom clusters, including depressed affect, lack of hope, feelings of guilt and shame, and somatic symptoms (e.g., disrupted sleep or appetite) with an emphasis on negative affect. Participants are asked to identify their experience with various symptoms over the past week. Sample items include "I thought my life had been a failure", "I felt that I could not shake off the blues even with help from my family or friends," and "I felt that everything I did was an effort". Each item is measured on a frequency scale (0 = Rarely or None of the Time, 1 = Some or a Little of the Time, 2 = Occasionally or a Moderate Amount of Time, 3 = Most or All of the Time). Four items are framed positively and reverse coded. Total scores can range from 0 to 60, and higher scores represent more depressive symptoms. The mean CES-D score was 7.9 (SD: 8.5).

Hostility was assessed using the Cook-Medley Hostility Scale [53]. The Cook-Medley Hostility Scale is a 50-item questionnaire derived from the Minnesota Multiphasic Personality Inventory and the key construct assessed by the scale is cynicism [54]. Sample items include "I think most people would lie to get ahead" and "Most people make friends because friends are likely to be useful to them". Each item is rated on a binary scale (0 = Probably False, 1 = Probably True). Hostility was assessed in exam 3 of CARDIA, exam 1 of JHS and in exam 2 of MESA. There are seven common items across the studies that were used in the primary analysis and these items were summed to create the hostility score. Scores range from 0 to 8, and higher scores indicate higher cynicism and hostility. The mean hostility score was 2.9 (SD:1.9).

Discrimination was assessed with the Major Experiences of Discrimination Scale [57,58]. This scale, also described as the Lifetime Discrimination Scale, assesses interpersonal experiences of unfair treatment that are attributed to one's group rather than one's own individual characteristics. Sample items include "Have you ever been unfairly fired" and "Have you ever been unfairly discouraged by a teacher or advisor from continuing your education". Each item is rated on a binary scale (0: No, 1: Yes). We considered discrimination attributed to any cause cumulatively, not merely racial discrimination. Discrimination was assessed in exam 1 of MESA and JHS and in exam 4 of CARDIA. There were four common items collected in all three studies and these items composed the discrimination score – a sum of the domains (e.g. work, school, community, etc.) where an individual has experienced discrimination. Scores range from 0 to 4, and higher scores indicate an experience of discrimination in more domains. The mean discrimination score was 1.4 (SD: 1.3).

Job strain was assessed using Karasek Job Content Questionnaire [59]. The scale evaluates two key domains: psychological demands and decision latitude. Psychological demands are an appraisal of stressors in the workplace and sample items include, "My job requires that I work fast" and "I have enough time to get the job done". Decision latitude assesses the extent of an individual's control over his/her tasks and sample items include, "I get to do a variety of different things on my job" and "I have very little freedom to decide how I do my work". Each item is rated on a frequency scale (0 = Rarely or None of the Time, 1 = Some or a Little of the Time, 2 = Occasionally or a Moderate Amount of Time, 3 = Most or All of the Time). Job strain was assessed in exam 2 of MESA and CARDIA and in the second-year annual follow up call in JHS. The cohort studies had four common items, half of which were worded positively and reverse coded. Using median cutoffs for decision latitude and psychological demands, we

constructed quadrants of job strain which included (1) low demand and high decision latitude (low strain), (2) high demand and high decision latitude (active jobs), (3) low demand and low decision latitude (passive jobs), and (4) high demand and low decision latitude (high strain). The median decision latitude score was 3.5 (IQR:1.0; Range: 0,4), and the median psychological demands score was 2.0 (IQR: 1.0; Range: 0,4). Twenty six percent of participants had low strain, 30% had active jobs, 12% had passive jobs, and 32% had high strain.

There was not repeated assessment for these psychosocial factors across all cohort studies. As a result, we model time-invariant psychosocial factors based on assessment at one point in time. The psychosocial assessment closest to baseline was used for the analysis. For additional information on the timing of psychosocial assessment, see Appendix A.

2.3.3 Outcome Measure

In 2014, the American Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure upheld the definition of hypertension as having systolic blood pressure of greater than or equal to 140 mmHG or diastolic blood pressure of greater than or equal to 90 mmHG 72. For the purposes of this study, hypertension is a dichotomous variable and defined as SBP >= 140 mmHg, DBP >= 90 mmHg, or the use of anti-hypertension medication. In CARDIA and MESA, three blood pressure assessments were averaged to get a final measure of blood pressure at each exam, and in JHS, two blood pressure assessments were averaged during each exam.

2.3.4 Covariates

We adjusted for a range of confounders that are risk factors for hypertension and associated with psychosocial characteristics. Covariates included age, sex, and geographic

region at the time of the corresponding exam. Geographic region was a categorical variable derived by the study site and defined by the U.S. Census Bureau as Northeast, South, Midwest or West [105].

Education was assessed differently by each study with varying degrees of specificity. To create a uniform measure of education across studies, responses were recoded into five condensed categories: (1) less than high school; (2) high school or GED completion or some college; (3) Technical school or associate degree; (4) bachelor's degree; and (5) graduate or professional school. For the cross-sectional analysis, education was operationalized as a 5-level ordinal variable based on data from baseline. For the survival analysis, education was operationalized as a time-varying ordinal variable, as there was repeated measurement in CARDIA.

Income was assessed as a categorical variable by each study; however, the income categories did not align across studies. To create a uniform measure of income across studies, responses were transformed into a continuous income variable. For discrete income categories, the midpoint value for each category was assigned to the individual. For the highest income category, we calculated the median income for individuals earning over 75,000 annually and over 100,000 annually using U.S. Census data, and that average income was used for individuals in the highest income category. For the cross-sectional analysis, income was operationalized as a continuous variable using income data from the corresponding exam. In the survival analysis, income was operationalized as a time-varying continuous variable, as there was repeated measurement in CARDIA and MESA. Participants with missing income data were assigned the mean income for their cohort study. In the study-specific analyses, income was used on the

original study-specific scale, and we conducted sensitivity analyses to address the impact of missing income data.

Smoking was collected similarly across all three studies: never smokers, former smokers and current smokers. For the cross-sectional analysis, smoking was operationalized as a 3-level categorical variable (current smokers, former smokers, and never smokers) using smoking data from the corresponding exam. For the survival analysis, smoking was operationalized using a time-varying categorical variable, as there was repeated measurement in all three studies.

Physical activity was assessed differently in all three studies, each study using a different questionnaire for physical activity items. Physical activity was assessed with a 28-item questionnaire in MESA, a 40-item questionnaire in JHS, and a 13-item questionnaire in CARDIA. There were 8 common activities across studies, but they were captured using such different frequencies that harmonization would have introduced substantial error. For example, JHS requested the frequency per month of leisurely walking at least 15 minutes; CARDIA requested the number of months where participants walked at least one hour a week for leisure; and MESA requested the number of hours a day where participants walked for leisure. As a result, physical activity was excluded in our pooled analyses but included in the study-specific analyses. Physical activity in MESA was operationalized as the sum of moderate and vigorous physical activity MET-hours/week. In JHS, physical activity was operationalized as a 3-level ordinal variable for light, moderate or heavy physical activity based on the American Heart Association's Life Simple Seven. In CARDIA, physical activity was operationalized as a continuous measure of heavy and moderate physical activity. Physical activity was time-varying in the MESA and CARDIA studies.

Body Mass Index (BMI) was collected similarly across all three studies. For the cross-sectional analysis, BMI was operationalized as a continuous variable using data from the corresponding exam. In the survival analysis, BMI was operationalized as a continuous, time-varying variable, as there was repeated measurement in all studies.

2.3.5 Statistical Analyses

Descriptive analyses assessed the distribution of covariates and outcome by study. We also assessed the distribution of covariates by tertiles of each psychosocial exposure. For the cross-sectional analysis, we used modified Poisson regression to estimate prevalence ratios for hypertension. Modified Poisson regression with robust error variances is recommended to estimate prevalence ratios and confidence intervals for binary outcomes when log-binomial models fail to converge [106–108]. These models have a Poisson distribution and a log link function and use the repeated statement for the sandwich variance estimator. We used baseline data for JHS and MESA which began in 2000; however, CARDIA participants were 18-35 years of age at baseline in 1985. To ensure comparability of age across studies, we used hypertension data from the year 2000 for CARDIA participants, at which point they were 33-50 years of age. We estimate the relevant associations for each cohort, as well as the pooled sample, and to test for differential effects by cohort, we include an interaction term for psychosocial indicator and the cohort study.

We adjusted for the covariates above in a stepwise manner. The purpose of this sequential modeling was to isolate the influence of health behaviors which may be on the causal pathway. The first model included adjustment for sex and cohort study, and the second model included socioeconomic position and geographic region. The third model included adjustment

for health behaviors. We adjusted for cohort study as a fixed effect, and tested for differences in the effect of psychosocial factors between cohorts using interaction terms in fully adjusted models.

For the survival analysis, we employed Cox regression to estimate the relationship between each stressor and incident hypertension in our pooled sample. We used age as the time scale, rather than time in study, because the study enrollment occurs at an arbitrary time point and is not clinically relevant [109–111]. We performed Cox regression with a stratification term for cohort, which allows each cohort to have a different baseline hazard function, and we adjusted for all covariates listed above in a stepwise manner. The exposure was assigned to baseline to maximize follow up time and the analysis included time-varying covariates for education, income, BMI, physical activity, and smoking status.

The final goal of this analysis was to assess whether the relationship between psychosocial characteristics and hypertension was modified by sociodemographic factors, including age, sex, and geographic region. Age was modeled linearly as we hypothesized a gradual increase in the effect of psychosocial factors by age; further, no threshold was identified in the literature whereby psychosocial factors increase in effect. Sex was modeled with a binary variable; and region with a categorical variable. We conducted this analysis using interaction terms between age, sex and geographic region with the psychosocial characteristics of interest in the fully-adjusted Cox models. We noted effect modification if $p \leq 0.10$ for the interaction term. For interpretation, we stratified results based on the effect modifier.

We conducted a range of sensitivity analyses to investigate whether the effects of the analysis held under different conditions. We assessed the impact of imputing income for missing

data by repeating the Cox model and excluding those for whom income was missing. We replicated the primary analyses within each cohort study using the abbreviated psychosocial scales and the full scales available in each study. Finally, we repeated the survival analysis using a parametric interval-censored model with a Weibull distribution to address the impact of left censored participants. Results for the sensitivity analyses can be found in the supplementary materials for this chapter.

2.4 Results

There were 8146 participants included in our cross-sectional analysis after exclusion for cardiovascular disease and missing covariate data (1739 CARDIA participants, 4529 JHS participants, and 1878 MESA participants). The prevalence of hypertension was 47% in the full sample, representing 3918 participants. There were 435 prevalent cases in CARDIA (16%), 2559 prevalent cases in JHS (56%), and 1126 prevalent cases in MESA (60%).

For the incident hypertension analysis, there were 5186 participants after the exclusions mentioned above (MESA=762, JHS=1986, CARDIA=2438). We observed 1544 new cases of hypertension over 54,628 person-years at risk. The hypertension incidence rate is 20 per 1,000 person years in CARDIA, 36 per 1,000 person years in JHS, and 86 per 1,000 person-years in MESA.

2.4.1 Characteristics of the study population

The mean age in our pooled sample was 53 (SD: 13). Forty percent of the participants were male. Much of the sample population resided in the South (63%), while 11% were in the Western region of the U.S., 16% were in the Midwest, and 10% were in the Northeast. More than 30% of the sample had attained a bachelor, graduate or professional degree, 12% had some

college and 42% of the sample has a maximum education attainment of a high school diploma or GED. The mean income in the study was roughly $44,000 per year. The mean BMI was 31 (SD: 7). Sixty percent of participants were never smokers, and roughly 20% were current smokers.

Depressive symptoms were highest in CARDIA and lowest in JHS and we observe some differences in dispersion between studies. Hostility and discrimination scores were highest in JHS and lowest in MESA, and we note differences in the dispersion of discrimination by cohort. Finally, high job strain is most prevalent in CARDIA and least prevalent in JHS, with notable differences in dispersion between studies (**Table 2.9-1**).

2.4.2 Cross-Sectional Analyses

One standard deviation increase in CES-D was associated with a 4% increase in hypertension prevalence in Blacks (CI: 1.01, 1.06), after adjusting for age, sex, geographic region, education, income, BMI or smoking status. We found that Blacks with higher hostility, discrimination and job strain scores did not have an increased risk of prevalent hypertension in the pooled sample.

There was a statistically significant difference in the effect of CES-D by cohort, whereby we noted a much stronger association between CES-D and prevalent hypertension in CARDIA compared to the other cohorts (p for interaction for MESA compared to CARDIA: 0.01, p for interaction for JHS compared to CARDIA 0.01). In stratified analyses, the prevalence ratio for CES-D and hypertension was 1.23 in CARDIA (CI: 1.07, 1.42), compared to 1.03 in JHS (CI: 0.97, 1.08), and 1.02 in MESA (CI: 0.94, 1.10) for fully adjusted models. There were no statistically significant differences in the effect of hostility, although we did note a greater

magnitude of effect in CARDIA than in other studies. Effect estimates for discrimination and job strain were similar across cohorts (Table 2.9-2).

2.4.3 Longitudinal Analyses

In the pooled sample, we found that CES-D and hostility were positively associated with incident hypertension after adjustment for age, sex, geographic region, education, income, smoking and BMI. One standard deviation increase in CES-D was associated with a 14% increase in the rate of hypertension (CI: 1.08, 1.20). Similarly, one standard deviation increase in hostility was associated with a 15% increase in the rate of hypertension (CI: 1.09, 1.21). High job strain was associated with a 27% increase in the rate of hypertension (CI:1.07, 1.50), but this effect was attenuated after adjusting for health behaviors. Discrimination was not associated with incident hypertension in the pooled sample. In MESA, though, discrimination is marginally associated with incident hypertension (HR: 1.10, CI: 0.97, 1.27) (Table 2.9-3).

There were no statistically significant differences in the effect of CES-D, hostility, discrimination or job strain by cohort. Qualitatively, we note larger hazard ratios for job strain in CARDIA and MESA compared to JHS, and the effects of CES-D and discrimination are slightly larger in MESA.

2.4.4 Effect Modification

The total number of interactions tested were 30, and three were statistically significant. We find that CES-D and discrimination are modified by sex (p for interaction 0.10 and 0.05, respectively), such that these characteristics appear to have stronger effects in Black men compared to Black women. Also, we find heterogeneous effects of hostility across geographic

regions. Hostility appears to have stronger effects in the Midwest compared to the South (p for interaction 0.03). We did not find evidence of effect modification by age. (Table 2.9-4)

We suspected that the observed heterogeneity of effect by sex and geographic region may be an artifact of cohort differences. As a result, we included an interaction term for depressive symptoms and cohort, in addition to the interaction between depressive symptoms and age (results not shown). After this adjustment, it appears that the depression-sex interaction was no longer significant. We did the same to test other effect modification results, and found that only the interaction between discrimination and sex remains statistically significant (p=0.05). A one standard deviation increase in discrimination is associated with a 9% increase in the rate of hypertension in men (CI: 1.00, 1.18), but discrimination and hypertension are not associated in women (HR: 0.98, CI: 0.91, 1.05).

2.5 Discussion

The current study was designed to examine the relationship between psychosocial characteristics and hypertension in a heterogeneous sample of Blacks in the U.S. We observed that depressive symptoms, hostility and job strain were salient risk factors for hypertension. These relationships were most apparent in longitudinal models where we assessed the risk of developing hypertension; cross-sectional models were inconclusive. Interestingly, the effect of discrimination was modified by the participant's sex, such that Black men were more vulnerable to the effects of discrimination than Black women.

This study confirmed that negative affect is independently associated with incident hypertension in a diverse sample of Blacks. We observe strong and stable effects of depressive symptoms and hostility across cohorts. Previous literature had suggested this association,

although much of this work was cross-sectional and lacked a great deal of diversity in the sample population[30,36,47]. We did not find evidence that depressive symptoms or hostility were modified by age, sex or geographic region.

One departure from previous literature was our finding that discrimination is not associated with hypertension in the pooled sample. Previous research on the relationship between hypertension and discrimination, particularly using the major experiences of discrimination scale, has been inconclusive [71,94,98]. However, our finding that discrimination might be modified by context may help to understand mixed findings. Our analysis demonstrates that discrimination poses greater hypertension risk for men compared to women. This finding was contrary to our hypothesis, although Hickson observed a relationship between discrimination and subcutaneous fat in Black men but not in Black women[112]. This finding may signal that the severity and implications of discrimination experienced by Black men are unique[72,113]. Also, coping behaviors may be patterned by sex. Sims and colleagues found that in women, discrimination is associated with more physical activity, compared to men [84]. There is still much to learn about the nature of discrimination and coping behaviors across sexes, but this finding is a substantive contribution to the literature.

This study was one of the first to identify job strain as a risk factor for incident hypertension in Blacks. The magnitude of this effect was quite strong, though it was attenuated after adjustment for health behaviors. This finding suggests that BMI and smoking are potential mediators of the relationship between job strain and hypertension. Support for this hypothesis is limited, as there are mixed findings on the relationship between job strain and health behaviors. The most in-depth study of BMI and job strain, a meta-analysis of 160,000 European

participants, found that job strain was associated with both weight gain and weight loss[15]. Another cohort study among women found that participants with higher BMI may be more vulnerable to BMI gain when exposed to constant work stress[114]. It appears that the relationship between job strain and BMI is nuanced and may be dependent on BMI prior to job strain. Regarding smoking, another meta-analysis of European cohort studies found no relationship between job strain and changes in smoking behavior; however, they did observe that smokers experiencing job strain smoked more cigarettes per day than smokers without job strain [115]. This finding has been replicated in other studies [116–119].

2.6 Limitations

This study is not without limitations. The three cohort studies employed in this analysis are unique in their target populations, survey administration and data collection. One key challenge was disparate measurement of confounders. We suspect health behaviors play a role in mediating the relationship between psychosocial characteristics and hypertension[120]; however, the cohort studies took such different approaches to measuring physical activity, nutrition, and alcohol consumption that harmonizing these variables for inclusion in the pooled analysis was not feasible. Although we corrected for physical activity in study-specific analyses, this may have had the effect of biasing our results.

Also, our assessment of psychosocial risk factors was often based on abbreviated and crude measurement due to pooling. The Cronbach's alpha for full versus abbreviated hostility scales was between 0.75 and 0.96 depending on the study ($p<0.001$ for all studies), discrimination was between 0.87 and 0.95 ($p<0.001$), and job strain was between 0.47 and 0.63 ($p<0.001$). Sensitivity analyses demonstrated that abbreviated psychosocial scales demonstrated

little bias with respect to hostility and discrimination, and substantial bias with respect to job strain (Table 2.9-7). We observed that high strain was associated with an 85% increase in the rate of hypertension (HR: 1.85, CI: 1.23, 2.79]. We conclude that the use of the abbreviated scale for job strain led to a substantial underestimation of its effect on incident hypertension.

Lastly, roughly half of our study population was excluded from the longitudinal analyses because participants developed hypertension prior to baseline. We were concerned about the impact that the exclusion of these left censored participants may have had on our results. We conducted sensitivity analyses using parametric survival models with a Weibull distribution and compared the results to that of the Cox model (Table 2.9-8). The Cox model and the parametric Weibull model perform similarly with respect to depressive symptoms and job strain. Regarding hostility, though, we observe a null association between hostility and incident hypertension in the parametric model. Further, we observe that a one-unit increase in discrimination is associated with a 5% increase in the rate of hypertension in the parametric model, while the Cox model demonstrated a null association. It is unclear if these differences are the result of the inclusion of left censored participants or the inability to adjust for time-varying confounders in the parametric model. While the source of this variation is unclear, future researchers should be aware of limitations of each model and potential implications of model selection on their results.

2.7 Conclusions

This study provided longitudinal evidence that depressive symptoms, hostility and job strain are risk factors for incident hypertension in a diverse sample of Blacks in the U.S. Discrimination may also be a salient risk factor for Black men and results were sensitive to

cohort study and modelling strategy. The size of this study allows for the detection of small effect sizes and effect modification of psychosocial characteristics. The diversity and breadth of this study distinguish it from previous work and help to elucidate the role of psychosocial risk factors in Blacks.

2.8 Supplementary Material

2.8.1 Covariates by Tertile of Psychosocial Characteristics

We created tertiles of each psychosocial characteristic to assess the distribution of covariates across the psychosocial indicators. Individuals in the lowest tertile of depressive symptoms identified fewer than 3 symptoms, the second tertile identified between 3 and 9 symptoms, and the highest tertile identified 10 or more symptoms. Individuals in the lowest tertile of hostility identified 0 or 1 symptoms, the second tertile identified 2 or 3 symptoms, and the highest tertile identified 4 or more symptoms. Individuals in the lowest tertile of discrimination identified no discrimination, the second tertile identified discrimination in 1 or 2 venues, and the highest tertile identified discrimination in 3 or more venues. For job strain, we investigate the distribution of covariates by categories (low strain, active job, passive job, and high strain).

Individuals with more psychosocial stress were most often CARDIA participants, younger and living in the West and Midwest regions of the country. Participants with higher depressive symptoms were more likely to be women, while participants with more hostility were more likely to be male. Participants with higher depressive symptoms, hostility and job strain were more likely to have lower education and income, while participants with more discrimination had

higher education and income. Finally, participants with higher depressive symptoms, hostility, and job strain were more likely to be current smokers. (Table 2.9-5)

2.8.2 Missing Income

There were 868 participants in the survival analysis for whom we imputed income data (MESA: 36, JHS: 301, CARDIA: 531). We conducted sensitivity analyses excluding participants with missing income data and we found that associations of similar magnitude as in the model with imputed income. Depressive symptoms and hostility were still significantly associated with incident hypertension, and discrimination and job strain were not associated after adjustment. We conclude that mean imputation for income had little effect in biasing our results. (Table 2.9-6)

2.8.3 Full Psychosocial Scales

We replicated the primary analyses within each cohort study using the full scales available in each study. The effect estimates for the full scales of hostility and discrimination demonstrated results similar in magnitude to the abbreviated scales. We did note a substantial difference in the effect of job strain using the full available scale. High strain was associated with an 85% increase in the rate of hypertension (HR: 1.85, CI: 1.23, 2.79]. We conclude that the use of the abbreviated scale for job strain led to a substantial underestimation of its effect on incident hypertension. (Table 2.9-7)

2.8.4 Parametric Weibull Models

Roughly half of study participants had hypertension at baseline and were excluded from the Cox analysis. We conducted sensitivity analyses using parametric interval-censored survival analyses with a Weibull distribution. This model maximizes statistical power through the inclusion of left-censored participants, who had developed hypertension prior to study

enrollment [121]. We used age as the time scale, rather than time in study, because the study enrollment occurs at an arbitrary time point and is not clinically relevant [109–111]. Prevalent cases were treated as left-censored, with an undefined age at the lower boundary and age at baseline as the upper boundary. Incident cases observed during the study had a lower boundary defined as the age at the last hypertension-free exam and an upper boundary defined as the age at the exam where hypertension was indicated. Right-censored participants, those hypertension-free at last follow-up or at the end of the study, had a lower boundary defined as the age at the last hypertension-free exam and an undefined upper bound. Our model controlled for study as a fixed effect, and we adjusted for all covariates listed above. This model does not allow for time varying covariates.

The Cox model and the parametric Weibull model perform similarly with respect to depressive symptoms and job strain. Regarding hostility, though, we observe a null association between hostility and incident hypertension in the parametric model. Further, we observe that a one-unit increase in discrimination is associated with a 5% increase in the rate of hypertension. The Cox model demonstrated a null association between discrimination and incident hypertension. It is unclear if these differences are the result of the inclusion of left censored participants or the inability to adjust for time-varying confounders in the parametric model. While the source of this variation is unclear, future researchers should be aware of limitations of each model and potential implications of model selection on their results. (Table 2.9-8)

2.9 Tables and Figures

Table 2.9-1 Selected Characteristics of Participants by Cohort Study (Exam 6 in CARDIA, Exam 1 in JHS and Exam 1 in MESA)

Population Characteristics	CARDIA	JHS	MESA	Pooled
Sample size	1739	4529	1878	8146
Age, Mean [Range]	39 [32,50]	54 [21,93]	62 [44,84]	53 [21,93]
Male	44%	35%	45%	40%
Region				
West	31%	0%	8%	11%
Midwest	44%	0%	16%	16%
Northeast	0%	0%	49%	10%
South	25%	100%	26%	63%
Education				
Less than high school	7%	18%	12%	14%
High school or GED	57%	37%	39%	42%
Technical School or Associate Degree	13%	11%	14%	12%
Bachelor's degree	19%	17%	17%	18%
Graduate or professional degree	5%	17%	17%	14%
Income, Mean [SD]	37,893 (29,742)	46,668 (34,319)	46,152 (29,270)	44,576 (32,419)
Body Mass Index, Mean [SD]	29 (7)	32 (7)	30 (6)	31 (7)
Smoking				
Never	58%	70%	45%	62%
Former	11%	18%	37%	20%
Current	32%	12%	18%	18%
Outcome Distribution				
Hypertension prevalence in 2000	16%	56%	60%	47%
New cases	763	424	357	1544
Person-years at risk	38,688	11,809	4,131	54,628
Incidence per 1,000 person-years	19.7	35.9	86.4	28.3
Psychosocial Distribution				
Depressive Symptoms, Mean [SD]	10.0 [9.1]	7.0 [8.3]	7.3 [7.3]	7.9 [8.5]
Hostility, Mean [SD]	2.9 [1.9]	3.2 [2.0]	2.3 [1.7]	2.9 [1.9]
Discrimination, Mean [SD]	1.4 [1.4]	1.6 [1.2]	0.9 [1.0]	1.4 [1.3]
Job Strain				
Low Strain	8%	36%	15%	26%
Active	37%	26%	32%	30%
Passive	4%	15%	14%	12%
High Strain	50%	22%	40%	32%

Table 2.9-2. Prevalence Ratios for Prevalent Hypertension for a 1-unit Increase in Standard Deviation of Psychosocial Characteristics in 2000

Psychosocial Characteristics	**CARDIA**	**JHS**	**MESA**	**Pooled**
CESD				
Model 1*	1.29 [1.13, 1.46]	1.04 [0.99, 1.09]	1.02 [0.95, 1.10]	1.05 [1.03, 1.08]
Model 2**	1.23 [1.08, 1.41]	1.04 [0.98, 1.09]	1.02 [0.94, 1.10]	1.04 [1.02, 1.07]
Model 3***	1.23 [1.07, 1.42]	1.03 [0.97, 1.08]	1.02 [0.94, 1.10]	1.04 [1.01, 1.06]
P for interaction	Ref	0.01	0.01	
Hostility				
Model 1*	1.17 [0.99, 1.39]	1.00 [0.96, 1.04]	1.03 [0.96, 1.11]	1.01 [0.98, 1.03]
Model 2**	1.11 [0.93, 1.32]	0.99 [0.95, 1.04]	1.01 [0.94, 1.09]	1.01 [0.98, 1.03]
Model 3***	1.12 [0.94, 1.34]	0.99 [0.95, 1.03]	1.00 [0.93, 1.08]	1.00 [0.98, 1.02]
P for interaction	Ref	0.21	0.33	
Lifetime Discrimination				
Model 1*	1.02 [0.87, 1.18]	1.02 [0.99, 1.08]	0.92 [0.84, 1.01]	1.01 [0.99, 1.04]
Model 2**	1.04 [0.89, 1.22]	1.03 [0.99, 1.08]	0.94 [0.85, 1.03]	1.02 [0.99, 1.05]
Model 3***	1.01 [0.86, 1.18]	1.03 [0.97, 1.08]	0.95 [0.85, 1.03]	1.02 [0.99, 1.04]
P for interaction	Ref	.078	0.45	
Job Strain				
Active Strain				
Model 1*	0.86 [0.45, 1.62]	0.90 [0.74, 1.09]	0.71 [0.45, 1.13]	0.93 [0.87, 0.99]
Model 2**	0.95 [0.48, 1.85]	0.87 [0.71, 1.08]	0.77 [0.47, 1.26]	0.93 [0.87, 0.99]
Model 3***	0.96 [0.49, 1.88]	0.86 [0.70, 1.07]	0.77 [0.47, 1.26]	0.92 [0.86, 0.99]
P for interaction	Ref	0.24	0.36	
Passive Strain				
Model 1*	0.32 [0.07, 1.41]	1.10 [0.90, 1.35]	0.88 [0.52, 1.47]	1.00 [0.93, 1.07]
Model 2**	0.35 [0.08, 1.59]	1.05 [0.84, 1.32]	0.87 [0.50, 1.49]	0.99 [0.92, 1.06]
Model 3***	0.37 [0.08, 1.69]	1.07 [0.86, 1.35]	0.82 [0.47, 1.43]	0.99 [0.92, 1.06]
P for interaction	Ref	0.29	0.44	
High Strain				
Model 1*	0.92 [0.49, 1.70]	0.91 [0.75, 1.11]	0.75 [0.48, 1.17]	0.99 [0.93, 1.06]
Model 2**	1.00 [0.52, 1.91]	0.85 [0.68, 1.06]	0.78 [0.49, 1.24]	0.97 [0.91, 1.04]
Model 3***	1.02 [0.53, 1.96]	0.86 [0.69, 1.07]	0.79 [0.50, 1.26]	0.97 [0.91, 1.04]
P for interaction	Ref	0.26	0.44	

*Adjusted for age, sex and cohort study
**Model 1, also adjusted for education, income, and geographic region
***Model 2, also adjusted for BMI and smoking status
Cohort-specific estimates are additionally adjusted for physical activity and income on its natural scale.

Table 2.9-3. Hazard Ratios for Incident Hypertension for a 1-unit Increase in Standard Deviation of Psychosocial Characteristics

Psychosocial Characteristics	**CARDIA**	**JHS**	**MESA**	**Pooled**
CESD				
Model 1*	1.10 [1.03, 1.17]	1.18 [1.06, 1.32]	1.14 [0.99, 1.31]	1.12 [1.07, 1.19]
Model 2**	1.11 [1.03, 1.19]	1.17 [1.04, 1.33]	1.22 [1.06, 1.40]	1.17 [1.11, 1.24]
Model 3***	1.07 [0.99, 1.16]	1.08 [0.95, 1.21]	1.26 [1.07, 1.47]	1.14 [1.08, 1.20]
P for interaction	Ref	0.61	0.56	
Hostility				
Model 1*	1.17 [1.08, 1.26]	1.13 [1.03, 1.24]	1.14 [1.01, 1.28]	1.15 [1.09, 1.21]
Model 2**	1.17 [1.08, 1.27]	1.16 [1.05, 1.29]	1.21 [1.07, 1.38]	1.15 [1.09, 1.21]
Model 3***	1.16 [1.06, 1.26]	1.12 [1.01, 1.24]	1.16 [1.00, 1.34]	1.15 [1.09, 1.21]
P for interaction	Ref	0.55	0.79	
Lifetime Discrimination				
Model 1*	1.02 [0.96, 1.09]	1.02 [0.92, 1.13]	1.10 [0.96, 1.25]	1.04 [0.98, 1.09]
Model 2**	0.97 [0.90, 1.04]	0.99 [0.89, 1.12]	1.10 [0.97, 1.27]	1.01 [0.96, 1.06]
Model 3***	1.00 [0.93, 1.08]	0.94 [0.84, 1.06]	1.10 [0.94, 1.28]	1.02 [0.96, 1.07]
P for interaction	Ref	0.89	0.23	
Job Strain				
Active Strain				
Model 1*	1.23 [0.89, 1.70]	1.02 [0.78, 1.31]	0.95 [0.62, 1.47]	1.05 [0.88, 1.24]
Model 2**	1.18 [0.85, 1.63]	0.95 [0.72, 1.26]	0.99 [0.64, 1.54]	1.05 [0.89, 1.25]
Model 3***	1.14 [0.81, 1.60]	0.93 [0.70, 1.23]	0.91 [0.56, 1.50]	1.03 [0.87, 1.23]
P for interaction	Ref	0.69	0.79	
Passive Strain				
Model 1*	1.31 [0.80, 2.13]	0.87 [0.65, 1.18]	0.92 [0.55, 1.56]	0.95 [0.76, 1.20]
Model 2**	1.30 [0.79, 2.12]	0.88 [0.63, 1.22]	0.86 [0.50, 1.48]	0.99 [0.79, 1.25]
Model 3***	1.04 [0.63, 1.72]	0.93 [0.67, 1.29]	0.71 [0.38, 1.34]	0.92 [0.73, 1.16]
P for interaction	Ref	0.49	0.66	
High Strain				
Model 1*	1.42 [1.03, 1.95]	1.11 [0.86, 1.44]	1.33 [0.88, 2.02]	1.23 [1.04, 1.45]
Model 2**	1.34 [0.97, 1.85]	1.08 [0.81, 1.44]	1.28 [0.84, 1.96]	1.27 [1.07, 1.50]
Model 3***	1.16 [0.83, 1.61]	1.03 [0.77, 1.37]	1.18 [0.73, 1.89]	1.15 [0.97, 1.37]
P for interaction	Ref	0.77	0.69	

*Adjusted for age, sex and cohort study
**Model 1, also adjusted for education, income, and geographic region
***Model 2, also adjusted for BMI and smoking status

Table 2.9-4. Associations of Psychosocial Risk Factors with Hypertension Incidence by Age at Baseline, Sex, and Geographic Region

	Hazard Ratios (per SD)					
	CES-D	Hostility	Discrimination	Job Strain		
				Active	***Passive***	***High***
Age						
Age 29 (25th percentile)	1.08 [1.02, 1.15]	1.10 [1.03, 1.17]	0.98 [0.93, 1.04]	0.98 [0.77, 1.24]	0.85 [0.60, 1.20]	0.91 [0.72, 1.15]
Age 62 (75th percentile)	1.17 [1.06, 1.29]	1.17 [1.08, 1.27]	0.98 [0.89, 1.08]	1.25 [0.95, 1.64]	1.07 [0.79, 1.44]	0.96 [0.74, 1.25]
P for interaction	*0.18*	*0.19*	*0.99*	*0.19*	*0.33*	*0.76*
Sex						
Female	1.11 [1.04, 1.19]	1.14 [1.06, 1.23]	0.98 [0.91, 1.05]	1.06 [0.84, 1.32]	1.05 [0.78, 1.41]	1.24 [0.99, 1.54]
Male	1.21 [1.10, 1.33]	1.17 [1.07, 1.27]	1.09 [1.00, 1.18]	0.98 [0.74, 1.30]	0.75 [0.51, 1.08]	1.01 [0.76, 1.33]
P for interaction	*0.10*	*0.65*	*0.05*	*0.81*	*0.13*	*0.31*
Region						
West	1.19 [1.05, 1.34]	1.11 [0.96, 1.28]	0.99 [0.88, 1.13]	1.06 [0.58, 1.92]	0.73 [0.29, 1.82]	1.23 [0.67, 2.26]
Midwest	1.10 [0.99, 1.23]	1.30 [1.15, 1.48]	1.03 [0.94, 1.14]	1.00 [0.62, 1.64]	1.29 [0.68, 2.45]	1.10 [0.68, 1.77]
Northeast	1.07 [0.87, 1.32]	0.97 [0.81, 1.16]	1.10 [0.88, 1.37]	2.01 [1.01, 3.98]	1.36 [0.56, 3.31]	2.47 [1.31, 4.64]
South	1.16 [1.07, 1.26]	1.13 [1.05, 1.22]	1.01 [0.93, 1.09]	1.01 [0.81, 1.25]	0.89 [0.68, 1.17]	1.07 [0.86, 1.32]
P for interaction for West, Midwest, NE compared to South	*0.96, 0.67, 0.68*	*0.59, 0.03, 0.17*	*0.74, 0.70, 0.63*	*0.88, 0.84, 0.44*	*0.82, 0.54, 0.72*	*0..64, 0.88, 0.15*
*All models adjusted for sex, cohort study, education, income, geographic region, BMI and smoking status						

Table 2.9-5. Mean Baseline Covariates at Each Tertile of Psychosocial Exposure

Population Characteristics	Depressive Symptoms			Hostility			Discrimination			Job Strain			
	T1	T2	T3	T1	T2	T3	T1	T2	T3	Low	Active	Passive	High
Total population	34	32	34	25	33	41	32	46	23	26	30	12	32
MESA	28	46	26	37	36	27	48	43	9	15	32	14	39
JHS	41	28	31	24	33	43	21	52	27	36	26	15	22
CARDIA	26	30	45	20	32	49	40	32	27	8	37	4	51
Age, years	50	48	43	49	45	42	51	51	46	52	43	55	41
Female	32	30	38	29	34	37	32	46	22	26	30	12	31
Male	36	35	29	20	32	48	30	45	25	24	29	12	34
Geographic Region													
West	24	34	41	27	37	37	40	37	23	7	40	5	48
Midwest	27	30	43	21	34	45	37	35	28	9	35	7	49
Northeast	22	47	31	33	36	31	51	41	8	14	31	14	42
South	39	30	31	25	32	43	26	49	24	33	27	14	26
Education													
Less than high school	42	22	37	14	29	57	43	43	14	21	21	21	37
High school or GED	31	31	38	21	33	46	34	44	22	21	30	11	38
Technical School or Associate Degree	32	35	34	24	37	39	28	49	23	27	32	12	29
Bachelor's degree	34	38	28	35	35	29	22	49	29	31	33	9	27
Graduate or professional degree	37	41	23	42	33	25	23	47	30	41	34	9	16
Mean Income	44,190	46,626	34,873	49,001	42,327	36,361	38,136	44,726	47,813	50,957	46,652	39,850	37,280
BMI	30	29	30	29	29	29	29	30	30	31	30	31	29
Smoking													
Never	34	32	34	26	33	41	31	46	24	28	30	11	31
Former	35	36	29	30	35	35	33	47	20	27	29	14	29
Current	31	28	41	18	33	49	33	43	23	18	29	13	41
Hypertensives in 2000	37	32	32	28	33	39	32	47	21	32	25	16	27
Incident hypertension cases	34	32	34	25	32	43	29	49	22	25	29	12	35

Table 2.9-6. Psychosocial Characteristics and Incident Hypertension Sensitivity Analysis: Income Imputation

Psychosocial Characteristics	**Sensitivity (excluding missing income)**	**Pooled (mean imputation)**
CESD	1.12 [1.06, 1.19]	1.14 [1.08, 1.20]
Hostility	1.13 [1.07, 1.20]	1.15 [1.09, 1.21]
Lifetime Discrimination	1.01 [0.96, 1.07]	1.02 [0.96, 1.07]
Job Strain		
Active Strain	1.01 [0.84, 1.21]	1.03 [0.87, 1.23]
Passive Strain	0.91 [0.71, 1.15]	0.92 [0.73, 1.16]
High Strain	1.08 [0.90, 1.29]	1.15 [0.97, 1.37]
*All models adjusted for sex, cohort study, education, income, geographic region, BMI and smoking status		

Table 2.9-7. Psychosocial Characteristics and Incident Hypertension Sensitivity Analysis: Full Psychosocial Scales

Psychosocial Characteristics	**Sensitivity (All available items from psychosocial scales)**	**Pooled (Abbreviated psychosocial scales)**
CESD	N/A	1.14 [1.08, 1.20]
Hostility	1.11 [1.06, 1.17]	1.15 [1.09, 1.21]
Lifetime Discrimination	1.04 [0.98, 1.10]	1.02 [0.96, 1.07]
Job Strain		
Active Strain	1.20 [0.80, 1.79]	1.03 [0.87, 1.23]
Passive Strain	1.07 [0.69, 1.66]	0.92 [0.73, 1.16]
High Strain	1.85 [1.23, 2.79]	1.15 [0.97, 1.37]
*All models adjusted for sex, cohort study, education, income, geographic region, BMI and smoking status		

Table 2.9-8. Psychosocial Characteristics and Incident Hypertension Sensitivity Analysis: Parametric Weibull

Psychosocial Characteristics	**Sensitivity (Parametric)**	**Pooled (Cox)**
CESD	1.10 (p<0.0001)	1.14 [1.08, 1.20]
Hostility	1.03 (p=0.06)	1.15 [1.09, 1.21]
Lifetime Discrimination	1.05 (p=0.01)	1.02 [0.96, 1.07]
Job Strain		
Low Strain	0.95 (p=0.26)	0.87 [0.73, 1.03]
Active Strain	0.93 (p=0.12)	0.89 [0.78, 1.02]
Passive Strain	0.86 (p=0.01)	0.81 [0.65, 0.99]
*All models adjusted for sex, cohort study, education, income, geographic region, BMI and smoking status		

CHAPTER 3. PSYCHOSOCIAL FACTORS AND DIABETES IN BLACKS

3.1 Abstract

Objectives. Examine the influence of depressive symptoms, hostility, discrimination and job strain on both prevalent and incident diabetes, as well as heterogeneity of effect by age, sex, and geographic region, in a diverse sample of Blacks.

Methods. We pooled individual-level data from 3 cohort studies comprising 8309 Black men and women who were free of cardiovascular disease at baseline. We used multivariate Poisson regression models to estimate prevalence ratios for prevalent diabetes as baseline, and we used Cox regression to estimate hazard ratios for incident diabetes. We tested for heterogeneity of effect using interaction terms.

Results. There were 1085 incident cases of diabetes over 76,922 person-years at risk. Depressive symptoms were associated with an 8% increase in incident diabetes in fully adjusted models (CI: 1.00, 1.16). Hostility was associated with an 8% increase in the rate of diabetes (CI: 1.01, 1.15), but this effect was attenuated after adjustment for BMI. Job strain was associated with 5 times the rate of diabetes in the Western region of the country (HR: 5.47, CI: 1.18, 25.34), but null associations were noted in other regions of the country. We did not observe an association between discrimination and diabetes, though we did observe greater magnitude of effect in the Multi-Ethnic Study of Atherosclerosis compared to the other cohort studies.

Conclusions. This study provides longitudinal evidence that depressive symptoms are independently risk factors for incident diabetes in a diverse sample of Blacks in the U.S. Hostility is marginally associated with incident diabetes. Discrimination and job strain were not associated with diabetes in the pooled sample, although their effects vary across cohort studies and geographic regions. The investigation of these risk factors on diabetes in a population of Blacks is novel, as well as the exploration of effect modification. Future research should seek to investigate the contexts in which these psychosocial risk factors are most detrimental for cardiovascular health.

3.2 Introduction

Diabetes Mellitus affects roughly 29 million people in the U.S., or 9% of the adult population[122]. Approximately one quarter of those with diabetes have not been diagnosed, and it is slightly more common in men than in women[123]. Diabetes increases the risk of heart attack by 1.8 times and stroke by 1.5 times, and it is the leading cause of kidney failure, causing 44% of all new cases in 2011[123]. Diabetes also causes a wide range of disability, ranging from amputations to blindness [122]. Due to the widespread impacts of this disease, the direct and indirect costs of diabetes were estimated at $245 billion in 2012 [122].

Blacks suffer with diabetes at nearly twice the rate of Whites [123]. The age-adjusted diabetes prevalence among people 20 years and older is 13.2% in Blacks, compared to 7.6% in Whites [123]. Among diabetics, Blacks tend to have higher HbA1c compared to Whites, poorer blood pressure control and lipid control and lower rates of self-monitoring of blood glucose[124–127]. As a consequence, Blacks are more likely to experience complications due to diabetes, such as lower limb amputations, retinopathy and kidney failure [128–130]. While these racial differences are

in part attributable to differences in socioeconomic status, health behaviors, and access to health care between groups, other causes of racial disparities in diabetes are still largely unknown[131].

Preliminary evidence suggests that psychosocial characteristics may be risk factors for diabetes through a variety of mechanisms. One study by Nowotny and colleagues found that acute stress induces spikes in blood glucose and insulin levels[17]. Another study found an additive effect of C-reactive protein (CRP) and depressive symptoms, such that participants with high depressive symptoms and high CRP experienced a greater risk of incident diabetes than participants with only high depressive symptoms or only high CRP [132]. Additional work by Wickrama and colleagues found that early adversity and stressful life events were directly associated with diabetes and prediabetes, but also indirectly associated through mechanisms of unhealthy eating and sedentary behavior [133]. In short, there is evidence of an independent effect of psychosocial stress on glucose metabolism and inflammation, as well as evidence of indirect effects of stress via coping behaviors.

Much of the epidemiologic evidence that psychosocial characteristics may be risk factors for diabetes comes from the depression literature; other psychosocial risk factors have not been explored to the same detail. The large majority of studies on depressive symptoms and diabetes demonstrate positive associations [134–139]. One study of the Multi-Ethnic Study of Atherosclerosis found that CES-D was not associated with impaired fasting glucose, but it was associated with treated diabetes in MESA. Another study of CARDIA participants found that a history of high depressive symptoms was associated with diabetes independent of BMI, smoking and physical activity. There is limited evidence that hostility and job strain may also be associated with diabetes [77,140–142]. The relationship between discrimination and diabetes is unknown.

Not only has there been little investigation of these risk factors overall, but even less so in Blacks. Although nearly all the aforementioned studies included Black participants, there has not been an investigation of heterogeneity of effect by race. Indeed, the severity of negative affect, chronicity of stress, buffering resources or coping behaviors may be patterned by race and may result in heterogeneity across race groups in the strength of the associations of psychosocial factors with diabetes[91,102]. As a result, additional attention to the relationships between psychosocial risk factors and diabetes within racial and ethnic groups is warranted.

The relationship between psychosocial characteristics and diabetes may also depend on a range of other sociodemographic characteristics. A "diabetes belt" consisting of 15 mostly southern states was described by Barker and colleagues [85]. Investigating causes of geographic differences in diabetes prevalence, they found that roughly one third of the difference was attributable to sedentary behavior and obesity and another third attributable to non-modifiable factors; however, other causes were unknown. If in fact, psychosocial characteristics are risk factors for diabetes, they may contribute disproportionately to health in different geographic regions if, for example, depressive symptoms are more strongly correlated with poor diet in the South compared to the Northeast.

While the relationship between psychosocial characteristics and geographic region is unknown, there is some literature describing differential effects of psychosocial characteristics on diabetes by sex and age. Demmer and Sui found that depressive symptoms and work-related stress, respectively, were associated with diabetes in women but not men [41,143]. Another study by Mutambudzi found stronger effects of job strain on diabetes in older adults, compared to middle aged adults, using the Health Retirement Study[77]. Evidence of effect modification is sparse, though, and it is unclear if these patterns will hold in Blacks.

To better understand these relationships, we designed a study to investigate the effects of selected psychosocial characteristics on diabetes risk in a diverse sample population of Blacks in the United States.

3.3 Methods

We pooled individual-level data from three prospective cohort studies: Coronary Artery Risk Development in Young Adults (CARDIA), Jackson Heart Study (JHS), and Multi-Ethnic Study of Atherosclerosis (MESA). The Coronary Artery Risk Development in Young Adults study began in 1985 with 2644 Black participants aged 18-35 at baseline. Participants were recruited from 4 study sites (Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA) and attended 8 examinations, the most recent ending in 2011 [86]. The Multi-Ethnic Study of Atherosclerosis began in 2000 with 1892 Black participants aged 45-84 years at baseline. Participants were recruited from 6 study sites (Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles, CA; New York, NY; and St. Paul, MN), attended 5 examinations, the most recent ending in 2012, and were asymptomatic of cardiovascular disease at baseline [87]. The Jackson Heart Study began in 2000 with 5301 Black participants aged 20-95 at baseline. Participants were recruited from three counties in Jackson, MS and attended 3 examinations, the most recent ending in 2012 [88].

3.3.1 Inclusion Criteria

To maximize comparability, cross-sectional analyses were based on data pooling exam 1 (calendar years 2000-2002) from MESA, exam 1 (calendar years 2000-2004) for JHS and exam 6 (calendar years 2000-2001) from CARDIA. For our analysis, we included participants who self-identified as Black, who were free of cardiovascular disease at the corresponding exam and for whom complete data on psychosocial risk factors and diabetes were available. Cardiovascular

disease was defined as physician-diagnosed heart attack, angina, stroke or transient ischemic attack, heart failure, current atrial fibrillation, peripheral vascular disease, deep vein thrombosis, or having undergone angioplasty, coronary bypass, catheterization, carotid endarterectomy, or another arterial revascularization procedure (MESA=0, JHS=741, CARDIA=32). After these exclusions, there were 8309 participants included in the cross-sectional analysis.

For the survival analysis, we included data from the start of all cohort studies (2000 for JHS and MESA, 1985 for CARDIA). Prevalent cases of diabetes at the start of follow up were excluded (MESA=407, JHS=871, CARDIA=135), leaving 7642 participants in the incident diabetes analysis. Participants participated in up to 3 exams in JHS, up to 5 exams in MESA and up to 8 exams in CARDIA. See the appendix for additional information on inclusion criteria and loss to follow up (Appendix B).

3.3.2 Exposure Measures

There are four psychosocial exposures that had been measured comparably across the three studies. Depressive symptoms were assessed using a 20-item Center for Epidemiologic Studies Depression Scale (CES-D) in all three cohort studies [42]. CES-D was assessed in exam 1 of MESA and JHS and in exam 3 of CARDIA. CES-D evaluates multiple symptom clusters, including depressed affect, lack of hope, feelings of guilt and shame, and somatic symptoms (e.g., disrupted sleep or appetite) with an emphasis on negative affect. Participants are asked to identify their experience with various symptoms over the past week. Sample items include "I thought my life had been a failure", "I felt that I could not shake off the blues even with help from my family or friends," and "I felt that everything I did was an effort". Each item is measured on a frequency scale (0 = Rarely or None of the Time, 1 = Some or a Little of the Time, 2 = Occasionally or a Moderate Amount of Time, 3 = Most or All of the Time). Four

items are framed positively and reverse coded. Total scores can range from 0 to 60, and higher scores represent more depressive symptoms. The mean CES-D score was 7.9 (Standard Deviation: 8.5).

Hostility was assessed using the Cook-Medley Hostility Scale [53]. The Cook-Medley Hostility Scale is a 50-item questionnaire derived from the Minnesota Multiphasic Personality Inventory and the key construct assessed by the scale is cynicism [54]. Sample items include "I think most people would lie to get ahead" and "Most people make friends because friends are likely to be useful to them". Each item is rated on a binary scale (0 = Probably False, 1 = Probably True). Hostility was assessed in exam 3 of CARDIA, exam 1 of JHS and in exam 2 of MESA. There are seven common items across the studies that were used in the primary analysis and these items were summed to create the hostility score. Scores range from 0 to 7, and higher scores indicate higher cynicism and hostility. The mean hostility score was 2.9 (SD:1.9).

Discrimination was assessed with the Major Experiences of Discrimination Scale [57,58]. This scale, also described as the Lifetime Discrimination Scale, assesses interpersonal experiences of unfair treatment that are attributed to one's group rather than one's own individual characteristics. Sample items include "Have you ever been unfairly fired" and "Have you ever been unfairly discouraged by a teacher or advisor from continuing your education". Each item is rated on a binary scale (0: No, 1: Yes). We considered discrimination attributed to any cause cumulatively, not merely racial discrimination. Discrimination was assessed in exam 1 of MESA and JHS and in exam 4 of CARDIA. There were four common items collected in all three studies and these items composed the discrimination score – a sum of the domains (e.g. (work, school, community, etc.) where an individual has experienced discrimination. Scores

range from 0 to 4, and higher scores indicate an experience of discrimination in more domains. The mean discrimination score was 1.4 (SD: 1.3).

Job strain was assessed using Karasek Job Content Questionnaire [59]. The scale evaluates two key domains: psychological demands and decision latitude. Psychological demands are an appraisal of stressors in the workplace and sample items include, "My job requires that I work fast" and "I have enough time to get the job done". Decision latitude assesses the extent of an individual's control over his/her tasks and sample items include, "I get to do a variety of different things on my job" and "I have very little freedom to decide how I do my work". Each item is rated on a frequency scale (0 = Rarely or None of the Time, 1 = Some or a Little of the Time, 2 = Occasionally or a Moderate Amount of Time, 3 = Most or All of the Time). Job strain was assessed in exam 2 of MESA and CARDIA and in the second-year annual follow up call in JHS. The cohort studies had four common items, half of which were worded positively and reverse coded. Using median cutoffs for decision latitude and psychological demands, we constructed quadrants of job strain which included (1) low demand and high decision latitude (low strain), (2) high demand and high decision latitude (active jobs), (3) low demand and low decision latitude (passive jobs), and (4) high demand and low decision latitude (high strain). The median decision latitude score was 3.5 (IQR:1.0; Range: 0,4), and the median psychological demands score was 2.0 (IQR: 1.0; Range: 0,4). Twenty six percent of participants had low strain, 30% had active jobs, 12% had passive jobs, and 32% had high strain.

There was not repeated assessment for these psychosocial factors across all cohort studies. As a result, we model time-invariant psychosocial factors based on assessment at one point in time. The psychosocial assessment closest to baseline was used for the analysis. For additional information on the timing of psychosocial assessment, see Appendix A.

3.3.3 Outcome Measure

In 2010, the American Diabetes Association established the definition of diabetes as having fasting plasma glucose of greater than or equal to 126 mg/dl or hemoglobin A1c greater than or equal to 6.5 mmol/mol [144]. For the purposes of this study, diabetes is a dichotomous variable and defined as FPG >= 126 mg/dl, HbA1c >= 6.5 mmol/mol, or the use of diabetes medication.

In MESA, fasting glucose and insulin and oral hypoglycemic medication use were assessed at every exam; however, serum Hemoglobin A1c was only assessed at exams 2 and 5. As a result, we used the information available at the corresponding exam to assess diabetes status at that time. In JHS and CARDIA, fasting glucose, HbA1c and medication use were available for every exam.

It was important for Type 1 diabetics to be excluded from this analysis because it is an autoimmune disease and risk factors are not modifiable. However, only the MESA study identified type of diabetes. Three participants with Type 1 diabetes from MESA were excluded. CARDIA did not ask explicitly about Type 1 diabetes, but did ask diabetics at what age they were diagnosed. We identified 17 participants with diabetes diagnoses by age 14 and excluded them as these were likely cases of Type 1 diabetes [145]. In JHS, we were not able to identify Type 1 diabetes, and as a result, our analyses may include several Type 1 diabetics. Given just 2% of Blacks in the U.S. have Type 1 Diabetes [146], we estimate that there may be as many as 90 participants in JHS that were misclassified as having Type 2 diabetes. The inclusion of these participants may have biased our effect estimates towards the null. After these exclusions, the prevalence of diabetes in the cross-sectional study is 16%, and over the course of follow up, we observe 1015 new cases of diabetes.

3.3.4 Covariates

We adjusted for a range of confounders that are risk factors for diabetes and associated with psychosocial characteristics. Covariates included age, sex, and geographic region at the time of the corresponding exam. Geographic region was a categorical variable derived by the study site and defined by the U.S. Census Bureau as Northeast, South, Midwest or West [105].

Education was assessed differently by each study with varying degrees of specificity. To create a uniform measure of education across studies, responses were recoded into five condensed categories: (1) less than high school; (2) high school or GED completion or some college; (3) Technical school or associate degree; (4) bachelor's degree; and (5) graduate or professional school. For the cross-sectional analysis, education was operationalized as a 5-level ordinal variable based on data from the corresponding exam. For the survival analysis, education was operationalized as a time-varying ordinal variable, as there was repeated measurement in CARDIA.

Income was assessed as a categorical variable by each study; however, the income categories did not align across studies. To create a uniform measure of income across studies, responses were transformed into a continuous income variable. For discrete income categories, the midpoint value for each category was assigned to the individual. For the highest income category, we calculated the median income for individuals earning over 75,000 annually and over 100,000 annually using U.S. Census data, and that average income was used for individuals in the highest income category. For the cross-sectional analysis, income was operationalized as a continuous variable using income data from the corresponding exam. In the survival analysis, income was operationalized as a time-varying continuous variable, as there was repeated measurement in CARDIA and MESA. Participants with missing income data were assigned the

mean income for their cohort study. In the study-specific sensitivity analyses, income was used on the original study-specific scale.

Smoking was collected similarly across all three studies: never smokers, former smokers and current smokers. For the cross-sectional analysis, smoking was operationalized as a 3-level categorical variable (current smokers, former smokers, and never smokers) using smoking data from the corresponding exam. For the survival analysis, smoking was operationalized using a time-varying categorical variable, as there was repeated measurement in all three studies.

Physical activity was assessed differently in all three studies, each study using a different questionnaire for physical activity items. Physical activity was assessed with a 28-item questionnaire in MESA, a 40-item questionnaire in JHS, and a 13-item questionnaire in CARDIA. There were 8 common activities across studies, but they were captured using such different frequencies that harmonization would have introduced substantial error. For example, JHS requested the frequency per month of leisurely walking at least 15 minutes; CARDIA requested the number of months where participants walked at least one hour a week for leisure; and MESA requested the number of hours a day where participants walked for leisure. As a result, physical activity was excluded in our pooled analyses but included in the study-specific analyses. Physical activity in MESA was operationalized as the sum of moderate and vigorous physical activity MET-hours/week. In JHS, physical activity was operationalized as a 3-level ordinal variable for light, moderate or heavy physical activity based on the American Heart Association's Life Simple Seven. In CARDIA, physical activity was operationalized as a continuous measure of heavy and moderate physical activity. Physical activity was time-varying in the MESA and CARDIA studies.

Body Mass Index (BMI) was collected similarly across all three studies. For the cross-sectional analysis, BMI was operationalized as a continuous variable using data from the corresponding exam. In the survival analysis, BMI was operationalized as a continuous, time-varying variable, as there was repeated measurement in all studies.

3.3.5 Statistical Analyses

Descriptive analyses assessed the distribution of covariates and outcome by study. We also assessed the distribution of covariates by tertiles of each psychosocial exposure. For the cross-sectional analysis, we used modified Poisson regression to estimate prevalence ratios for diabetes. Modified Poisson regression with robust error variances is recommended to estimate prevalence ratios and confidence intervals for binary outcomes when log-binomial models fail to converge [106–108]. These models have a Poisson distribution and a log link function and use the repeated statement for the sandwich variance estimator [106]. We used baseline data for JHS and MESA which began in 2000; however, CARDIA participants were 18-35 years of age at baseline in 1985. To ensure comparability of age across studies, we used diabetes data from the year 2000 for CARDIA participants, at which point they were 33-50 years of age. We estimate the relevant associations for each cohort, as well as the pooled sample, and to test for differential effects by cohort, we include an interaction term for psychosocial indicator and the cohort study.

We adjusted for the covariates above in a stepwise manner. The purpose of this sequential modeling was to isolate the effects of health behaviors which may be on the causal pathway. The first model included adjustment for sex and cohort study, and the second model included socioeconomic position and geographic region. The third model included adjustment for health behaviors. We adjusted for cohort study as a fixed effect, and tested for differences in

the effect of psychosocial factors between cohorts using interaction terms in fully adjusted models.

For the survival analysis, we employed Cox regression to estimate the relationship between each stressor and incident diabetes in our pooled sample. We used age as the time scale, rather than time in study, because the study enrollment occurs at an arbitrary time point and is not clinically relevant [109–111]. We performed Cox regression with a stratification term for cohort, which allows each cohort to have a different baseline hazard function, and we adjusted for all covariates listed above in a stepwise manner. Exposures were assigned to baseline, and we included time-varying covariates for education, income, BMI, physical activity, and smoking status.

The final goal of this analysis was to assess whether the relationship between psychosocial characteristics and diabetes was modified by sociodemographic factors, including age, sex, and geographic region. Age was modeled linearly as we hypothesized a gradual increase in the effect of psychosocial factors by age; further, no threshold was identified in the literature whereby psychosocial factors increase in effect. Sex was modeled with a binary variable; and region with a categorical variable. We conducted this analysis using interaction terms between age, sex and geographic region with the psychosocial characteristics of interest in the fully-adjusted Cox models. We noted effect modification if $p \leq 0.10$ for the interaction term. For interpretation, we stratified results based on the effect modifier.

We conducted a range of sensitivity analyses to investigate whether the effects of the analysis held under different conditions. We assessed the impact of imputing income for missing data by repeating the Cox model and excluding those for whom income was missing, and we

replicated the primary analyses within each cohort study using the abbreviated psychosocial scales and the full scales available in each study. Results for the sensitivity analyses can be found in the supplementary materials for this chapter.

3.4 Results

The total number of participants in the cross-sectional analysis was 8309 (1889 CARDIA participants, 4538 JHS participants, and 1882 in MESA. The prevalence of diabetes was 16% in the full sample, representing 1343 participants. There were 135 prevalent cases in CARDIA, 871 prevalent cases in JHS, and 337 prevalent cases in MESA.

For the incident diabetes analysis, there were 7642 participants after the exclusions mentioned above (MESA=1468, JHS=3647, CARDIA=2527). We observed 1085 new events of diabetes over the course of follow up. The diabetes incidence rate was 7 per 1,000 person years in CARDIA, 23 per 1,000 person years in JHS, and 12 per 1,000 person-years in MESA.

3.4.1 Characteristics of the study population

The mean age in the pooled sample was 53 (SD: 13 years). Forty percent of the participants were male. Much of the sample population resided in the South (63%), while 11% were in the Western region of the U.S., 16% were in the Midwest, and 10% were in the Northeast. More than 30% of the sample had attained a bachelor, graduate or professional degree, 12% had some college and 42% of the sample had a maximum education attainment of a high school diploma or GED. The mean income in the study was roughly $44,000 per year. The mean BMI was 31 (SD: 7). Sixty percent of participants were never smokers, and roughly 20% were current smokers.

Depressive symptoms were highest in CARDIA and lowest in JHS and we observe some differences in dispersion between studies. Hostility and discrimination scores were highest in JHS and lowest in MESA, and we note differences in the dispersion of discrimination by cohort. Finally, high job strain is most prevalent in CARDIA and least prevalent in JHS, with notable differences in dispersion between studies. (Table 3.9-1)

3.4.2 Cross-Sectional Analyses

We found that one standard deviation increase in CES-D and hostility were associated with a 6% increased risk for prevalent diabetes after adjustment for age and sex (CI: 1.01, 1.12 and CI: 1.01, 1.11, respectively); these associations, though, were attenuated after adjustment for socioeconomic position. In fully adjusted models, neither CES-D, hostility, discrimination nor job strain were associated with prevalent diabetes. There were no statistically significant differences in the effect of CES-D, hostility, discrimination or job strain by cohort, although in CARDIA we do see greater magnitude of effect for hostility and job strain than in other cohorts. (Table 3.9-2)

3.4.3 Longitudinal Analyses

In the pooled sample, we found that CES-D was positively associated with incident diabetes after adjustment for age, sex, geographic region, education, income. One standard deviation increase in CES-D was associated with a 13% increase in the rate of diabetes (HR: 1.12, CI: 1.05, 1.122). The effects of CES-D were slightly attenuated after adjustment for health behaviors, however, CES-D remained a significant predictor. We did not observe significant differences in the effect of CES-D across cohorts. (Table 3.9-3)

Hostility was also positively associated with incident diabetes after adjustment for age, sex, geographic region, education and income. We found that a one standard deviation increase in hostility was associated with an 8% increase in the rate of diabetes (HR: 1.08, CI: 1.01, 1.15). After adjusting for health behaviors, the effect of hostility was no longer significant. We observed that the effects of hostility differed substantially across cohorts. In MESA, we observed a hazard ratio of 1.40 (CI: 1.12, 1.75), while the hazard ratio for hostility in CARDIA was 0.96 (CI: 0.85, 1.09). (Table 3.9-3)

We did not observe an effect of discrimination or job strain in the pooled sample, however within cohorts, we did observe a few noteworthy associations. Generally, the effects for discrimination and job strain were larger in MESA than other cohorts, though they did not reach statistical significance (HR: 1.20, CI: 0.94, 1.53 and HR: 1.14, CI: 0.53, 2.46, respectively). Similarly, in CARDIA we observe a larger hazard ratio for job strain than in other samples, but this effect is not statistically significant (HR: 1.45, CI: 0.88, 2.39). (Table 3.9-3)

3.4.4 Effect Modification

The total number of interactions tested were 30, and three were statistically significant. We found that hostility was marginally modified by age (p for interaction: 0.10), such that the effects of hostility were stronger in older Blacks compared to younger Blacks. Also, we found heterogeneous effects of CES-D and job strain across geographic regions. CES-D appeared to have inverse effects in the Midwest compared to the South (p for interaction 0.03), and job strain appeared to have stronger effects in the West compared to the South (p for interaction: 0.08). (Table 3.9-4)

We suspected that the observed heterogeneity of effect by age and geographic region may be an artifact of cohort differences. As a result, we included an interaction term for hostility and cohort, in addition to the interaction between hostility and age. After this adjustment, it appears that the hostility-age interaction was no longer significant. We did the same to test effect modification by geographic region, and found that only the interaction between job strain and geography remain significant (p=0.05). Participants experiencing job strain in the West had 5 times the rate of diabetes than those in the West with low job strain (HR: 5.47, CI: 1.18, 25.34).

3.5 Discussion

This study was designed to examine the relationship between psychosocial characteristics and diabetes in a heterogeneous sample of Blacks in the U.S. We observed that depressive symptoms are consistently associated with diabetes in both cross sectional and longitudinal studies. Hostility is marginally associated with prevalent and incident diabetes, although the effects are strongest in MESA. The relationship between discrimination and diabetes is strongest in the MESA cohort, although this relationship does not achieve statistical significance. Finally, with respect to job strain, we see stronger effects in the CARDIA and MESA cohorts, and in the Western region of the U.S.

The findings discussed here are supported by prior work identifying depressive symptoms as a risk factor for diabetes. Many researchers have replicated the finding that depressive symptoms are risk factors for incident diabetes in multi-ethnic samples. Specifically, one meta-analysis by Mezuk and colleagues found a 60% increase in incident diabetes among individuals with high depressive symptoms[147]. Research in Blacks has been mixed, but one study by Knox found stronger effects of depressive symptoms on diabetes in Blacks in CARDIA[69]. This is the first within-group study to demonstrate a positive and consistent association.

Prior research on the role hostility in diabetes development is more meager. Studies conducted by Wylie-Rossett and Suarez found that hostility was positively associated with insulin resistance and diabetes incidence, respectively[140,148]; however, evidence in Black populations is limited. The attenuation of hostility noted in our study is likely a result of BMI. Surwit and colleagues also found that adjusting for BMI attenuated the effect of hostility on fasting glucose[149], suggesting that BMI may be a confounder or mediator of the relationship between hostility and diabetes.

One novel finding of this paper is that discrimination and job strain are not uniformly associated with diabetes in a diverse group of Black Americans. We do observe differences between cohorts, suggesting that discrimination and job strain may be independent risk factors for diabetes depending on context; however, given the scarcity of prior work, this hypothesis cannot be validated. Additional research is necessary to investigate the effects of discrimination and job strain on diabetes.

We could not identify any previous studies of effect modification of psychosocial characteristics by geographic region; however, we have observed that job strain may be a more salient predictor of diabetes in the Western region of the country. We hypothesized that the effect of psychosocial stressors would be strongest in the South where we see the greatest prevalence diabetes, but in fact, that was not the case. While regional culture may have implications for stress perception, coping behaviors, social support or economic opportunity [150], there is no clear explanation for the patterns we see by geographic region. Future research should replicate these analyses in other cohort studies and explore further the relationship between psychosocial risk factors and geographic region of the U.S.

3.6 Limitations

This study is not without limitations. The three cohort studies employed in this analysis are unique in their target populations, survey administration and data collection. One key challenge was disparate measurement of confounding variables. One risk factor that was notably absent from the analysis was diet. Diet is a strong predictor of diabetes, and also, it is associated with psychosocial risk factors[100,151]. As a result, our study may be vulnerable to residual confounding from this and other important risk factors that were not included in this analysis.

Second, there was not repeated assessment for these psychosocial factors across all cohort studies. As a result, we model time-invariant psychosocial factors based on assessment at one point in time. Hostility is a stable personality trait, and that characteristic would not likely experience a great deal of variation; however, time-invariant exposures may have caused bias in our estimation of depressive symptoms, discrimination and job strain. Additional research is necessary to better understand the effect that psychosocial exposures over the lifecourse may have on cardiovascular health.

Finally, we were limited in our exploration of other psychosocial characteristics that may be associated with diabetes incidence in Blacks. Social support, for example, is an independent risk factor for diabetes management, and it may also interact with negative affect to have a synergistic effect on health[152,153]. A measure of social support was not available for this study; however, future research should investigate a broader range of psychosocial factors, as well as interactions between psychosocial characteristics.

3.7 Conclusions

This study pooled individual-level data from three cohort studies to assess the

relationship between psychosocial risk factors and diabetes in a diverse sample of Blacks. Depressive symptoms have a consistent and direct effect on diabetes incidence that is apparent in cross-sectional and longitudinal studies. Hostility is marginally associated with prevalent and incident diabetes, although the effects of hostility on diabetes across cohorts varies substantially. Cohort differences in the effects of discrimination and job strain on diabetes were also observed, though we noted little evidence of effect modification by sociodemographic factors. The exploration of psychosocial risk factors and diabetes is novel, and future research should seek to replicate these findings.

3.8 Supplementary Material

3.8.1 Covariates by Tertile of Psychosocial Characteristics

We created tertiles of each psychosocial characteristic to assess the distribution of covariates across the psychosocial indicators. Individuals in the lowest tertile of depressive symptoms identified fewer than 3 symptoms, the second tertile identified between 3 and 9 symptoms, and the highest tertile identified 10 or more symptoms. Individuals in the lowest tertile of hostility identified 0 or 1 symptoms, the second tertile identified 2 or 3 symptoms, and the highest tertile identified 4 or more symptoms. Individuals in the lowest tertile of discrimination identified no discrimination, the second tertile identified discrimination in 1 or 2 venues, and the highest tertile identified discrimination in 3 or more venues. For job strain, we investigate the distribution of covariates by categories (low strain, active job, passive job, and high strain).

Individuals with more psychosocial stress were most often CARDIA participants, younger and living in the West and Midwest regions of the country. Participants with higher depressive

symptoms were more likely to be women, while participants with more hostility were more likely to be male. Participants with higher depressive symptoms, hostility and job strain were more likely to have lower education and income, while participants with more discrimination had higher education and income. Finally, participants with higher depressive symptoms, hostility, and job strain were more likely to be current smokers. (Table 3.9-5)

3.8.2 Missing Income

There were 1167 participants in the survival analysis for whom we imputed income data (MESA: 36, JHS: 565, CARDIA: 566). We conducted sensitivity analyses excluding participants with missing income data and we found that associations of similar magnitude as in the model with imputed income. We found that depressive symptoms were significantly associated with incident diabetes in both models (HR in both models: 1.08, CI: 1.00, 1.16]. The hazard ratios for hostility, discrimination and job strain in the models with missing data were not statistically significant, and the magnitude was similar to the hazard ratios in the models with imputed income. In summary, mean imputation of income was not likely a source of bias in our study. (Table 3.9-6)

3.8.3 Full Psychosocial Scales

We replicated the primary analyses within each cohort study using the full scales available in each study. Generally, the full scales demonstrated associations in the same direction but slightly higher magnitude as the abbreviated psychosocial scales. Including the full scale for hostility strengthens the estimate such that it achieves statistical significance. One standard deviation increase in hostility is associated with an 8% increase in the rate of diabetes (HR: 1.08, CI: 1.02, 1.14). Discrimination still does not reach statistical significance with the inclusion of additional items, nor does the job strain scale. We conclude that the inclusion of the partial scales

led to an underestimation of the effect of hostility, but did not bias the estimate of discrimination or job strain. (Table 3.9-7)

3.9 Tables and Figures

Table 3.9-1 Selected Characteristics of Participants by Cohort Study (Exam 6 in CARDIA, Exam 1 in JHS, Exam 1 in MESA)

Population Characteristics	CARDIA	JHS	MESA	Pooled
Sample size	1889	4538	1882	8309
Age, Mean [Range]	39 [32,50]	54 [21,93]	62 [44,84]	53 [21,93]
Male	44%	35%	45%	40%
Region				
West	31%	0%	8%	11%
Midwest	44%	0%	16%	16%
Northeast	0%	0%	49%	10%
South	25%	100%	26%	63%
Education				
Less than high school	7%	18%	12%	14%
High school or GED	57%	37%	39%	42%
Technical School or Associate Degree	13%	11%	14%	12%
Bachelor's degree	19%	17%	17%	18%
Graduate or professional degree	5%	17%	17%	14%
Income, Mean [SD]	37,936 (29,808)	46,688 (34,339)	46,152 (29,270)	44,607 (32,453)
Body Mass Index, Mean [SD]	29 (7)	32 (7)	30 (6)	31 (7)
Smoking				
Never	57%	70%	45%	62%
Former	11%	18%	37%	20%
Current	32%	12%	18%	18%
Outcome Distribution				
Diabetes prevalence	7%	19%	18%	16%
New cases	304	514	267	1085
Person-years at Risk	43,821	22,439	10,662	76,922
Incidence Rate per 1,000 PY	7.1	22.9	11.9	14.1
Psychosocial Distribution				
Depressive Symptoms, Mean [SD]	10.0 [9.1]	7.0 [8.3]	7.3 [7.3]	7.9 [8.5]
Hostility, Mean [SD]	2.9 [1.9]	3.2 [2.0]	2.3 [1.7]	2.9 [1.9]
Discrimination, Mean [SD]	1.4 [1.4]	1.6 [1.2]	0.9 [1.0]	1.4 [1.3]
Job Strain				
Low Strain	8%	36%	15%	26%
Active	37%	26%	32%	30%
Passive	4%	15%	14%	12%
High Strain	51%	22%	39%	32%

Table 3.9-2. Prevalence Ratios for Prevalent Diabetes for a 1-unit Increase in Standard Deviation of Psychosocial Characteristics in 2000

Psychosocial Characteristics	CARDIA	JHS	MESA	Pooled
CES-D				
Model 1*	0.99 [0.85, 1.18]	1.08 [0.99, 1.16]	1.06 [0.95, 1.19]	1.06 [1.01, 1.12]
Model 2**	1.00 [0.84, 1.19]	1.05 [0.96, 1.14]	1.05 [0.93, 1.19]	1.04 [0.99, 1.10]
Model 3***	1.01 [0.85, 1.21]	1.02 [0.93, 1.11]	1.05 [0.92, 1.19]	1.03 [0.98, 1.09]
P for interaction	Ref	0.94	0.99	
Hostility				
Model 1*	1.18 [0.97, 1.43]	1.05 [0.98, 1.12]	1.09 [0.97, 1.22]	1.06 [1.01, 1.11]
Model 2**	1.14 [0.93, 1.40]	1.05 [0.98, 1.13]	1.06 [0.93, 1.19]	1.05 [0.99, 1.10]
Model 3***	1.12 [0.90, 1.38]	1.03 [0.96, 1.11]	1.03 [0.91, 1.16]	1.03 [0.98, 1.08]
P for interaction	Ref	0.98	0.83	
Lifetime Discrimination				
Model 1*	0.99 [0.83, 1.19]	0.99 [0.93, 1.07]	1.02 [0.88, 1.17]	0.99 [0.95, 1.06]
Model 2**	1.02 [0.84, 1.23]	0.99 [0.92, 1.08]	1.06 [0.91, 1.23]	1.03 [0.97, 1.08]
Model 3***	0.99 [0.82, 1.20]	0.98 [0.90, 1.06]	1.05 [0.91, 1.22]	1.01 [0.95, 1.07]
P for interaction	Ref	0.79	0.62	
Job Strain				
Active Strain				
Model 1*	1.14 [0.61, 2.11]	0.92 [0.82, 1.03]	0.94 [0.70, 1.27]	0.88 [0.75, 1.02]
Model 2**	1.31 [0.69, 2.52]	0.93 [0.83, 1.05]	0.96 [0.71, 1.32]	0.87 [0.75, 1.01]
Model 3***	1.41 [0.71, 2.78]	0.93 [0.82, 1.04]	0.97 [0.71, 1.33]	0.86 [0.74, 0.99]
P for interaction	Ref	0.85	0.70	
Passive Strain				
Model 1*	1.17 [0.48, 2.86]	0.99 [0.88, 1.12]	1.08 [0.78, 1.51]	1.04 [0.88, 1.23]
Model 2**	1.26 [0.51, 3.16]	0.99 [0.88, 1.12]	1.05 [0.74, 1.49]	0.98 [0.83, 1.16]
Model 3***	1.51 [0.59, 3.85]	0.98 [0.86, 1.12]	1.06 [0.74, 1.51]	1.00 [0.85, 1.18]
P for interaction	Ref	0.14	0.27	
High Strain				
Model 1*	1.20 [0.65, 2.19]	0.98 [0.88, 1.10]	1.04 [0.78, 1.38]	0.90 [0.77, 1.04]
Model 2**	1.28 [0.68, 2.41]	0.95 [0.84, 1.08]	1.01 [0.75, 1.36]	0.84 [0.73, 0.98]
Model 3***	1.36 [0.70, 2.62]	0.95 [0.84, 1.08]	1.03 [0.76, 1.39]	0.84 [0.72, 0.98]
P for interaction	Ref	0.86	0.74	

*Adjusted for age, sex and cohort study
**Model 1, also adjusted for education, income, and geographic region
***Model 2, also adjusted for BMI and smoking status
Cohort-specific estimates are additionally adjusted for physical activity and income on its natural scale.

Table 3.9-3. Hazard Ratios for Incident Diabetes for a 1-unit Increase in Standard Deviation of Psychosocial Characteristics

Psychosocial Characteristics	CARDIA	JHS	MESA	Pooled
CES-D				
Model 1*	1.07 [0.96, 1.18]	1.11 [1.00, 1.24]	1.05 [0.89, 1.23]	1.09 [1.01, 1.17]
Model 2**	1.06 [0.95, 1.18]	1.16 [1.04, 1.31]	1.11 [0.94, 1.32]	1.13 [1.05, 1.22]
Model 3***	1.03 [0.91, 1.17]	1.10 [0.98, 1.24]	1.11 [0.93, 1.33]	1.08 [1.00, 1.16]
P for interaction	Ref	0.57	0.57	
Hostility				
Model 1*	1.08 [0.96, 1.21]	1.07 [0.98, 1.16]	1.23 [1.00, 1.50]	1.08 [1.02, 1.16]
Model 2**	0.96 [0.85, 1.09]	1.05 [0.96, 1.15]	1.40 [1.12, 1.75]	1.08 [1.01, 1.15]
Model 3***	0.93 [0.81, 1.07]	1.03 [0.94, 1.14]	1.33 [1.07, 1.67]	1.06 [0.99, 1.13]
P for interaction	Ref	0.20	0.08	
Lifetime Discrimination				
Model 1*	1.05 [0.95, 1.16]	1.07 [0.97, 1.17]	1.19 [0.95, 1.51]	1.07 [1.00, 1.14]
Model 2**	0.97 [0.87, 1.09]	1.03 [0.93, 1.14]	1.20 [0.94, 1.53]	1.04 [0.97, 1.11]
Model 3***	1.01 [0.90, 1.15]	0.98 [0.89, 1.09]	1.09 [0.84, 1.42]	1.04 [0.97, 1.12]
P for interaction	Ref	0.28	0.09	
Job Strain				
Active Strain				
Model 1*	1.24 [0.75, 2.04]	1.09 [0.86, 1.37]	1.18 [0.56, 2.47]	1.07 [0.88, 1.28]
Model 2**	1.20 [0.73, 1.99]	0.98 [0.77, 1.26]	1.09 [0.50, 2.37]	1.11 [0.91, 1.34]
Model 3***	1.29 [0.71, 2.35]	0.96 [0.75, 1.23]	0.90 [0.40, 2.00]	1.06 [0.87, 1.29]
P for interaction	Ref	0.74	0.92	
Passive Strain				
Model 1*	0.85 [0.37, 1.20]	0.92 [0.71, 1.20]	0.95 [0.39, 2.28]	0.91 [0.71, 1.15]
Model 2**	1.03 [0.44, 2.38]	0.87 [0.65, 1.16]	0.88 [0.34, 2.31]	0.96 [0.76, 1.22]
Model 3***	0.90 [0.35, 2.25]	0.92 [0.69, 1.23]	0.94 [0.35, 2.48]	0.89 [0.70, 1.13]
P for interaction	Ref	0.71	0.72	
High Strain				
Model 1*	1.29 [0.79, 2.10]	0.90 [0.71, 1.15]	1.15 [0.56, 2.47]	1.00 [0.83, 1.22]
Model 2**	1.45 [0.88, 2.39]	0.90 [0.68, 1.18]	1.14 [0.53, 2.46]	1.10 [0.90, 1.33]
Model 3***	1.33 [0.74, 2.41]	0.93 [0.71, 1.22]	1.18 [0.54, 2.57]	0.99 [0.82, 1.21]
P for interaction	Ref	0.27	0.87	

*Adjusted for sex and cohort study
**Model 1, also adjusted for education, income, and geographic region
***Model 2, also adjusted for BMI and smoking status

Table 3.9-4. Associations of Psychosocial Risk Factors with Diabetes Incidence by Age at Baseline, Sex, and Geographic Region

	Hazard Ratios (per SD)					
	CES-D	Hostility	Discrimination	Job Strain		
				Active	***Passive***	***High***
Age						
Age 29 (25th percentile)	1.04 [0.95, 1.15]	0.95 [0.86, 1.05]	0.96 [0.87, 1.05]	0.98 [0.71, 1.36]	0.82 [0.51, 1.32]	0.98 [0.71, 1.37]
Age 62 (75th percentile)	1.06 [0.94, 1.19]	1.06 [0.97, 1.17]	0.97 [0.87, 1.08]	1.14 [0.87, 1.51]	0.95 [0.71, 1.27]	0.97 [0.74, 1.26]
P for interaction	*0.85*	*0.10*	*0.86*	*0.49*	*0.60*	*0.95*
Sex						
Female	1.04 [0.95, 1.14]	1.07 [0.98, 1.17]	1.06 [0.97, 1.16]	1.10 [0.86, 1.41]	1.02 [00.75, 1.38]	1.06 [0.82, 1.37]
Male	1.20 [1.04, 1.37]	1.09 [0.97, 1.22]	1.03 [0.91, 1.16]	1.01 [0.72, 1.42]	0.81 [0.54, 1.22]	0.92 [0.65, 1.29]
P for interaction	*0.45*	*0.46*	*0.84*	*0.17*	*0.33*	*0.13*
Region						
West	0.99 [0.79, 1.24]	1.15 [0.90, 1.47]	0.94 [0.76, 1.17]	3.63 [0.88, 14.96]	1.98 [0.28, 14.19]	5.47 [1.18, 25.34]
Midwest	0.92 [0.75, 1.12]	1.03 [0.83, 1.29]	1.12 [0.95, 1.32]	2.08 [0.88, 4.93]	1.79 [0.55, 5.81]	1.83 [0.77, 4.38]
Northeast	1.11 [0.71, 1.75]	1.44 [0.93, 2.22]	1.20 [0.70, 2.06]	0.84 [0.31, 2.29]	0.87 [0.26, 2.93]	0.84 [0.32, 2.24]
South	1.13 [1.03, 1.24]	1.07 [0.99, 1.16]	1.06 [0.97, 1.15]	0.97 [0.78, 1.21]	0.89 [0.69, 1.16]	0.94 [0.75, 1.18]
P for interaction for West, Midwest, NE compared to South	*0.35, 0.03, 0.65*	*0.84, 0.90, 0.22*	*0.41, 0.96, 0.61*	*0.17, 0.13, 0.21*	*0.46, 0.13, 0.53*	*0.08, 0.22, 0.70*

*All models adjusted for sex, cohort study, education, income, geographic region, BMI and smoking status

Table 3.9-5. Mean Baseline Covariates at Each Tertile of Psychosocial Exposure

Population Characteristics	Depressive Symptoms			Hostility			Discrimination			Job Strain			
	T1	T2	T3	T1	T2	T3	T1	T2	T3	Low	Active	Passive	High
Total population	34	32	34	25	33	41	32	46	23	26	30	12	32
MESA	28	46	26	37	36	27	48	43	9	15	32	14	39
JHS	41	28	31	24	33	43	21	52	27	36	26	15	22
CARDIA	26	30	45	20	32	49	40	32	27	8	37	4	51
Age, years	50	48	43	49	45	42	51	51	46	52	43	55	41
Female	32	30	38	29	34	37	32	46	22	26	30	12	31
Male	36	35	29	20	32	48	30	45	25	24	29	12	34
Geographic Region													
West	24	34	41	27	37	37	40	37	23	7	40	5	48
Midwest	27	30	43	21	34	45	37	35	28	9	35	7	49
Northeast	22	47	31	33	36	31	51	41	8	14	31	14	42
South	39	30	31	25	32	43	26	49	24	33	27	14	26
Education													
Less than high school	42	22	37	14	29	57	43	43	14	21	21	21	37
High school or GED	31	31	38	21	33	46	34	44	22	21	30	11	38
Technical School or Associate Degree	32	35	34	24	37	39	28	49	23	27	32	12	29
Bachelor's degree	34	38	28	35	35	29	22	49	29	31	33	9	27
Graduate or professional degree	37	41	23	42	33	25	23	47	30	41	34	9	16
Mean Income	44,190	46,626	34,873	49,001	42,327	36,361	38,136	44,726	47,813	50,957	46,652	39,850	37,280
BMI	30	29	30	29	29	29	29	30	30	31	30	31	29
Smoking													
Never	34	32	34	26	33	41	31	46	24	28	30	11	31
Former	35	36	29	30	35	35	33	47	20	27	29	14	29
Current	31	28	41	18	33	49	33	43	23	18	29	13	41
Diabetes in 2000	36	31	33	27	32	42	31	47	22	32	24	17	27
Incident diabetes cases	28	36	36	30	32	38	32	45	23	24	31	12	33

Table 3.9-6. Psychosocial Characteristics and Incident Diabetes Sensitivity Analysis: Income Imputation

Psychosocial Characteristics	**Sensitivity (excluding missing income)**	**Pooled (mean imputation)**
CESD	1.08 [1.00, 1.16]	1.08 [1.00, 1.16]
Hostility	1.07 [0.99, 1.14]	1.06 [0.99, 1.13]
Lifetime Discrimination	1.02 [0.95, 1.09]	1.04 [0.97, 1.12]
Job Strain		
Active Strain	1.00 [0.82, 1.23]	1.06 [0.87, 1.29]
Passive Strain	1.03 [0.86, 1.22]	0.89 [0.70, 1.13]
High Strain	0.87 [0.69, 1.12]	0.99 [0.82, 1.21]
*All models adjusted for sex, cohort study, education, income, geographic region, BMI and smoking status		

Table 3.9-7. Psychosocial Characteristics and Incident Diabetes Sensitivity Analysis: Full Psychosocial Scales

Psychosocial Characteristics	**Sensitivity (All available items from psychosocial scales)**	**Pooled (Abbreviated psychosocial scales)**
CESD	N/A	1.08 [1.00, 1.16]
Hostility	1.08 [1.02, 1.14]	1.06 [0.99, 1.13]
Lifetime Discrimination	1.06 [0.99, 1.14]	1.04 [0.97, 1.12]
Job Strain		
Active Strain	0.73 [0.35, 1.53]	1.06 [0.87, 1.29]
Passive Strain	1.02 [0.53, 1.98]	0.89 [0.70, 1.13]
High Strain	0.74 [0.35, 1.53]	0.99 [0.82, 1.21]
*All models adjusted for sex, cohort study, education, income, geographic region, BMI and smoking status		

CHAPTER 4. PSYCHOSOCIAL FACTORS AND INCIDENT CARDIOVASCULAR DISEASE IN BLACKS

4.1 Abstract

Objectives. Examine the influence of depressive symptoms, hostility, discrimination and job strain on incident cardiovascular disease (CVD), as well as heterogeneity of effect by age, sex, and geographic region, in a diverse sample of Blacks.

Methods. We pooled individual-level data from 3 cohort studies comprising 9301 Black men and women who were free of cardiovascular disease at baseline. We used Cox regression to estimate hazard ratios for incident cardiovascular disease and tested for heterogeneity of effect using interaction terms.

Results. There were 590 incident cases of cardiovascular disease over 91,159 person-years at risk. Depressive symptoms were associated with a 20% increase in incident myocardial infarction (CI: 1.03, 1.40) and a 13% increase in a composite measure of CVD (CI: 1.03, 1.25). Hostility was marginally associated with a 15% increase in the rate of myocardial infarction (CI: 0.99, 1.31) and showed a stronger association with CVD in younger participants compared to older participants (p for interaction = 0.002). Discrimination nor job strain were associated with incident CVD in the pooled sample, but passive jobs were a stronger predictor of CVD in the Northeast compared to other regions (p for interaction = 0.10).

Conclusions. This study provides longitudinal evidence that depressive symptoms are independently risk factors for incident CVD in a diverse sample of Blacks in the U.S. Hostility may also increase the risk of incident myocardial infarction. The effects of psychosocial characteristics on CVD depends greatly on cohort, age and geographic region. Efforts to minimize the prevalence and impact of negative affect may be promising strategies to reduce CVD incidence in Blacks.

4.2 Introduction

Cardiovascular diseases (CVD) are a persistent threat to public health in the U.S. Roughly 1 in every 3 deaths is due to CVD in the U.S., and CVD has been the leading cause of death annually since 1918 [1]. Though many of these deaths occur late in life, one third of deaths due to CVD occur prior to age 75, well before the average life expectancy of 77.9 years [2]. Recent decades have seen marked decreases in CVD mortality largely due to medical therapies and the changing distribution of CVD risk factors [2]. However, cardiovascular diseases continue to be major sources of morbidity and disability in the U.S., where we observe roughly 1.5 million heart attacks and strokes each year [3].

It is well established that African Americans are at a higher risk for CVD than Whites. The MESA study found that the risk of developing congestive heart failure over a four-year period was higher among Black compared with White participants (HR: 1.8, CI: 1.1-3.1) [5]. The REGARDS study found that Blacks were 4 times as likely to experience a stroke during ages 45–54 years compared to Whites (CI: 1.23–13.11)[6]. Black-White disparities in CVD incidence and mortality remain relatively stable over the life course until age 65 where we see reductions in disparities, likely due to survival bias [3]. A range of socioeconomic and behavioral risk factors for

CVD contribute to this disparity, but these risk factors fail to account for all of the observed racial differences [3].

There is a growing body of evidence establishing a relationship between specific psychosocial factors and CVD. Psychosocial characteristics may be involved in the etiology of cardiovascular disease indirectly by altering individual's behavior, namely increasing smoking, decreasing physical activity and compromising diet. These behaviors, then, increase susceptibility to cardiovascular risk factors and disease. Certainly, this hypothesis has been partially validated in prior research [12–14,30]. However, psychosocial stressors have also been found to have a direct impact on physiological processes. Chronic stress can cause the excessive activation of the sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenal (HPA) axis. The cumulative effect of the hyperactivity of the HPA axis and SNS is insulin resistance, hypertension and atherosclerosis, substantiating the link between psychosocial stress and cardiovascular disease. Indeed, psychosocial stressors have been found to have a direct effect on coronary artery calcification [19–22], inflammation [23–26] , and metabolic syndrome [16,27,28].

There is clear evidence that depressive symptoms are a risk factor for multiple forms of CVD. Prior research describes that depressive symptoms are associated with myocardial infarction, stroke, coronary revascularization, coronary heart disease and mortality due to cardiovascular disease [37–39,154–157]. Though few of these studies have been conducted within ethnic groups, they have been conducted in multi-ethnic and otherwise diverse populations; however, the degree to which the effect of depressive symptoms vary by context is unknown.

The study of the link between hostility and CVD has been less thorough and the findings more mixed. A number of studies have demonstrated positive associations between hostility and

myocardial infarction, coronary heart disease, and stroke [48,49,51,158], while others have demonstrated null associations with coronary heart disease, CVD mortality, and stroke [50,159,160]. The inconclusiveness of this research hints that there may be certain contexts in which hostility poses a greater risk; however, there has not been a great deal of work conducted in this area to validate this hypothesis.

The evidence on discrimination and cardiovascular disease is substantially more meager. Only one previous study has assessed the relationship between discrimination and incident heart disease. Everson-Rose found that there is a positive relationship between the discrimination and incident CVD in MESA[161]. Two additional studies have investigated the link between discrimination and CVD cross-sectionally, but they had conflicting results [162,163]. Indeed, more longitudinal research is needed to investigate the effect of discrimination on various forms of CVD in diverse populations.

Finally, the evidence that job strain is a risk factor for incident CVD is consistent and convincing. Job strain has been found to be strongly associated with coronary heart disease angina, coronary artery disease, stroke, and myocardial infarction [64,65,164–166], though there has been some evidence to the contrary [167–169]. Two great limitations of this work have been the lack of racial and ethnic diversity in study samples and the applicability of this research to populations in the U.S., as much of this work has been conducted abroad.

Psychosocial characteristics may contribute uniquely to the cardiovascular health of Blacks in the U.S. Negative affect and chronic stress may have more adverse effects in Blacks due to the chronicity and severity of stress, as well of the co-occurrence and clustering of stressors. Further, coping behaviors for depression or discrimination, for example, may be

different by race, and this may result in differential associations of psychosocial factors with CVD. This hypothesis has been confirmed by several studies finding effect modification of psychosocial characteristics by race. The majority of these show a stronger effect of psychosocial stress in Blacks compared to whites [38,39,163,170]. This evidence provides support for the within group study of psychosocial stress and CVD in Black Americans.

There is also evidence that psychosocial characteristics may have heterogeneous effects on cardiovascular disease by other sociodemographic characteristics, as well. There are mixed findings that psychosocial stressors are modified by sex. Many studies demonstrate that the effects of psychosocial stress to be stronger in women [38,63,169,171]; however, there has been some evidence to the contrary[48,17265,173]. With respect to age, most evidence suggests that older participants are more vulnerable to psychosocial stress than younger participants[40,78,174]; but again there is evidence to the contrary[65,175]. While much of this work has been conducted in ethnically diverse populations, the role of sex, age and place may interplay with psychosocial characteristics in a unique way to impact the cardiovascular health of Black Americans.

To better understand the role of psychosocial characteristics in the etiology of CVD, we designed a study to investigate the effects of negative affect and stress on incident cardiovascular disease in a diverse sample population of Blacks in the United States.

4.3 Methods

We pooled individual-level data from three prospective cohort studies: Coronary Artery Risk Development in Young Adults (CARDIA), Jackson Heart Study (JHS), and Multi-Ethnic Study of Atherosclerosis (MESA). CARDIA began in 1985 with 2644 Black participants aged 18-35 at baseline. Participants were recruited from 4 study sites (Birmingham, AL; Chicago, IL;

Minneapolis, MN; and Oakland, CA) and attended 8 examinations, the most recent ending in 2011 [86]. MESA began in 2000 with 1892 Black participants aged 45-84 years at baseline. Participants were recruited from 6 study sites (Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles, CA; New York, NY; and St. Paul, MN), attended 5 examinations, the most recent ending in 2012, and were asymptomatic of cardiovascular disease at baseline [87]. JHS began in 2000 with 5301 Black participants aged 20-95 at baseline. Participants were recruited from three counties in Jackson, MS and attended 3 examinations, the most recent ending in 2012 [88].

4.3.1 Inclusion Criteria

For our analysis, we included participants who self-identified as Black, who were free of cardiovascular disease at baseline and for whom complete data on psychosocial risk factors and cardiovascular disease were available. There were 741 JHS participants a history of CVD at baseline, and these participants were excluded from the study. After these exclusions, there were 9031 participants included in the analysis. We included data from the start of all cohort studies (2000 for JHS and MESA, 1985 for CARDIA). Study participants participated in up to 3 exams in JHS, up to 5 exams in MESA and up to 8 exams in CARDIA.

4.3.2 Exposure Measures

There are four psychosocial exposures that had been measured comparably across the three studies. Depressive symptoms were assessed using a 20-item Center for Epidemiologic Studies Depression Scale (CES-D) in all three cohort studies [42]. CES-D was assessed in exam 1 of MESA and JHS and in exam 3 of CARDIA. CES-D evaluates multiple symptom clusters, including depressed affect, lack of hope, feelings of guilt and shame, and somatic symptoms (e.g., disrupted sleep or appetite) with an emphasis on negative affect. Participants are asked to

identify their experience with various symptoms over the past week. Sample items include "I thought my life had been a failure", "I felt that I could not shake off the blues even with help from my family or friends," and "I felt that everything I did was an effort". Each item is measured on a frequency scale (0 = Rarely or None of the Time, 1 = Some or a Little of the Time, 2 = Occasionally or a Moderate Amount of Time, 3 = Most or All of the Time). Four items are framed positively and reverse coded. Total scores can range from 0 to 60, and higher scores represent more depressive symptoms. The mean CES-D score was 7.9 in the pooled sample (SD: 8.5).

Hostility was assessed using the Cook-Medley Hostility Scale [53]. The Cook-Medley Hostility Scale is a 50-item questionnaire derived from the Minnesota Multiphasic Personality Inventory and the key construct assessed by the scale is cynicism [54]. Sample items include "I think most people would lie to get ahead" and "Most people make friends because friends are likely to be useful to them". Each item is rated on a binary scale (0 = Probably False, 1 = Probably True). Hostility was assessed in exam 3 of CARDIA, exam 1 of JHS and in exam 2 of MESA. There are seven common items across the studies that were used in the primary analysis and these items were summed to create the hostility score. Scores range from 0 to 7, and higher scores indicate higher cynicism and hostility. The mean hostility score was 2.9 in the pooled sample (SD: 1.9).

Discrimination was assessed with the Major Experiences of Discrimination Scale [57,58]. This scale, also described as the Lifetime Discrimination Scale, assesses interpersonal experiences of unfair treatment that are attributed to one's group rather than one's own individual characteristics. Sample items include "Have you ever been unfairly fired" and "Have you ever been unfairly discouraged by a teacher or advisor from continuing your education".

Each item is rated on a binary scale (0: No, 1: Yes). We considered discrimination attributed to any cause cumulatively, not merely racial discrimination or sex discrimination independently, for example. Discrimination was assessed in exam 1 of MESA and JHS and in exam 4 of CARDIA. There were four common items collected in all three studies and these items composed the discrimination score – a sum of the domains (e.g. (work, school, community, etc.) where an individual has experienced discrimination. Scores range from 0 to 4, and higher scores indicate an experience of discrimination in more domains. The mean discrimination score was 1.4 in the pooled sample (SD: 1.3).

Job strain was assessed using Karasek Job Content Questionnaire [59]. The scale evaluates two key domains: psychological demands and decision latitude. Psychological demands are an appraisal of stressors in the workplace and sample items include, "My job requires that I work fast" and "I have enough time to get the job done". Decision latitude assesses the extent of an individual's control over his/her tasks and sample items include, "I get to do a variety of different things on my job" and "I have very little freedom to decide how I do my work". Each item is rated on a frequency scale (0 = Rarely or None of the Time, 1 = Some or a Little of the Time, 2 = Occasionally or a Moderate Amount of Time, 3 = Most or All of the Time). Job strain was assessed in exam 2 of MESA and CARDIA and in the second-year annual follow up call in JHS. The cohort studies had four common items, half of which were worded positively and reverse coded. Using median cutoffs for decision latitude and psychological demands, we constructed quadrants of job strain which included (1) low demand and high decision latitude (low strain), (2) high demand and high decision latitude (active jobs), (3) low demand and low decision latitude (passive jobs), and (4) high demand and low decision latitude (high strain). The median decision latitude score was 3.5 (IQR:1.0; Range: 0,4), and the median psychological

demands score was 2.0 (IQR: 1.0; Range: 0,4). Twenty six percent of participants had low strain, 30% had active jobs, 12% had passive jobs, and 32% had high strain.

There was not repeated assessment for these psychosocial factors across all cohort studies. As a result, we model time-invariant psychosocial factors based on assessment at one point in time. The psychosocial assessment closest to baseline was used for the analysis and the exposure was assigned to baseline to maximize follow up time. For additional information on the timing of psychosocial assessment, see Appendix A.

4.3.3 Outcome Measure

The primary outcome for this study was incident cardiovascular disease, defined as stroke, myocardial infarction, congestive heart failure or fatal cardiovascular disease. The assessment of these outcomes was consistent across all three studies. Data for other conditions, including transient ischemic attack, resuscitated cardiac arrest, peripheral vascular/arterial disease, and cardiac procedures, were not collected uniformly across all the cohort studies, and as a result, these data could not be harmonized.

Participants were contacted at 6-month intervals in CARDIA, 9 to 12 month intervals in MESA, and annually in JHS to identify hospitalizations and possible CVD events. Hospitalizations for CVD were adjudicated by trained physicians, and deaths were primarily identified via next of kin or the National Death Index. Cause of death was adjudicated using information obtained from proxies, medical history, death certificates, and autopsy reports. Definitions of each outcome and descriptions of the adjudication process have been previously described for CARDIA [176], MESA [177], and JHS [178].

4.3.4 Covariates

We adjusted for a range of confounders that are risk factors for CVD and associated with psychosocial characteristics. Covariates included age at baseline, sex, geographic region, education, income, smoking status, physical activity, and body mass index. Geographic region was derived by the study site and defined by the U.S. Census Bureau as Northeast, South, Midwest or West [105]. Geographic region was included in the analysis as a categorical variable.

Education was assessed differently by each study with varying degrees of specificity. To create a uniform measure of education across studies, responses were recoded into five condensed categories: (1) less than high school; (2) high school or GED completion or some college; (3) Technical school or associate degree; (4) bachelor's degree; and (5) graduate or professional school. Education was operationalized as a time-varying, 5-level ordinal variable, as there was repeated measurement in CARDIA.

Income was assessed as a categorical variable by each study; however, the income categories did not align across studies. To create a uniform measure of income across studies, responses were transformed into a continuous income variable. For discrete income categories, the midpoint value for each category was assigned to the individual. For the highest income category, we calculated the median income for individuals earning over 75,000 annually and over 100,000 annually using U.S. Census data, and that average income was used for individuals in the highest income category. Income was operationalized as a time-varying continuous variable, as there was repeated measurement in CARDIA and MESA. Participants with missing income data were assigned the mean baseline income for their cohort study. In the study-specific sensitivity analyses, income was used on the original study-specific scale.

Smoking was collected similarly across all three studies: never smokers, former smokers and current smokers. Smoking was operationalized as a time-varying, 3-level categorical variable (current smokers, former smokers, and never smokers), as there was repeated measurement in all three studies.

Physical activity was assessed differently in all three studies, each study using a different questionnaire for physical activity items. Physical activity was assessed with a 28-item questionnaire in MESA, a 40-item questionnaire in JHS, and a 13-item questionnaire in CARDIA. There were 8 common activities across studies, but they were captured using such different frequencies that harmonization would have introduced substantial error. For example, JHS requested the frequency per month of leisurely walking at least 15 minutes; CARDIA requested the number of months where participants walked at least one hour a week for leisure; and MESA requested the number of hours a day where participants walked for leisure. As a result, physical activity was excluded in our pooled analyses but included in the study-specific analyses. Physical activity in MESA was operationalized as the sum of moderate and vigorous physical activity MET-hours/week. In JHS, physical activity was operationalized as a 3-level ordinal variable for light, moderate or heavy physical activity based on the American Heart Association's Life Simple Seven. In CARDIA, physical activity was operationalized as a continuous measure of heavy and moderate physical activity. Physical activity was time-varying in the MESA and CARDIA studies.

Body Mass Index (BMI) was collected similarly across all three studies. BMI was operationalized as a continuous, time-varying variable, as there was repeated measurement in all studies.

4.3.5 Statistical Analyses

Descriptive analyses assessed the distribution of covariates and outcome by study. We also assessed the distribution of covariates by tertiles of each psychosocial exposure. We employed Cox regression to estimate the relationship between each stressor and incident CVD in our pooled sample. In addition to assessing the hazard of cardiovascular disease, we also assess the hazard of myocardial infarction, stroke and cardiovascular mortality independently. We used age as the time scale, rather than time in study, because the study enrollment occurs at an arbitrary time point and is not clinically relevant [109–111]. We performed Cox regression with a stratification term for cohort, which allows each cohort to have a different baseline hazard function, and we tested for differences in the effect of psychosocial factors between cohorts using interaction terms in fully adjusted models. We estimate the relevant associations for each cohort, as well as the pooled sample, and to test for differential effects by cohort, we include an interaction term for psychosocial indicator and the cohort study.

Further, we adjusted for all covariates listed above in a stepwise manner. The purpose of this sequential modeling was to isolate the influence of health behaviors and proximal health outcomes which may be on the causal pathway. The first model included adjustment for sex, and the second model included socioeconomic position and geographic region. The third model included adjustment for health behaviors and the final model included hypertension and diabetes as covariates. We included time-varying covariates for education, income, BMI, physical activity, smoking status, hypertension and diabetes when available.

The second goal of this analysis was to assess whether the relationship between psychosocial characteristics and CVD was modified by sociodemographic factors, including age, sex, and geographic region. Age was modeled linearly as we hypothesized a gradual increase in

the effect of psychosocial factors by age; further, no threshold was identified in the literature whereby psychosocial factors increase in effect. Sex was modeled with a binary variable; and region with a categorical variable. We conducted this analysis using interaction terms between age, sex and geographic region with the psychosocial characteristics of interest in the fully-adjusted Cox models. We noted effect modification if $p \leq 0.10$ for the interaction term. For interpretation, we stratified results based on the effect modifier.

We conducted a range of sensitivity analyses to investigate whether the effects of the analysis held under different conditions. We assessed the impact of imputing income for missing data by repeating the Cox model and excluding those for whom income was missing. We replicated the primary analyses using the abbreviated psychosocial scales and the full scales available in each study to better understand the effect of using partial psychosocial scales. Finally, we also replicated analyses using a more inclusive definition of CVD, which included conditions that were not available in all three studies. These analyses can be found in the Supplementary Material for this chapter.

4.4 Results

The total number of participants in the analysis was 9031 (2630 CARDIA participants, 4523 JHS participants, and 1878 MESA participants). We observed 590 new cases of cardiovascular disease over 91,159 person-years at risk during a mean follow-up of 10 years. The incidence rate was 3.2 per 1,000 person-years in CARDIA, 8.1 per 1,000 person-years in JHS, and 14.4 per 1,000 person-years in MESA.

4.4.1 Characteristics of the study population

At baseline, the mean age in our pooled sample was 47 (SD: 18 years). Forty percent of the participants were male. The majority of the sample population resided in the South (63%), while 11% were in the Western region of the U.S., 16% were in the Midwest, and 10% were in the Northeast. Nearly 30% of the sample had attained a bachelor, graduate or professional degree, 10% had some college and 47% of the sample had a maximum education attainment of a high school diploma or GED. The mean income in the study was roughly $42,000 per year. The mean BMI was 30 (SD: 7). Sixty percent of participants were never smokers, and roughly 20% were current smokers.

Depressive symptoms were highest in CARDIA and lowest in JHS and we observe some differences in dispersion between studies. Hostility and discrimination scores were highest in JHS and lowest in MESA, and we note differences in the dispersion of discrimination by cohort. Finally, high job strain is most prevalent in CARDIA and least prevalent in JHS, with notable differences in dispersion between studies. (Table 4.9-1)

4.4.2 Longitudinal Analyses

In the pooled sample, we found that CES-D was positively and consistently associated with incident cardiovascular disease. One standard deviation increase in CES-D was associated with a 14% increase in the rate of CVD in the pooled sample (Hazard Ratio: 1.14, CI: 1.04, 1.26), after adjustment for age, sex, geographic region, education and income. Additional adjustment for health behaviors and cardiovascular risk factors did not change the association. The relationship between CES-D was consistent across all three cohort studies, where we observe similar magnitudes of effect (Table 4.9-2). CES-D was also a strong independent predictor of myocardial infarction (HR: 1.20, CI: 1.03, 1.40) and stroke (HR: 1.12, CI: 0.97,

1.29), although the latter was only marginally significant (Table 4.9-3). The effects were magnified in sensitivity analyses where we expanded the definition of CVD. We find that a one standard deviation increase in CES-D is associated with a 19% increase in the rate of incident CVD (HR: 1.19, CI: 1.09, 1.29). (Table 4.9-9)

With respect to hostility, we observe that the association with incident CVD in the pooled sample is not statistically significant (HR: 1.02, CI: 0.94, 1.12) (Table 4.9-2). In CARDIA, though, one standard deviation increase in hostility is associated with a 34% increase in the rate of incident CVD after adjusting for age, sex, geographic region, education and income (HR: 1.34, CI: 1.09, 1.65). We do see an effect of hostility on an expanded definition of CVD (HR: 1.09, CI: 1.01, 1.18), as well as with MI specifically (HR: 1.15, 0.99, 1.31), in the pooled sample (Table 4.9-3).

Discrimination was not associated with a composite measure of CVD, nor with MI or stroke. Rather, discrimination appears to have an inverse relationship with incident CVD in the pooled sample (HR: 0.87, CI: 0.78, 0.96). There do not appear to be suggestive effects within or across cohort studies. (Table 4.9-2)

Finally, we observe that the association between job strain and incident CVD in the pooled sample is not significant (HR: 0.97, CI: 0.72, 1.31) (Table 4.9-2). In MESA, we observe a positive association although the confidence interval is very large (HR: 1.40, CI: 0.37, 5.29). We conducted sensitivity analyses to assess the relationship between CVD and job strain using the full scale, and this too suggests a positive association, although the results still do not achieve statistical significance (HR: 1.62, CI: 0.69, 3.82). (Table 4.9-7)

4.4.3 Effect Modification

The total number of interactions tested were 30, and three were statistically significant. We found that hostility was strongly modified by age (p for interaction: 0.002), such that the effects of hostility on CVD are stronger in younger Blacks compared to older Blacks. A 29-year-old with higher hostility had 1.2 times the rate of developing CVD than a 29-year-old without hostility (HR: 1.19, CI: 1.03, 1.37); this association did not hold for older participants. (Table 4.9-4) We suspected that the observed heterogeneity of effect by age may be an artifact of cohort differences. As a result, we included an interaction term for hostility and cohort, in addition to the interaction between hostility and age (results not shown). After this adjustment, it appears that the hostility-age interaction was still significant (p=0.09), so we conclude that hostility is a stronger predictor of CVD in younger participants than in older participants and that this effect is not merely due to cohort difference.

Also, there was a great degree of variability in the effects of psychosocial characteristics across geographic regions, but this was accompanied by a great deal of imprecision. Having a passive job compared to a low strain job may be associated with greater CVD risk in the Northeast compared to the South, but this difference was only marginally significant (p=0.10). Further hostility appeared to be more strongly associated with CVD in the Midwest than in the South (p=0.02). (Table 4.9-4) Again, we considered if this effect modification might be attributable to cohort differences rather than true heterogeneity of effect by geographic region. When we controlled for the interaction between both the psychosocial predictor and cohort, and between psychosocial predictor and geographic region, we found that the passive job-geographic region interaction remained significant (p=0.06). As a result, we conclude that passive jobs are

more strongly associated with incident CVD in the Northeast than in other regions of the country (HR: 4.14, CI: 0.81, 21.10).

4.5 Discussion

This study was designed to examine the relationship between psychosocial characteristics and cardiovascular disease in a heterogeneous sample of Blacks in the U.S. We observed that depressive symptoms were a salient risk factor for incident cardiovascular disease and the effects were relatively stable across populations. Hostility was significantly associated with an inclusive measure of cardiovascular disease in all participants, but the effects of hostility on CVD are greatest in younger populations. Job strain may also be associated with cardiovascular disease as suggested in the MESA cohort, but passive jobs, specifically, were more strongly associated with CVD in the Northeast. We do not find evidence of an association between discrimination and incident CVD.

Depressive symptoms are a well-established risk factor for cardiovascular disease. Many studies of diverse participants have demonstrated positive associations between depressive symptoms and CVD but this study is one of the first to document this association in Blacks. We find a consistent pattern across cohort studies and across various CVD outcomes that is independent of health behaviors and cardiovascular risk factors. Our findings that the effects of CES-D are not modified by sociodemographic characteristics are consistent with a recent publication by Gilsanz who found no evidence of effect modification of depressive symptoms on CVD by age or sex[173].

Previous studies have found contradicting evidence regarding the role of hostility in cardiovascular disease. Some of this variability is attributed to the specific CVD outcome. While

the majority of studies on hostility and myocardial infarction demonstrate positive associations [49,51,159,179], there are more conflicting results when other cardiovascular conditions or composite CVD measures are used [50,159,160]. This finding is mirrored in our analysis where we see an effect of hostility on MI and an inclusive measure of CVD, but not stroke or a narrowly defined CVD measure. Future research might consider what is driving this variability as it may have relevance for the mechanisms through which hostility increases susceptibility to CVD.

Conflicting results on the effect of hostility may also signal effect modification. This study is the first to document effect modification of hostility on CVD by age. Though this finding was contrary to our hypothesis, it might indicate a critical period in which psychosocial characteristics are particularly influential in the etiology of cardiovascular disease[180]. Further, there may be characteristics of hostility that vary by age. One study conducted by Jorgensen found that a specific form of hostility, defensive hostility, was associated with coronary blockage, while other forms of hostility were not[181]. If younger participants were more likely to embody defensive hostility, and older participants a different form of hostility, this might explain these findings.

Only one previous study assessed the effect of discrimination on incident cardiovascular events. Everson-Rose found that discrimination was associated with increased risk of CVD in an older and ethnically diverse sample population [161]. Our results demonstrate an inverse relationship between lifetime discrimination and incident CVD. We believe this discrepancy is due to sample population characteristics or the assessment of discrimination. Given there are now only two studies on the effects of discrimination and incident CVD, more research is warranted using varied assessment of the construct and across diverse populations to better understand the role of unfair treatment in the etiology of CVD.

Finally, we found that job strain was not significantly associated with CVD in the pooled sample. This finding was contrary to our hypothesis given a great volume of work demonstrates that job strain is indeed a risk factor for various forms of cardiovascular disease[64,65,164–166]. Our findings were likely driven by abbreviated assessment of job strain, and the lack of power to detect an association in individual cohorts. We did however observe that passive jobs were more strongly associated with incident CVD in the Northeast. While regional culture may have implications for stress perception and coping behaviors[150], there is no clear explanation for the patterns we see by geographic region. Future research should replicate these analyses in other cohort studies and explore further the relationship between psychosocial risk factors and geographic region of the U.S.

4.6 Limitations

This study is not without limitations. The types of cardiovascular disease we could investigate in the pooled sample was limited to those conditions that were collected similarly across all three cohorts. We conducted sensitivity analyses using a more inclusive definition of CVD, and we observed that the effect of CES-D and hostility is greater when applying a more inclusive definition of CVD (Table 4.9-9). We conclude that the exclusion of additional cardiovascular conditions led to an underestimation of the effect of CES-D and hostility.

Second, our conceptualization of job strain was constrained by the variables included in each of the cohort studies. Only four of 49 items assessing job strain were available for the pooled analysis based on our need to harmonize the data across the studies. As a result, our study may not have adequately captured the construct of job strain in a manner sufficient to reproduce the relationships noted in previous literature. This hypothesis is supported by our sensitivity analysis that shows that when we use the full scales for job strain, we find that participants with

high strain are 1.6 times as likely to develop CVD (HR: 1.62, CI: 0.69, 3.82) compared to low strain (Table 4.9-7). This result likely did not reach statistical significance because our sample size for this analysis was 848 participants. We conclude that the use of the abbreviated job strain scale led us to substantially underestimate the effect of job strain on cardiovascular risk in these cohorts.

Finally, this study was limited by time-invariant psychosocial exposures. Although some studies had repeated assessment of these exposures, we could not include them due to our need to harmonize across the studies. Hostility is presumed to be a stable personality trait; however, there is certainly evidence that depressive symptoms can vary over time as a result of sleep quality, physical activity or treatment for depression, for example[182–184]. Further, participants' degree of job strain is likely to change due to changing employment and promotion opportunities. We expect the greatest degree of variability of psychosocial characteristics in the CARDIA study, where we observe participants for up to 25 years. Our approach relies on the assumption that psychosocial status at one point in time can be predict cardiovascular outcomes occurring much later in life; however, this may not be true. Future research should investigate the degree to which changes in psychosocial factors affect cardiovascular health.

4.7 Conclusions

This study is the first to investigate the effect of psychosocial factors on incident CVD in a diverse population of Blacks in the U.S. We find that depressive symptoms are a consistent and independent risk factor for incident cardiovascular disease in Blacks. Hostility, too, is a predictor of incident CVD, and the effects of hostility on CVD are greatest in younger populations. Evidence describing the effect of job strain and discrimination was inconclusive; however additional research is necessary to better understand the role of psychosocial factors in the

etiology of CVD in Blacks. In summary, the prevention and management of negative affect is a hopeful strategy to reduce the incidence of CVD in Blacks.

4.8 Supplementary Material

4.8.1 Covariates by Tertile of Psychosocial Characteristics

We created tertiles of each psychosocial characteristic to assess the distribution of covariates across the psychosocial indicators. Individuals in the lowest tertile of depressive symptoms identified fewer than 3 symptoms, the second tertile identified between 3 and 9 symptoms, and the highest tertile identified 10 or more symptoms. Individuals in the lowest tertile of hostility identified 0 or 1 symptoms, the second tertile identified 2 or 3 symptoms, and the highest tertile identified 4 or more symptoms. Individuals in the lowest tertile of discrimination identified no discrimination, the second tertile identified discrimination in 1 or 2 venues, and the highest tertile identified discrimination in 3 or more venues. For job strain, we investigate the distribution of covariates by categories (low strain, active job, passive job, and high strain).

Individuals with more psychosocial stress were most often CARDIA participants, younger and living in the West and Midwest regions of the country. Participants with higher depressive symptoms were more likely to be women, while participants with more hostility were more likely to be male. Participants with higher depressive symptoms, hostility and job strain were more likely to have lower education and income, while participants with more discrimination had higher education and income. Finally, participants with higher depressive symptoms, hostility, and job strain were more likely to be current smokers. (Table 4.9-5)

4.8.2 Missing Income

There were 1309 participants in the survival analysis for whom we imputed income data (MESA: 36, JHS: 705, CARDIA: 568). We conducted sensitivity analyses excluding participants with missing income data to assess what effect, if any, imputing income had on our analyses. We found associations of similar magnitude as in the model with imputed income. CES-D remained significantly associated with incident CVD, and the other measures of psychosocial stress were not significant. In summary, imputing income did not bias the results of this analysis. (Table 4.9-6)

4.8.3 Full Psychosocial Scales

We replicated the primary analyses within each cohort study using the full scales available in each study. We felt this sensitivity analysis was necessary because for some of the psychosocial scales, we are using as few as four items to assess the construct and this may fundamentally alter the constructs ability to predict CVD outcomes. In the case of hostility and discrimination, we found that the full scales demonstrated associations of the same magnitude as the abbreviated psychosocial scales. With the job strain measure, we observed a great difference in the magnitude of effect between the full and partial scales. High strain was associated with a 60% increase in the rate of CVD, although the effect of job strain still did not reach statistical significance likely due to small sample size (HR: 1.62, CI: 0.69, 3.82). We conclude that the inclusion of the partial scales may have led to an underestimation of the effect of job strain, but did not bias the estimate of hostility or discrimination. (Table 4.9-7)

4.8.4 Inclusive Cardiovascular Disease Definition

For the primary analyses, we had to limit our investigation to outcomes that were measured consistently across all three cohort studies. This measure of CVD, though, did not include other

key conditions and may cause an underestimation of the effect of psychosocial risk factors. For the sensitivity analysis, we expanded the definition of CVD to include transient ischemic attack, resuscitated cardiac arrest, peripheral vascular/arterial disease, cardiac procedures (e.g. coronary bypass graft, revascularization, and angioplasty), and fatal CVD. Data for these conditions were not collected uniformly across all the cohort studies, and as a result, these data could not be harmonized across studies. Incident cases of CVD by type of CVD and by cohort study can be found in Table 4.9-8.

We replicated the longitudinal analyses using a more inclusive definition of CVD. We observed that the effect of CES-D and hostility is higher considering a more inclusive definition of CVD. A one unit increase in CES-D is associated with a 19% increase in incident CVD (HR: 1.19, CI: 1.09, 1.29), and hostility is associated with a 9% increase in incident CVD (HR: 1.09, CI: 1.01, 1.18). There is also a change in the effect of discrimination, such that the effect no longer appears to be protective but null when a more inclusive definition of CVD is applied. The definition of CVD has little impact on the effect of job strain. We conclude that the exclusion of additional cardiovascular conditions led to an underestimation of the effect of CES-D and hostility. (Table 4.9-9)

4.8.5 Healthy Participant Effect

We conducted several sensitivity analyses to ensure that the effects of our study were not biased by the health of participants at baseline. First, we conducted sensitivity analyses including the participants who developed cardiovascular disease prior to study enrollment. There were 729 participants (all from Jackson Heart Study) who had diagnosed cardiovascular disease at baseline. We excluded these participants from the primary analyses because we could not be sure that poor psychosocial health was not a result of cardiovascular disease; however, it was

necessary to conduct sensitivity analyses to assess if we had biased our results in doing so. We conducted this analysis using parametric survival models with a Weibull distribution and found that there was little difference in the results when we included these participants and when we excluded these participants. As a result, we posit that the exclusion of participants who develop CVD prior to baseline did not bias our results in a meaningful way. (Table 4.9-10)

Second, we replicated the analyses among those who were still CVD-free at age 45. The Multi-Ethnic Study of Atherosclerosis had inclusion criteria that stated that participants must still be CVD free by age 45; however, Jackson Heart Study and the Coronary Artery Risk Development in Young Adults study had no such exclusions. As a result, there were 404 participants included in the pooled sample who develop CVD prior to age 45. When we exclude those participants, the effect of CES-D, hostility and discrimination are attenuated. This supports the hypothesis that psychosocial risk factor may play a role in the premature development of cardiovascular disease. (Table 4.9-11)

4.9 Tables and Figures

Table 4.9-1 Selected Characteristics of Participants by Cohort Study at Baseline

Population Characteristics	CARDIA	JHS	MESA	Pooled
Sample size	2630	4523	1878	9031
Age, Mean [Range]	24 [17,35]	54 [21,93]	62 [44,84]	47 [17,93]
Male	44%	35%	45%	40%
Region				
West	31%	0%	8%	11%
Midwest	44%	0%	16%	16%
Northeast	0%	0%	49%	10%
South	25%	100%	26%	63%
Education				
Less than high school	14%	18%	12%	16%
High school or GED	71%	37%	39%	47%
Technical School or Associate Degree	14%	11%	14%	10%
Bachelor's degree	9%	17%	17%	15%
Graduate or professional degree	1%	17%	17%	12%
Income, Mean [SD]	30,244 (21, 561)	46,722 (34,339)	46,152 (29,368)	41,811 (30,994)
Body Mass Index, Mean [SD]	25 (7)	32 (7)	30 (6)	30 (7)
Smoking				
Never	57%	70%	45%	61%
Former	9%	18%	37%	19%
Current	34%	12%	18%	20%
Outcome Distribution				
Incident Cardiovascular Disease	151	241	198	590
Person-Years at Risk	47,697	29,694	13,768	91,159
Incidence Rate per 1,000 Person-Years	3.2	8.1	14.4	6.5
Psychosocial Distribution				
Depressive Symptoms, Mean [SD]	10.0 [9.1]	7.0 [8.3]	7.3 [7.3]	7.9 [8.5]
Hostility, Mean [SD]	2.9 [1.9]	3.2 [2.0]	2.3 [1.7]	2.9 [1.9]
Discrimination, Mean [SD]	1.4 [1.4]	1.6 [1.2]	0.9 [1.0]	1.4 [1.3]
Job Strain				
Low Strain	8%	36%	15%	26%
Active Job	37%	26%	32%	30%
Passive Job	4%	15%	14%	12%
High Strain	51%	22%	39%	32%

Table 4.9-2. Hazard Ratios for Incident Cardiovascular Disease for a 1-unit Increase in Standard Deviation of Psychosocial Characteristics

Psychosocial Characteristics	CARDIA	JHS	MESA	Pooled
CES-D				
Model 1*	1.18 [1.02, 1.38]	1.13 [0.97, 1.31]	1.23 [1.02, 1.50]	1.17 [1.06, 1.28]
Model 2**	1.18 [0.99, 1.40]	1.14 [0.97, 1.34]	1.17 [0.91, 1.53]	1.14 [1.04, 1.26]
Model 3***	1.14 [0.94, 1.37]	1.02 [0.86, 1.20]	1.16 [0.90, 1.50]	1.14 [1.04, 1.25]
Model 4****	1.11 [0.99, 1.24]	1.01 [0.86, 1.20]	1.15 [0.89, 1.48]	1.13 [1.03, 1.25]
P for interaction	Ref	0.47	0.99	
Hostility				
Model 1*	1.31 [1.11, 1.55]	0.97 [0.85, 1.10]	0.99 [0.82, 1.18]	1.06 [0.97, 1.15]
Model 2**	1.34 [1.09, 1.65]	0.99 [0.87, 1.14]	0.99 [0.76, 1.28]	1.02 [0.94, 1.12]
Model 3***	1.33 [1.07, 1.65]	0.92 [0.81, 1.06]	0.95 [0.73, 1.23]	1.03 [0.94, 1.12]
Model 4****	1.30 [1.04, 1.63]	0.92 [0.80, 1.05]	0.95 [0.73, 1.23]	1.02 [0.94, 1.12]
P for interaction	Ref	0.002	0.05	
Lifetime Discrimination				
Model 1*				
Model 2**	0.82 [0.69, 0.98]	1.01 [0.87, 1.17]	0.89 [0.69, 1.14]	0.92 [0.83, 1.02]
Model 3***	0.87 [0.71, 1.06]	0.97 [0.83, 1.14]	0.76 [0.53, 1.10]	0.87 [0.78, 0.96]
Model 4****	0.89 [0.73, 1.11]	0.88 [0.75, 1.04]	0.77 [0.53, 1.10]	0.87 [0.79, 0.97]
P for interaction	0.85 [0.68, 1.05]	0.88 [0.75, 1.04]	0.76 [0.53, 1.09]	0.87 [0.78, 0.96]
	Ref	0.78	0.93	
Job Strain				
Active Strain				
Model 1*	0.99 [0.48, 2.03]	0.93 [0.62, 1.39]	0.99 [0.42, 2.33]	0.96 [0.71, 1.31]
Model 2**	1.12 [0.50, 2.53]	0.81 [0.52, 1.26]	1.15 [0.28, 4.69]	0.95 [0.70, 1.29]
Model 3***	1.08 [0.48, 2.45]	0.71 [0.45, 1.10]	1.17 [0.28, 4.83]	0.94 [0.69, 1.28]
Model 4****	1.04 [0.46, 2.36]	0.70 [0.45, 1.10]	1.22 [0.29, 5.12]	0.95 [0.70, 1.29]
P for interaction	Ref	0.49	0.52	
Passive Strain				
Model 1*	1.36 [0.48, 3.66]	0.86 [0.57, 1.29]	1.19 [0.50, 2.83]	0.95 [0.67, 1.34]
Model 2**	1.14 [0.36, 3.64]	0.81 [0.51, 1.27]	0.83 [0.16, 4.40]	1.03 [0.72, 1.45]
Model 3***	1.18 [0.37, 3.78]	0.79 [0.50, 1.25]	0.79 [0.15, 4.19]	1.03 [0.73, 1.47]
Model 4****	1.12 [0.35, 3.61]	0.79 [0.50, 1.24]	0.81 [0.20, 5.82]	1.04 [0.70, 1.29]
P for interaction	Ref	0.54	0.97	
High Strain				
Model 1*	0.87 [0.43, 1.77]	0.99 [0.62, 1.39]	1.38 [0.42, 2.33]	0.98 [0.71, 1.31]
Model 2**	0.88 [0.39, 1.97]	1.12 [0.75, 1.67]	1.40 [0.37, 5.29]	0.98 [0.72, 1.32]
Model 3***	0.85 [0.38, 1.91]	1.05 [0.70, 1.56]	1.35 [0.35, 5.17]	0.98 [0.72, 1.32]
Model 4****	0.81 [0.37, 1.70]	1.04 [0.70, 1.55]	1.34 [0.35, 5.11]	0.97 [0.72, 1.31]
P for interaction	Ref	0.79	0.92	

*Adjusted for sex and cohort study
**Model 1, also adjusted for education, income, and geographic region
***Model 2, also adjusted for BMI and smoking status
****Model 3, also adjusted for hypertension and diabetes status

Table 4.9-3. Hazard Ratios for Incident Cardiovascular Disease for a 1-unit Increase in Standard Deviation of Psychosocial Characteristics

Psychosocial Characteristics*	MI (n=197)	Stroke (n=252)	CVD Mortality (n=116)
CES-D	1.20 [1.03, 1.40]	1.12 [0.97, 1.29]	1.13 [0.85, 1.50]
Hostility	1.15 [0.99, 1.31]	1.01 [0.89, 1.15]	0.92 [0.70, 1.20]
Lifetime Discrimination	0.92 [0.78, 1.09]	1.05 [0.91, 1.21]	0.79 [0.56, 1.11]
Job Strain			
Active Strain	0.91 [0.55, 1.49]	1.09 [0.71, 1.67]	1.04 [0.33, 3.29]
Passive Strain	0.82 [0.47, 1.43]	0.93 [0.57, 1.50]	1.43 [0.46, 4.47]
High Strain	1.01 [0.63, 1.61]	0.99 [0.66, 1.51]	1.07 [0.36, 3.20]

*Models adjusted for sex, cohort study, education, income, geographic region, BMI, smoking status, hypertension and diabetes

Table 4.9-4. Associations of Psychosocial Risk Factors with Cardiovascular Disease Incidence by Age at Baseline, Sex, and Geographic Region

	Hazard Ratios (per SD)					
	CES-D	Hostility	Discrimination	Job Strain		
				Active	Passive	High
Age						
Age 29 (25th percentile)	1.15 [1.01, 1.30]	1.19 [1.03, 1.37]	0.87 [0.75, 1.02]	1.04 [0.60, 1.81]	0.90 [0.42, 1.92]	1.33 [0.76, 2.31]
Age 62 (75th percentile)	1.04 [0.93, 1.17]	0.93 [0.84, 1.02]	0.86 [0.76, 0.97]	1.17 [0.81, 1.69]	1.10 [0.77, 1.58]	0.99 [0.72, 1.36]
P for interaction	0.28	0.002	0.83	0.69	0.60	0.31
Sex						
Female	1.08 [0.96, 1.22]	0.94 [0.83, 1.07]	0.88 [0.76, 1.02]	0.99 [0.67, 1.49]	1.02 [0.65, 1.60]	0.96 [0.65, 1.42]
Male	1.12 [0.96, 1.30]	1.03 [0.91, 1.17]	0.85 [0.73, 0.99]	0.93 [0.57, 1.51]	0.85 [0.48, 1.48]	0.91 [0.57, 1.46]
P for interaction	0.78	0.32	0.58	0.64	0.68	0.51
Region						
West	0.79 [0.55, 1.14]	1.21 [0.87, 1.69]	0.64 [0.43, 0.97]	1.55 [0.19, 12.62]	1.61 [0.10, 26.83]	1.72 [0.21, 13.86]
Midwest	1.33 [1.07, 1.65]	1.34 [1.05, 1.70]	0.88 [0.70, 1.10]	1.68 [0.39, 7.37]	1.35 [0.23, 7.84]	1.64 [0.38, 7.10]
Northeast	1.29 [0.94, 1.77]	0.85 [0.60, 1.21]	0.76 [0.36, 1.64]	1.84 [0.33, 10.10]	4.14 [0.81, 21.10]	2.17 [0.45, 10.57]
South	1.08 [0.95, 1.22]	0.94 [0.84, 1.05]	0.90 [0.79, 1.02]	0.90 [0.64, 1.28]	0.84 [0.57, 1.24]	0.82 [0.58, 1.16]
P for interaction for West, Midwest, NE compared to South	0.16, 0.15, 0.69	0.11, 0.02, 0.56	0.12, 0.62, 0.41	0.59, 0.25, 0.63	0.90, 0.55, 0.10	0.47, 0.24, 0.33

*All models adjusted for sex, cohort study, education, income, geographic region, BMI, smoking status, hypertension and diabetes status.

Table 4.9-5. Mean Baseline Covariates at Each Tertile of Psychosocial Exposure

Population Characteristics	Depressive Symptoms			Hostility			Discrimination			Job Strain			
	T1	T2	T3	T1	T2	T3	T1	T2	T3	Low	Active	Passive	High
Total population	34	32	34	25	33	41	32	46	23	26	30	12	32
MESA	28	46	26	37	36	27	48	43	9	15	32	14	39
JHS	41	28	31	24	33	43	21	52	27	36	26	15	22
CARDIA	26	30	45	20	32	49	40	32	27	8	37	4	51
Age, years	50	48	43	49	45	42	51	51	46	52	43	55	41
Female	32	30	38	29	34	37	32	46	22	26	30	12	31
Male	36	35	29	20	32	48	30	45	25	24	29	12	34
Geographic Region													
West	24	34	41	27	37	37	40	37	23	7	40	5	48
Midwest	27	30	43	21	34	45	37	35	28	9	35	7	49
Northeast	22	47	31	33	36	31	51	41	8	14	31	14	42
South	39	30	31	25	32	43	26	49	24	33	27	14	26
Education													
Less than high school	42	22	37	14	29	57	43	43	14	21	21	21	37
High school or GED	31	31	38	21	33	46	34	44	22	21	30	11	38
Technical School or Associate Degree	32	35	34	24	37	39	28	49	23	27	32	12	29
Bachelor's degree	34	38	28	35	35	29	22	49	29	31	33	9	27
Graduate or professional degree	37	41	23	42	33	25	23	47	30	41	34	9	16
Mean Income	44,190	46,626	34,873	49,001	42,327	36,361	38,136	44,726	47,813	50,957	46,652	39,850	37,280
BMI	30	29	30	29	29	29	29	30	30	31	30	31	29
Smoking													
Never	34	32	34	26	33	41	31	46	24	28	30	11	31
Former	35	36	29	30	35	35	33	47	20	27	29	14	29
Current	31	28	41	18	33	49	33	43	23	18	29	13	41
Incident CVD Cases	36	31	32	27	36	37	39	45	16	27	25	16	32

Table 4.9-6. Psychosocial Characteristics and Incident CVD Sensitivity Analysis: Income Imputation

Psychosocial Characteristics	**Sensitivity (excluding missing income)**	**Pooled (mean imputation)**
CESD	1.11 [1.01, 1.23]	1.13 [1.03, 1.25]
Hostility	1.02 [0.93, 1.12]	1.02 [0.94, 1.12]
Lifetime Discrimination	0.89 [0.80, 0.99]	0.87 [0.78, 0.96]
Job Strain		
Active Strain	1.05 [0.77, 1.44]	0.95 [0.70, 1.29]
Passive Strain	0.91 [0.68, 1.22]	1.04 [0.70, 1.29]
High Strain	0.94 [0.66, 1.35]	0.97 [0.72, 1.31]
*All models adjusted for sex, cohort study, education, income, geographic region, BMI, smoking status, hypertension and diabetes status.		

Table 4.9-7. Psychosocial Characteristics and Incident CVD Sensitivity Analysis: Full Psychosocial Scales

Psychosocial Characteristics	**Sensitivity (All available items from psychosocial scales)**	**Pooled (Abbreviated psychosocial scales)**
CESD	N/A	1.13 [1.03, 1.25]
Hostility	0.97 [0.89, 1.04]	1.02 [0.94, 1.12]
Lifetime Discrimination	0.87 [0.79, 0.97]	0.87 [0.78, 0.96]
Job Strain		
Active Strain	1.30 [0.54, 3.12]	0.95 [0.70, 1.29]
Passive Strain	1.43 [0.60, 3.45]	1.04 [0.70, 1.29]
High Strain	1.62 [0.69, 3.82]	0.97 [0.72, 1.31]
*All models adjusted for sex, cohort study, education, income, geographic region, BMI, smoking status, hypertension and diabetes status.		

Table 4.9-8. Cases of Incident Cardiovascular Disease (Expanded Definition) by Cohort Study

Condition	CARDIA	JHS	MESA
Stroke	51	142	59
Myocardial Infarction	48	100	49
Congestive Heart Failure	57	4	81
CVD Death	27	19	70
Resuscitated Cardiac Arrest	N/A	N/A	13
Transient Ischemic Attack	10	N/A	23
Peripheral vascular/arterial disease	6	1	32
Cardiac Procedures	27	58	68
Total CVD	159	302	285

Table 4.9-9. Psychosocial Characteristics and Incident CVD Sensitivity Analysis: Expanded CVD Definition

Psychosocial Characteristics	**Sensitivity (Expanded CVD)**	**Pooled (CVD)**
CESD	1.19 [1.09, 1.29]	1.13 [1.03, 1.25]
Hostility	1.09 [1.01, 1.18]	1.02 [0.94, 1.12]
Lifetime Discrimination	0.98 [0.89, 1.07]	0.87 [0.78, 0.96]
Job Strain		
Low Strain	0.98 [0.74, 1.29]	0.95 [0.70, 1.29]
Active Strain	0.93 [0.69, 1.26]	1.04 [0.70, 1.29]
Passive Strain	0.99 [0.77, 1.30]	0.97 [0.72, 1.31]
*All models adjusted for sex, cohort study, education, income, geographic region, BMI, smoking status, hypertension and diabetes status.		

Table 4.9-10. Psychosocial Characteristics and Incident CVD Sensitivity Analysis: Parametric Weibull Models

Psychosocial Characteristics	**Sensitivity (Parametric)**	**Pooled (Cox)**
CESD	1.14 (p<0.0001)	1.18 (0.002)
Hostility	1.02 (0.42)	1.02 (0.64)
Lifetime Discrimination	1.01 (0.85)	1.02 (0.75)
Job Strain		
Low Strain	0.85 (0.31)	0.98 (0.80)
Active Strain	0.91 (0.59)	1.02 (0.81)
Passive Strain	0.78 (0.18)	0.80 (0.03)
*All models adjusted for sex, cohort study, education, income, geographic region, BMI, smoking status, hypertension and diabetes status.		

Table 4.9-11. Psychosocial Characteristics and Incident CVD Sensitivity Analysis: Free of Cardiovascular Disease at Age 45

Psychosocial Characteristics	**Sensitivity (CVD Free at Age 45)**	**Pooled (CVD Free at Baseline)**
CESD	1.03 [0.92, 1.15]	1.13 [1.03, 1.25]
Hostility	0.91 [0.82, 1.01]	1.02 [0.94, 1.12]
Lifetime Discrimination	1.00 [0.89, 1.13]	0.87 [0.78, 0.96]
Job Strain		
Low Strain	1.04 [0.73, 1.47]	0.95 [0.70, 1.29]
Active Strain	0.77 [0.53, 1.13]	1.04 [0.70, 1.29]
Passive Strain	0.83 [0.59, 1.16]	0.97 [0.72, 1.31]
*All models adjusted for sex, cohort study, education, income, geographic region, BMI, smoking status, hypertension and diabetes status.		

CHAPTER 5. CONCLUSIONS

5.1 Review of major findings

This dissertation investigated the relationship between four psychosocial characteristics (depressive symptoms, hostility, discrimination and job strain) and cardiovascular health. We found that psychosocial characteristics were not universally risk factors for CVD-related outcomes in Blacks, but several trends did emerge.

5.1.1 Depressive Symptoms

The evidence that depressive symptoms are an independent risk factor for the etiology of cardiovascular disease is consistent and convincing. Fifteen percent of our sample population had CES-D scores greater than or equal to 16. We found that higher levels of depressive symptoms are associated with incident hypertension, incident diabetes mellitus, and incident cardiovascular disease. We also found that depressive symptoms are a greater predictor of myocardial infarction than stroke or cardiovascular mortality. Given the relationship between depressive symptoms and CVD varies by type of CVD, this may provide insight into potential physiologic mechanisms. Within Blacks, we did not find evidence of heterogeneity of effect of depressive symptoms by age, sex, or geographic region.

Meta-analyses have demonstrated much greater effects for depressive symptoms than were noted in this study. Prior research has demonstrated 40% increases in incident hypertension, 60%

increases in incident diabetes, and 30% increases for incident stroke[30–32]. Given the great deal of work demonstrating that Blacks are more vulnerable to the effect of depressive symptoms than Whites[36–39], it is unlikely that we would observe the smaller effect sizes. However, many of these meta-analyses use a dichotomous measure of CES-D, while we assumed a linear relationship based on our theoretical framework and functional form analyses. Second, given that these meta analyses rely on data published in peer-reviewed journals, they may be vulnerable to publication bias. In short, we do not believe that smaller observed effect sizes in our study signal bias.

Further, we did not observe significant attenuation of the effect of CES-D by socioeconomic position and health behaviors. We posit, then, that depressive symptoms have an independent effect on the etiology of cardiovascular outcomes. There is a great volume of literature devoted to better understanding mechanisms of this relationship. They find that depressive symptoms increase coronary artery calcification (CAC), which is highly correlated with atherosclerosis [20,22]. Though health behaviors likely do not mediate the relationship between depressive symptoms and CAC, there may be a synergistic relationship between smoking and depressive symptoms related to CAC [185]. Other studies have found a plausible link between depressive symptoms and markers of inflammation that are implicated in the progression and instability of atherosclerotic plaque [186–188]. This research identifies two clear pathways through which depressive symptoms influence cardiovascular health.

5.1.2 Hostility

Hostility has not been researched to a great degree in longitudinal studies or in Black populations, so this study is a valuable contribution to the literature. Approximately 29% of our sample population had hostility scores of 5 or more (Range: 0 to 8), and the evidence this study provides on the relationship between hostility and cardiovascular risk is suggestive. We found

that hostility is a risk factor for incident hypertension, myocardial infarction, and an inclusive composite measure of cardiovascular disease. We did not find evidence that hostility is associated with diabetes or other forms of CVD independent of health behaviors. These findings reflect mixed findings in prior literature [47,140,158–160].

The inconclusiveness of this research may be caused by the abbreviation of the Cook-Medley scale. The scale was validated in full, but many cohort studies use abbreviated scales to assess the effects of hostility. We noted differences in the effect of hostility when we used the 7 items that were available across all three cohort studies and the 50 items available in CARDIA. Missing from our hostility score were items that assessed social avoidance and aggressive responding. These characteristics measure key constructs of hostility, which may be driving associations with CVD. While hostility was not significantly associated with diabetes using the abbreviated scale, we observed a strong independent effect of hostility on diabetes using the full questionnaire in CARDIA.

The inconclusiveness in prior research may also signal heterogeneity of effect. We found that the effects of hostility were modified by age, such that younger participants were more vulnerable to the effects of hostility with respect to incident CVD than older participants. This was contrary to our hypothesis that older Blacks, having experienced weathering over the lifecourse would demonstrate increased vulnerability. Future research should elucidate the characteristics of cynicism among younger individuals, as well as co-occurring stressors, which may help to explain these findings.

5.1.3 Discrimination

Approximately 31% of our sample population reported no experiences of discrimination, 23% reported discrimination in one domain, and 46% reported discrimination in two or more domains. Previous research on the effect of discrimination, particularly using the major experiences of discrimination scale, has been inconclusive [71,98,189]. We thought this inconsistency could be addressed with a larger sample size and a within group study of race; however, we observed null associations with incident hypertension, diabetes and cardiovascular events in the pooled sample. We did observe, though, a marginally significant effect of discrimination on hypertension and diabetes in the MESA cohort. The effects of discrimination did not achieve statistical significance in MESA; however, the relationship was suggestive.

The major experiences of discrimination scale evaluates the domains in which participants experience discrimination. Higher scores indicate experiences of discrimination in multiple domains, and while this is a rough proxy for frequency of discrimination, it would be inadequate to assess the experience of someone who encounters perpetual discrimination within one domain. It is unclear if experiencing discrimination in multiple domains would induce more stress than experiencing discrimination in one domain chronically. Further, it is unclear if discrimination in certain domains induces greater stress response than other domains (e.g. education, workforce, housing, healthcare, justice system). It is reasonable to assume that the threat of unjust incarceration, for example, may induce more stress than being unfairly denied a promotion; however, this has not yet been tested empirically. In short, a more thoughtful conceptual framework may best support future research in the discrimination literature.

Our finding that discrimination might be modified by context may also help to understand mixed findings. We observed that the effect of discrimination on hypertension was stronger in

men than women. This finding was supported by Hickson and colleagues, who found an effect of discrimination on subcutaneous fat in Black men, but not in Black women [112]. This finding is reasonable if we consider that discrimination in Black men, particularly in the domains of education and the criminal justice system, often has more severe consequences than for Black women[72,190,191]. Further, Black men and women may cope differently with discrimination-related stress. Sims and colleagues found that in women, discrimination is associated with more physical activity compared to men, and this may help to explain more deleterious consequences of discrimination in men [84]. There is still much to learn about sex-specific characteristics of discrimination in Blacks and sex-specific coping mechanisms.

5.1.4 Job Strain

The effect of job strain varies by health outcome. We demonstrated that job strain was a risk factor for hypertension. Job strain, though, was not associated with incident diabetes or incident cardiovascular disease in the pooled sample. The mixed findings observed in this study were contrary to our hypothesis given a great volume of work demonstrates that job strain is indeed a risk factor for various cardiovascular outcomes. Likely the cause of these findings was our conceptualization of job strain. Only four of 49 items assessing job strain were available for the pooled analysis. Missing from our job strain measurement were items that assessed the participant's opportunity to learn new things, develop their own abilities, exercise creativity, or balance conflicting demands. These characteristics measure key constructs of professional development, autonomy, and decision making skills, which may be driving associations with CVD. Further, the four questions used in our analyses to assess job strain, may not be the most relevant to assess job strain in Blacks.

As a result, our study may not have adequately captured the construct of job strain in a manner sufficient to reproduce this positive relationship observed in previous literature. This hypothesis is supported by our sensitivity analysis that shows that when we use the full scales for job strain, we find that participants with high strain have an increased rate of incident hypertension and CVD. In summary, future research should insist on the comprehensive measurement of job strain lest we underestimate its effects.

However, we should also consider that job strain may operate differently in Blacks and Whites. This study is the first within group study of Blacks to investigate the effect of job strain on cardiovascular health. The Job Content Questionnaire was validated in White male workers, and it is reasonable to question it validity for women and ethnic minorities, who may experience job stressors related to discrimination, job typing or multiple social roles[70]. Validation and differential item functioning for job strain in Blacks should be the subject of future research.

Our study also revealed that the effect of job strain on hypertension was attenuated after adjustment for health behaviors, suggesting that BMI and smoking are potential mediators of this relationship. Support for this hypothesis is limited, as there are mixed findings on the relationship between job strain and health behaviors. The most in-depth study of BMI and job strain, a meta-analysis of 160,000 European participants, found that job strain was associated with both weight gain and weight loss [15]. Another more recent study of women found that those with higher BMI may be more vulnerable to BMI gain when exposed to constant work stress [114]. It appears that the relationship between job strain and BMI is nuanced and may be dependent on BMI prior to job strain. Regarding smoking, another meta-analysis of European cohort studies found no relationship between job strain and changes in smoking behavior; however, they did observe that smokers experiencing job strain smoked more cigarettes per day than smokers

without job strain [115]. This finding has been replicated in other studies [116–119]. In short, there is support for our finding that health behaviors mediate the relationship between job strain and hypertension.

Finally, we observed regional differences, whereby participants in the west and northeast experienced greater risk associated with job strain than participants in other regions of the country. Passive jobs, characterized by low psychological demands and low decision latitude, appear particularly detrimental in the Northeast with respect to incident CVD, and high strain jobs, characterized by high psychological demands and low decision latitude, were associated with increased risk of diabetes in the West. These findings were contrary to our hypotheses that individuals in the South would be more vulnerable to the effects of psychosocial characteristics, and there is no clear explanation for this geographic patterning. These findings may be noise generated from pooling; however, given such little previous research on these trends, it is unclear. Regional culture could have implications for stress perception, as well as coping behaviors, social support or economic opportunties[150], which could in turn increase cardiovascular risk. Namely, individuals in the South may have the benefit of additional social support through religious and other community organization which serves as a buffer against the effects of stress and negative affect. As a result, additional consideration into characteristics of geographic regions that are associated with increased CVD risk help to understand geographic patterning of CVD.

5.2 Strengths and Limitations

The great strength of our study was the pooling of individual-level data from three cohort studies. The cohort studies were unique in their population characteristics, but they complemented one another to form a diverse sample of Blacks in the U.S. The advantage of

having younger participants was that we likely minimized the effect of survival bias, and the heterogeneity of age among participants also allowed us to test the hypotheses of effect modification, such as the weathering hypothesis. Throughout this study, we observed that often study-specific results did not meet statistical significance. In an analysis of one cohort study, we might have concluded a null association between psychosocial factors and cardiovascular outcomes. Conducting a meta-analysis, though, improved our power to detect these effects, which were often quite small in magnitude.

Another asset of this study was the rigor of the three data sources utilized. Each of these studies collected nuanced psychosocial profiles for their participants. Further, while many studies in this area use self-reported health metrics, each of these cohort studies had detailed and adjudicated data on cardiovascular health. These key features make these cohorts optimal candidates for inclusion in this study. Further, we had access to longitudinal data spanning up to 25 years. Prior research illustrates the bidirectional relationship between negative affect and health conditions[31]. As a result, cross sectional research designs are inadequate to describe the impact of these risk factors on health. In the event of highly prevalent outcomes, we benefitted from applying novel methods to include left-censored participants who would have otherwise been excluded from the study.

The greatest limitations of this study also result from the data source. First, our assessment of psychosocial characteristics may not have been adequate to capture the true relationship to cardiovascular health. Our analysis was limited to the psychosocial concepts available across each of the cohort studies, and within each concept, we were limited by the number of items that were available across all three studies. The result was that we used abbreviated scales for hostility, discrimination and job strain that were not highly correlated with

the full studies. The Cronbach's alpha for the full and abbreviated scales were between 0.75 and 0.96 for the hostility ($p<0.001$ for all studies), between 0.87 and 0.95 for discrimination ($p<0.001$), and between 0.47 and 0.63 ($p<0.001$) for job strain. In sensitivity analyses, we found that the abbreviated scales attenuated the effect of hostility and job strain in several of the analyses, but in large part, the psychosocial measures do not achieve statistical significance (perhaps due to small sample sizes for these cohort-specific analyses). As a result, we conclude that our results may be a conservative estimate of the effects of psychosocial stress, and there may also be other psychosocial characteristics, not assessed in this study, that are meaningful for cardiovascular health as well.

Also, we did not have repeated measurement of psychosocial characteristics consistently across studies and could not investigate changes in stress, as a result. Given hostility is a stable personality trait, there would likely be little effect on our results if we had repeated measurement. This is likely not the case, though, for depressive symptoms and job stress, where participants likely experienced varied exposure over a follow up period of 25 years. The value of this study, though, still holds as, particularly with depressive symptoms, we observed a great degree of cardiovascular risk associated with measurement at just one point in time. Future studies should seek to investigate how changes in psychosocial characteristics impact cardiovascular outcomes.

Third, we attempted to limit reverse causation by excluding left censored participants from the longitudinal analysis. This is particularly relevant for CES-D, given that chronic conditions, such as diabetes and cardiovascular disease, are known risk factors for depression[147]. There may still be some potential for reverse causation, though, because we assigned the psychosocial exposures to baseline, when actually, they were assessed at different time points.

Although this decision was intended to extend follow up time, it may also have introduced some reverse causation and bias as a result.

Finally, as is the case in much epidemiologic research, our study is likely vulnerable to selection and participation bias[192]. Our study may have been vulnerable to selection bias due to our exclusion of participants with CVD prior to baseline or loss to follow up. Participants with CVD at baseline were all from Jackson Heart Study and there were no differences in psychosocial factors. They were, however, older on average and they had higher BMI and smoking prevalence, and lower education and income. In sensitivity analyses of participants with baseline CVD, we noted no differences in the associations between psychosocial indicators and CVD compared to the pooled sample; and as a result, we do not anticipate that the exclusion of these participants was a great source of bias.

Regarding loss to follow up, we noted attrition of 7% in MESA (124 participants), 16% in JHS (822 participants), and 5% in CARDIA (130 participants). Because psychosocial evaluation occurs after visit 1 in many studies, many participants lost to follow up have missing psychosocial data. Specifically, participants who only attended exam 1 in MESA have missing data for job strain and hostility, participants lost to follow up in JHS have missing data for job strain, and those lost to follow up in CARDIA have missing data for all psychosocial characteristics. However, analyzing the data of participants who completed psychosocial questionnaires prior to being lost to follow up, we observe that they had lower depressive symptoms and hostility and were less likely to experience job strain compared to participants who attended at least one follow up visit. In regression analyses, Midwest residence, lower education, currently smoking were significant predictors of attrition. Depressive symptoms and discrimination were inversely associated with attrition, suggesting that individuals with greater

psychosocial burden may be less likely to be lost to follow up. Relying on these results, we might conclude that our findings were potentially biased away the null; however, because we cannot assess the psychosocial characteristics of many participants lost to follow up, the impact of this attrition is challenging to assess.

Finally, individuals with the greatest degree of chronic stress are less likely to participate in research studies, as are individuals with chronic conditions[193]. Additionally, many epidemiologic cohort studies exclude institutionalized individuals who may be most susceptible to the effects of psychosocial risk factors. The absence of these individuals introduces participation bias and limits the generalizability of our results.

5.3 Significance and Implications

The goal of this study was to understand the role of psychosocial characteristics on cardiovascular health in Blacks. Psychosocial risk factors are contributing to premature cardiovascular disease in Blacks. Given prior evidence suggests that the prevalence of psychosocial risk factors is substantially higher among Blacks compared with Whites and evidence that psychosocial risk factors have stronger effects in Blacks, these risk factors are likely contributing to CVD disparities[36,55,70,71].

In this study, we found heterogeneous effects of psychosocial characteristics by age, sex and geographic region as hypothesized; but also, we noted differential effects of psychosocial characteristics across cohort studies, by the length of our psychosocial scales, and depending upon our statistical methods. These mixed findings may help bring some clarity to our interpretation of the inconsistency found in previous research. Future research must strive to

replicate findings across cohorts, keeping in mind how cohort characteristics, inadequate psychosocial assessment and statistical methods may impact research findings.

Our results indicate that depressive symptoms, hostility and job strain are associated with cardiovascular risk in Blacks. Our within group analysis was particularly valuable in demonstrating features of these associations that are unique to Blacks. For example, prior work has been consistent in demonstrating that the effects of psychosocial stress and negative affect are stronger in women compared to men; however, our study found that discrimination was a stronger predictor of hypertension in Black men compared to Black women. Future work should investigate sex-specific risk and protective factors which may predispose certain populations to CVD risk, keeping in mind these relationships may vary by race and ethnicity.

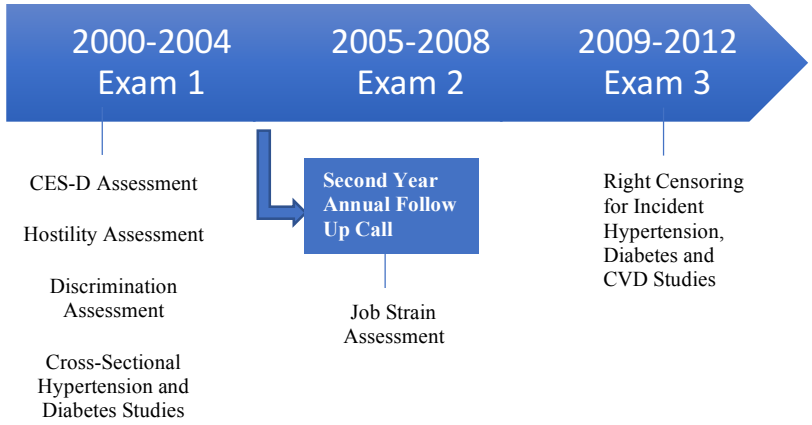
Depressive symptoms emerged as the most consistent psychosocial threat to cardiovascular health in Blacks in our study, and this finding has important clinical implications. Blacks are more likely to have higher depressive symptoms, and yet, mental health care is characterized by racial and ethnic disparities in access to care, delay of care, and quality of care[194]. There is evidence that minority patients are less likely to receive the best available treatment for depression and anxiety, as well as evidence of provider discrimination[194,195]. Improvements in the detection, access to care and treatment of depression in Blacks is likely to have a notable effect not only on the mental health of Blacks, but also cardiovascular health. Similarly, other efforts to buffer the effects of negative affect and stress, or prevent upstream determinants of negative affect and stress, may have implications for cardiovascular health. Future research would benefit from a framework which emphasizes macrosocial constraints on mental health and health behavior, as well as interventions to address the social and environment context which predisposes Blacks to psychosocial stress and premature morbidity and mortality.

Prior research has found that Blacks are more vulnerable to the effects of psychosocial stress and negative affect, and we hypothesize that these racial differences are in part due to the chronicity, severity and clustering of stressors among Blacks. Given these characteristics of psychosocial stress and negative affect are not often investigated, we encourage a research agenda that can address some of these key features. Chronicity of stress and negative affect can be investigated with assessment of the duration of the stressor, as well as repeated measurement of the stressor in cohort studies. Severity can be assessed through the consideration of not merely the number of domains in which a participant experiences discrimination, for example, but also the number of times that discrimination occurs and the characteristic to which the discrimination is attributed (e.g. race, sex, sexual orientation, etc). Finally, an investigation of clustering might include an analysis of the social patterning of stressors and the co-occurrence or interaction between various forms of social disadvantage. The clustering hypothesis was supported by the high correlations of psychosocial characteristics seen in this study. The features of psychosocial stress and the contexts in which they occur are likely to vary across ethnic groups, and as a result, there is a continued need for within group, as well as between group, research to identify risk and protective factors for CVD in Blacks.

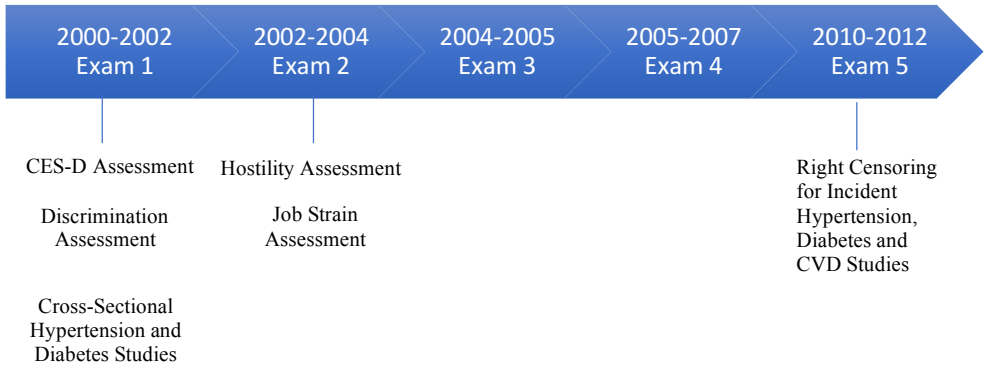
In conclusion, despite enormous reductions in premature CVD over the last 50 years, there remain persistent racial disparities in CVD incidence, severity and mortality. This dissertation has demonstrated that psychosocial stress and negative affect contribute to the increased prevalence of cardiovascular disease in Blacks in the U.S. It is unlikely that these psychosocial characteristics explain Black/White disparities entirely; however, it is likely that reductions in stress and negative affect would decrease the incidence of hypertension, diabetes and CVD among Blacks.

APPENDIX A Psychosocial Assessment

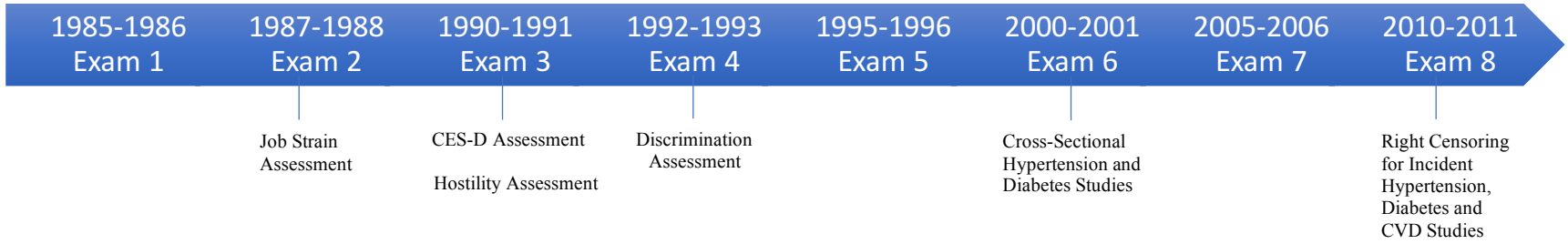
A.1. Psychosocial Assessment in Jackson Heart Study



A.2. Multi-Ethnic Study of Atherosclerosis

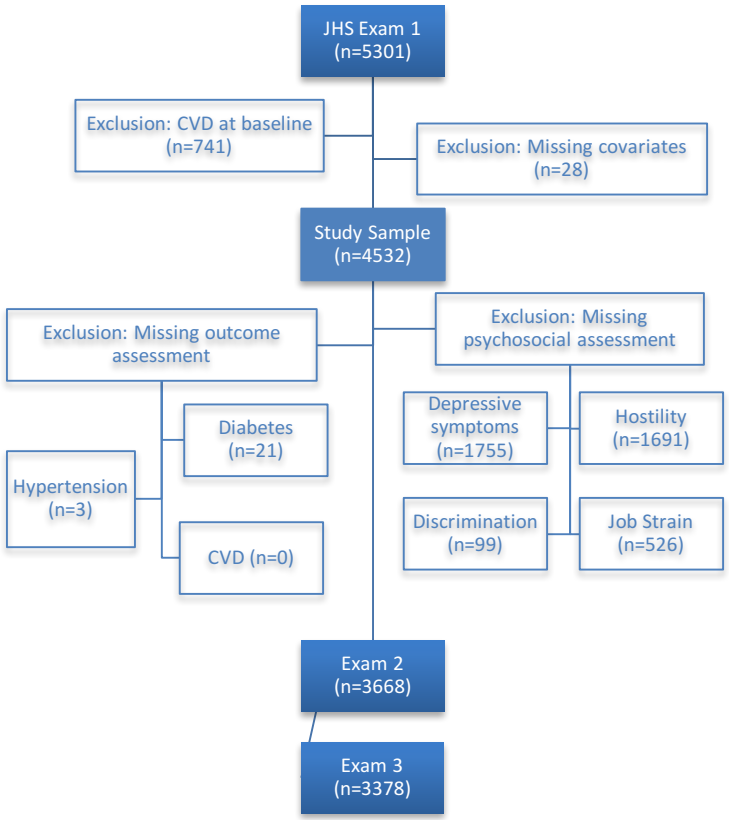


A.3. Coronary Artery Risk Developments in Young Adults

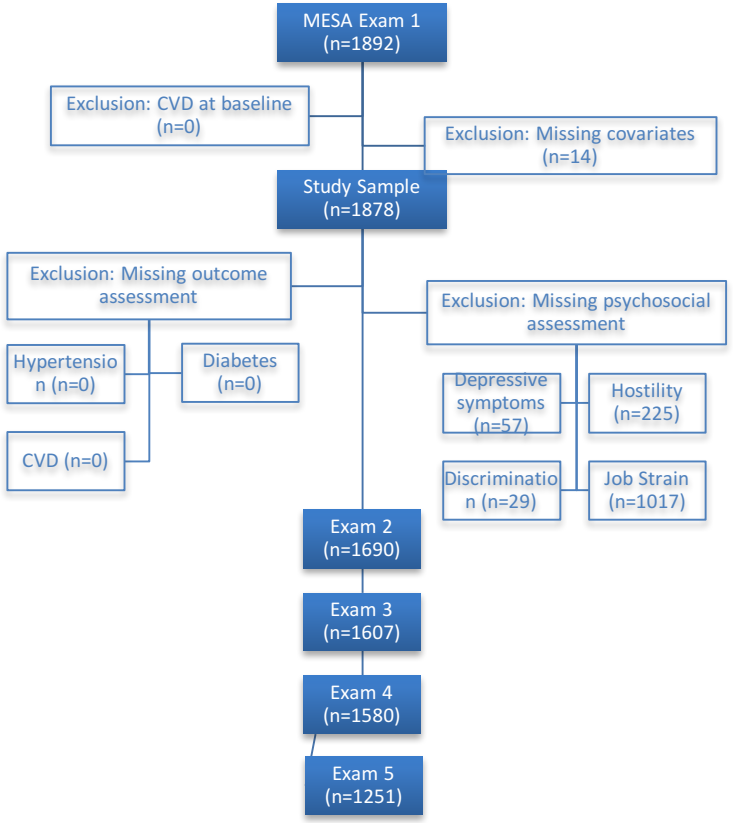


APPENDIX B Inclusion Criteria and Loss to Follow Up

B.1. Jackson Heart Study

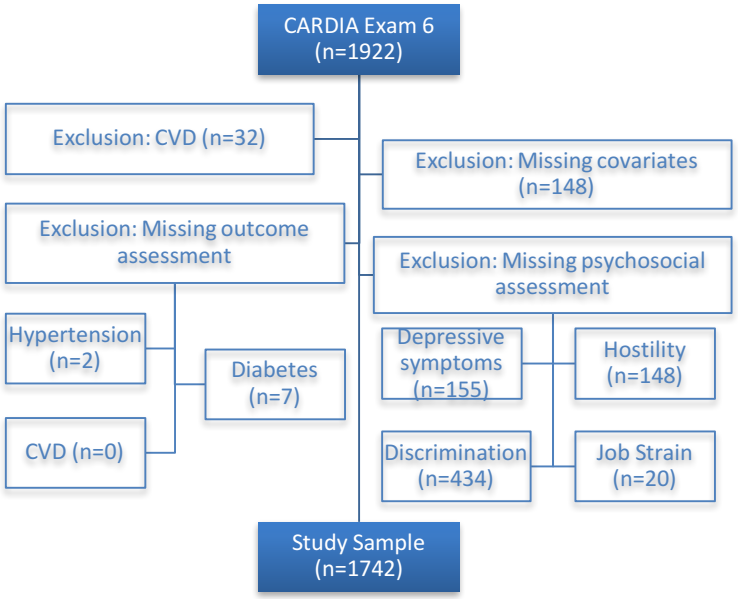


B.2. Multi Ethnic Study of Atherosclerosis



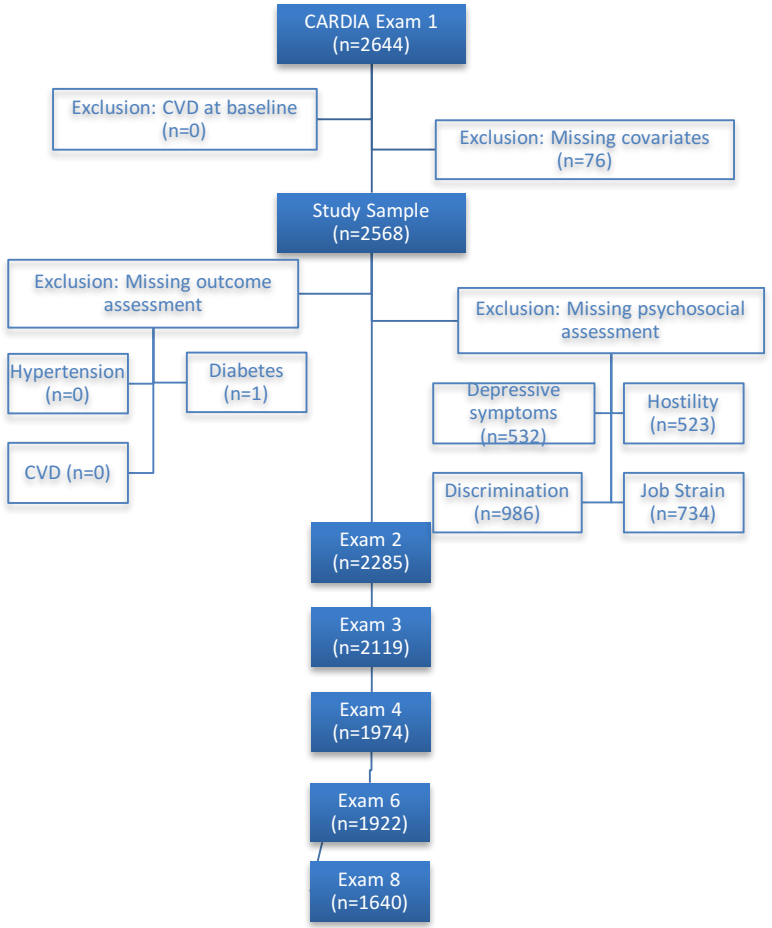
B.3. Coronary Artery Risk Development in Young Adults

Cross Sectional Study



B.4. Coronary Artery Risk Development in Young Adults

Longitudinal Study



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