DEPRESSIVE SYMPTOMS AND SUBCLINICAL VASCULAR DISEASE:

A CROSS-CULTURAL COMPARISON

APPROVED BY SUPERVISORY COMMITTEE

Munro Cullum, Ph.D., ABPP

Myron Weiner, M.D.

Linda Hynan, Ph.D.

Heidi Rossetti, Ph.D.

Martin Deschner, Ph.D.

Kevin King, M.D.

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PATRICIA SINCLAIR MOORE, B.A.

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PATRICIA SINCLAIR MOORE

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C. MUNRO CULLUM, PH.D.

Abstract

While rates of depression are similar across ethnic groups, severity of symptoms and disability related to depression are greater in African Americans when compared with other groups (Breslau, Kendler, Su, Gaxiola-Aguilar, & Kessler, 2005). Markers of subclinical cardiovascular disease have been associated with depression, and rates of most cardiovascular risk factors are higher in African Americans than Caucasians (Shaya, Gu, & Saunders, 2007). Whereas rates of atherosclerosis are similar across these groups (Jain et al., 2004), atherosclerosis has been shown to be associated with depression in mostly

Caucasian samples (Bus et al., 2011; Gebara & Santos, 2010). A more direct marker of subclinical cerebrovascular impact is cerebral white matter hyperintensity volume (WMHv). Differences in WMHv have been reported across ethnic groups, and WMHv is more closely associated with the cardiovascular risk factors that are higher in African Americans. White matter hyperintensities (WMH) have been independently associated with increased depressive symptoms in late-life depression (Pompili et al., 2007; 2008; Sneed et al., 2011; Tham, Woon, Sum, Lee, & Sim, 2011), although the relationship between vascular disease and depression is poorly understood.

This study aimed to examine the relationship between atherosclerosis, WMHv, and depressive symptoms in Caucasians and African Americans over age 50 to determine the association between subclinical vascular disease and depressive symptoms across ethnic groups. To this end, specific measures of subclinical vascular diseases (measures of atherosclerosis, WMHv) were compared to identify the best predictors of depressive symptoms within ethnic groups.

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List of Abbreviations

IMT: Intima Media Thickness

CAC: Carotid Artery Calcification

AWT: Aortic Wall Thickness

EBCT: Electron Beam Computed Tomography (Measures Coronary Artery Calcium)

MDCT: Multi-Detector Computed Tomography (Measures Coronary Artery Calcium)

ABI: Ankle Brachial Index

DHS: Dallas Heart Study

HPA: Hypothalamic-Pituitary Axis

OR: Odds Ratio

WMH: White Matter Hyperintensities

DTI: Diffusion Tensor Imaging

HRSD: Hamilton Rating Scale for Depression

QIDS-SR: Quick Inventory of Depressive Symptomatology- Self Report

FOV: Field of View

Chapter One: Overview

Introduction

Depression is a common mental illness and significant public health problem with significant impact upon rates of disability and economic burden (Mathers & Loncar, 2006). Numerous epidemiological studies have reported differential prevalence rates of depression across ethnic groups in the U.S.. However, formal diagnosis and treatment are often not pursued, notably among African Americans (L. A. Cooper et al., 2003; Das, Olfson, McCurtis, & Weissman, 2006; González et al., 2008). Despite higher rates of major depression among Caucasians in the United States, depression among African Americans may be more persistent and disabling (Williams et al., 2007).

One possible explanation for the disproportionate impact of depression on African Americans is the higher prevalence rates of many vascular diseases and risk factors associated with cerebrovascular disease (Liao & Cooper, 1995; Ford, Giles, & Dietz, 2002; Shaya et al., 2007). For example, Ferdinand (2006) reported a significant increase in premature cardiovascular deaths in African Americans over age 65 (>30% of total deaths) when compared with a similar cohort of Caucasians (15% of total deaths).

It has been proposed that depression and vascular disease often co-occur in middle-aged and older adults (de Groot et al., 2000; Firbank et al., 2005;

Krishnan, Hays, & Blazer, 1997; M. Santos et al., 2012; Seldenrijk et al., 2011). There is evidence that cardio- and cerebrovascular disease may predispose to, precipitate, or aggravate depression, and conversely, that depression may be a sign of microvascular disease.

Formal study of a potential connection between vascular disease and depression originated with two oft-cited papers. In 1995 Krishnan and McDonald published a theory in which subtle cerebrovascular changes in brain areas sensitive to stress regulation result in vulnerability to depressive symptoms. Initially referred to as "arteriosclerotic depression," investigators began to explore and attempt to validate this theorized phenomenon and described the "vascular depression hypothesis" as an explanation for the relationship between subclinical vascular disease and depression.
(Krishnan & McDonald, 1995; Krishnan et al., 1997).

Krishan, Hays, and Blazer (1997) and Alexopoulos, Barnett, Meyers, Young, Kakuma, Silbersweig, and Charlson (1997) simultaneously released clinical and MRI definitions of "vascular depression." Alexopoulos et al. (1997) compared symptom presentation in 65 consecutively recruited elderly depressed patients diagnosed as having either vascular or nonvascular depression based upon reported vascular disease burden. These investigators indicated that patients with vascular depression demonstrated greater disability and a unique symptom profile characterized by greater psychomotor symptoms, less guilt, and less

insight.

Krishnan et al. (1997) compared 33 patients with vascular depression and 57 patients with nonvascular depression diagnosed by MRI. Patients with deep white matter hyperintensities were categorized as vascular depression. These cerebrovascular changes as reflected by cerebral white matter hyper intensities (WMH) visualized on MRI were found to be associated with depressive symptoms in older adults (Krishnan & McDonald, 1995). This group also reported that patients with vascular depression had greater anhedonia and, consistent with previous report, greater degree of disability. To date, no studies have been published investigating ethnic differences or comparing the cardiovascular with cerebrovascular measures in their association with depressive symptoms.

Research groups in the United States, Europe, and Africa have begun to separately study cerebrovascular and cardiovascular disease variables and their relationship with depressive symptoms. In exploring cardiovascular disease and depression, links between subclinical atherosclerosis and depression have been demonstrated and replicated in primarily elderly samples (Agatisa et al., 2005; Faramawi et al., 2007; Haas et al., 2005; Hamer, Malan, Harvey, & Malan, 2011; Jones, Bromberger, Sutton-Tyrrell, & Matthews, 2003; Pizzi et al., 2010; Seldenrijk et al., 2011; 2010; Spitzer et al., 2008). Notably, despite the potential ethnic differences in cardiovascular disease, no studies have exclusively explored

potential cross-cultural differences in the relationships between cardiovascular disease and depression, and instead race is often viewed as a covariate.

To better understand the association between subclinical cerebrovascular disease and depressive symptoms, investigators have often utilized WMH as the marker of subtle cerebrovascular change suggested by the vascular depression hypothesis. The positive relationship between WMH and depressive symptoms has been primarily elucidated in individuals with late-life depression, which is defined as depression with first onset between ages 45 and 65 (Figiel et al., 1991; Firbank, Lloyd, Ferrier, & O'Brien, 2004; Herrmann, Le Masurier, & Ebmeier, 2007; Jorm et al., 2005; O'Brien et al., 2006; Thomas, O'Brien, et al., 2002a). WMH have also been associated with extended chronicity (Heiden et al., 2005), increased disability (Firbank et al., 2004; González, Tarraf, Whitfield, & Gallo, 2012), and treatment resistance (Baldwin et al., 2004; Simpson, Baldwin, Jackson, & Burns, 1998; Sneed et al., 2011) of depression in older adults. Conspicuously, possibly due to sample size limitations or difficulty recruiting minorities, investigations of ethnic differences have not been specifically reported.

Rationale

Despite ethnic differences in cardiovascular risk and mortality, the majority of the literature exploring the relationship between subclinical vascular disease and depressive symptoms has been performed in small and predominantly Caucasian

samples. Further, the state of the literature at present does not specifically compare subclinical cardiovascular and cerebrovascular measures to identify factors most closely associated with or potentially predictive of depression. The primary aim of the proposed investigation is to study and compare the relationships between subclinical cerebral microvascular disease (WMH volume), subclinical large vessel disease (atherosclerosis), and depressive symptoms in African Americans and Caucasians.

Chapter Two: Review of the Literature

Depression

Description. Depression is one of the most common mental illnesses. In the United States alone, the 12-month prevalence rate of diagnosed mood disorders is 9.5% (Kessler, Chiu, Demler, & Walters, 2005) based upon criteria put forth in American Psychiatric Association's Diagnostic and Statistical Manual (4th ed., text rev.; *DSM-IV-TR*; American Psychiatric Association, 2000). Depression is characterized by symptoms that may include depressed mood, decreased interest, dyssomnia, changes in appetite, feelings of guilt or worthlessness, fatigue, poor concentration, psychomotor changes, and/or suicidal ideation (Association, 2000). Depressive symptoms can range from mild to severe, and the condition may include isolated or recurrent episodes.

According to the DSM-IV-TR, a diagnosis of major depression requires that the aforementioned symptoms (at least five of the aforementioned symptoms in addition to depressed mood or anhedonia for at least two weeks) impair social or occupational functioning and/or result in significant distress (American Psychiatric Association, 2000). A diagnosis of *dysthymic disorder* requires consistent presence of at least two of the aforementioned depressive symptoms across a two-year period (Association, 2000). Last *depressive disorder- not otherwise specified*, is a clinical diagnosis that reflects depressive symptoms that

do not otherwise meet criteria for major depression or dysthymic disorder. Even in the absence of a formal diagnosis, depressive symptoms can have significant impact on an individual's ability to function. These symptoms can manifest early in life, and remain chronic, or present with a sudden onset later in life following psychosocial stressors or, sometimes, without a noticeable precipitating event (Weissman, 2009). The negative impact on functioning is often amplified by psychiatric comorbidities, including anxiety and substance use disorders (Kessler, Nelson, McGonagle, Liu, et al., 1996). Impaired functioning on such a large scale has implications for society at large.

In 2000, the estimated economic burden of depression in the United States rose to $83.1 billion, with most of this being attributed to lost productivity and absenteeism (Greenberg et al., 2003). Though the impact is substantial throughout the American population, the burden of depression-related disability is differentially dispersed across ethnic groups (González, Tarraf, Whitfield, & Vega, 2010).

Depression and Ethnicity. Ethnic differences in depression rates have been consistently reported in the psychological epidemiologic literature. Rates of major depressive disorder among African Americans are often reported as being lower than those of Caucasians. For example, reported 12-month prevalence rates of formally diagnosed depression among individuals over age 18 range between 7% and 10% for African Americans, but analogous rates among Caucasians have

been reported to be 18% to 20% (Breslau et al., 2005; González et al., 2010; Williams et al., 2007). Despite these lower prevalence rates of major depression diagnoses in African Americans, Miller et al. (2004) reported higher frequency (21%) of clinically relevant (yet often undiagnosed) depressive *symptoms* in a sample of 998 community-dwelling older African American adults. These lower rates of formal depression diagnoses, when compared with higher rates of depressive symptoms, in African Americans may be reflective of limited access to and/or an aversion to mental health treatment settings where they might otherwise receive a diagnosis (Carrington, 2006; Das et al., 2006).

When depression is examined in African Americans, some studies report increased levels of disease *severity* (Williams et al., 2007) and overall disability when severity is controlled (González et al., 2010). A recent large epidemiological report including 3,570 African Americans indicated that among depressed African Americans 56.5% of cases were classified as chronic, whereas 38.6% of depression cases were chronic in Caucasians (Williams et al., 2007).

Further support for increased depression chronicity and persistence among African Americans was provided by Breslau et al. (2005), as part of a nationally representative survey on mental illness comorbidity. These investigators examined relationships between psychiatric comorbidity, race, ethnicity, and socioeconomic status (SES). This study reported that among individuals diagnosed with depression in their lifetime, when followed annually, African

Americans more often reported experiencing depression within the past year. These differences in the nature of depressive symptoms among African Americans persisted even when additional demographic factors (SES, education) are controlled (Breslau et al., 2005). In fact, in a large epidemiological study (*N*=20,013) SES, as measured by income and education, appears to have no effect on rates of depression in African American samples, (Gavin et al., 2010b; Riolo, Nguyen, Greden, & King, 2005), despite the impact of SES on depression among Caucasians (Gavin et al., 2010b).

Two hypotheses that have been put forth to explain the differences in rates of depression between Caucasians and African Americans. Distinct symptom profiles have been described in African American samples, with greater prevalence of somatic symptoms (Brown, Schulberg, & Madonia, 1996; Das et al., 2006; McKnight-Eily et al., 2009). Persons with greater somatic symptoms are more likely to seek treatment with a primary care physician, who may miss a diagnosis of depression as an explanation for their somatic complaints (Brown et al., 1996; Das et al., 2006; Scott, Matsuyama, & Mezuk, 2011).

A primary explanation for the greater disability secondary to depression in African Americans may be disparity in use, acceptance, and availability of treatment. For example, multiple studies have reported that African Americans are less likely to seek treatment for depression even when suffering from severe symptoms (Cooper et al., 2003; Das et al., 2006; González et al., 2008; Pickett,

Weissman, & Bruce, 2012; Scott et al., 2011). In one recent epidemiological study (*N*=9,723), 32.4% of depressed Caucasians pursued antidepressant treatment, but only 14% of depressed African Americans did so (González et al., 2008).

Vascular Depression. A cardiovascular connection to depression had been hypothesized since the early 1960's (Krishnan & McDonald, 1995), but Rabkin, Charles, and Kass (1983) first documented an increased rate of depression among hypertensive patients. The first proposed models accounting for connections between atherosclerosis and depression focused on elderly populations. Krishnan and McDonald (1995) first described "arteriosclerotic depression," whereby hypertension, diabetes, and hyperlipidemia work in concert to result in subclinical atherosclerosis, subtle cerebrovascular changes, and depressive symptoms (Krishnan & McDonald, 1995). Alexopoulos and colleagues formalized these observations in defining a "vascular depression" characterized by late onset of illness, co-morbid vascular risk, distinct depressive symptom profiles, secondary cognitive dysfunction, and negative family history of depression (Alexopoulos et al., 1997).

Alexopoulos et al. (1997) attributed vascular depression to subclinical damage in basal ganglia, prefrontal areas, and associated connections. They proposed the likelihood for a frontal lobe syndrome including psychomotor retardation, poor insight, and impaired executive function. Krishnan and

McDonald (1995) hypothesized a mechanism whereby subtle cerebrovascular changes in the frontal lobe, basal ganglia, and white matter would reduce norepinephrine turnover and damage noradrenergic neurons. They proposed that this would reduce catecholamine response to stress resulting in depressive symptoms.

Recent epidemiologic literature estimates that 2.64 million Americans over the age of 50 meet criteria for vascular depression (González et al., 2012). The same study reported that 22% of people treated for depression over age 50 had cerebrovascular disease. The nature of depression with cerebrovascular involvement is such that patients suffer from greater functional impairment than those diagnosed only with major depression, potentially due to the increased treatment resistance in this population (Baldwin et al., 2004; González et al., 2012; Simpson et al., 1998; Sneed et al., 2011). The mechanism of increased treatment resistance remains unclear. This implication requires that the field continues to explore and elucidate the nature of relationship (Ramasubbu, 2000).

Cardiovascular Disease

Description. Cardiovascular diseases are the leading cause of death in the United States (Hoyert, Arias, & Smith, 2012). Cardiovascular diseases refer to a class of illnesses that affect the heart and vascular systems. This term encompasses a wide range of diseases including congenital cardiac abnormalities

and cardiac/vascular damage secondary to ischemic stenosis or occlusion as a result of hypertension and atherosclerosis.

Arteriosclerosis refers broadly to vascular disease, while alternative descriptors are employed depending on the type of vasculature involved. Atherosclerosis affects medium and large arteries and has been extensively studied (Robinson, Fox, Bullano, & Grandy, 2009). Relatively less attention has historically been given to arteriolosclerosis, which is a type of microvascular disease indicative of damage to small arteries and arterioles.

Atherosclerosis can be assessed through several markers, including carotid intima media thickness (IMT), coronary artery calcification (CAC), carotid plaque, and abdominal aortic wall thickness (AWT). Carotid IMT (cIMT) is obtained through MRI or ultrasound measurement of the thickness of the two innermost layers of arterial wall. This measurement evaluates the integration of encrusted arterial lesions into the arterial wall through fibrocellular thickening (Hollander, 1976; Stary et al., 1994). CAC is measured by a electron-beam computed tomography (EBCT) or multi-detector computed tomography (MDCT) and demonstrates the calcification of lesions in the arterial wall (Piers et al., 2008). AWT is assessed through abdominal MRI and is believed to reflect earlier stages in atherosclerotic disease, as plaque formation in the abdominal aorta often precedes manifestation of clinical atherosclerotic symptoms.

Cardiovascular Risk. Non-congenital cardiovascular diseases are often the result of modifiable risk and genetic predisposition. Wilson et al. (1998) utilized a population-based sample from the landmark Framingham Study to establish risk categories that effectively predicted development of cardiovascular disease. The risk factors most closely associated with cardiovascular disease based on the Framingham Risk Score algorithm include age, gender, smoking status, cholesterol levels, and hypertension (Wilson et al., 1998).

Multiple risk factors for cardiovascular disease often coincide in what has been termed the *metabolic syndrome* (Grundy, 2004). Metabolic syndrome is a constellation of cardiovascular risk factors formally defined as three or more of the following: (1) High blood pressure: ≥130/85 mm Hg or antihypertensive medication use; (2) High triglycerides: ≥150 mg/dL; (3) Low HDL cholesterol: <40 mg/dL in men or <50 mg/dL in women; (4) High fasting glucose: ≥110 mg/dL or antidiabetic medication use; or (5) Abdominal obesity: waist circumference >102 cm in men or >88 cm in women (Grundy, 2004; Kinder, 2004).These factors, along with family history of cardiovascular disease, may result in acute cardiovascular events such as myocardial infarctions, or in more insidious disease processes such as atherosclerosis.

Ethnicity and Cardiovascular Disease. Cardiovascular risk and mortality is disproportionately higher in African Americans (Ferdinand, 2006; Kurian & Cardarelli, 2007). Epidemiological research has demonstrated that while rates of

metabolic syndrome in the general population are as high as 23%, among urban African Americans this rate exceeds 40% (Ford et al., 2002; Shaya et al., 2007). Individual cardiovascular risk factors have been found equally elevated among African Americans.

A recent review of epidemiologic studies comparing cardiovascular risk in one or more ethnic groups reported that 12 of the 13 studies reviewed found significant differences across ethnic groups, with highest rates of hypertension and family history of hypertension among African Americans (Kurian & Cardarelli, 2007). Another factor included in metabolic syndrome is obesity, which is closely associated with increased prevalence of atherosclerosis (Burkhauser & Cawley, 2008). The most recent and comprehensive epidemiological study of obesity reported prevalence significantly higher among African Americans when compared with Caucasians and Mexican Americans, regardless of gender (Flegal, Carroll, Ogden, & Curtin, 2010).

The higher rates of cardiovascular risk factors have been associated with increased cardiovascular mortality among African Americans (Ferdinand, 2006). Despite decreasing mortality rates among Caucasians, cardiovascular mortality rates for African Americans remained constant from 1980 to 1991 (Liao & Cooper, 1995). A recent international study of patients with atherothrombotic risk (*N*=49,602) found cardiovascular mortality to be 6.1% among African American

participants after two-year follow-up; a significant increase compared to other ethnic groups (3.9%) (Meadows et al., 2011).

Atherosclerosis

Description. The process of atherosclerotic change in arterial walls often begins in adolescence with accumulation of low-density lipoproteins at vulnerable areas of the innermost layer of the arterial wall, the tunica intima, which is made of endothelial cells. These fatty streaks are then oxidized and initiate the inflammatory response of endothelial cells. This response involves the secretion of adhesion molecules, which draws monocytes, neutrophils, mast cells, and lymphocytes into the lesion (Insull, 2009; Stary et al., 1994). The oxidized cholesterol stimulates the monocytes to transform into cholesterol-consuming macrophages (Insull, 2009; Stary et al., 1994).

Elegantly described by Insull (2009), as macrophages begin to consume cholesterol they transform into foam cells. If the associated inflammatory response is left unchecked, these lipid-engulfing macrophages, foam cells, accumulate into a lipid-rich plaque. This atheromatic plaque then develops lipid-rich necrotic core as foam cells die and attract more macrophages. Fibrous connective tissue eventually creates a cap to cover the plaque. Throughout this process, the plaque becomes increasingly calcified, and results in intima medial thickening, luminal narrowing, ischemia, and potentially vascular rupture. These

plaques become acutely dangerous as the thin fibrous cap can erode, releasing the plaque to travel to upstream sites in the heart, lungs, brain, and other large arterial sites; reducing or completely occluding blood flow to tissue.

Atherosclerosis and Ethnicity. Despite oft-reported increased mortality rates in African Americans with cardiovascular disease, consistent results describing the relationship between race and atherosclerosis remain elusive. While few studies comment specifically on this relationship, a report from the Dallas Heart Study (DHS), a large, epidemiologic study of cardiovascular risk in Dallas County, described similar rates of atherosclerosis (as assessed by CAC) in African Americans and Caucasians (Jain et al., 2004). Despite these findings, investigators later proposed different rates of atherosclerosis in multi-ethnic samples, with African Americans actually demonstrating *lower* rates of atherosclerosis than their Caucasian counterparts (Bild, 2005; Manolio et al., 2008). These same studies suggest that atherosclerosis in African Americans appears to be less related to coronary artery disease than in Caucasians, and thus may result in different symptoms than in Caucasians (Bild, 2005; Manolio et al., 2008). These results being inconsistent with findings on other cardiovascular measures may suggest different relationships between small and large vascular beds.

Atherosclerosis and Depression

Mechanisms. While the vascular/arteriosclerotic depression hypothesis proposes a mechanism of action whereby atherosclerosis leads to subtle cerebrovascular changes affecting stress-regulating neural circuitry resulting in depression, additional pathophysiological actions have been proposed to account for the relationship between subclinical atherosclerosis and depression. These hypothesized mechanisms include impaired platelet activation in depressed subjects (Laghrissi-Thode, Wagner, Pollock, Johnson, & Finkel, 1997) and the inability of depressed individuals to adjust pulse rate to variability in blood pressure (Watkins & Grossman, 1999). Furthermore, one of the most discussed hypotheses across the literature is the moderating influence of hypothalamic-pituitary axis (HPA) reactivity. HPA axis dysregulation in depression is believed to result in hypercortisolemia. Hypercortisolemia has not only been documented in depression (Carroll, Curtis, Davies, Mendels, & Sugerman, 1976), but also appears to have deleterious effects on vascular health (Hajat, Diez-Roux, Sánchez, & Holvoet, 2012).

Findings. The vascular depression hypothesis spurred greater exploration of associations between subclinical cardiovascular disease and late-onset depression in older adults. Seldenrijk et al. (2011) found that carotid intima media thickness was associated with late-onset (>40 years old) depression, rather than early-onset depression (N=470, p= 0.004) (Seldenrijk et al., 2011). In a large,

Dutch, population-based study of cardiovascular risk (*N*= 3,704), Tiemeier et al. (2003) reported that regardless of history of clinical cardiovascular disease (i.e. heart attack or stroke), atherosclerosis was associated with greater risk of having a depressive disorder among a sample of individuals aged 60 and older (*OR*=1.24). Tiemeier et al. (2004) then utilized more extensive measures of atherosclerosis and reported that individuals (*N*=4,019) with severe CAC were nearly four times as likely to experience a depressive disorder (*OR*=3.89). Additionally, each standard deviation increase in atherosclerosis resulted in a 30% increased risk for depression.

Similar results have been reported in younger samples. For example, middle-aged adults with past-year depressive or anxiety disorders (*N*= 2,717) were found to have two or three times the risk of increased ankle-brachial index (ABI), a measure of atherosclerosis (*OR*=2.78) (Seldenrijk et al., 2010). In the only study that utilized a sample from Sub-Saharan Africa (*N*=389), Hamer et al. (2011) reported an independent association between depressive symptoms and subclinical atherosclerosis in a sample of middle-aged adults (β=0.003, 95% CI 0.001-0.005, *p*=0.005).

Among middle-aged adults, depressive symptoms may precede development of atherosclerosis. As part of an ongoing longitudinal exploration of a cohort free from cardiovascular disease (*N*=324), Stewart et al. (2009) reported that elevated depressive symptoms during baseline measurements predicted

development of atherosclerotic change after three year follow-up (ΔR^2=0.026, p=.002). Haas et al. (2005) found that among 219 middle-aged (30 to 60) adults, depressive symptoms at baseline more than doubled the risk of carotid plaque presence at ten-year follow up (*OR*= 2.29) (Haas et al., 2005).

Recent work has uncovered a potential dose-response effect of depression, with each depressive episode accelerating atherosclerosis development. A history of recurrent, rather than single, major depressive episodes more than doubled risk of carotid plaque in 336 middle-aged women (*OR*=2.29) (Jones et al., 2003). Agatisa et al. (2005) confirmed this dose-response effect even when 210 female participants were determined to be free from known cardiovascular disease at the time of assessment. They reported that history of recurrent depression, compared with single episode depression, resulted in a significant increased risk for high levels of coronary artery calcification (*OR*=2.71).

Atherosclerosis, Depression, and Ethnicity. Higher prevalence of chronic depressive symptoms among the African American population and recent evidence linking atherosclerosis with long-standing depressive symptoms suggest that depressive symptoms associated with subclinical vascular disease may disproportionately affect African Americans. As minority populations often lack access to mental healthcare, an understanding of depression associated with vascular disease may improve rates of treatment through primary care physicians.

Unfortunately, only two of the reviewed studies exploring this relationship reported ethnic-specific results.

Hamer (2011) reported that black Africans between ages 25 and 60 (n=186) reported significantly more depressive symptoms (OR=3.72) than their Caucasian counterparts (n=203). Despite non-significant differences in mean age across ethnic groups the black African sample in this study also had the highest levels of carotid IMT, but the interaction between depressive symptoms, carotid IMT, and ethnicity was inconsistent. Jones (2003) reported somewhat more consistent findings in that ethnicity was differentially associated with atherosclerosis measure. African American race was associated with cIMT score (p<0.001) and Caucasian race was associated with CAC score (p=0.01), but no results were reported with reference to depressive symptoms. Similarly, Agatisa et al. (2005) noted that African American women were more likely to have any level of coronary calcification than their Caucasian counterparts (p=0.06), but no associations with depressive symptoms were described.

Cerebrovascular Disease

Description and Mechanisms. Cerebrovascular disease is the third leading cause of death behind cardiovascular disease and cancers (Hoyert et al., 2012). Cerebrovascular disease refers to a class of abnormalities related to the vascular system in the brain. Cardiovascular disease is often associated with large

vessel cerebrovascular accidents (stroke). There are two forms of strokes: ischemic and hemorrhagic. Large vessel ischemic strokes can result from atherosclerosis if a blood clot (thrombus) or debris from elsewhere in the body (embolus), which breaks away from an atherosclerotic wall occludes vasculature in the brain. Another form of stroke is known as a lacunar stroke. Small vessel, or lacunar, stroke is a subcortical occlusion in a single branch of a penetrating cerebral artery, and is often the result of chronic arteriolosclerosis (Arboix & Martí-Vilaita, 2009). These small infarcts represent approximately 25% of all reported strokes (Arboix & Martí-Vilaita, 2009). Hemorrhagic strokes occur when a vessel ruptures, often secondary to hypertension combined with weak, atherosclerotic vessel walls, and releases neurotoxic blood into brain tissue.

In addition to type of lesion, location of infarct has significant implications for symptoms and prognosis. Through exploration of the "lesion-deficit model" modern neuroscience has mapped many of the neural correlates of behavior through study of stroke location and associated deficits (G. E. Alexander, DeLong, & Strick, 1986; L. D. Alexander et al., 2010; Devlin & Watkins, 2007). Thus, stroke location can have implications for behavior and affective response, including depression. Modern neuroimaging technology permits exploration of brain-behavior associations in vivo through neuroimaging techniques to better understand the potential behavioral and affective correlates of lesions.

Risk. Because cerebrovascular disease often occurs as a downstream effect of cardiovascular disease, many of the risk factors overlap. Hypertension, hyperlipidemia, and resultant atherosclerosis lead to cerebrovascular disease. While atherosclerosis and hypertension have each been independently implicated in the development of cerebrovascular disease and ischemic stroke (Davila-Roman et al., 1994; Ohira, 2006; Zhang, Zhang, & Zhong, 2009), hypertension appears to be more directly associated with the microvascular changes in the brain (arteiolosclerosis), which can result in more subtle clinical manifestations (Hajjar et al., 2011; Veglio et al., 2009). Essentially, cardiovascular risk factors are differently associated with cerebrovascular disease.

The incidence and mortality of stroke in African Americans is nearly double that of Caucasians (Gorelick, 1998). Ruland et al. (2003) indicated stroke risk factors are less likely to be recognized or treated in African Americans than in Caucasian or Hispanic samples (Ruland, Raman, Chaturvedi, Leurgans, & Gorelick, 2003). Further, after controlling for modifiable cerebrovascular risk factors, African decent was associated with greater hypertensive damage to cerebral white matter (Birns, Morris, Jarosz, Markus, & Kalra, 2008). This finding was supported by the Northern Manhattan Stroke Study when investigators demonstrated the increased prevalence of intracranial occlusive disease among African Americans when compared with Caucasians (Sacco, Kargman, Gu, & Zamanillo, 1995). This disparity in incidence, mortality, and

mechanism of cerebrovascular risk suggests the potential for increased rates of vascular depression in African Americans. To date, there is a dearth of literature exploring this phenomenon as it relates to the African American community.

Cerebrovascular Disease and Depression. The first suggestion of cerebrovascular involvement in depression was in Gaupp's 1905 "Depressive States in Old Age." In his clinical observations, he postulated association between an accumulation of vascular lesions and depression (Gaupp, Pomarol-Clotet, & Berrios, 2000; Santos et al., 2012). Nearly 80 years later, in four influential descriptive papers, Robinson et al. (1982, 1983, 1983, 1984) expanded and described the phenomenon of post-stroke mood disorders (Robinson & Price, 1982; Robinson, Kubos, Starr, Rao, & Price, 1983a; Robinson, Starr, Kubos, & Price, 1983b).

Specifically, Robinson reported that 50% of acute stroke patients studied (*N*=103) suffered from clinically significant depression, and it was noted that these depressive symptoms were slow to remit and could not be accounted for by neurological symptoms, functional impairment, or demographic factors (Robinson et al., 1983b; Robinson & Price, 1982). Though the vascular depression hypothesis describes subclinical cerebrovascular disease as an underlying mechanism, the description of depressive symptoms as specifically slow to remit mirror those described by Robinson (Alexopoulos et al., 1997; Krishnan & McDonald, 1995). When initial stroke-related depression theories arose

neuroimaging was in its infancy allowing only crude measures of large brain lesions to be detected. Increased sensitivity in neuroimaging techniques now allow for detection of subtle cerebrovascular disease, including small basal ganglia infarcts and WMH. These subtle processes have now also been found to be associated with depressive symptoms (Krishnan, 2000; Murray, Staff, & McNeil, 2012; Rao, 2000; Santos et al., 2012; Schwartz et al., 1993; Steffens, Helms, Krishnan, & Burke, 1999).

White Matter Hyperintensities

Description. While gray matter is made up of the cell bodies of neurons, white matter is predominantly comprised of axons and oligodendrocytes that form their encasing myelin sheath. These axons crisscross the brain forming functional connections between gray matter regions. This communication network rapidly carries electrical impulses between cell bodies throughout the brain. Effective myelination is essential for the process of salutatory conduction, which greatly increases conduction of the electrical signal. Functional circuits are thought to rely on requisite temporal relationship, which may be disrupted if the speed of axonal transmission is altered, such as in ischemic demyelination. This communication allows for integration of cortical and subcortical structures (Bartzokis, 2004).

Axons vary in length and morphology and appear as a webbed matrix strategically connecting neural areas. Much like rubber casing around copper wires, the myelin sheaths provide insulation and prevent the electrical impulses travelling along the axon from dispersing randomly. In the central nervous system, myelin is produced by oligodendrocytes, a form of glial cell. As the oligodendrocyte produces myelin, it begins to wrap the axon, eventually encasing the string-like axon. Interference by demyelinating diseases or ischemic injury can disrupt neural communication. Both of these conditions can prevent effective electrical communication in the brain, and may result in dysfunction of associated areas of grey matter.

Initially the term “leukoaraiosis” was used to described white matter thinning. Neuroimaging literature has since specified WMH as foci of hyper-intense signal in white matter regions seen on T2-weighted MRI scans. Neuroimaging studies report that areas of hyper-intense signal are reflective of increased content of free water and is a sign of structural disruption (Awad, Johnson, Spetzler, & Hodak, 1986; Modir, Gardener, & Wright, 2012; Thomas, O'Brien, et al., 2002a; Thomas, Perry, et al., 2002b). Diffusion tensor imaging (DTI) allowed more precise measurement of this change in microstructure by precisely defining the directionality of water diffusion as indicated by its fractional anisotropy. Loss of fractional anisotropy in WMH demonstrated that water was then able to move freely in any direction and that the function of

myelin to confine diffusion parallel to the course of the axon had been disrupted by demonstrating that increased water diffusion represents disruptions of white matter tracts (Colloby et al., 2011; Taylor et al., 2001).

WMH are a common finding first believed to have no clinical relevance. Wen and Sachdev (2004) described WMH prevalence in a 477 healthy subjects aged 60-64. These investigators found that 100% of T2-weighted MRI scans showed periventricular WMH, and 96% of the subjects demonstrated deep WMH (Wen & Sachdev, 2004). In 2009 Wen, Sachdev, Li, Chen and Anstey then reported that among a younger healthy sample (N=428), aged 44-48, 34% had deep WMH (Wen, Sachdev, Li, Chen, & Anstey, 2009). Consistent with these findings, a report by Hopkins et al. (2006) indicated that in a healthy sample aged 16-65, the older group (>55 years) demonstrated ten times the rate of WMH (OR=10.01, p<0.001).

Although WMH appear to increase with even healthy aging, the rate of accumulation varies depending on presence of cardiovascular comorbidities and identification of underlying mechanisms and clinical implications of these white matter hyperintensities remains an ongoing process. WMH now are thought to primarily result from arteriolosclerosis, but a range of pathological abnormalities ranging from blood brain barrier disruption to regions of frank infarctions have been demonstrated (Awad et al., 1986; Black, Gao, & Bilbao, 2009; Herrmann et al., 2007; Hopkins et al., 2006; Moody, Brown, Challa, & Anderson, 1995; Taylor

et al., 2001; Thomas, O'Brien, et al., 2002a). A recent review of neuropathological studies of WMH by Modir, Gardener, and Wright (2012) elegantly summarized the current hypothesized mechanisms for WMH presence:

1. Low-level vascular insufficiency and structural changes, associated with hypertension, result in chronic hypoperfusion and ischemia.
2. Hypertension-related endothelial dysfunction compromises the blood-brain barrier allowing neurotoxins to diffuse into the white matter.
3. Venous collagenosis occurs secondary to collagen fiber deposition in venula resulting in luminal narrowing, disruption of the blood-brain barrier, and increased perfusion pressure (Moody et al., 1995).

Yet another possibility is that WMH are secondary to mechanistic injury. As arterioles expand and contract violently with increased hypertension, neighboring white matter becomes injured. All of these mechanisms are likely upstream results of cardiovascular disease, but most notably hypertension.

WMH Association with Cardiovascular Disease. Recent work has begun to elucidate the relationship between WMH, hypertension, and atherosclerosis. Compared with atherosclerosis, hypertension is more likely to affect small arteries and arterioles (Hollander, 1976). As WMH are hypothesized to reflect ischemic microvascular disease, it is not surprising that hypertension has been reported to be the cardiovascular risk factor most closely associated with WMH (Herrmann et al., 2007; Modir et al., 2012; Santos et al., 2012). Reports of

associations between WMH and carotid atherosclerosis were initially inconsistent, and several explorations refuted the connection (Heiden et al., 2005; Kwee et al., 2011; Pico et al., 2002; Takahashi et al., 2006). A study published by Lee et al. (2011) described results that may explain the inconsistent report. WMH were found to be more closely related to intracranial, rather than extracranial, atherosclerosis (Lee et al., 2011).

Ethnic Differences in WMH. As previously mentioned, the prevalence of hypertension among African Americans is significantly higher than Caucasian counterparts (Kurian & Cardarelli, 2007; Stavitsky et al., 2010). Unfortunately, only one report was identified specifically comparing WMH across ethnic groups. Brickman et al. (2008) reported significantly greater WMH burden (β=0.36, t=4.44) in older African Americans (n=264) compared with Caucasians (n=205). Clearly, given the cardiovascular predisposition for WMH in the African American community, further exploration into the impact of the clinical manifestations of WMH is needed.

White Matter Hyperintensities and Depression

Mechanisms. Despite reported associations between lesion location and symptom manifestation in many neuropsychiatric syndromes, clear delineation of the neural circuitry of depression remains elusive (Nestler et al., 2002). In an oft-cited early paper, Alexander et al. (1986) elegantly summarized previous research

findings to first describe three distinct functional neural circuits potentially associated with depression (Alexander et al., 1986; Naismith, Norrie, Mowszowski, & Hickie, 2012). Mayberg's seminal works in neuroimaging and neurophysiology have specifically implicated white matter structures and dysregulation of subcortical circuits in depression (Hamani et al., 2011; Mayberg, 1997; Mayberg et al., 1999).

Nestler et al. (2002) concluded that likely numerous brain regions are associated with individual depressive symptoms including at least prefrontal and cingulate cortex, hippocampus, striatum, amygdala, and thalamus. A recent work from Naismith et al. (2012) synthesized neuroimaging and post-mortem findings related to the neurobiology of depression and reported that circuits involving the anterior cingulate cortex, dorsolateral prefrontal cortex, and orbitofrontal cortex are associated with depression (Naismith et al., 2012). While at cortical levels neural circuits are more spatially distinct, at subcortical levels, circuits are closer together, allowing for potentially greater impact with smaller lesions (Naismith et al., 2012). Thus, subcortical white matter hyperintensities may affect multiple systems in subtle ways, including those circuits implicated in depression.

Findings. The vascular depression hypothesis focus has been in late-life depression and is associated with cardio- and cerebrovascular pathology in older adults. Using this hypothesis, investigators have reported associations between WMH and depression in older adults (> age 50). WMH burden has been

associated with depressive symptoms, chronicity, and treatment resistance in this population (Colloby et al., 2011; Herrmann et al., 2007; O'Brien et al., 2006; Santos et al., 2012; Stavitsky et al., 2010; Tham et al., 2011; Vasudev et al., 2012).

Prior to the publication of the vascular depression hypothesis, Figiel, Krishnan, Doraiswamy, Nemeroff, and Boyko (1991) published an early study comparing WMH volume and location in late-onset (n=10) versus early-onset (n=9) depression in a small elderly sample (age 61-80). This work indicated a greater volume of caudate and deep WMH in the late-onset group (p=0.039) (Figiel et al., 1991). Following these and earlier observations of white matter abnormalities in elderly depressed individuals (Krishnan et al., 1988), Krishnan and McDonald (1995) published the vascular depression hypothesis. Two years later, Krishnan (1997) characterized depressed subjects as having vascular (n=37) or nonvascular (n=52) depression based upon MRI analysis of WMH. Subjects with vascular depression were more likely to be at least 60 years of age (X^2= 21.9, df=1, p=0.0001), have late-onset depressive symptoms (OR=7.16), and lack psychotic features (OR=0.08). Following Krishnan's initial work in this area, numerous investigators have followed to further elaborate upon and confirm the vascular depression hypothesis utilizing WMH.

In association with the Rotterdam Scan Study, de Groot et al. (2000) indicated that among elderly individuals (N=1,077), those with severe WMH

(*n*=212) were three to five times more likely to suffer from depressive symptoms (as measured by the Center for Epidemiologic Studies Depression Scale) when compared with elderly individuals with mild or no evidence of WMH (de Groot et al., 2000). Jorm et al. (2005) described a smaller, yet still significant association (*OR*=1.49) between depressive symptoms and total WMH volume in a sample aged 60-64 (*N*=475). Firbank et al. (2004) explored WMH location in association with depressive symptoms in 61 older adults. They reported that although whole brain WMH volume was significantly different in depressed and non-depressed samples (p=0.021), the largest difference was seen when frontal WMH were examined (p<0.001) (Firbank et al., 2004). One year later this same research group published a follow-up study with a notably larger sample (*N*=629) comparing mild versus severe whole brain WMH and confirmed that severity was associated with higher scores on a clinician-administered depression scale (*OR*=1.52). The difference remained significant even with quality of life was controlled.

WMH in older populations may be an important prognostic indicator of depression. Heiden et al. (2005) described WMH volume and depression severity based upon Hamilton Rating Scale for Depression (HRSD) score at baseline and at five-year follow-up in 21 depressed subjects aged 61-78. This group reported that although no HRSD differences were significant at baseline, subjects with visual ratings of "moderate/severe" deep WMH (*n*=6) had higher scores at follow-

up than those with “absent/slight” deep WMH (p=0.010). Additionally, none of the subjects with “moderate/severe” deep WMH (n=6) achieved full inter-episode recovery from depression, while 86% of the “absent/slight” deep WMH recovered (p<0.001) suggesting a more chronic course.

In addition to the potential for greater chronicity, several reports have implicated WMH in antidepressant treatment resistance. For example, an early report from Simpson et al. (1998) combined neurological exam components, neuropsychological measures, and neuroimaging findings to uncover independent predictors of depression in an elderly sample of major depressives (N=75). WMH status alone correctly predicted response to monotherapy with 84% specificity (Simpson et al., 1998). Regardless of age or lesion location, depressed patients older than 45 years of age who demonstrated high WMH volume (n=10) were significantly less likely to remit following antidepressant treatment (OR=7.00 p=0.02) (Sneed et al., 2011). As WMH are associated with increased chronicity, disability, and treatment resistance, in late-life depression, a greater understanding of the underlying pathology is needed.

Neuropathological studies are describing the underlying biology to perhaps provide further evidence for the relationship between WMH and depression. There is support for an ischemic etiology resulting in demyelination and cell death. Utilizing post-mortem immunohistochemistry, Thomas et al. (2002) reported that 100% of WMH in elderly individuals with depression (N=20)

were found to be ischemic, while fewer than one third of the WMH were ischemic in the non-depressed elderly control group (*N*=20) (Thomas, O'Brien, et al., 2002a).

A follow-up study using the same sample conducted by the same team employed intercellular cell adhesion molecules, a marker of ischemia-induced white matter lesions. Thomas et al. (2003) reported ischemic demyelination, predominantly in the dorsolateral prefrontal cortex, in elderly depressed patients' brains (*N* =20). Regenold et al. (2007) supported this finding and described significantly decreased deep white matter myelin staining in brains of patients with depressive disorders (Regenold et al., 2007). Such demyelination secondary to ischemia may be best explained by the significant reduction of myelin-producing oligodendrocytes in prefrontal areas in brains of patients who were diagnosed with major depression (Uranova, Vostrikov, Orlovskaya, & Rachmanova, 2004). Further neuropathological understanding of WMH will permit greater clarity in the cardiovascular risk factors involved and allow for prevention.

WMH, Depression, and Ethnicity. Despite the elevated rates of hypertension and WMH among African Americans (Brickman et al., 2008; Kurian & Cardarelli, 2007), no studies specifically explore ethnicity and the vascular depression hypothesis. As previously noted, depression among African Americans, as in the proposed vascular depression hypothesis, results in greater

disability and chronicity (Heiden et al., 2005; Williams et al., 2007), yet the connection between vascular disease and depressive symptoms remains unexplored in African Americans compared with Caucasians. Evidence suggests that African Americans may disproportionately suffer from depression as secondary to vascular disease. The research suggesting an ischemic etiology of WMH secondary to cardiovascular disease, and difference in the manifestation of these diseases, warrants exploration of potential ethnic differences in the association between vascular disease and depressive symptoms.

Rationale

Investigators in psychological epidemiology have begun to explore depression as a neuropsychiatric disorder often associated with vascular disease, particularly in middle aged and older adults. Depression-related disability and chronicity of depressive symptoms impact African Americans more severely than Caucasians. One potential explanation for this difference arises from the vascular depression hypothesis, which suggests that depression can be the result of subclinical cerebrovascular disease secondary to cardiovascular disease with impact to the circuits of the brain associated with depression. Work in this area has delineated a unique symptom profile in patients with "vascular depression." It should be noted that this symptom profile is similar to that commonly reported in depressed African Americans.

To date, studies exploring the relationship between vascular disease and depression have focused exclusively on large vessel disease (atherosclerosis) or small vessel disease (WMHv). Though associations have been reported between depression and each of these forms of vascular disease, none has specifically compared their association with depression. This void in the literature is particularly relevant with recent suggestions that evolution of small and large vessel disease may be distinct processes. Additionally, though numerous studies have documented increased rates of cardiovascular and cerebrovascular disease in African Americans and differences in the rates of depression, no studies have been conducted to compare potential differences in the association between vascular disease and depression.

The results of this study may impact clinical practice by alerting practitioners to explore depressive symptoms in patients diagnosed with vascular disease. Should ethnic differences be uncovered, it may encourage the general practice physicians with whom African Americans are more likely to seek treatment to prophylactically treat depressive symptoms when associated with vascular risk.

Chapter Three: Methodology

Dallas Heart Study Design

The current study will be conducted as a retrospective analysis of data from The Dallas Heart Study (DHS). DHS is a large, population-based, longitudinal investigation of factors related to cardiovascular disease (Victor et al., 2004). In order to provide greater opportunities to explore relationships between these factors and ethnicity, African Americans were over-sampled to represent 50% of the cohort (Victor et al., 2004). This large, ethnically diverse sample allows for exploration of subtle cerebrovascular measures such as WMH. Further, with an emphasis on cardiovascular disease, the DHS collected multiple measures of atherosclerosis to enable a holistic view of coronary artery disease. The nature of this study provides an ideal sample for exploring ethnicity as a factor in the relationships between cardio- and cerebrovascular disease with depression.

Participants

DHS data were collected during two time points (DHS-I and DHS-II). Data collection for DHS-I was started in 1999 (N=2,971), and subjects were recruited from that sample to participate in DHS-II (Victor et al., 2004). Data collection for DHS-II ran from September 2007 through January 2010. DHS-I

subjects were recruited from a stratified random sample of Dallas County residents. Participants were then recruited for follow-up into DHS-II (N=3,402), which included an expanded study to add a self-report measure of depression and structural brain imaging. All subjects for this study were drawn from the DHS-II sample in order to include these measures.

Only subjects who reported race as Non-Hispanic African American or Non-Hispanic Caucasian were included. Hispanics were excluded for several reasons. First, the rate of foreign-born Hispanics in Dallas is higher than rates of foreign-born Caucasians or African Americans. There is also a greater heterogeneity of nativity within the Hispanic population, and differences have been reported in Hispanic country of origin and association with depression (Torres Stone, Rivera, & Berdahl, 2004) as well as level of acculturation and depressive symptoms (Golding, Karno, & Rutter, 1990). Further, Gavin et al. (2010b) reported inconsistency in the association between SES and depression in individuals of Hispanic ethnicity when compared with African Americans and Caucasians.

Subjects over age 50 were included based on the age cut-off for late-life depression described in the largest epidemiologic study of vascular depression to date, Gonzales et al. (2012). Only subjects with complete data including WMH measures, QIDS-SR, and measures of atherosclerosis (multi-detector computed tomography (MDCT)) were considered for analysis. Following review of

inclusion criteria, participants with a history of stroke or myocardial infarction were excluded. Utilizing these points, sample size included 738 subjects.

Measures

Survey Data. Survey data were collected via a self-report questionnaire that included medical history, demographics, income information, medication lists, and health beliefs. Variables including ethnicity, age, gender, education, income, history of myocardial infarction, and history of stroke were selected for consideration.

Depression Measurement. Depressive symptoms were assessed using the Quick Inventory of Depressive Symptoms- Self Report (QIDS-SR). This 16-item screening measure assesses past week self-reported depressive symptoms from each of the Major Depressive Disorder symptom domains including depressed mood, anhedonia, dyssomnia, appetite changes, feelings of guilt or worthlessness, decreased concentration, psychomotor changes, fatigue, and suicidal ideation. The QIDS-SR items have been described in detail elsewhere (Rush et al., 2003).

The QIDS-SR has been confirmed as a psychometrically sound measure of depressive symptoms. Rush et al. (2003) reported good internal consistency (n=596 Cronbach's **α**=.86) among adults diagnosed with major depressive disorder. This same investigation found that QIDS-SR was highly correlated with other validated measures of depression including the Hamilton Rating Scale for

Depression- 24 item (r=.84) (Rush et al., 2003). Trivedi et al. (2004) described the concurrent validity of the QIDS-SR based upon scores of the Medical Outcomes Study 12-item Short Form. The QIDS-SR has been made open source by investigators and can be reprinted without cost. The version utilized in DHS-II can be viewed in Appendix A.

The descriptive ranges for the QIDS-SR were used in this study as published in Rush et al. (2003): no depressive symptoms (0-5), mild depressive symptoms (≥6-10), moderate depressive symptoms (≥11-15), severe depressive symptoms (≥16-20), and very severe depressive symptoms (≥21-27). In data analysis QIDS-SR score was used both as a continuous variable and as a dichotomous variable. When analyzed as a dichotomous variable a QIDS-SR score ≥6 was operationalized as relevant depressive symptoms.

Coronary Artery Calcification. Coronary artery calcium (CAC) was measured by multi-detector computed tomography (MDCT) on a single scanner (Toshiba Aquilon 64-Slice MDCT). Each participant was scanned twice and the calcium score was averaged between the two scans. Calcium scoring followed the protocol of the Multi Ethnic Study of Atherosclerosis, and detection of calcium was based on a focus of calcium with ≥3 contiguous pixels at ≥130 Hounsfield units {Agatston:1990vd, Jain:2004dw}.

Carotid Intima Media Thickness. Carotid magnetic resonance imaging (MRI) was obtained via a Phillips Achieva 3.0T MRI system. The index carotid

artery was imaged using four contrast-weightings (T1, T2, proton density, and time of flight) covering 20 slices (2mm thickness) centered at the bifurcation. A trained technologist blind to study population characteristics interpreted the images using semi-automated software (VesselMASS).

White Matter Hyperintensities. The MRI protocol was conducted as previously described in DHS MRI studies (Hulsey et al., 2012; King, Peshock, & Warren, 2012). WMH volume (in milliliters) automatically quantified from two-dimensional fluid-attenuated inversion recovery and three-dimensional magnetization-prepared rapid acquisition gradient-echo brain images obtained during follow-up evaluation as part of DHS-2 with a 3.0-T MR unit (Achieva; Philips Medical Systems, Best, the Netherlands). WMH segmentation method and validation has previously been described (Hulsey et al., 2012; King et al., 2012).

Analysis. De-identified data were obtained from a central repository compliant with University of Texas Southwestern Medical Center Institutional Review Board standards. Analyses were conducted utilizing IBM® SPSS® Statistics (Version 20). Figures were created with SigmaPlot (Version 12).

Study Aims, Hypotheses, and Proposed Analyses

The first aim was to describe the frequency and severity of depressive symptoms in a population-based sample of African Americans and Caucasians over age 50. To determine potential differences in the proportion of depressive

symptoms across ethnic groups, the QIDS-SR score was dichotomized into positive (QIDS-SR score ≥6) and negative depressive symptom status (QIDS-SR score <6). Mantel-Haenszel Chi Square tests were used to compare ethnic groups stratified by gender. Additional analyses examined ethnic differences within males and females separately. Stepwise logistic regression was used to determine if ethnicity was a significant predictor of depressive symptom status following adjustment for significant covariates. Variables considered as potential covariates included age, education, income, ethnicity, gender, diabetes status, hypertensive status, hypercholesterolemic status, and metabolic syndrome status in addition to significant interactions. It was hypothesized that presence of depressive symptoms (defined as QIDS-SR score ≥6) would be more frequent in the Caucasian sample (Hypothesis 1a).

The second question of the first aim was to determine ethnic differences in depressive symptom severity in the described sample. Using the QIDS-SR total score as a continuous variable, significant covariates were identified for the total sample and for each ethnic-gender group combination. As QIDS-SR total data were not normally distributed, nonparametric tests were used to confirm all results. This was done by comparing results of parametric analyses with the QIDS-SR total score (non-transformed) with QIDS-SR total rank scores, and log10 (log10) transformed QIDS-SR total scores where applicable. It was hypothesized that depressive symptom severity would be greater in the African

American sample when compared with the Caucasian participants (Hypothesis 1b).

The second aim of the study was to compare the relationship between atherosclerosis (cIMT and CAC) and depressive symptoms in Caucasians and African Americans over 50, controlling for significant covariates. Two separate analyses were conducted for cIMT and CAC score. CAC score was used as a dichotomous variable for regressions (present was categorized as $\geq$10 Agatston units). CAC score was used as a continuous variable for correlations. Significant covariates of QIDS-SR scores, identified in previous analyses (age, education, BMI, income, ethnicity*metabolic syndrome), were included in all analyses. Group-specific multiple regression models examined group-specific covariates and the variable of interest.

To evaluate potential associations between depressive symptoms and atherosclerosis, partial and zero-order correlations were conducted using QIDS-SR score and the relevant measure of atherosclerosis. Partial correlations included significant covariates of QIDS-SR total score, including age, education, income, BMI and ethnicity*gender. As none of the primary variables of interest were normally distributed, all analyses were first conducted using parametric statistical procedures, and then confirmatory analyses were conducted using rank scores and Log10 transformed scores of CAC, cIMT, and QIDS-SR total score. It was hypothesized that CAC (Hypothesis 2a) and cIMT (Hypothesis 2b) would be

similarly associated with depressive symptoms in African Americans and Caucasians.

The third aim of the study was to determine if there was an association between cerebral microvascular disease (assessed by WMH volume) and depressive symptoms in African Americans and Caucasians over age 50, controlling for significant covariates. Significant covariates of QIDS-SR scores (age, education, BMI, income, ethnicity*metabolic syndrome) were included in all analyses.

As WMH were not normally distributed, the raw score was adjusted for total cranial volume and then an inverse sine transformation was performed. An inverse sine transformation ($2\arcsin\sqrt{x}$) was selected as WMH adjusted for total cranial volume resulted in a proportion. The transformed WMH variable was included in the multiple regression model along with significant predictors identified in previous analyses for each the total sample and ethnic-gender group combinations. All analyses were first conducted using parametric statistical procedures, and then confirmatory analyses were conducted using rank scores and Log10 transformed scores of WMH and QIDS-SR total score.

To further evaluate potential associations between depressive symptoms and WMH, partial and zero-order correlations of using QIDS-SR score and inverse sine transformed WMHv were performed for each ethnic-gender group combination. As none of the primary variables of interest were normally

distributed, analyses were repeated using rank and Log10 transformed scores of QIDS-SR score and the rank of WMHv, log10 transformed WMHv, and inverse sine transformed WMHv adjusted for total cranial volume to confirm results. It was hypothesized that African Americans would demonstrate greater volumes of WMH (Hypothesis 3a), and that there would be a stronger association between WMH volume and depressive symptoms in African Americans than Caucasians (Hypothesis 3b).

Chapter Four: Results

Sample Characteristics

Sample Size. From the 1,754 DHS-II participants over age fifty, 127 subjects were excluded for history of myocardial infarction. To arrive at the total sample of 738 subjects, 617 subjects who did not have MRI with WMH measures, 43 without MDCT mean measurements for CAC, 68 without carotid IMT measures, and 62 without complete QIDS-SR were excluded. In addition, 3 subjects with unknown ethnicity, 18 with 'other' ethnicity, and 78 Hispanic subjects were excluded in order to directly compare African Americans with Caucasian participants.

Demographic Characteristics. Due to significant differences in gender distribution across health and socio-demographic characteristics, analyses comparing ethnic groups included stratification by gender. Full descriptive demographic characteristics are presented in Table 1a. The total sample was predominantly (60%) female and included 49% African American participants. The mean age for the combined sample was 58.56 years (SD=6.02). A two-way ANOVA revealed a significant interaction for gender and ethnicity (p=0.021). Analyses of education categorical variables revealed that 70.6% of the combined sample completed at least a high school education. A Kruskal-Wallis test for four independent groups was used to evaluate differences in the median education

category (completion of high school) across the four ethnic-gender group combinations. There were significant differences across groups ($p<0.001$) and the median education of African Americans was lower than that of Caucasians. These results were confirmed with a significant Mantel-Hansel Chi Square evaluating differences in education stratified by gender [$X^2(3, N=734)=31.07$, $p<0.001$]. The combined sample median income range was $40,000 to $49,000. A Kruskal-Wallis test revealed significant differences in income across race and gender groups [$X^2(3, N=738)=105.72$, $p<0.001$]. Caucasian males demonstrated the highest median income range and African Americans females had the lowest.

Health Characteristics. Descriptive information on health characteristics of the samples can be found in Tables 1b and 1c. The total sample mean Body Mass Index (BMI) was 29.52 (SD=5.44). A Two-Way ANOVA was utilized to identify differences in means across the groups defined by ethnicity and gender [$F(1, 734)=12.65$, $p<0.001$]; African American females demonstrated the highest mean BMI [M(SD)=31.62(5.82)] and Caucasian females the lowest [M(SD)=28.41(5.65)]. These results were confirmed with nonparametric tests. The total sample mean was slightly higher than the U.S. average based upon the report presented by Wang & Beydoun, 2007 (28.2 for women; 27.6 for men). As the sample was comprised of Dallas, Texas residents, regional differences in BMI and increased BMI in areas of urban sprawl may best account for the increased

BMI in this sample (Scott, Dubowitz, & Cohen, 2009; Vandegrift & Yoked, 2004; Wang & Beydoun, 2007).

More than 60% of the total sample was determined to be hypertensive. A Mantel-Haenszel Chi Square revealed significant differences across ethnic groups when gender was held constant. Seventy-five percent of the African American sample was hypertensive, compared to 46% of the Caucasian group [$X^2(1, N=738)=63.98, p<0.001$].

Across the total sample, 15.7% of participants were determined to have diabetes. A Mantel-Haenszel Chi Square revealed significant differences in frequency of diabetes across ethnic groups when gender was held constant [$X^2(1, N=738)=22.85, p<0.001$], with the African American male group having the highest prevalence (23%) and the Caucasian male group having the lowest (7.7%).

Across the total sample, 38.5% of participants were hypercholesterolemic. Mantel-Haenszel Chi Square tests did not reveal differences between ethnic groups stratified by gender [$X^2(2, N=738)=3.02, p=0.09$].

While 36.9% of the total sample met criteria for metabolic syndrome, Chi Square test revealed ethnic differences when stratifying for gender [$X^2(2, N=738)=7.884, p=0.008$], with African American females demonstrating the greatest prevalence (47%). More specifically, the significant difference between

ethnic groups was found in the females only [X^2(1, n=443)=12.529, p<0.001], with non-significant ethnic group differences among males.

The total sample mean CAC score was 146.52 (SD=453.3). A two-way ANOVA suggested a non-significant interaction between ethnicity and gender [F(1, 734)=0.05, p=0.83]. The analysis revealed significant group differences across gender [F(1, 734)=16.1, p<0.001], with men demonstrating higher scores, but ethnic differences were not significant [F(1, 734)=1.19, p=0.28]. This result was confirmed with nonparametric tests. When CAC score was dichotomized, using 10 (Agatston et al., 1990) units as the cut-off for CAC plaque presence, differences were commensurate with CAC total score results with non-significant ethnic differences. Using Mantel-Haenszel Chi Square, difference in CAC plaque presence among ethnic groups stratified by gender was not significant [X^2(1, N=738)=0.12, p=0.727].

The total sample mean cIMT score was 1.36 (SD=0.24), and a Two-Way ANOVA revealed a significant interaction between ethnicity and gender [F(1, 734)=4.91, p<0.027]. There were significant effects of gender (p<0.001) and ethnicity (p<0.001). Non-parametric tests confirmed group differences.

In terms of small vessel measures, the total sample mean of WMHv (mL) was 2.25 (SD=5.17) with a range of 0.119 to 83.181. Ethnic and gender group differences were not significant using a two-way ANOVA [F(1, 734)=0.031, p=0.86]. Total sample mean for the inverse sine-transformed WMHv adjusted for

total cranial volume (InverseSineWMH) was 0.08 (SD=0.05). Though the ethnic-gender interaction and gender group differences were non-significant, ethnic differences were significant [$F(1, 734)=4.40$, $p=0.036$], with African Americans demonstrating higher volumes of WMH. Though this is consistent with Brickman et al. (2008), due to the relative dearth of information related to ethnic differences in WMHv, further comparisons were conducted including covariates (See Results Section and Appendix B).

Depression Characteristics. Of the 34.6% of subjects who reported depressive symptoms, the majority reported symptoms in the "mild" range as described by Rush et al. (2003). Only 7.3% of the total sample reported symptoms in the "moderate" range, 2.2% of the sample had scores in the "severe" range, and 0.5% fell in the "very severe" range (See Table 2a). When QIDS-SR scores were dichotomized based upon the aforementioned depressive symptom severity ranges using a score of 6 ("mild") as a cut-off, 34.6% of the sample was found to have "present" depressive symptoms (See Table 2b).

Descriptive statistics for depression symptom scores can be found in table 2c. QIDS-SR mean for the total sample was 5.27 (SD=3.94). According to the ranges published in Rush et al. (2003) this mean suggests no significant depressive symptoms, although no formal studies have reported normative means. Though this dataset does not include information regarding psychiatric diagnoses, 11.9% of the sample reported taking an antidepressant.

Prior to analyses including potential covariates for hypothesis 1, significant differences were found in QIDS-SR total score between gender groups and between ethnic groups. A two-way ANOVA indicated that the interaction between ethnicity and gender was not significant [F(1, 734)=0.81, p=0.37]. Effects of gender and ethnicity were significant in the analysis. Females demonstrated a significantly higher mean score than the males [F(1, 734)=18.89, p<0.001]. Differences in depressive symptom severity were also found across ethnic groups with African Americans demonstrating higher QIDS-SR scores than Caucasians [F(1, 734)=12.95, p<0.001]. As QIDS-SR total scores were not normally distributed, efforts were made to support the use of parametric tests by using non-parametric tests to confirm results. When results were similar, parametric analyses were reported.

Hypotheses 1a and 1b: Ethnic Differences in Depressive Symptoms

Hypothesis 1a: Ethnic Differences in Depressive Symptom Status. In order to evaluate group differences in depressive symptom status, QIDS-SR scores were dichotomized, as previously described, into "positive" depressive symptom status (QIDS-SR≥6, reflecting at least mild depressive symptoms) and "negative" depressive symptom status (QIDS-SR<6). Based upon previous reports, Caucasians were hypothesized to demonstrate higher frequencies of positive depressive symptoms when adjusting the model for cardiovascular risk

(BMI, hypercholesterolemia, hypertension, diabetes status, and metabolic status) and socio-demographic (age, gender, income, and education) factors were controlled. Complete analyses for this hypothesis can be found in Tables 2b and 3a.

The comparison of depressive symptoms in the two racial groups holding constant gender using a Mantel-Haenszel Chi Square is located in Table 2b. Holding constant the effects of each gender, positive depressive symptoms were found to be significantly different across groups [$X^2(1, N=738)=6.94$, $p=0.008$]. Though overall females demonstrated greater frequency of depressive symptom presence [$X^2(1, n=443)=8.95$, $p=0.003$], ethnicity did not affect depressive symptom presence for this gender group ($p=0.252$). Within the male group, however, African Americans demonstrated greater frequency of depressive symptoms than Caucasians [$X^2(1, n=295)=6.94$, $p=0.004$].

A stepwise logistic regression was used to compare positive versus negative depressive symptom status for ethnic and gender groups and included covariates for age, education, income, BMI, metabolic syndrome status, hypertension status, hypercholesterolemia status, diabetes status, along with significant interactions. As indicated in Table 3a, the regression model for the total sample included income, education, gender, and BMI. Neither ethnicity nor an interaction between gender and ethnicity were predictive of depressive symptom status.

Separate stepwise regression analyses (See Table 3a) were employed to identify ethnicity by gender combination group differences in covariate contribution in predictions of depressive symptom status. For African American females, younger age independently predicted presence of depressive symptoms [OR=0.943, 95% CI=0.901-0.988, p=0.012]. Higher BMI [OR=1.103, 95% CI=1.044-1.165, p<0.001] and lower level of education [OR=0.627, 95% CI=0.421-0.935, p=0.022] were the significant predictive variables of depressive symptom status for Caucasian females. Lower level of income was significantly predictive of depressive symptom status for Caucasian males [OR=0.884, 95%CI=0.79-0.99, p=0.032]. None of these variables was significantly predictive of depressive symptom status for African American males.

While the inverse was hypothesized above, African Americans have a higher proportion of depressive symptoms, but further analysis suggested that this difference was actually attributable to age, education, income, and body mass index. However, separate analyses for ethnic and gender group combinations demonstrated different relationships were found for each of these covariates.

Hypothesis 1b: Ethnic Differences in Depressive Symptom Severity. African Americans were hypothesized to demonstrate greater severity of depressive symptoms when compared with Caucasians. Means and standard deviations are presented in Table 2c. A non-significant interaction between ethnicity and gender [F(1, 734)=0.81, p=0.370] was found in the non-adjusted

ANOVA model. Significant differences were found between males and females [$F(1, 734)=18.89$, $p<0.001$] and between Caucasians and African Americans [$F(1, 734)=12.95$, $p<0.001$].

In the adjusted model, a two-way ANCOVA included the significant covariates. Age, gender, income, education, ethnicity, and the significant interaction between ethnicity and metabolic syndrome presence together accounted for 11.7% ($R^2=0.117$) of the variance in symptom severity across groups (See Table 3b). Ethnic differences in depressive symptom severity remained significant when these covariates were included [$F(1, 734)=7.211$, $p=0.007$], with African Americans demonstrating higher QIDS-SR scores than Caucasians. In the total group regression model (Table 3c) African American ethnicity was found to be predictive of increased depressive symptom severity ($p=0.015$).

Further effects of ethnicity were demonstrated with a significant interaction between ethnicity and metabolic syndrome status (Figure 1). Unlike other ethnic and gender groups, depressive symptom severity appears to increase in Caucasian females with the presence of metabolic syndrome. As QIDS-SR scores were not normally distributed, results were separately confirmed with the same analyses utilizing QIDS-SR rank scores.

A stepwise regression was performed to more clearly identify potential group differences in covariate contribution to depressive symptom severity as

measured by QIDS-SR total score. The model for the total sample revealed that gender (p<0.001) and African American ethnicity (p=0.015), along with age, education, BMI, and income, were predictive of depressive symptom severity. Complete results of this analysis can be found in Table 3c.

A separate model examining ethnic-gender group combinations suggested that the strongest predictors of depressive symptom severity for African American females were younger age and fewer years of education (See Table 3c for complete results). Together, these factors accounted for 6.1% the variance in depressive symptom severity (R^2=0.061). For Caucasian females, education and BMI were predictive of depressive symptom severity for this group. Together, these variables accounted for 11.5% of the variance in QIDS-SR scores (R^2=0.115). The models for predictors of depressive symptom severity were more similar for the male groups as income was the only significantly predictive variable for both Caucasian (R^2=0.038) and African American (R^2=0.053) males.

Ethnic Differences in Depressive Symptoms: Summary of Findings. These results support the hypothesis that African Americans would demonstrate greater depressive symptom severity. However, African Americans also demonstrated greater frequency of depressive symptoms, but this higher frequency was actually explained by differences in socioeconomic variables. Exploring depressive symptoms both in terms of presence and severity suggested that while ethnicity was not independently associated with depressive symptom

presence, African American ethnicity was predictive of increased symptom severity. It was additionally uncovered that demographic and health factors differentially contributed to variance in depressive symptom presence and severity in ethnic-gender group combinations.

Hypothesis 2: Ethnic Differences in the Relationship Between Depressive Symptoms and Atherosclerosis.

In order to determine the association between atherosclerosis and depressive symptoms, separate analyses were conducted using two measures of atherosclerosis (CAC and cIMT) and QIDS-SR total score. CAC is believed to measure relatively stable calcified plaques, while cIMT measure describes overall carotid luminal narrowing. It was hypothesized that these measures of atherosclerosis would be similarly associated with depressive symptoms in both African Americans and Caucasians. All results related to this hypothesis can be viewed in Tables 4a through 5c.

Hypothesis 2a: Ethnic Differences in the Relationship Between Depressive Symptoms and Coronary Artery Calcification. Multiple regression analyses were used to determine if CAC presence was predictive of depressive symptoms, and whether relationships differed in ethnic and gender groups. CAC scores were dichotomized into present or absent defined as greater or less than 10 Agatston units (Agatston et al., 1990). The log10 regression model for the total

sample, combining ethnic and gender groups, suggested that CAC presence was not predictive of depressive symptom severity. Rather, gender, age, income, education, and BMI together accounted for 7.8% of the variance in QIDS-SR total score (See Table 4a). CAC presence was also not predictive of log10 QIDS-SR score for any group when ethnicity was included as a predictor (See Table 4a).

In order to further clarify any potential association between CAC score and depressive symptoms, partial and zero order (Pearson correlations) were calculated using CAC score as a continuous variable. CAC scores were skewed, necessitating duplicate analyses using raw and log10 transformed CAC scores. Correlations including significant covariates (age, income, education, BMI, ethnicity by metabolic syndrome) found that CAC was not significantly correlated with depressive symptoms in any of the four ethnic-gender group combinations. In sum, CAC was not identified as either a significant predictor or correlate of depressive symptoms in this sample.

Hypothesis 2b: Ethnic Differences in the Relationship Between Depressive Symptoms and Carotid Intima Media Thickness. A second analysis was conducted to further explore the relationship between atherosclerosis and depressive symptoms by evaluating cIMT score and QIDS-SR total score. Regression analyses were used to evaluate the relationship in the total sample including the significant covariates of QIDS-SR score (age, income, education, gender, BMI, and ethnicity by metabolic syndrome). The regression model for the

sample suggested that cIMT was not predictive of depressive symptom severity (p=0.25) in the total sample. Additionally, the interaction between ethnicity and metabolic syndrome was not a significant covariate (See Table 5a).

Analyses were then conducted separately evaluating ethnic-gender group combinations (See Table 5a). Initial analysis utilizing raw cIMT score and raw QIDS-SR suggested that cIMT was significantly predictive of depressive symptoms for Caucasian males (p=0.029). However, due to the skewness in both QIDS-SR scores and cIMT, the log10 model (results shown) and the nonparametric tests (rank; not shown) did not confirm this result. Carotid intima media thickness was not a significant predictor of depressive symptoms for any of the ethnic-gender combination groups.

Zero-order (Pearson) and partial correlations including the aforementioned significant covariates were utilized to clarify the association between log10 cIMT and QIDS-SR total score (See Table 5b). Though zero-order correlations suggested an association between log10 cIMT and QIDS-SR scores for Caucasian females, (r=0.195; p=0.005) and Caucasian males (r=0.163; p=0.042), these associations were not signficant in partial correlations when covariates were accounted for. Thus, while an association appeared between cIMT and depressive symptoms in Caucasian females and males, it was accounted for by differences in education, income, age, and BMI.

Ethnic Differences in the Relationship Between Depressive Symptoms and Atherosclerosis: Summary of Findings. It was hypothesized that both measures of atherosclerosis would be similarly associated with depressive symptoms in Caucasians and African Americans. In contrast, these results indicated that CAC was not associated with depressive symptoms in any of the four groups. One measure, cIMT, appeared to be associated with depressive symptoms in Caucasian females and males, though the association was better accounted for by income, education, age, and BMI. Thus, neither measure of atherosclerosis was found to be associated with depressive symptoms in this sample.

Hypothesis 3: Ethnic Differences in the Relationship Between Depressive Symptoms and White Matter Hyperintensities

In order to identify hypothesized ethnic differences in the relationship between WMH volume (WMHv) and depressive symptoms, WMHv data preprocessing was required. To account for individual differences in brain volume, WMHv was adjusted for total cranial volume. This percentage of total cranial volume was then transformed using an inverse sine transformation [(2arcsin$\sqrt{x}$); (InverseSineWMH)]. Analyses were first conducted to confirm group differences in WMHv volume including appropriate health and socio-

demographic covariates. All analyses related to hypothesis 3 can be viewed in Appendix B along with Tables 6a and 6b.

Hypothesis 3a: Ethnic Differences in WMH. ANOVA results showed ethnic differences following inverse sine transformation, with African Americans demonstrating significantly higher volumes of WMH [$F(1, 734)=4.40$, $p=0.04$]. Two-way ANOVAs identified age, diabetes status, cIMT, and CAC as the significant covariates of InverseSineWMH (See Appendix B). There was no significant interaction between gender and ethnicity [$F(1, 730)=0.171$, $p=0.68$]. WMHv differences in ethnic groups was not signficant with the inclusion of these important covariates [$F(1, 730)=2.484$, $p=0.115$]. Notably, gender differences emerged with inclusion of these covariates, suggesting that the females in this sample had higher WMHv [M(SD)=0.078(0.049)] than males [M(SD)=0.071(0.049)], a finding which has been previously reported by researchers (Sachdev, Parslow, Wen, Anstey, & Easteal, 2009).

Hypothesis 3b: Depressive Symptom Association with WMHv. Potential differences in the relationship between WMHv and depressive symptoms were explored in the total sample and by ethnic-gender group combinations using InverseSineWMH and QIDS-SR total. The final regression model for the total sample (See Table 6a) including significant covariates of log10 QIDS-SR suggested that WMHv was not predictive of depressive symptoms

(p=0.334). As in previous models, only age, income, education, and gender were predictive of depressive symptoms in the total sample.

When ethnic-gender group combinations were compared, again, only previously identified covariates of QIDS-SR score were found to be predictive of depressive symptoms (See Table 6a). In this sample, InverseSineWMH was not a significant predictor of depressive symptoms for any group.

Partial and zero-order Pearson correlations also suggested no significant associations between depressive symptoms (log10 QIDS-SR total) and WMHv (InverseSineWMH) for either ethnic-gender group combination. Correlation analyses can be viewed in Table 6c.

Ethnic Differences in the Relationship Between Depressive Symptoms and White Matter Hyperintensities: Summary of Findings. While there initially appeared to be differences in WMHv across ethnic groups in initial descriptive statistics, inclusion of covariates indicated that these differences were actually accounted for by age, education, BMI, and income. Gender differences remained significant when covariates were included in the analysis. Women appeared to have higher volumes of WMH, which is consistent with previous literature (Sachdev et al., 2009) . Contrary to prediction, there was no association between WMHv and depressive symptoms. As such, no ethnic differences in the relationship were revealed. In this sample, no association between WMHv and depressive symptoms emerged.

Chapter Five: Discussion

Introduction

This study provides a unique perspective of the relationship between subclinical vascular disease and depressive symptoms. Previous works have primarily explored this relationship in individuals with major depression diagnoses and/or symptomatic vascular disease. Depressive symptoms do not always warrant a major depressive disorder diagnosis, and can occur in the context of almost any psychiatric diagnosis, or within psychologically healthy individuals from time to time or when facing a psychosocial stressor. Examination of depressive symptoms and subclinical vascular disease as variables in a population-based sample provides a clearer understanding of this relationship as it manifests in the general population. In order to better understand how vascular variables may be associated with depressive symptoms across ethnic groups, it is essential to first describe and compare depressive symptom manifestation and characterize socio-demographic contributors

Sample Characteristics

The results describing the cardiovascular health characteristics of the current sample are primarily consistent with previously reported prevalence rates. For example though African Americans were found to have higher rates of

hypertension, these results are consistent with a recently published cardiovascular epidemiology study that reported 71.1% of African American adults were hypertensive compared with 45% of Caucasian adults (Avery et al., 2012). Additionally, though 15.7% of the current sample were determined to have diabetes, this is similar to a previously published figure (15.3%) in an oft-cited epidemiologic study of health among older adults in the United States (Selvin, Coresh, & Brancati, 2006). The current finding that African Americans had higher rates of diabetes than Caucasian counterparts supports previous work describing ethnic differences in diabetes prevalence (Go et al., 2013; McBean, Li, Gilbertson, & Collins, 2004). Consistent with previous literature, no ethnic differences in hypercholesterolemia were identified in the current sample, and the sample prevalence rate (38.%) is consistent with the national prevalence (37.1% for age 40-59) released in the most recent AHA (American Heart Association) report on national cardiovascular statistics (Go et al., 2013).

Unlike the aforementioned cardiovascular variables, the atherosclerosis measures of primary interest in the current examination are less frequently explored in large, predominantly healthy, ethnically diverse epidemiologic samples. Of primary interest was examining ethnic differences across these measures. Previous reports have provided conflicting evidence with regard to the relationship between ethnicity and atherosclerosis (Orakzai et al., 2006; Budhoff et al., 2005). The current finding of non-significant differences in coronary artery

calcification between African Americans and Caucasians is consistent with a previous report of these data in a larger sample from the Dallas Heart Study (Jain et al., 2004). Carotid intima media thickness, however, was determined to be different across ethnic groups, suggesting that ethnic and gender differences in atherosclerosis are measure dependent. This phenomenon has been described previously (Winston et al., 2013).

The one measure of health in the current sample that differed from normative means was BMI. The total sample mean [M (SD)=29.52 (5.44)]was slightly higher than the U.S. average based upon the report presented by Wang & Beydoun, 2007 (28.2 for women; 27.6 for men). As the sample was comprised of Dallas County, Texas residents, regional differences in BMI and increased BMI in areas of urban sprawl may best account for the increased BMI in this sample (Scott, Dubowitz, & Cohen, 2009; Vandegrift & Yoked, 2004; Wang & Beydoun, 2007).

Perhaps related to the increased BMI in the current sample, the prevalence of metabolic syndrome appeared to be elevated among the African American females (47%) in the sample. This prevalence rate is higher than previous population studies which have indicated that approximately 40% of African Americans meet criteria for metabolic syndrome (Ford & Erlinger, 2004; Go et al., 2013; Shaya, Gu, & Saunders, 2007). None of these reports explored gender

differences, but suggested that African American females may be at greater risk for development of metabolic syndrome.

Ethnicity and Depressive Symptoms

Depressive Symptom Presence. When QIDS-SR scores were dichotomized based upon the depressive symptom severity ranges by Rush et al. (2003), the majority of the current sample denied any depressive symptoms (65.4%). Though a recent large epidemiologic study (N=34,653) reported that 11% of the general U.S. population met criteria for "sub-threshold depression (Pietrzak et al., 2012)," researchers focused on lifetime history, rather than recent (i.e. past-week) symptoms (as the QIDS-SR does), and utilized a more specific threshold for inclusion (depressed mood and/or anhedonia along with additional depressive symptoms). However, the current finding is consistent with two large epidemiologic studies that suggested that between 27% and 39% of individuals in the general population, particularly in older adults, report subclinical depressive symptoms (Glaesmer, Riedel-Heller, Braehler, Spangenberg, & Luppa, 2011; Henderson & Pollard, 1992).

Based upon previous works suggesting that Caucasians demonstrate higher frequency of *major depressive disorder* and more often seek treatment for depression in general (Riolo et al., 2005; Williams et al., 2007), it was anticipated that Caucasians would demonstrate a higher frequency of *depressive symptoms*

than African Americans. The studies utilized to formulate this hypothesis focused on diagnoses of major depressive disorder among the general population rather the current examination of depressive symptoms in the general population. The current results revealed that ethnic differences in this domain were accounted for by variance in socio-demographic and health characteristics including income, age, education, and BMI.

There has been ongoing debate among social and clinical psychology researchers regarding the potential differential contributions of socioeconomic factors to depression, utilizing various definitions (Das et al., 2006; Gavin, Rue, & Takeuchi, 2010a; Gavin et al., 2010b; Myers et al., 2002). These reports have maintained that socioeconomic variables do not account for ethnic differences in *major depression* incidence. The current findings indicate that socioeconomic and health factors do, however, account for ethnic differences in presence of *depressive symptoms*. Therefore, among the general population, age, education, income, and BMI are most associated with risk for experiencing any depressive symptoms, regardless of etiology or association with a diagnosable mental illness, the result of a normal reaction to a psychosocial stressor, or as part of the spectrum of normal human experience.

Depressive Symptom Severity. Among the 37.5% of participants with *present* depressive symptoms, the majority of symptoms fell into the "mild" range (71%). Though the depressive symptom severity among this sample was far lower

than has been reported in previous literature, past studies have exclusively reported severity among patients diagnosed with major depressive disorder (Kessler et al., 2005).

Within the total sample, females demonstrated a significantly higher QIDS-SR mean score than males, which is consistent with previous reports of increased depression severity among females (McGuire, Strine, Vachirasudlekha, Mokdad, & Anderson, 2008; Van de Velde, Bracke, & Levecque, 2010). Various hypotheses have been put forth for this increased impact upon females, though gender roles and self-esteem appear to have promninent support (Cambron, Acitelli, & Pettit, 2009; Nazroo, Edwards, & Brown, 1998).

The current results revealed that African Americans demonstrated higher depressive symptom scores than Caucasians. Previous reports have suggested that African Americans with major depressive disorder experience greater symptom severity (Miller et al., 2004; Myers et al., 2002; Williams et al., 2007), though no previous studies have examined and identified ethnic differences in self-report depressive symptoms in the general population (Mills & Henretta, 2001). The current finding suggests that although the difference is small, this increased symptom severity in African Americans extends from clinical samples into the general population.

Researchers examining major depressive disorder among African Americans have put forth several hypotheses to explain the disproportionate

severity. Perceived racism has been thought to be associated with depression among African Americans (Pieterse, Todd, Neville, & Carter, 2012), though such information is not collected in most clinical studies. It was anticipated that poverty might contribute to ethnic differences, though African American ethnicity remained a significant predictor of symptom severity even following control for varying income levels. It remains possible that differences in mental health treatment pursuit account for this discrepancy. African Americans with significant depressive symptoms, through lack of treatment pursuit, are vulnerable to greater symptom chronicity, which may exacerbate hopelessness and increase severity indicators. In sum, when covariates were controlled, African American ethnicity did not predict *presence* of depressive symptoms, but did predict *increased severity* of depressive symptoms.

Perhaps the most notable and unexpected findings in the comparison of depressive symptoms across ethnic groups were the differential contributions of socio-demographic and health characteristics to depressive symptoms. Previous reports have indicated that socio-economic variables do not influence depression in African Americans (Ennis, Hobfoll, & Schröder, 2000; Gavin, Walton, Chae, Alegría, et al., 2010b; Williams et al., 2007). However, a recent report by Hudson et al. (2011) suggested *gender* differences in the effect of socioeconomic variables on depression in African Americans. These researchers encouraged the use of multiple measures of SES (income, education, and others) to more accurately

determine effects. The current results support Hudson et al. (2011) and replicated that socio-demographic characteristics do contribute to depressive symptom frequency and severity in African Americans as well as Caucasians.

The results of the present study revealed that lower income was associated with increased depressive symptom severity for both African American and Caucasian males. This finding is supported by a previous investigation suggesting that among older males, household income and employment are important determinants of life satisfaction (Beutel, Glaesmer, Wiltink, Marian, & Brähler, 2010), and significant predictors of depression among African American males, but not females (Hudson, Neighbors, Geronimus, & Jackson, 2011). Further, males who see themselves as "inadequate breadwinners" report lower levels of subjective well-being and more depression than males who see themselves as "adequate" earners (Crowley, 1998). Thus, the current finding supports those by Hudson et al. (2011) and may be a reflection of the association between subjective well-being and depression (Gargiulo & Stokes, 2008).

Though income was similarly associated with depressive symptoms in both African American and Caucasian males, some differences in contributors to depressive symptoms emerged across ethnic groups among females in the sample. For example, while not a predictor in males, lower education was predictive of depressive symptoms for both African American and Caucasian females. Previous research has found gender differences in the impact of education on depressive

symptoms (Ross & Mirowsky, 2006). Ross and Mirowsky (2006) reported that while depressive symptoms decline with increasing levels of education in both genders, the trajectory of decline was significantly steeper for females. In essence, while both genders benefit (in terms of decreased depressive symptoms) from increasing years of education, females appear to profit more (Ross & Mirowsky, 2006).

The influence of age and BMI on depressive symptoms diverged across ethnic groups among the female sample. Younger age was predictive of depressive symptoms among African American, but not Caucasian, females. Previous research has suggested that depressive symptoms increase with age in women until the mid-40's, when a decline in symptoms begins (Jorm, 2000; Kasen, Cohen, Chen, & Castille, 2003; Scarinci et al., 2002). However, these previous works did not specifically explore ethnic differences. The demographic composition of the current sample allowed for such a comparison, and the current results indicate that age differently impacts depressive symptoms across these ethnic groups.

In addition to education, higher BMI was a predictor of depressive symptoms for Caucasian females. Though previous work did not find differences between U.S.-born African Americans and Caucasians in the relationship between obesity and depression (Gavin, Rue, & Takeuchi, 2010a), a recently published study reported that obesity had a greater association with depression among

Caucasian females than African American females (Hicken et al., 2013). It is of note that none of the cardiovascular measures typically associated with increased BMI (diabetes, hypertension, hyperlipidemia, or metabolic syndrome) were linked with increased depressive symptoms for Caucasian females in this sample. Thus, it appears that body image, rather than health factors, account for this connection. Such an hypothesis is supported by Gavin et al. (2010a) who reported that "body image dissatisfaction" mediated the relationship between depression and obesity. Furthermore, psychological distress and depression have been previously associated with negative body image among Caucasian, rather than African American females (Grabe & Jackson, 2009; Walker, Timmerman, Kim, & Sterling, 2002). This difference appears to be reflective of ethnic differences in desirable female body image, with Caucasians preferring thinner body types, and African American women viewing larger body types as more attractive (Kumanyika, Wilson, & Guilford-Davenport, 1993).

Overall, the results of this study demonstrated increased severity of depressive symptoms (as measured by higher QIDS-SR scores) in African Americans compared with Caucasians. Socio-demographic and health factors differently influenced depressive symptoms among ethnic and gender groups. As these factors interacted with depressive symptoms across ethnic groups, it was expected that vascular disease, too, would be related to depressive symptoms

Ethnicity and the Relationship Between Vascular Factors and Depressive Symptoms

Depressive Symptom Relationship to Atherosclerosis. Using the "vascular depression hypothesis" and previous findings of ethnic similarities in measures of atherosclerosis as a guiding model, it was anticipated that large vessel disease would be similarly associated with depressive symptoms in African Americans and Caucasians. It appears that the underlying assumption of a positive association between atherosclerosis and depressive symptoms across the ethnic-gender group combinations in this investigation was not supported.

CAC, the measure reported to be more predictive of cardiovascular disease (Folsom, 2008), was found to be unrelated to depressive symptoms in any of the four ethnic-gender combined groups. This result is consistent with very recent findings in a population-based sample comprised of randomly selected 50 and 60 year-old Caucasians (N=617) from the Danish population (Devantier et al., 2013). Devantier et al. (2013) concluded that CAC was not associated with self-reported depressive symptoms in the context of major depressive disorder. Thus, even among individuals whose depressive symptoms were sufficiently severe to warrant a major depressive disorder diagnosis, CAC was not associated with the disorder. Though the present study exclusively examined individuals with subclinical vascular disease and depressive symptoms across the diagnostic spectrum, the current findings are consistent with Devantier et al. (2013).

Though cIMT has been the primary measure utilized in examining the relationship between atherosclerosis and depression, CAC has been previously shown to be associated with depressive disorders (Tiemeier et al., 2004) and recurrent, not single episode, major depression (Agatisa et al., 2005). The present findings suggest that the relationship between CAC and depressive symptoms does not persist in the general population. Seldenrijk et al. (2012) reported that CAC was only associated with prolonged psychological distress rather than current psychological distress. Based upon the national prevalence rate of major depressive disorder (9.5%), a state that would indicate prolonged distress, it is likely that relatively few participants in the current sample would meet the severity/chronicity threshold to demonstrate an association between CAC and depressive symptoms.

An additional measure of atherosclerosis, cIMT, has been more widely used in the field to elucidate the relationship between atherosclerosis and depression (Seldenrijk et al., 2011; Jones et al., 2003; Stewart et al., 2009). Despite previous works suggesting a positive relationship between depression and cIMT, was not found to be predictive of depressive symptoms. It was anticipated that the relationship would remain significant in the general population based upon previous findings. Further, cIMT is closely associated with cerebrovascular disease (Folsom, 2008), which is often associated with depression.

A recent study conducted to explore connections between atherosclerosis and self-reported menopause symptoms also found that self-reported depression was not associated with cIMT (Wolff et al., 2013). Wolff et al. (2013) also selected participants regardless of psychiatric status and utilized self-report depressive symptoms, which may explain the similar results. Additionally, Stewart et al. (2009) emphasized the element of change in the relationship through findings suggesting that depressive symptoms precede the development of atherosclerosis (cIMT).

Though past research has reported a link between a major depressive diagnosis and at least subclinical atherosclerosis, the findings of this study indicate that the connection is not present in a population-based sample with depressive symptoms predominantly classified as subclinical or "mild." Past studies focused on patients with severe (Hamer et al., 2011) or clinician-confirmed major depressive disorder assessed via psychiatric interview or Structured Clinical Interview for DSM-IV (SCID) (Agatisa et al., 2005; Jones et al., 2003).

A recent review by Baune et al. (2012) suggested that clinical characteristics of depression including symptom severity are required to facilitate the bidirectional relationship between depression and atherosclerosis. Unfortunately, as the current sample was population-based, only a small proportion (10%; n=74), could be categorized as having "moderate" to "very

severe" depressive symptoms. Utilizing such small subsample sizes with the number of comparisons required would limit statistical power preventing certainty in any findings. As no relationship between depressive symptoms and atherosclerosis was uncovered, conclusions regarding potential ethnic differences in the connection between atherosclerosis and depressive symptoms cannot be drawn. While previous reports suggest a strong link between atherosclerosis and depression, the current results indicate that the association between depressive symptoms and subclinical atherosclerosis is not applicable to the incident depressive symptoms found in the general population

Depression and White Matter Hyperintensities. Based upon the "vascular depression hypothesis" and the increased presence of cerebrovascular risk factors in African Americans, it was anticipated that subclinical cerebrovascular disease, as measured by volume of WMH, would be more closely associated with depressive symptoms in African Americans. Ethnic differences in the relationship between depressive symptoms and volume of WMH could not be examined, however, as no significant associations between volume of WMH and depressive symptoms could be identified in any groups.

Several potential hypothesized explanations for the lack of association between WMH and depressive symptoms exist. First, similar to the studies conducted with large vessel disease, the majority of research conducted in this area has utilized patients with a history of major depressive disorder as

determined by clinician interview or SCID (Iosifescu et al., 2006; Murrough, Iacoviello, Neumeister, Charney, & Iosifescu, 2011; Pompili et al., 2007; 2008; Krishnan & McDonald, 1995; Sneed et al., 2011; Tham et al., 2011; Thomas et al., 2002; Vasudev et al., 2012), compared with the current investigation which used a self-report checklist of depressive symptoms in a general population, non-clinical sample. There may be an element unique to major depressive disorder that explains the relationship. Perhaps depressive symptoms, regardless of severity, require the social or occupational dysfunction associated with a major depressive disorder diagnosis to interact with cerebrovascular disease. It is possible that symptoms must be debilitating in some domain, and this debilitation is driving the association with WMH. Additionally, it is known that multiple major depressive episodes have a dose-response effect on large vessel disease (Jones et al., 2003; Agatisa et al., 2005; Steward et al., 2009). Perhaps the chronicity and severity are the key elements of a major depressive disorder diagnosis that explains the relationship between WMH and depression as in the "neurotoxic hypothesis" of depression (Sapolsky, 2000). Further study is required to isolate the components of major depressive disorder that are necessary for an association with cerebrovascular disease.

The current study focused on recent (i.e. past week), self-reported depressive symptoms among individuals in a general population sample, and found no relationship with WMH. Previous studies utilizing community-based

samples found mixed results in terms of the relationship between depression and WMH. De Groot et al. (2000) found a strong positive association in a large sample (N=1,077), though this work specifically identified individuals with a lifetime history of major depressive episodes, relied upon clinical ratings of WMH, and included participants with cerebral infarcts. The current study focused on depressive *symptoms*, utilized a semi-automated grading algorithm for WMH, and excluded participants with a history of stroke in order to comment on depressive symptom association with subclinical vascular disease. Versluis et al. (2006) also utilized a population-based sample, a self-report measure to evaluate depressive symptoms, and a semi-automated WMH grading algorithm, and were unable to identify an association between volume of WMH and depressive symptoms. Taken together, it appears that the relationship between WMH and depression is limited to individuals with major depressive disorder and does not extend to individuals in the general population with depressive symptoms.

Past research that reported a positive relationship between WMH and depression also included analysis of location and type of WMH (deep versus periventricular) (Murray et al., 2013; Sneed et al., 2011; Taylor, Aizenstein, & Alexopoulos, 2013). As previously mentioned, deep WMH in frontal areas have been found to be most closely associated with depression (Murray et al., 2013; O'Brien et al., 2006; Steffens, Helms, Krishnan, & Burke, 1999). The dataset utilized for the current study did not include location or type of white matter

hyperintensity. However, Versluis et al. (2006) did utilize WMH location and progression in a similar sample to the current study and were unable to find a significant association with even severe depressive symptoms.

Limitations

Several limitations of this study warrant mention. First, though the QIDS-SR has been well-established as a measure of severity of depressive symptoms (Bernstein et al., 2010; Doraiswamy et al., 2010; Rush et al., 2003; Trivedi et al., 2004), and it correlates strongly with other measures of depressive symptoms (Bernstein et al., 2010), no studies to date have established an average score for the general population. Furthermore, the QIDS-SR has not been normed in African Americans. Though none of the most commonly used self-report depression screening measures (e.g. Hamilton Rating Scale for Depression, Inventory of Depressive Symptomatology, Montgomery-Asberg Depression Rating Scale) have ethnic-specific norms, the psychometrics of the Center for Epidemiologic Studies Depression Scale (CES-D) were recently evaluated to determine utility across ethnic groups (Coman, Iordache, Schensul, & Coiculescu, 2012; Heller, Viken, & Swindle, 2010). These studies reported that though African Americans scored higher, ethnic differences in total score were not significant. While the QIDS-SR has not been normed among African Americans,

based upon current results and recent work with the CES-D, it is likely that separate may not be needed.

Additionally, comparisons among psychiatric diagnoses cannot be made as no mental health history was included in the dataset. This limits the generalizability of these results to the general population. It is possible that within this sample there are individuals with diagnosed mental illness whose data may be have provided greater detail for interpretation. Further, the lack of information on the duration depressive symptoms prevents potential comments regarding chronicity, a variable important in other reports on the relationship between depression and vascular disease.

Potential concerns may also be raised with regard to the statistical analyses conducted in this study. While it may appear that this study is vulnerable to experiment-wise error due to the number of analyses, additional nonparametric analyses were conducted as confirmatory rather than primary. As such, for the major hypotheses a total of three sets of primary analyses were conducted (two nonparametric, one parametric). Due to the large number of subjects and the use of confirmatory analyses, this method is viewed as a part of a conservative analysis plan.

Finally, as is a limitation in most clinical research, the sample was likely biased toward overall health. In order to participate in the Dallas Heart Study, subjects had to be sufficiently healthy to leave home and travel to clinic visits.

Further, individuals with metal implants or other contraindications for MRI would have been unable to participate.

Implications for the "Vascular Depression Hypothesis"

Since the initiation of the present study, Taylor, Aizenstein, and Alexopoulos (2013) have released an updated model of the "vascular depression hypothesis" based upon the current state of the field with increased focus on lesion location (uncinate fasciculus and superior longitudinal fasciculus) and progression of WMH over time in relationship to depression. This update suggests that WMH location and longitudinal changes over time, not WMH volume, are more important in the association with depression. The current study relied upon WMH volume, though Versluis et al (2006) did employ these additional variables and did not report an association with self-reported depressive symptoms. Therefore, the "vascular depression hypothesis" may not extend beyond diagnosable depression to self-reported symptoms.

Future Directions

The current study demonstrated increased depressive symptom severity in African Americans in the general population, and uncovered differential impacts of socio-demographic variables across ethnic-gender groups. The results suggest that ethnic differences in depressive symptoms do exist and that African American ethnicity is associated with severity, but not presence of symptoms.

Unfortunately, associations with subclinical vascular disease remain elusive. A direct comparison between patients diagnosed with major depressive disorder, those with subclinical depressive symptoms, and those with depressive symptoms in the context of other mental disorders (i.e. personality, anxiety disorders) would further clarify the association between depression and vascular disease.

As other population-based samples have found mixed results in examining the relationship between vascular disease and depressive symptoms, further study is warranted to better understand the potential ethnic differences in this relationship. Elucidation of ethnic differences may explain the disproportionate impact of depression on African Americans. Though this study did not find ethnic differences in the association between depressive symptoms and subclinical vascular disease, ethnic differences may be uncovered in comparing the relationship between major depressive disorder and clinical vascular disease across ethnic groups. The disproportionate burden of vascular disease and depression severity upon African Americans may be mitigated by research connecting the two through increased depression screening by general practitioners and cardiologists- physicians with whom African Americans may be more willing to seek treatment.

Comparing the relationships between depressive symptoms in the context of mental illnesses, socio-demographic variables, and vascular disease across ethnic groups may better characterize the heterogeneity among patients with

depressive syndromes. The current findings demonstrate that the relationship between vascular disease and depression does not persist in subclinical vascular disease and depressive symptoms in the general population. Working to better clarify the thresholds (vascular and depressive) required for a connection may provide greater understanding of the connections between physical and mental health, will lead to greater precision in research, and improve treatment efficacy.

Tables

Table 1a. *Demographic Characteristics*

		Caucasians		African Americans		Gender by Ethnicity
	Total Sample	**Females**	**Males**	**Females**	**Males**	***p*-value**
Total N (% of Total)	738 (100)	207 (28)	167 (22)	236 (32)	128 (17)	
Age Mean (SD)	58.6 (6.0)	59.2 (6.1)	58.3 (6.0)	58.6 (5.9)	57.8 (5.9)	**0.021**[a]
Education, %≥High School	70.6	77.8	82	61.4	60.9	**<0.001** [b]
Income Median, US$	40-49,999	40-49,999	50-74,999	25-29,999	30-34,999	**<0.001**

Note. [a]ANOVA: Gender (p=0.070); Ethnicity (p=0.220)
[b] Mantel Haenszel Chi Square: Males [X^2(1,292)=17.702; p=<0.001]
Females [X^2(1, 442)=13.621;p=<0.001]
[c]Kruskal Wallis H Test: Gender by Income (p=<0.001); Ethnicity by Income (p=<0.001)

Table 1b. *Health Characteristics*

		Caucasians		African Americans				
	Total Sample	**Females**	**Males**	**Females**	**Males**	**Gender by Ethnicity Interaction *p*-value**	**Gender *p*-value**	**Ethnicity *p*-value**
BMI Mean (SD)	29.52 (5.44)	28.41 (5.65)	28.45 (3.97)	31.62 (5.82)	28.83 (4.95)	**<0.001**	**<0.001**	**<0.001**
CAC Score Mean (SE)	146.5 (435.3)	72.7 (203.9)	210.8 (412.5)	115.5 (387.6)	239.1 (712.1)	0.825	**<0.001**	0.280
WMH (mL) Mean (SE)	2.25 (5.17)	1.99 (3.36)	2.01 (4.52)	2.45 (5.29)	2.61 (7.62)	0.860	0.830	0.180
Inverse Sine Transformed WMH	0.0754 (0.0492)	0.0753 (0.0409)	0.0668 (0.0452)	0.0809 (0.0552)	0.0768 (0.0535)	0.560	0.090	0.036
Common cIMT Mean (SD)	1.34 (0.25)	1.27 (0.17)	1.30 (0.20)	1.33 (0.22)	1.48 (0.34)	**0.027**	**<0.001**	**<0.001**

Note. BMI=Body Mass Index; CAC=Coronary Artery Calcification; WMH=White Matter Hyperintensities; cIMT=Carotid Intima Media Thickness

Table 1c. *Health Characteristics Continued*

		Caucasians		African Americans				
	Total	**Females**	**Males**	**Females**	**Males**	**Ethnicity Stratified by Gender[a] *p*-value**	**Ethnic Differences in Females *p*-value**	**Ethnic Differences in Males *p*-value**
HTN N (% of Group)	448 (60.7)	97 (46.9)	76 (46.5)	179 (75.8)	96 (75)	**<0.001**	**<0.001**	**<0.001**
Diabetic N (% of Group)	116 (15.7)	16 (7.7)	19 (11.4)	51 (21.6)	30 (23.4)	**<0.001**	**<0.001**	**0.006**
HCL N (% of Group)	284 (38.5)	86 (41.5)	70 (41.9)	89 (37.7)	39 (30.5)	0.082	0.407	0.061
MetS N (% of Group)	272 (36.9)	64 (30.9)	56 (33.5)	111 (47.0)	41 (32)	**0.008**	**<0.001**	0.933
CAC Present (>10 Agatston Units) N (% of Group)	321 (56.5)	68 (32.9)	101 (60.5)	89 (37.7)	63 (49.2)	0.727	0.286	0.054

Note. [a]Mantel Haenszel Chi Square stratified by gender
HTN=Hypertensive; HCL=Hypercholesterolemic; MetS=Metabolic Syndrome; CAC=Coronary Artery Calcification

Table 2a. *Depressive Symptom Severity Levels by Selected Group*

	QIDS-SR Total Score, n (%)				
	No Sxs (0-5)	**Mild (≥6-10)**	**Moderate (≥11-15)**	**Severe (≥16-20)**	**Very Severe (≥21-27)**
Total Sample	483 (65.4)	181 (24.5)	54 (7.3)	16 (2.2)	4 (0.5)
Ethnicity					
African Americans	219 (60.2)	95 (26.1)	36 (9.9)	12 (3.3)	2 (0.5)
Caucasians	264 (70.6)	86 (23.0)	18 (4.8)	4 (1.1)	2 (0.5)
Gender					
Females	271 (61.2)	113 (25.5)	42 (9.5)	14 (3.2)	3 (0.7)
Males	212 (71.9)	68 (23.1)	12 (4.1)	2 (0.7)	1 (0.3)
Ethnicity by Gender					
African Americans					
Females	138 (58.5)	59 (25.0)	27 (11.4)	11 (4.7)	1 (0.4)
Males	81 (63.3)	36 (28.0)	9 (7.0)	1 (0.8)	1 (0.8)
Caucasians					
Females	133 (64.3)	54 (26.1)	15 (7.2)	3 (1.4)	2 (1.0)
Males	131 (78.4)	32 (19.2)	3 (1.8)	1 (0.6)	0 (0.0)

Table 2b. *Presence of Depressive Symptoms by Gender, Ethnicity, and Total Sample*

	Females	**Males**	**Total Sample**
Total Sample QIDS-SR Positive N (%)	172 (38.8)	83 (28.1)	255 (34.6)
Caucasians QIDS-SR Positive N (%)	74 (35.7)	36 (21.6)	110 (29.4)
African Americans QIDS-SR Positive N (%)	98 (58.5)	47 (36.7)	145 (39.8)
Chi Square *p*-value	0.252[a]	**0.004**[b]	**0.008**[c]

Note. [a]Chi-Square p-value comparing race and presence of depressive symptoms for females
[b]Chi-Square p-value comparing race and presence of depressive symptoms for females
[c] Stratifying by gender using Mantel Haenszel Chi Square

Table 2c. *ANOVA Result: Depressive Symptom Severity (QIDS-SR total score) for Ethnicity by Gender*

	QIDS-SR Total Score Mean (SD)	**QIDS-SR Total Score Range**	**ANOVA Unadjusted *p* value**
Total Sample	5.27 (3.94)	0-27	
Ethnicity			**<0.001**
African Americans	5.84 (4.20)	0-24	
Caucasians	4.72 (3.61)	0-27	
Gender			**<0.001**
Females	5.83 (4.31)	0-27	
Males	4.44 (3.17)	0-21	
Ethnicity by Gender Interaction			0.370
African American Females	6.19 (4.50)	0-24	
Caucasian Females	5.41 (4.10)	0-27	
African American Males	5.19 (3.61)	0-21	
Caucasian Males	3.87 (2.66)	0-16	

Table 3a. *Stepwise Logistic Regression Models: Predictors of Positive Depressive Symptom Status (QIDS-SR≥6) for Total Sample and Ethnic-Gender Group Combinations*

	Variables	Odds Ratio (OR)	95%CI for OR	*p*	Hosmer and Lemeshow Test (*p*)
Total Sample					
	Income	0.939	0.897-0.983	**0.007**	
	Education	0.770	0.627-0.946	**0.013**	0.705
	BMI	1.029	1.000-1.059	**0.049**	
	Gender	0.706	0.509-0.980	**0.038**	
African American Females	Age	0.943	0.901-0.988	**0.012**	0.849
Caucasian Females					
	BMI	1.103	1.044-1.165	**<0.001**	0.672
	Education	0.627	0.421-0.935	**0.022**	
Caucasian Males					
	Income	0.884	0.79-0.99	**0.032**	0.349

Note. No significant predictors for African American males

Table 3b. *ANCOVA Result: Depressive Symptom Severity (QIDS-SR total score) for Ethnicity by Gender*

	β	**ANCOVA Adjusted *p* value**
Total Sample		
Ethnicity	0.765	**0.007**
African Americans		
Caucasians		
Gender	0.909	**0.001**
Females		
Males		
Ethnicity by Gender	0.21	0.249
Interaction		
African American Females		
Caucasian Females		
African American Males		
Caucasian Males		
Covariates		
Age	0.788	**0.006**
Income	0.915	**0.001**
Education	0.959	**<0.001**
BMI	0.284	0.165
Metabolic Syndrome	0.306	0.241
Ethnicity by Metabolic Syndrome Interaction	0.769	**0.011**
Gender by Metabolic Syndrome Interaction	0.05	0.14

ANCOVA R^2=0.117

Table 3c. *Stepwise Regression Model: Predictors of Depressive Symptom Severity (QIDS-SR Total Score) for Total Sample and Ethnic-Gender Group Combinations*

	Variables	β	*p*	R^2
Total Sample				0.045
	Age	-0.078	**0.030**	
	Income	-0.159	**<0.001**	
	Education	-0.213	**<0.001**	
	Gender (M=1)	-0.152	**<0.001**	
	BMI	0.104	**0.004**	
	Ethnicity (C=1)	-0.091	**0.015**	
African American Females				0.061
	Age	-0.195	**0.003**	
	Education	-0.166	**0.010**	
Caucasian Females				0.115
	BMI	-0.246	**<0.001**	
	Education	0.209	**0.002**	
African American Males				0.053
	Income	-0.230	**0.009**	
Caucasian Males				0.038
	Income	-0.195	**0.012**	

Note. F=Female; AA=African American

Table 4a. *Multiple Regression Model: Presence of CAC as a Predictor of Depressive Symptom Severity (QIDS-SR Total Score) for Total Sample and Ethnic-Gender Group Combinations*

		QIDS-SR Total Score			Log10 QIDS-SR Total Score		
	Variable	**β**	***p***	***R^2***	**β**	***p***	***R^2***
Total Sample				0.101			0.078
	Age	-0.091	**0.010**		-0.098	**0.007**	
	Income	-0.146	**<0.001**		-0.156	**<0.001**	
	Education	-0.145	**<0.001**		-0.142	**<0.001**	
	Gender	-0.134	**<0.001**		-0.127	**0.001**	
	BMI	0.077	**0.031**		0.052	0.153	
	CAC Score	0.038	0.314		0.028	0.473	
African American Females				0.061			0.056
	Age	-0.195	**0.003**		-0.191	**0.003**	
	Education	-0.166	**0.010**		-0.154	**0.018**	
	CAC	0.029	0.463		0.036	0.416	
Caucasian Females				0.115			0.098
	BMI	0.209	**0.002**		0.227	**0.001**	
	Education	-0.246	**<0.001**		-0.192	**0.005**	
	CAC	0.042	0.996		-0.005	0.910	
African American Males				0.053			0.065
	Income	-0.230	**0.009**		-0.256	**0.004**	
	CAC	0.097	0.999		0.103	0.106	
Caucasian Males				0.038			0.033
	Income	-0.195	**0.012**		-0.183	**0.022**	
	CAC	0.013	0.997		-0.031	0.701	

Table 4c. *Pearson and Partial Correlations Between Depressive Symptom Severity and CAC Scores*

	QIDS-SR Total Score and CAC Score				**Log10 QIDS-SR Total Score and Log10 CAC Score**			
	Zero-Order (Pearson) Correlation		**Partial Correlation** [a]		**Zero-Order (Pearson) Correlation**		**Partial Correlation** [a]	
Group	***r***	***p***	***r***	***p***	***r***	***p***	***r***	***p***
African American Females	-0.570	0.380	-0.068	0.300	-0.010	0.884	0.006	0.929
Caucasian Females	-0.090	0.196	-0.041	0.565	-0.036	0.611	0.002	0.977
African American Males	0.070	0.431	0.052	0.565	0.127	0.161	0.138	0.133
Caucasian Males	0.144	0.063	0.152	0.055	0.055	0.497	0.076	0.353

Note. [a] Significant covariates of QIDS-SR total score partialled out.

Table 5a. *Regression Model: cIMT Score as Predictor of Depressive Symptom Severity (QIDS-SR Total Score) for Total Sample and Ethnic-Gender Group Combinations*

		QIDS-SR Total Score			Log10 QIDS-SR Total Score		
	Variable	**β**	***p***	***R^2***	**β**	***p***	***R^2***
Total Sample				0.103			0.056
	Age	-0.094	**0.008**		-0.098	**0.007**	
	Income	-0.144	**<0.001**		-0.156	**<0.001**	
	Education	-0.143	**<0.001**		-0.142	**<0.001**	
	Gender	-0.144	**<0.001**		-0.127	**0.001**	
	BMI	0.070	**0.050**		0.052	0.153	
	cIMT	0.042	0.252		0.067	0.068	
African American Females				0.061			0.056
	Age	-0.197	**0.003**		-0.191	**0.003**	
	Education	-0.166	**0.010**		-0.154	**0.018**	
	cIMT	0.009	0.829		0.026	0.693	
Caucasian Females				0.115			0.098
	BMI	0.186	**0.006**		-0.192	**0.005**	
	Education	-0.234	**0.001**		0.227	**0.001**	
	cIMT	0.113	0.079		0.134	0.051	
African American Males				0.054			0.065
	Income	-0.227	**0.011**		-0.256	**0.004**	
	cIMT	-0.036	0.679		0.001	0.994	
Caucasian Males				0.063			0.033
	Income	-0.176	**0.021**		-0.183	**0.022**	
	cIMT	0.167	**0.029**		0.147	0.064	

Table 5c. *Pearson and Partial Correlations Between Depressive Symptom Severity and cIMT Scores*

	QIDS-SR Total Score and cIMT Score				**Log10 QIDS-SR Total Score and cIMT Score**			
	Zero-Order (Pearson) Correlation		**Partial Correlation** [a]		**Zero-Order (Pearson) Correlation**		**Partial Correlation** [a]	
Group	***r***	***p***	***r***	***p***	***r***	***p***	***r***	***p***
African American Females	-0.014	0.832	0.009	0.891	-0.05	0.451	-0.03	0.657
Caucasian Females	0.185	**0.008**	0.116	0.099	0.195	**0.005**	0.129	0.069
African American Males	-0.056	0.529	-0.033	0.716	-0.018	0.841	0.016	0.865
Caucasian Males	0.173	**0.026**	0.155	**0.050**	0.163	**0.042**	0.152	0.062

Note. [a] Significant covariates of QIDS-SR total score partialled out. Covariates included in analyses: age, education, BMI, income, ethnicity*metabolic syndrome. Results confirmed with rank cIMT scores and rank QIDS-SR total score

Table 6a. *Regression Model: Inverse Sine WMHv as Predictor of Depressive Symptom Severity (QIDS-SR Total Score) for Total Sample and Ethnic-Gender Group Combinations*

		QIDS-SR Total Score and Inverse Sine WMHv			**Log10 QIDS-SR Total Score and Inverse Sine WMHv**		
	Variable	**β**	***p***	***R^2***	**β**	***p***	***R^2***
Total Sample				0.101			0.089
	Age	-0.096	**0.011**		-0.098	**0.007**	
	BMI	0.078	**0.030**		0.052	0.153	
	Income	-0.145	**<0.001**		-0.156	**<0.001**	
	Education	-0.144	**<0.001**		-0.142	**<0.001**	
	Gender	-0.133	**<0.001**		-0.127	**0.001**	
	InverseSin WMH	0.015	0.697		0.037	0.334	
African American Females				0.065			0.056
	Age	-0.211	**0.002**		-0.191	**0.003**	
	Education	-0.167	**0.009**		-0.154	**0.018**	
	InverseSin WMH	0.065	0.320		0.056	0.403	
Caucasian Females				0.118			0.098
	BMI	-0.253	**<0.001**		-0.192	**0.005**	
	Education	0.209	**0.002**		0.227	**0.001**	
	InverseSin WMH	-0.057	0.391		0.036	0.051	
African American Males				0.053			0.065
	Income	-0.230	**0.010**		-0.256	**0.004**	
	InverseSin WMH	0.002	0.984		0.057	0.524	
Caucasian Males				0.090			0.033
	Income	-0.180	**0.018**		-0.183	**0.022**	
	CAC	0.167	**0.029**		0.054	0.064	
	cIMT	0.153	**0.050**		0.147	0.501	
	InverseSin WMH	-0.052	0.165		-0.062	0.436	

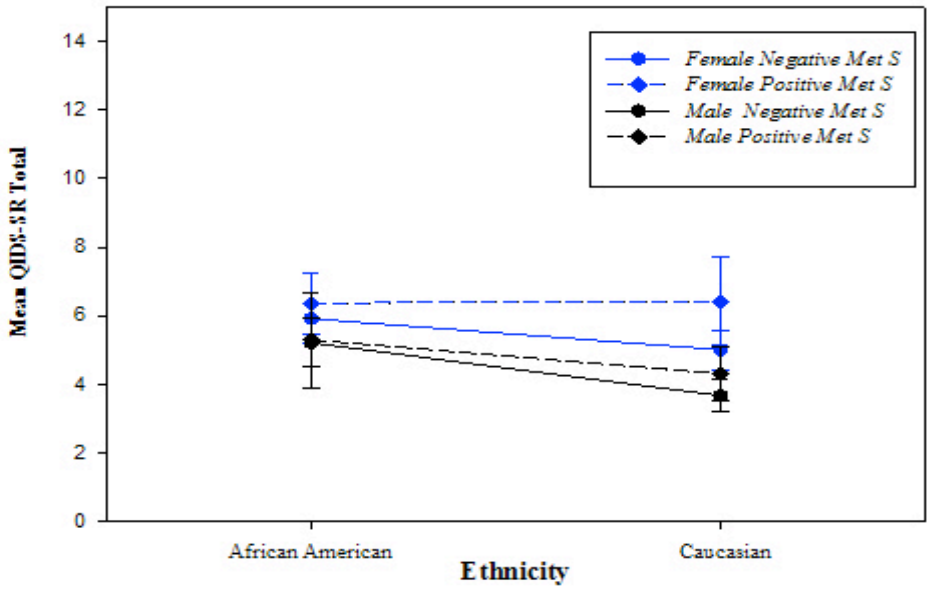
Table 6c. *Pearson and Partial Correlations Between Depressive Symptom Severity and Inverse Sine Transformed WMH in Ethnic Groups Stratified by Gender*

	QIDS-SR Total Score and Inverse Sine Transformed WMH				**Log10 Transformed QIDS-SR Total Score and Inverse Sine Transformed WMH**			
	Zero-Order (Pearson) Correlation		**Partial Correlation [a]**		**Zero-Order (Pearson) Correlation**		**Partial Correlation [a]**	
Group	***r***	***p***	***r***	***p***	***r***	***p***	***r***	***p***
African American Females	0.014	0.833	0.073	0.270	-0.001	0.983	0.073	0.270
Caucasian Females	-0.022	0.757	-0.035	0.618	0.040	0.570	-0.035	0.618
African American Males	0.031	0.731	-0.018	0.844	0.046	0.608	-0.018	0.844
Caucasian Males	-0.042	0.594	-0.068	0.389	-0.040	0.610	-0.068	0.389

Note. [a] Significant covariates for the model predicting QIDS-SR total score partialled out. Covariates included in analyses: age, education, BMI, income, ethnicity*metabolic syndrome.

Figures

Figure 1. *Ethnicity*Gender*Metabolic Syndrome Status Interaction in Depressive Symptom Severity (QIDS-SR Total)*[a]



Note. [a]Means have been adjusted for the covariates in the model

Appendices

Appendix A: Quick Inventory of Depressive Symptomatology-Self Report

The Quick Inventory of Depressive Symptomatology (16-Item) (Self-Report) (QIDS-SR16)

Name or ID: _____ Date: _____

CHECK THE ONE RESPONSE TO EACH ITEM THAT BEST DESCRIBES YOU FOR THE PAST SEVEN DAYS.

During the past seven days...

1. Falling Asleep:

☐ 0 I never take longer than 30 minutes to fall asleep.

☐ 1 I take at least 30 minutes to fall asleep, less than half the time.

☐ 2 I take at least 30 minutes to fall asleep, more than half the time.

☐ 3 I take more than 60 minutes to fall asleep, more than half the time.

2. Sleep During the Night

☐ 0 I do not wake up at night.

☐ 1 I have a restless, light sleep with a few brief awakenings each night.

☐ 2 I wake up at least once a night, but I go back to sleep easily.

☐ 3 I awaken more than once a night and stay awake for 20 minutes or more, more than half the time.

3. Waking Up Too Early:

☐ 0 Most of the time, I awaken no more than 30 minutes before I need to get up.

☐ 1 More than half the time, I awaken more than 30 minutes before I need to get up.

☐ 2 I almost always awaken at least one hour or so before I need to, but I go back to sleep eventually.

☐ 3 I awaken at least one hour before I need to, and can't go back to sleep.

4. Sleeping Too Much:

☐ 0 I sleep no longer than 7-8 hours/night, without napping during the day.

☐ 1 I sleep no longer than 10 hours in a 24-hour period including naps.

☐ 2 I sleep no longer than 12 hours in a 24-hour period including naps.

☐ 3 I sleep longer than 12 hours in a 24-hour period including naps.

During the past seven days...

5. Feeling Sad:

☐ 0 I do not feel sad.

☐ 1 I feel sad less than half the time.

☐ 2 I feel sad more than half the time.

☐ 3 I feel sad nearly all of the time.

Please complete either 6 or 7 (not both)

6. Decreased Appetite:

☐ 0 There is no change in my usual appetite.

☐ 1 I eat somewhat less often or lesser amounts of food than usual.

☐ 2 I eat much less than usual and only with personal effort.

☐ 3 I rarely eat within a 24-hour period, and only with extreme personal effort or when others persuade me to eat.

- OR -

7. Increased Appetite:

☐ 0 There is no change from my usual appetite.

☐ 1 I feel a need to eat more frequently than usual.

☐ 2 I regularly eat more often and/or greater amounts of food than usual.

☐ 3 I feel driven to overeat both at mealtime and between meals.

Please complete either 8 or 9 (not both)

8. Decreased Weight (Within the Last Two Weeks):

☐ 0 I have not had a change in my weight.

☐ 1 I feel as if I have had a slight weight loss.

☐ 2 I have lost 2 pounds or more.

☐ 3 I have lost 5 pounds or more.

- OR -

9. Increased Weight (Within the Last Two Weeks):

☐ 0 I have not had a change in my weight.

☐ 1 I feel as if I have had a slight weight gain.

☐ 2 I have gained 2 pounds or more.

☐ 3 I have gained 5 pounds or more.

The Quick Inventory of Depressive Symptomatology (16-Item) (Self-Report) (QIDS-SR16)

During the past seven days...

10. Concentration / Decision Making:

☐ 0 There is no change in my usual capacity to concentrate or make decisions.

☐ 1 I occasionally feel indecisive or find that my attention wanders.

☐ 2 Most of the time, I struggle to focus my attention or to make decisions.

☐ 3 I cannot concentrate well enough to read or cannot make even minor decisions.

11. View of Myself:

☐ 0 I see myself as equally worthwhile and deserving as other people.

☐ 1 I am more self-blaming than usual.

☐ 2 I largely believe that I cause problems for others.

☐ 3 I think almost constantly about major and minor defects in myself.

12. Thoughts of Death or Suicide:

☐ 0 I do not think of suicide or death.

☐ 1 I feel that life is empty or wonder if it's worth living.

☐ 2 I think of suicide or death several times a week for several minutes.

☐ 3 I think of suicide or death several times a day in some detail, or I have made specific plans for suicide or have actually tried to take my life.

13. General Interest

☐ 0 There is no change from usual in how interested I am in other people or activities.

☐ 1 I notice that I am less interested in people or activities.

☐ 2 I find I have interest in only one or two of my formerly pursued activities.

☐ 3 I have virtually no interest in formerly pursued activities.

During the past seven days...

14. Energy Level:

☐ 0 There is no change in my usual level of energy.

☐ 1 I get tired more easily than usual.

☐ 2 I have to make a big effort to start or finish my usual daily activities (for example, shopping, homework, cooking, or going to work).

☐ 3 I really cannot carry out most of my usual daily activities because I just don't have the energy.

15. Feeling Slowed Down:

☐ 0 I think, speak, and move at my usual rate of speed.

☐ 1 I find that my thinking is slowed down or my voice sounds dull or flat.

☐ 2 It takes me several seconds to respond to most questions and I'm sure my thinking is slowed.

☐ 3 I am often unable to respond to questions without extreme effort.

16. Feeling Restless:

☐ 0 I do not feel restless.

☐ 1 I'm often fidgety, wringing my hands, or need to shift how I am sitting.

☐ 2 I have impulses to move about and am quite restless.

☐ 3 At times, I am unable to stay seated and need to pace around.

Appendix B: Group Differences and Significant Covariates of WMHv

ANOVA: Group Differences in WMHv with Significant Covariates

	df	*F*	*Partial Eta Square*	*p*
Covariates				
Age	1	72.837	0.091	**<0.001**
CAC Score	1	5.501	0.007	**0.019**
cIMT	1	6.951	0.009	**0.009**
Diabetes Status	1	5.140	0.007	**0.024**
Factors				
Gender[a]	1	4.852	0.007	**0.028**
Ethnicity	1	2.484	0.003	0.115
Gender*Ethnicity	1	0.171	0.000	0.680

R^2=0.145

Note. [a]Gender means in InverseSineWMH: Males [M(SD)=0.071(0.049)]; Females [M(SD)=0.078(0.049)].

References

Agatisa, P. K., Matthews, K. A., Bromberger, J. T., Edmundowicz, D., Chang, Y. F., & Sutton-Tyrrell, K. (2005). Coronary and aortic calcification in women with a history of major depression. *Archives of Internal Medicine*, *165*(11), 1229-1236.

Agatston, A. S., Janowitz, W. R., Hildner, F. J., Zusmer, N. R., Viamonte, M., & Detrano, R. (1990). Quantification of coronary artery calcium using ultrafast computed tomography. *Journal of the American College of Cardiology*, *15*(4), 827–832.

Alexander, G. E., DeLong, M. R., & Strick, P. L. (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annual Review of Neuroscience*, *9*(1), 357–381.

Alexander, L. D., Black, S. E., Gao, F., Szilagyi, G., Danells, C. J., & McIlroy, W. E. (2010). Correlating lesion size and location to deficits after ischemic stroke: The influence of accounting for altered peri-necrotic tissue and incidental silent infarcts. *Behavioral and Brain Functions*, *6*(1), 6. doi:10.1186/1744-9081-6-6

Alexopoulos, G. S., Meyers, B. S., Young, R. C., Kakuma, T., Silbersweig, D., & Charlson, M. (1997). Clinically defined vascular depression. *American Journal of Psychiatry*, *154*(4), 562–565.

Arboix, A., & Martí-Vilaita, J. L. (2009). Lacunar stroke. *Expert Review of Neurotherapeutics*, *9*(2), 179–196.

American Psychiatric Association. (2000). Diagnostic and statistical manual of mental disorders (4th ed., text revision). Washington, DC: Author

Avery, C. L., Loehr, L. R., Baggett, C., Chang, P. P., Kucharska-Newton, A. M., Matsushita, K., et al. (2012). The population burden of heart failure attributable to modifiable risk factors: The ARIC (Atherosclerosis Risk in Communities) Study. *Journal of the American College of Cardiology*, *60*(17), 1640–1646. doi:10.1016/j.jacc.2012.07.022

Awad, I. A., Johnson, P.C., Spetzler, R. F., & Hodak, J. A. (1986). Incidental subcortical lesions identified on magnetic resonance imaging in the elderly. Postmortem pathological correlations. *Stroke*, *17*(6), 1090–1097. doi:10.1161/01.STR.17.6.1090

Baldwin, R., Jeffries, S., Jackson, A., Sutcliffe, C., Thacker, N., Scott, M., & Burns, A. (2004). Treatment response in late-onset depression: relationship to neuropsychological, neuroradiological and vascular risk factors. *Psychological Medicine*, *34*(1), 125–136.

Bartzokis, G. (2004). Age-related myelin breakdown: a developmental model of cognitive decline and Alzheimer's disease. *Neurobiology of Aging*, *25*(1), 5–18. doi:10.1016/j.neurobiolaging.2003.03.001

Baune, B. T., Stuart, M., Gilmour, A., Wersching, H., Arolt, V., & Berger, K.

(2012). Moderators of the relationship between depression and cardiovascular disorders: a systematic review. *General Hospital Psychiatry, 34*(2012), 478-492.

Bernstein, I. H., Rush, A. J., Stegman, D., Macleod, L., Witte, B., & Trivedi, M. H. (2010). A comparison of the QIDS-C 16, QIDS-SR 16, and the MADRS in an adult outpatient clinical sample. *CNS Spectrums*, *15*(7), 458–468.

Beutel, M. E., Glaesmer, H., Wiltink, J., Marian, H., & Brähler, E. (2010). Life satisfaction, anxiety, depression and resilience across the life span of men. *The Aging Male*, *13*(1), 32–39. doi:10.3109/13685530903296698

Bild, D. E. (2005). Ethnic Differences in Coronary Calcification: The Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation*, *111*(10), 1313–1320. doi:10.1161/01.CIR.0000157730.94423.4B

Birns, J., Morris, R., Jarosz, J., Markus, H., & Kalra, L. (2008). Ethnic differences in the cerebrovascular impact of hypertension. *Cerebrovascular Diseases*, *25*(5), 408–416. doi:10.1159/000121341

Black, S., Gao, F., & Bilbao, J. (2009). Understanding white matter disease: Imaging-pathological correlations in vascular cognitive impairment. *Stroke*, *40*(3 SUPPL. 1), S48–S52.

Breslau, J., Kendler, K. S., Su, M., Gaxiola-Aguilar, S., & Kessler, R. C. (2005). Lifetime risk and persistence of psychiatric disorders across ethnic groups in the United States. *Psychological Medicine*, *35*(3), 317–327.

doi:10.1017/S0033291704003514

Brickman, A. M., Schupf, N., Manly, J. J., Luchsinger, J. A., Andrews, H., Tang, M. X.,…Brown, T. R. (2008). Brain morphology in older African Americans, Caribbean Hispanics, and whites from northern Manhattan. *Archives of Neurology*, *65*(8), 1053-1061.

Brown, C., Schulberg, H. C., & Madonia, M. J. (1996). Clinical presentations of major depression by African Americans and whites in primary medical care practice. *Journal of Affective Disorders*, *41*(3), 181–191.

Budoff, M. J., Nasir, K., Mao, S., Tseng, P. H., Chau, A., Liu, S. T., et al. (2006). Ethnic differences of the presence and severity of coronary atherosclerosis. *Atherosclerosis*, *187*(2), 343–350. doi:10.1016/j.atherosclerosis.2005.09.013

Burkhauser, R. V., & Cawley, J. (2008). Beyond BMI: The value of more accurate measures of fatness and obesity in social science research. *Journal of Health Economics*, *27*(2), 519–529. doi:10.1016/j.jhealeco.2007.05.005

Bus, R. M., Marijnissen, S., Holewijn, B., Franke, N., Purandare, J., de Graaf, M.,… Oude Voshaar, R. (2011). Depressive symptom clusters are differentially associated with atherosclerotic disease. *Psychological Medicine*, *41*(7), 1419-1428. doi:10.1017/S0033291710002151

Cambron, M. J., Acitelli, L. K., & Pettit, J. W. (2009). Explaining Gender Differences in Depression: an Interpersonal Contingent Self-Esteem Perspective. *Sex Roles*, *61*(11-12), 751–761. doi:10.1007/s11199-009-9616-6

Carrington, C. H. (2006). Clinical depression in African American women: Diagnoses, treatment, and research. *Journal of Clinical Psychology*, *62*(7), 779–791. doi:10.1002/jclp.20289

Carroll, B. J., Curtis, G. C., Davies, B. M., Mendels, J., & Sugerman, A. A. (1976). Urinary free cortisol excretion in depression. *Psychological Medicine*, *6*(1), 43–50.

Colloby, S. J., Firbank, M. J., Thomas, A. J., Vasudev, A., Parry, S. W., & O'Brien, J. T. (2011). White matter changes in late-life depression: A diffusion tensor imaging study. *Journal of Affective Disorders*, 135(1-3), 216-20. doi:10.1016/j.jad.2011.07.025

Coman, E. N., Iordache, E., Schensul, J. J., & Coiculescu, I. (2012). Comparisons of CES-D depression scoring methods in two older adults ethnic groups. The emergence of an ethnic-specific brief three-item CES-D scale. *International Journal of Geriatric Psychiatry*, *28*(4), 424–432. doi:10.1002/gps.3842

Cooper, L. A., Gonzales, J. J., Gallo, J. J., Rost, K. M., Meredith, L. S., Rubenstein, L. V.,…Ford, D. E. (2003). The acceptability of treatment for depression among African-American, Hispanic, and white primary care patients. *Medical Care*, *41*(4), 479–489.

Crowley, M. S. (1998). Men's Self-Perceived Adequacy as the Family Breadwinner: Implications for Their Psychological, Marital, and Work-Family Well-Being. *Journal of Family and Economic Issues*, *19*(1), 7–23.

Das, A. K., Olfson, M., McCurtis, H. L., & Weissman, M. M. (2006). Depression in African Americans: Breaking barriers to detection and treatment. *Journal of Family Practice*, *55*(1), 30-39.

Davila-Roman, V. G., Barzilai, B., Wareing, T. H., Murphy, S. F., Schechtman, K. B., & Kouchoukos, N. T. (1994). Atherosclerosis of the ascending aorta. Prevalence and role as an independent predictor of cerebrovascular events in cardiac patients. *Stroke*, *25*(10), 2010–2016. doi:10.1161/01.STR.25.10.2010

de Groot, J. C., de Leeuw, F. E., Oudkerk, M., Hofman, A., Jolles, J., & Breteler, M. M. B. (2000). Cerebral white matter lesions and depressive symptoms in elderly adults. *Archives of General Psychiatry*, *57*(11), 1071–1076.

Devantier, T. A., Nørgaard, B. L., Sand, N. P., Mols, R. E., Foldager, L., Diederichsen, A. C. P., et al. (2013). Lack of correlation between depression and coronary artery calcification in a non-selected Danish population. *Psychosomatics*, 1–8. doi:10.1016/j.psym.2013.01.005

Devlin, J. T., & Watkins, K. E. (2007). Stimulating language: insights from TMS. *Brain*, *130*(3), 610–622. doi:10.1093/brain/awl331

Doraiswamy, P. M., Bernstein, I. H., Rush, A. J., Kyutoku, Y., Carmody, T. J., Macleod, L., et al. (2010). Diagnostic utility of the Quick Inventory of Depressive Symptomatology (QIDS-C16 and QIDS-SR16) in the elderly. *Acta Psychiatrica Scandinavica*, *122*(3), 226–234. doi:10.1111/j.1600-0447.2009.01531.x

Ennis, N. E., Hobfoll, S. E., & Schröder, K. E. (2000). Money doesn't talk, it swears: How economic stress and resistance resources impact inner-city women's depressive mood. *American Journal of Community Psychology*, *28*(2), 149–173.

Faramawi, M. F., Gustat, J., Wildman, R. P., Rice, J., Johnson, E., & Sherwin, R. (2007). Relation between depressive symptoms and common carotid artery atherosclerosis in American persons ≥65 years of age. *The American Journal of Cardiology*, *99*(11), 1610–1613. doi:10.1016/j.amjcard.2006.12.090

Ferdinand, K. C. (2006). Coronary artery disease in minority racial and ethnic groups in the United States. *The American Journal of Cardiology*, *97*(2), 12–19. doi:10.1016/j.amjcard.2005.11.011

Figiel, G. S., Krishnan, K., Murali Doraiswamy, P., Rao, V. P., Nemeroff, C. B., & Boyko, O. B. (1991). Subcortical hyperintensities on brain magnetic resonance imaging: a comparison between late age onset and early onset elderly depressed subjects. *Neurobiology of Aging*, *12*(3), 245–247.

Firbank, M. J., Lloyd, A. J., Ferrier, N., & O'Brien, J. T. (2004). A volumetric study of MRI signal hyperintensities in late-life depression. *American Journal of Geriatric Psychiatry*, *12*(6), 606–612.

Firbank, M. J., O'Brien, J. T., Pakrasi, S., Pantoni, L., Simoni, M., Erkinjuntti, T.,…Inzitari, D. (2005). White matter hyperintensities and depression—preliminary results from the LADIS study. *International Journal of Geriatric*

Psychiatry, *20*(7), 674–679. doi:10.1002/gps.1342

Flegal, K. M., Carroll, M. D., Ogden, C. L., & Curtin, L. R. (2010). Prevalence and trends in obesity among U.S. adults, 1999-2008. *JAMA: The Journal of the American Medical Association*, *303*(3), 235–241.

Folsom, A. R. (2008). Coronary artery calcification compared with carotid intima-media thickness in the prediction of cardiovascular disease incidence: The Multi-Ethnic Study of Atherosclerosis (MESA). *Archives of Internal Medicine*, *168*(12), 1333. doi:10.1001/archinte.168.12.1333

Ford, E. S., Giles, W. H., & Dietz, W. H. (2002). Prevalence of the metabolic syndrome among US adults. *JAMA: The Journal of the American Medical Association*, *287*(3), 356–359.

Ford, D. E., & Erlinger, T. P. (2004). Depression and c-reactive protein in US adults: Data from the Third National Health and Nutrition Examination Survey. *Archives of Internal Medicine*, *164*(9), 1010-1014.

Gargiulo, R. A., & Stokes, M. A. (2008). Subjective well-being as an indicator for clinical depression. *Social Indicators Research*, *92*(3), 517–527. doi:10.1007/s11205-008-9301-0

Gaupp, R., Pomarol-Clotet, E., & Berrios, G. E. (2000). Depressive states in old age (Die Depressionszustände des höheren Lebensalters'. Münchener medizinische Wochenschrift, 8 August 1905, 1531-7). *History of Psychiatry*, *11*(42), 216–225. doi:10.1177/0957154X0001104205

Gavin, A. R., Rue, T., & Takeuchi, D. (2010a). Racial/ethnic differences in the association between obesity and major depressive disorder: Findings from the Comprehensive Psychiatric Epidemiology Surveys. *Public Health Reports*, *125*(5), 698-708.

Gavin, A. R., Walton, E., Chae, D. H., Alegría, M., Jackson, J. S., & Takeuchi, D. (2010b). The associations between socio-economic status and major depressive disorder among Blacks, Latinos, Asians and Whites: findings from the Collaborative Psychiatric Epidemiology Studies. *Psychological Medicine*, *40*(01), 51–61. doi:10.1017/S0033291709006023

Gebara, O. C., & Santos, R. D. (2010). Persistency of depression is associated with subclinical coronary atherosclerosis in males: Commentary on the study of Hamer et al. *Atherosclerosis*, *210*(1), 41–42. doi:10.1016/j.atherosclerosis.2010.01.039

Glaesmer, H., Riedel-Heller, S., Braehler, E., Spangenberg, L., & Luppa, M. (2011). Age-and gender-specific prevalence and risk factors for depressive symptoms in the elderly: a population-based study. *International Psychogeriatrics*, *23*(8), 1294-1300. doi:10.1017/S1041610211000780

Go, A. S., Mozaffarian, D., Roger, V. L., Benjamin, E. J., Berry, J. D., Borden, W. B., et al. (2013). Heart disease and stroke statistics 2013 Update: A report from the American Heart Association. *Circulation*, *127*(1), e6–e245.

Golding, J. M., Karno, M., & Rutter, C. M. (1990). Symptoms of major

depression among Mexican-Americans and Whites. *The American Journal of Psychiatry*.

González, H. M., Croghan, T. W., West, B. T., Tarraf, W., Williams, D. R., Nesse, R.,…Jackson, J. (2008). Antidepressant Use among Blacks and Whites in the United States. *Psychiatric services (Washington, DC)*, *59*(10), 1131-1138.

González, H. M., Tarraf, W., Whitfield, K. E., & Vega, W. A. (2010). The epidemiology of major depression and ethnicity in the United States. *Journal of Psychiatric Research*, *44*(15), 1043–1051. doi:10.1016/j.jpsychires.2010.03.017

González, H. M., Tarraf, W., Whitfield, K., & Gallo, J. J. (2012). Vascular depression prevalence and epidemiology in the United States. *Journal of Psychiatric Research*, *46*(4), 456–461. doi:10.1016/j.jpsychires.2012.01.011

Gorelick, P. B. (1998). Cerebrovascular Disease in African Americans. *Stroke*, *29*(12), 2656–2664. doi:10.1161/01.STR.29.12.2656

Grabe, S., & Jackson, B. (2009). Self-objectification and depressive symptoms: Does their association vary among Asian American and White American men and women? *Body Image*, *6*(2), 141–144. doi:10.1016/j.bodyim.2009.02.001

Greenberg, P. E., Kessler, R. C., Birnbaum, H. G., Leong, S. A., Lowe, S. W., Berglund, P. A., & Corey-Lisle, P. K. (2003). The economic burden of depression in the United States: How did it change between 1990 and 2000?

The Journal of clinical psychiatry, *64*(12), 1465–1475.

Grundy, S. M. (2004). Definition of Metabolic Syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association Conference on Scientific Issues Related to Definition. *Circulation*, *109*(3), 433–438. doi:10.1161/01.CIR.0000111245.75752.C6

Haas, D. C., Davidson, K. W., Schwartz, D. J., Rieckmann, N., Roman, M. J., Pickering, T. G.,…Schwartz, J. E. (2005). Depressive symptoms are independently predictive of carotid atherosclerosis. *The American Journal of Cardiology*, *95*(4), 547–550. doi:10.1016/j.amjcard.2004.10.032

Hajat, A., Diez-Roux, A. V., Sánchez, B. N., Holvoet, P., Lima, J. A., Merkin, S. S., Wu, M. (2012). Examining the association between salivary cortisol levels and subclinical measures of atherosclerosis: The Multi-Ethnic Study of Atherosclerosis. *Psychoneuroendocrinology*. doi:10.1016/j.psyneuen.2012.10.007

Hajjar, I., Quach, L., Yang, F., Chaves, P. H. M., Newman, A. B., Mukamal, K.,…Lipsitz, L.A. (2011). Hypertension, white matter hyperintensities, and concurrent impairments in mobility, cognition, and mood: The Cardiovascular Health Study. *Circulation*, *123*(8), 858–865. doi:10.1161/ 110.978114

Hamani, C., Mayberg, H., Stone, S., Laxton, A., Haber, S., & Lozano, A. M. (2011). The subcallosal cingulate gyrus in the context of major depression. *Biological Psychiatry; Biological Psychiatry*, *69*(4), 301–308.

doi:10.1016/j.biopsych.2010.09.034

Hamer, M., Malan, N. T., Harvey, B. H., & Malan, L. (2011). Depressive symptoms and sub-clinical atherosclerosis in Africans: Role of metabolic syndrome, inflammation and sympathoadrenal function. *Physiology & Behavior*, *104*(5), 744–748. doi:10.1016/j.physbeh.2011.07.024

Heiden, A., Kettenbach, J., Fischer, P., Schein, B., Ba-Ssalamah, A., Frey, R.,…Kasper, S. (2005). White matter hyperintensities and chronicity of depression. *Journal of Psychiatric Research*, *39*(3), 285–293. doi:10.1016/j.jpsychires.2004.07.004

Heller, K., Viken, R. J., & Swindle, R. W., Jr. (2010). Screening for depression in African American and Caucasian older women. *Aging & mental health*, *14*(3), 339–346. doi:10.1080/13607860903228820

Henderson, J. G., & Pollard, C. A. (1992). Prevalence of various depressive symptoms in a sample of the general population. *Psychological Reports*, *71*(1), 208–210.

Herrmann, L. L., Le Masurier, M., & Ebmeier, K. P. (2007). White matter hyperintensities in late life depression: A systematic review. *Journal of Neurology, Neurosurgery & Psychiatry*, *79*(6), 619–624. doi:10.1136/jnnp.2007.124651

Hicken, M. T., Lee, H., Mezuk, B., Kershaw, K. N., Rafferty, J., & Jackson, J. S. (2013). Racial and ethnic differences in the association between obesity and

depression in women. *Journal of Women's Health*, *22*(5), 445–452.

Hollander, W. (1976). Role of hypertension in atherosclerosis and cardiovascular disease. *The American Journal of Cardiology*, *38*(6), 786–800.

Hopkins, R. O., Beck, C. J., Burnett, D. L., Weaver, L. K., Victoroff, J., & Bigler, E. D. (2006). Prevalence of white matter hyperintensities in a young healthy population. *Journal of Neuroimaging*, *16*(3), 243–251. doi:10.1111/j.1552-6569.2006.00047.x

Hoyert, D. L., Kung, H.-C., & Smith, B. L. (2005). Deaths: preliminary data for 2003. *National Vital Statistics Reports*, *53*(15), 1–48.

Hudson, D. L., Neighbors, H. W., Geronimus, A. T., & Jackson, J. S. (2011). The relationship between socioeconomic position and depression among a US nationally representative sample of African Americans. *Social Psychiatry and Psychiatric Epidemiology*, *47*(3), 373–381. doi:10.1007/s00127-011-0348-x

Hulsey, K. M., Gupta, M., King, K. S., Peshock, R. M., Whittemore, A. R., & McColl, R. W. (2012). Automated quantification of white matter disease extent at 3 T: Comparison with volumetric readings. *Journal of Magnetic Resonance Imaging*, *36*(2), 305–311. doi:10.1002/jmri.23659

Insull, W., Jr. (2009). The pathology of atherosclerosis: plaque development and plaque responses to medical treatment. *The American Journal of Medicine*, *122*(1), S3–S14. doi:10.1016/j.amjmed.2008.10.013

Iosifescu, D. V., Renshaw, P. F., Lyoo, I. K., Lee, H. K., Perlis, R. H.,

Papakostas, G. I., et al. (2006). Brain white-matter hyperintensities and treatment outcome in major depressive disorder. *The British Journal of Psychiatry*, *188*(2), 180–185. doi:10.1192/bjp.188.2.180

Jain, T., Peshock, R., McGuire, D. K., Willett, D., Yu, Z., Vega, G. L., et al. (2004). African Americans and Caucasians have a similar prevalence of coronary calcium in the Dallas Heart Study. *Journal of the American College of Cardiology*, *44*(5), 1011–1017. doi:10.1016/j.jacc.2004.05.069

Jenkinson, M., & Smith, S. (2001). A global optimisation method for robust affine registration of brain images. *Medical Image Analysis*, *5*(2), 143–156.

Jones, D. J., Bromberger, J. T., Sutton-Tyrrell, K., & Matthews, K. A. (2003). Lifetime history of depression and carotid atherosclerosis in middle-aged women. *Archives of General Psychiatry*, *60*(2), 153-160-.

Jorm, A. F., Anstey, K. J., Christensen, H., de Plater, G., Kumar, R., Wen, W., & Sachdev, P. (2005). MRI hyperintensities and depressive symptoms in a community sample of individuals 60–64 years old. *American Journal of Psychiatry*, *162*(4), 699–705.

Kasen, S., Cohen, P., Chen, H., & Castille, D. (2003). Depression in adult women: age changes and cohort effects. *American Journal of Public Health*, *93*(12), 2061-2066.

Kessler, R. C., Chiu, W. T., Demler, O., & Walters, E. E. (2005). Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National

Comorbidity Survey Replication. *Archives of General Psychiatry*, *62*(6), 617-627.

Kessler, R. C., Nelson, C. B., McGonagle, K. A., Liu, J., Swartz, M., & Blazer, D. G. (1996). Comorbidity of DSM-III-R major depressive disorder in the general population: Results from the US National Comorbidity Survey. *The British journal of psychiatry. Supplement*, (30), 17–30.

Kinder, L. S. (2004). Depression and the metabolic syndrome in young adults: Findings from the Third National Health and Nutrition Examination Survey. *Psychosomatic Medicine*, *66*(3), 316–322. doi:10.1097/01.psy.0000124755.91880.f4

King, K. S., Peshock, R. M., Warren, M. W., Alhilali, L., Hulsey, K., McColl, R.,…Whittemore, A. (2012). Evaluation of a practical visual MRI rating scale of brain white matter hyperintensities for clinicians based on largest lesion size regardless of location. *American Journal of Neuroradiology*. doi:10.3174/ajnr.A3283

Krishnan, K. (2000). Depression as a contributing factor in cerebrovascular disease. *American Heart Journal*, *140*(4), 70–76. doi:10.1067/mhj.2000.109980

Krishnan, K. R., Hays, J. C., & Blazer, D. G. (1997). MRI-defined vascular depression. *American Journal of Psychiatry*, *154*(4), 497–501.

Krishnan, K., Goli, V., Ellinwood, E. H., France, R. D., Blazer, D. G., &

Nemeroff, C. B. (1988). Leukoencephalopathy in patients diagnosed as major depressive. *Biological Psychiatry*, *23*(5), 519–522.

Krishnan, K., & McDonald, W. M. (1995). Arteriosclerotic depression. *Medical Hypotheses*, *44*(2), 111–115.

Kumanyika, S., Wilson, J. F., & Guilford-Davenport, M. (1993). Weight-related attitudes and behaviors of black women. *Journal of the American Dietetic Association*, *93*(4), 416–422.

Kurian, A. K., & Cardarelli, K. M. (2007). Racial and ethnic differences in cardiovascular disease risk factors: a systematic review. *Ethnicity & Disease*, *17*(1), 143-152.

Laghrissi-Thode, F., Wagner, W. R., Pollock, B. G., Johnson, P.C., & Finkel, M. S. (1997). Elevated platelet factor 4 and β-thromboglobulin plasma levels in depressed patients with ischemic heart disease. *Biological Psychiatry*, *42*(4), 290–295.

Lee, S. J., Kim, J. S., Chung, S. W., Kim, B. S., Ahn, K. J., & Lee, K. S. (2011). White matter hyperintensities (WMH) are associated with intracranial atherosclerosis rather than extracranial atherosclerosis. *Archives of Gerontology and Geriatrics*, *53*(2), e129–e132. doi:10.1016/j.archger.2010.07.008

Liao, Y., & Cooper, R. S. (1995). Continued adverse trends in coronary heart disease mortality among blacks, 1980-91. *Public Health Reports*, *110*(5),

572–579.

Magnus, J. H., Shankar, A., & Broussard, D. L. (2010). Self-report of depressive symptoms in African American and white women in primary care. *Journal of the National Medical Association*, *102*(5), 389–395.

Manolio, T. A., Arnold, A. M., Post, W., Bertoni, A. G., Schreiner, P. J., Sacco, R. L.,…Szklo, M. (2008). Ethnic differences in the relationship of carotid atherosclerosis to coronary calcification: The Multi-Ethnic Study of Atherosclerosis. *Atherosclerosis*, *197*(1), 132–138. doi:10.1016/j.atherosclerosis.2007.02.030

Mathers, C. D., & Loncar, D. (2006). Projections of global mortality and burden of disease from 2002 to 2030. *PLoS medicine*, *3*(11), 2011–2030.

Mayberg, H. (1997). Limbic-cortical dysregulation: A proposed model of depression. *The Journal of Neuropsychiatry and Clinical Neurosciences,* 9, 471-481.

Mayberg, H. S., Liotti, M., Brannan, S. K., McGinnis, S., Mahurin, R. K., Jerabek, P. A.,…Fox, P.T. (1999). Reciprocal limbic-cortical function and negative mood: Converging PET findings in depression and normal sadness. *American Journal of Psychiatry*, *156*(5), 675–682.

McBean, A. M., Li, S., Gilbertson, D. T., & Collins, A. J. (2004). Differences in diabetes prevalence, incidence, and mortality among the elderly of four racial/ethnic groups: whites, blacks, Hispanics, and Asians. *Diabetes Care*,

27(10), 2317–2324.

McGuire, L. C., Strine, T. W., Vachirasudlekha, S., Mokdad, A. H., & Anderson, L. A. (2008). The Prevalence of depression in older U.S. women: 2006 behavioral risk factor surveillance system. *Journal of Women's Health*, *17*(4), 501–507. doi:10.1089/jwh.2008.0815

McKnight-Eily, L. R., Presley-Cantrell, L., Elam-Evans, L. D., Chapman, D. P., Kaslow, N. J., & Perry, G. S. (2009). Prevalence and correlates of current depressive symptomatology and lifetime diagnosis of depression in Black women. *Women's Health Issues*, *19*(4), 243–252. doi:10.1016/j.whi.2009.04.003

Meadows, T. A., Bhatt, D. L., Cannon, C. P., Gersh, B. J., Röther, J., Goto, S.,…Steg, P.G. (2011). Ethnic differences in cardiovascular risks and mortality in atherothrombotic disease: insights from the Reduction of Atherothrombosis for Continued Health (REACH) registry, *86*(10), 960–967. doi:10.4065/mcp.2011.0010

Miller, D. K., Malmstrom, T. K., Joshi, S., Andresen, E. M., Morley, J. E., & Wolinsky, F. D. (2004). Clinically relevant levels of depressive symptoms in community-dwelling middle-aged African Americans. *Journal of the American Geriatrics Society*, *52*(5), 741–748.

Modir, R., Gardener, H., & Wright, C. B. (2012). Blood pressure and white matter hyperintensity volume - a review of the relationship and implications for

stroke prediction and prevention. *European Neurological Review*, *7*(3), 174–177. Retrieved from http://www.scopus.com/inward/record.url?eid=2-s2.0-84867040463&partnerID=40&md5=729cd141ac06448694cc0317382f5b51

Moody, D. M., Brown, W. R., Challa, V. R., & Anderson, R. L. (1995). Periventricular venous collagenosis: Association with leukoaraiosis. *Radiology*, *194*(2), 469–476.

Murray, A. D., Staff, R. T., & McNeil, C. J. (2012). Depressive symptoms in late life and cerebrovascular disease: The importance of intelligence and lesion location. *Depression and Anxiety*, *30*(1), 77–84. doi:10.1002/da.22022

Murrough, J. W., Iacoviello, B., Neumeister, A., Charney, D. S., & Iosifescu, D. V. (2011). Cognitive dysfunction in depression: Neurocircuitry and new therapeutic strategies. *Neurobiology of Learning and Memory*, 1–11. doi:10.1016/j.nlm.2011.06.006.

Myers, H. F., Lesser, I., Rodriguez, N., Mira, C. B., Hwang, W.-C., Camp, C., et al. (2002). Ethnic differences in clinical presentation of depression in adult women. *Cultural Diversity & Ethnic Minority Psychology*, *8*(2), 138–156. doi:10.1037//1099-9809.8.2.138

Naismith, S. L., Norrie, L. M., Mowszowski, L., & Hickie, I. B. (2012). The neurobiology of depression in later-life: Clinical, neuropsychological, neuroimaging and pathophysiological features. *Progress in Neurobiology*, *98*(1), 99–143. doi:10.1016/j.pneurobio.2012.05.009

Nazroo, J. Y., Edwards, A. C., & Brown, G. W. (1998). Gender differences in the prevalence of depression: Artefact, alternative disorders, biology or roles? *Sociology of Health & Illness*, *20*(3), 312–330.

Nestler, E. J., Barrot, M., DiLeone, R. J., Eisch, A. J., Gold, S. J., & Monteggia, L. M. (2002). Neurobiology of depression. *Neuron*, *34*(1), 13–25.

O'Brien, J. T., Firbank, M. J., Krishnan, M. S., van Straaten, E. C. W., van der Flier, W. M., Petrovic, K.,…Inzitari, D. (2006). White matter hyperintensities rather than lacunar infarcts are associated with depressive symptoms in older people: The LADIS study. *American Journal of Geriatric Psychiatry*, *14*(10), 834–841.

Ohira, T. (2006). Risk factors for ischemic stroke subtypes: The Atherosclerosis Risk in Communities Study. *Stroke*, *37*(10), 2493–2498. doi:10.1161/01.STR.0000239694.19359.88

Orakzai, S. H., Orakzai, R. H., Nasir, K., Santos, R. D., Edmundowicz, D., Budoff, M. J., & Blumenthal, R. S. (2006). Subclinical coronary atherosclerosis: Racial profiling is necessary! *American Heart Journal*, *152*(5), 819–827. doi:10.1016/j.ahj.2006.08.008

Pickett, Y. R., Weissman, J., & Bruce, M. L. (2012). Racial Differences in Antidepressant Use Among Older Home Health Care Patients. *Psychiatric Services*, *63*(8), 827–829.

Pico, F., Dufouil, C., Levy, C., Besancon, V., de Kersaint-Gilly, A., Bonithon-

Kopp, C.,…Alperovitch, A. (2002). Longitudinal study of carotid atherosclerosis and white matter hyperintensities: the EVA-MRI cohort. *Cerebrovascular Diseases*, *14*(2), 109–115.

Piers, L., Salachova, F., Slart, R., Vliegenthart, R., Dikkers, R., Hospers, F.,…Tio, R.A. (2008). The role of coronary artery calcification score in clinical practice. *BMC Cardiovascular Disorders*, *8*(1), 38. doi:10.1186/1471-2261-8-38

Pieterse, A. L., Todd, N. R., Neville, H. A., & Carter, R. T. (2012). Perceived racism and mental health among Black American adults: A meta-analytic review. *Journal of Counseling Psychology*, *59*(1), 1–9. doi:10.1037/a0026208

Pietrzak, R. H., Kinley, J., Afifi, T. O., Enns, M. W., Fawcett, J., & Sareen, J. (2012). Subsyndromal depression in the United States: prevalence, course, and risk for incident psychiatric outcomes. *Psychological Medicine*, *43*(07), 1401–1414. doi:10.1017/S0033291712002309

Pizzi, C., Manzoli, L., Mancini, S., Bedetti, G., Fontana, F., & Costa, G. M. (2010). Autonomic nervous system, inflammation and preclinical carotid atherosclerosis in depressed subjects with coronary risk factors. *Atherosclerosis*, *212*(1), 292–298. doi:10.1016/j.atherosclerosis.2010.04.038

Pompili, M., Ehrlich, S., Pisa, E., Mann, J. J., Innamorati, M., Cittadini, A.,…Giardi, P. (2007). White matter hyperintensities and their associations with suicidality in patients with major affective disorders. *European Archives*

of Psychiatry and Clinical Neuroscience, *257*(8), 494–499. doi:10.1007/s00406-007-0755-x

Pompili, M., Innamorati, M., Mann, J. J., Oquendo, M. A., Lester, D., Del Casale, A., et al. (2008). Periventricular white matter hyperintensities as predictors of suicide attempts in bipolar disorders and unipolar depression. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *32*(6), 1501–1507. doi:10.1016/j.pnpbp.2008.05.009

Rabkin, J. G., Charles, E., & Kass, F. (1983). Hypertension and DSM-III depression in psychiatric outpatients. *American Journal of Psychiatry*, *140*(8), 1072–1074.

Ramasubbu, R. (2000). Relationship between depression and cerebrovascular disease: conceptual issues. *Journal of Affective Disorders*, *57*(1), 1–12.

Rao, R. (2000). Cerebrovascular disease and late life depression: an age old association revisited. *International Journal of Geriatric Psychiatry*, *15*(5), 419–433.

Regenold, W. T., Phatak, P., Marano, C. M., Gearhart, L., Viens, C. H., & Hisley, K. C. (2007). Myelin staining of deep white matter in the dorsolateral prefrontal cortex in schizophrenia, bipolar disorder, and unipolar major depression. *Psychiatry Research*, *151*(3), 179–188. doi:10.1016/j.psychres.2006.12.019

Riolo, S. A., Nguyen, T. A., Greden, J. F., & King, C. A. (2005). Prevalence of depression by race/ethnicity: findings from the National Health and Nutrition Examination Survey III. *American Journal of Public Health*, *95*(6), 998.

Robinson, J. G., Fox, K. M., Bullano, M. F., Grandy, S. (2009). Atherosclerosis profile and incidence of cardiovascular events: a population-based survey. *BMC Cardiovascular Disorders*, *9*(1), 46. doi:10.1186/1471-2261-9-46

Robinson, R. G., & Price, T. R. (1982). Post-stroke depressive disorders: a follow-up study of 103 patients. *Stroke*, *13*(5), 635–641. doi:10.1161/01.STR.13.5.635

Robinson, R. G., Kubos, K. L., Starr, L. B., Rao, K., & Price, T. R. (1983a). Mood changes in stroke patients: relationship to lesion location. *Comprehensive Psychiatry*, *24*(6), 555–566.

Robinson, R. G., Starr, L. B., Kubos, K. L., & Price, T. R. (1983b). A two-year longitudinal study of post-stroke mood disorders: findings during the initial evaluation. *Stroke*, *14*(5), 736–741. doi:10.1161/01.STR.14.5.736

Ross, C. E., & Mirowsky, J. (2006). Sex differences in the effect of education on depression: Resource multiplication or resource substitution? *Social Science & Medicine*, *63*(5), 1400–1413. doi:10.1016/j.socscimed.2006.03.013

Ruland, S., Raman, R., Chaturvedi, S., Leurgans, S., & Gorelick, P. B. (2003). Awareness, treatment, and control of vascular risk factors in African Americans with stroke. *Neurology*, *60*(1), 64–68.

doi:10.1001/archinte.153.2.154

Rush, A. J., Trivedi, M. H., Ibrahim, H. M., Carmody, T. J., Arnow, B., Klein, D. N.,…Keller, M.B. (2003). The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): A psychometric evaluation in patients with chronic major depression. *Biological Psychiatry*, 54(5), 573-583. doi:10.1016/S0006-3223(03)01866-8

Sacco, R. L., Kargman, D. E., Gu, Q., & Zamanillo, M. C. (1995). Race-Ethnicity and Determinants of Intracranial Atherosclerotic Cerebral Infarction: The Northern Manhattan Stroke Study. *Stroke*, *26*(1), 14–20.

Sachdev, P. S., Parslow, R., Wen, W., Anstey, K. J., & Easteal, S. (2009). Sex differences in the causes and consequences of white matter hyperintensities. *Neurobiology of Aging*, *30*(6), 946–956. doi:10.1016/j.neurobiolaging.2007.08.023

Santos, M., Xekardaki, A., Kövari, E., Gold, G., Bouras, C., & Giannakopoulos, P. (2012). Microvascular pathology in late-life depression. *Journal of the Neurological Sciences*, *322*(1-2), 46–49. doi:10.1016/j.jns.2012.05.048

Sapolsky, R. M. (2000). The possibility of neurotoxicity in the hippocampus in major depression: A primer on neuron death. *Biological Psychiatry*, *48*(8), 755–765.

Scarinci, I. C., Beech, B. M., Naumann, W., Kovach, K. W., Pugh, L., & Fapohunda, B. (2002). Depression, socioeconomics status, age, and marital

status in black women: A national study. *Ethnicity & Disease*, *12*(3), 421–428.

Schwartz, J. A., Speed, N. M., Brunberg, J. A., Brewer, T. L., Brown, M., & Greden, J. F. (1993). Depression in stroke rehabilitation. *Biological Psychiatry*, *33*(10), 694–699.

Scott, M. M., Dubowitz, T., & Cohen, D. A. (2009). Regional differences in walking frequency and BMI: what role does the built environment play for Blacks and Whites? *Health & Place*, *15*(3), 897–902. doi:10.1016/j.healthplace.2009.02.010

Scott, T., Matsuyama, R., & Mezuk, B. (2011). The relationship between treatment settings and diagnostic attributions of depression among African Americans. *General Hospital Psychiatry*, *33*(1), 66–74. doi:10.1016/j.genhosppsych.2010.12.002

Seldenrijk, A., van Hout, H. P., van Marwijk, H. W., de Groot, E., Gort, J., Rustemeijer, C.,…Pennix, B.W. (2011). Carotid atherosclerosis in depression and anxiety: associations for age of depression onset. *The World Journal of Biological Psychiatry*, *12*(7), 549–558. doi:10.3109/15622975.2011.583942

Seldenrijk, A., Vogelzangs, N., van Hout, H. P., van Marwijk, H. W., Diamant, M., & Penninx, B. W. (2010). Depressive and anxiety disorders and risk of subclinical atherosclerosis. *Journal of Psychosomatic Research*, *69*(2), 203–210. doi:10.1016/j.jpsychores.2010.01.005

Selvin, E., Coresh, J., & Brancati, F. L. (2006). The burden and treatment of diabetes in elderly individuals in the US. *Diabetes Care*, *29*(11), 2415–2419. doi:10.2337/dc06-1058

Shaya, F. T., Gu, A., & Saunders, E. (2007). Metabolic syndrome prevalence in an urban African American population. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*, *1*(3), 151–157. doi:10.1016/j.dsx.2007.05.003

Simpson, S., Baldwin, R. C., Jackson, A., & Burns, A. S. (1998). Is subcortical disease associated with a poor response to antidepressants? Neurological, neuropsychological and neuroradiological findings in late-life depression. *Psychological Medicine*, *28*(5), 1015–1026.

Smith, P. J., Blumenthal, J. A., Babyak, M. A., Doraiswamy, P. M., Hinderliter, A., Hoffman, B. M., …Sherwood, A. (2009). Intima-media thickness and age of first depressive episode. *Biological Psychology*, *80*(3), 361–364.

Smith, S. M. (2002). Fast robust automated brain extraction. *Human Brain Mapping*, *17*(3), 143–155. doi:10.1002/hbm.10062

Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E. J., Johansen-Berg, H.,…Matthews, P.M. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage*, *23*, S208–S219. doi:10.1016/j.neuroimage.2004.07.051

Sneed, J. R., Culang-Reinlieb, M. E., Brickman, A. M., Gunning-Dixon, F. M., Johnert, L., Garcon, E., & Roose, S. P. (2011). MRI signal hyperintensities

and failure to remit following antidepressant treatment. *Journal of Affective Disorders*, *135*(1-3), 315–320. doi:10.1016/j.jad.2011.06.052

Spitzer, C., Völzke, H., Barnow, S., Krohn, U., Wallaschofski, H., Lüdemann, J.,…Grabe, H. J. (2008). Association between depression and subclinical carotid atherosclerosis in patients with Type 1 diabetes. *Diabetic Medicine*, *25*(3), 349–354. doi:10.1111/j.1464-5491.2007.02369.x

Stary, H. C., Chandler, A. B., Glagov, S., Guyton, J. R., Insull, W., Rosenfeld, M. E.,…Wissler, R. W. (1994). A definition of initial, fatty streak, and intermediate lesions of atherosclerosis. A report from the Committee on Vascular Lesion of the Council on Arteriosclerosis, American Heart Association. *Circulation*, *89*(5), 2462–2478. doi:10.1161/01.CIR.89.5.2462

Stavitsky, K., Du, Y., Seichepine, D., Laudate, T. M., Beiser, A., Seshadri, S.,…Au, R. (2010). White Matter Hyperintensity and Cognitive Functioning in the Racial and Ethnic Minority Cohort of the Framingham Heart Study. *Neuroepidemiology*, *35*(2), 117–122. doi:10.1159/000313443

Steffens, D. C., Helms, M. J., Krishnan, K. R. R., & Burke, G. L. (1999). Cerebrovascular disease and depression symptoms in the cardiovascular health study. *Stroke*, *30*(10), 2159–2166. doi:10.1161/01.STR.30.10.2159

Stewart, J. C., Janicki, D. L., Muldoon, M. F., Sutton-Tyrrell, K., & Kamarck, T. W. (2007). Negative emotions and 3-year progression of subclinical atherosclerosis. *Archives of General Psychiatry*, *64*(2), 225-233.

Takahashi, T., Murata, T., Narita, K., Hamada, T., Kosaka, H., Omori, M.,…Wada, Y. (2006). Multifractal analysis of deep white matter microstructural changes on MRI in relation to early-stage atherosclerosis. *Neuroimage*, *32*(3), 1158–1166. doi:10.1016/j.neuroimage.2006.04.218

Taylor, W. D., Payne, M. E., Krishnan, K., Wagner, H. R., Provenzale, J. M., Steffens, D. C., & MacFall, J. R. (2001). Evidence of white matter tract disruption in MRI hyperintensities. *Biological Psychiatry*, *50*(3), 179–183.

Taylor, W. D., Aizenstein, H. J., & Alexopoulos, G. S. (2013). The vascular depression hypothesis: mechanisms linking vascular disease with depression. *Molecular Psychiatry*, 1–12. doi:10.1038/mp.2013.20

Tham, M. W., Woon, P. S., Sum, M. Y., Lee, T.-S., & Sim, K. (2011). White matter abnormalities in major depression: Evidence from post-mortem, neuroimaging and genetic studies. *Journal of Affective Disorders*, *132*(1-2), 26–36. doi:10.1016/j.jad.2010.09.013

Thomas, A. J., O'Brien, J. T., Davis, S., Ballard, C., Barber, R., Kalaria, R. N., & Perry, R. H. (2002a). Ischemic basis for deep white matter hyperintensities in major depression: A neuropathological study. *Archives of General Psychiatry*, *59*(9), 785-792.

Thomas, A. J., Perry, R., Kalaria, R. N., Oakley, A., McMeekin, W., & O'Brien, J. T. (2002b). Neuropathological evidence for ischemia in the white matter of the dorsolateral prefrontal cortex in late-life depression. *International Journal*

of Geriatric Psychiatry, *18*(1), 7–13. doi:10.1002/gps.720

Torres Stone, R., Rivera, F. I., & Berdahl, T. (2004). Predictors of depression among Whites, Mexicans and Puerto Ricans: A look at race/ethnicity as a reflection of social relations. *Race and Society*, *7*(2), 79–94. doi:10.1016/j.racsoc.2005.05.003

Trivedi, M. H., Rush, A. J., Ibrahim, H. M., Carmody, T. J., Biggs, M. M., Suppes, T., et al. (2004). The Inventory of Depressive Symptomatology, Clinician Rating (IDS-C) and Self-Report (IDS-SR), and the Quick Inventory of Depressive Symptomatology, Clinician Rating (QIDS-C) and Self-Report (QIDS-SR) in public sector patients with mood disorders: A psychometric evaluation. *Psychological Medicine*, *34*(1), 73–82. doi:10.1017/S0033291703001107

United States Census Bureau. (2008). An Older and More Diverse Population by Midcentury [Press Release]. Retrieved from http://www.census.gov/newsroom/releases/archives/population/cb08-123.html

Uranova, N. A., Vostrikov, V. M., Orlovskaya, D. D., & Rachmanova, V. I. (2004). Oligodendroglial density in the prefrontal cortex in schizophrenia and mood disorders: a study from the Stanley Neuropathology Consortium. *Schizophrenia Research*, *67*(2-3), 269–275. doi:10.1016/S0920-9964(03)00181-6

Van de Velde, S., Bracke, P., & Levecque, K. (2010). Gender differences in depression in 23 European countries. Cross-national variation in the gender gap in depression. *Social Science & Medicine*, *71*(2), 305–313. doi:10.1016/j.socscimed.2010.03.035

Vandegrift, D., & Yoked, T. (2004). Obesity rates, income, and suburban sprawl: an analysis of US states. *Health & Place*, *10*(3), 221–229. doi:10.1016/j.healthplace.2003.09.003

Vasudev, A., Saxby, B. K., O'Brien, J. T., Colloby, S. J., Firbank, M. J., Brooker, H.,…Thomas, A. J. (2012). Relationship between cognition, magnetic resonance white matter hyperintensities, and cardiovascular Autonomic changes in late-life depression. *American Journal of Geriatric Psychiatry*, *20*(8), 691–699. doi:10.1097/JGP.0b013e31824c0435

Veglio, F., Paglieri, C., Rabbia, F., Bisbocci, D., Bergui, M., & Cerrato, P. (2009). Hypertension and cerebrovascular damage. *Atherosclerosis*, *205*(2), 331–341. doi:10.1016/j.atherosclerosis.2008.10.028

Versluis, C. E., van der Mast, R. C., van Buchem, M. A., Bollen, E. L. E. M., Blauw, G. J., Eekhof, J. A. H., et al. (2006). Progression of cerebral white matter lesions is not associated with development of depressive symptoms in elderly subjects at risk of cardiovascular disease. The PROSPER Study. *International Journal of Geriatric Psychiatry*, *21*(4), 375–381. doi:10.1002/gps.1477

Victor, R. G., Haley, R. W., Willett, D. L., Peshock, R. M., Vaeth, P. C., Leonard, D.,…Hobbs, H. H. (2004). The Dallas Heart Study: a population-based probability sample for the multidisciplinary study of ethnic differences in cardiovascular health. *The American Journal of Cardiology*, *93*(12), 1473–1480. doi:10.1016/j.amjcard.2004.02.058

Walker, L., Timmerman, G. M., Kim, M., & Sterling, B. (2002). Relationships between body image and depressive symptoms during postpartum in ethnically diverse, low income women. *Women and Health*, *36*(3), 101–121.

Wang, Y., & Beydoun, M. A. (2007). The obesity epidemic in the United States gender, age, socioeconomic, racial/ethnic, and geographic characteristics: A systematic review and meta-regression analysis. *Epidemiologic Reviews*, *29*(1), 6–28. doi:10.1093/epirev/mxm007

Watkins, L. L., & Grossman, P. (1999). Association of depressive symptoms with reduced baroreflex cardiac control in coronary artery disease. *American Heart Journal*, *137*(3), 453–457.

Weissman, M. (2009). Depression. *Annals of Epidemiology*, *19*(4), 264–267.

Wen, W., & Sachdev, P. (2004). The topography of white matter hyperintensities on brain MRI in healthy 60-to 64-year-old individuals. *Neuroimage*, *22*(1), 144–154. doi:10.1016/j.neuroimage.2003.12.027

Wen, W., Sachdev, P. S., Li, J. J., Chen, X., & Anstey, K. J. (2009). White matter hyperintensities in the forties: their prevalence and topography in an

epidemiological sample aged 44–48. *Human Brain Mapping*, *30*(4), 1155–1167. doi:10.1002/hbm.20586

Williams, D. R., González, H. M., Neighbors, H., Nesse, R., Abelson, J. M., Sweetman, J., & Jackson, J. S. (2007). Prevalence and distribution of major depressive disorder in African Americans, Caribbean blacks, and whites: results from the National Survey of American Life. *Archives of General Psychiatry*, *64*(3), 305-315.

Wilson, P. W., D'Agostino, R. B., Levy, D., Belanger, A. M., Silbershatz, H., & Kannel, W. B. (1998). Prediction of coronary heart disease using risk factor categories. *Circulation*, *97*(18), 1837–1847. doi:10.1161/01.CIR.97.18.1837

Winston, G. J., Palmas, W., Lima, J., Polak, J. F., Bertoni, A. G., Burke, G., et al. (2013). Pulse pressure and subclinical cardiovascular disease in the Multi-Ethnic Study of Atherosclerosis. *American Journal of Hypertension, 26*(5), 636-642. doi:10.1093/ajh/hps092

Wolff, E. F., He, Y., Black, D. M., Brinton, E. A., Budoff, M. J., Cedars, M. I…Taylor, H.S. (2013). Self-reported menopausal symptoms, coronary artery calcification, and carotid intima-media thickness in recently menopausal women screened for the Kronos early estrogen prevention study (KEEPS). *Fertility and Sterility*, *99*(5), 1385–1391. doi:10.1016/j.fertnstert.2012.11.053

Zhang, A. J., Zhang, A. Y., & Zhong, C. (2009). Carotid atherosclerosis in ischemic cerebrovascular patients. *Journal of Clinical Medicine Research*,

1(1), 40-44. doi:10.4021/jocmr2009.03.1226

Zhang, Y., Brady, M., & Smith, S. (2001). Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. *Medical Imaging, 20*(1), 45–57.