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DEPRESSIVE SYMPTOM SEVERITY, STRESSFUL LIFE EVENTS, AND SUBCLINICAL ATHEROSCLEROSIS IN AFRICAN AMERICAN ADULTS

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DEPRESSIVE SYMPTOM SEVERITY, STRESSFUL LIFE EVENTS, AND SUBCLINICAL ATHEROSCLEROSIS IN AFRICAN AMERICAN ADULTS

A Thesis

Submitted to the Faculty

of

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by

Jessica Berntson

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ABSTRACT

Berntson, Jessica. M.S., Purdue University, December 2015. Depressive Symptom Severity, Stressful Life Events, and Subclinical Atherosclerosis in African American Adults. Major Professor: Jesse C. Stewart.

Prospective epidemiologic evidence indicates that both stressful life events (SLEs) and depression are associated with an increased risk of subclinical atherosclerosis and cardiovascular disease (CVD) events. Even though stressful life events (SLEs) and depression co-occur and may act together to influence cardiovascular disease (CVD) risk, these psychosocial factors have been mainly examined in isolation. For instance, depression may moderate the relationship between SLEs and CVD outcomes. I hypothesized that depressive symptoms would potentiate the deleterious effect of SLEs on subclinical atherosclerosis. This hypothesis is plausible, given that depressed adults exhibit exaggerated and prolonged sympathetic nervous system, hypothalamic-pituitary-adrenal (HPA) axis, and inflammatory responses to stress, which in turn could promote atherosclerosis. As compared to their nondepressed counterparts, depressed individuals may also be more likely to engage in maladaptive methods to cope with SLEs (e.g., increased tobacco use, alcohol use, and consumption of low-nutrient, energy dense foods), which could also promote atherosclerosis. I examined cross-sectional data from 274 to 279 (depending on the outcome measure) older, African American adults (mean

age = 66 years, 67% female) with no evidence of clinical CVD or dementia who participated in the St. Louis African American Health-Heart study (2009–2011). Number of SLEs was assessed using the Life Events Calendar, a structured interview. From this interview, a continuous SLEs variable was computed (number of adult SLEs: 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or 11+). Severity of depression symptoms was measured using the 17-item Hamilton Rating Scale for Depression (HAM-D). Two measures of subclinical atherosclerosis were obtained: carotid intima-media thickness (CIMT; assessed by ultrasonography) and coronary artery calcification (CAC; assessed by multi-detector computerized tomography). I conducted linear (CIMT) and logistic (CAC) regression models, first adjusted for demographics (age, sex, education) and then fully-adjusted (demographics; mean arterial pressure; low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C); hemoglobin A1c; BMI; tobacco use; diabetes diagnosis; and use of antihypertensitve, lipid lowering, antidiabetic, and antidepressant medications). No main effects of SLEs or HAM-D were found for CIMT or CAC. There were also no SLEs by HAM-D interactions for CIMT or CAC. Because the current results are largely inconsistent with prior literature and there is a paucity of studies utilizing African American samples, future research is needed to examine the independent and interactive associations of SLEs and depressive symptoms with measures of subclinical atherosclerosis. If the present results are replicated, it may suggest that SLEs, depressive symptoms, and their interactive effect are not cardiotoxic among African American adults.

INTRODUCTION

Cardiovascular Disease

Epidemiology

CVD refers to disorders of the heart and the vascular system, which include coronary artery disease, congestive heart failure, stroke, and hypertension. The prevalence of CVD is on the rise in the U.S., with estimates of more than 1 in 3 Americans currently experiencing some form of CVD (Rosamond et al., 2007). Perhaps more concerning, CVD is the number one cause of mortality in adults, accounting for 39% of all deaths (Clouse, 2006). Moreover, there are exorbitant costs for treating advanced CVD. The American Heart Association forecasts that, by 2030, the total cost of CVD will exceed $1 trillion (Heidenreich et al., 2011). Also by that time, it is expected 41% of the U.S. population will have some form of CVD.

Given the immense burden of CVD, it is important to consider those at greatest risk of the disease. African Americans are one group at increased risk for both CVD morbidity and mortality. Among African Americans adults, 44% of men and 49% of women have CVD (Go et al., 2013). Not only is CVD the leading cause of death in African Americans but more African Americans experience fatal CVD events than any other racial/ethnic groups in the U.S. (Yancy & Sica, 2004). Specifically, the death rate

from CVD in 2009 was 39% higher for African Americans than for Caucasians (Go et al., 2013). Furthermore, although deaths attributable to CVD have been declining in recent years, this decline has been less pronounced for African Americans than for Caucasians (Mensah, Mokdad, Ford, Greenlund, & Croft, 2005).

Due to the increasing prevalence and costs of CVD, the need for prevention efforts is greater now than ever before. Fortunately, many CVD risk factors are modifiable. Moreover, among the preventive strategies recommended by the American Heart Association is the early detection and management of CVD risk factors (Heidenreich et al., 2011). To achieve this goal, it is imperative to enhance our understanding of conventional and emerging CVD risk factors and their interactions, especially in high-risk populations such as African Americans.

Pathophysiology

Although CVD includes a variety of conditions, the focus of this study is the type that arises from atherosclerosis. Therefore, from this point forward, CVD will refer to atherosclerotic CVD, a progressive systemic disease process involving the thickening and hardening of the blood vessels in the heart, brain, and peripheral circulation (Santos & Nasir, 2009). The arterial walls of these blood vessels are composed of three layers: adventitia, tunica media, and tunica intima (Libby, 2004). The outer layer (adventitia) contains collagen fibrils in a loose array and elastin, which facilitates blood flow by allowing the vessels to expand and contract. The middle layer (media) is composed of smooth muscle cells in an elastin-laden extracellular matrix. The inner layer (intima) is the single layer of vascular endothelial cells that is in direct contact with blood flow.

Injury to the intima layer due to sheer forces in blood flow instigates the process of atherosclerosis by increasing the adhesiveness and permeability of vessel walls (Libby, 2004; Ross, 1999; Santos & Nasir, 2009). In response, lipids flowing in the blood stream begin to accumulate as deposits on the intima. Chemical modifications to the lipid deposits results in endothelial dysfunction. Endothelial dysfunction triggers an inflammatory response, which causes (a) cytokines to increase expression of adhesion molecules on the intima and (b) leukocytes (e.g., monocytes) to adhere and then migrate into the intima to become macrophages and engulf lipid deposits before expanding to become foam cells. At this point, blood vessels are classified as having a fatty streak. Subsequently, lymphocytes (e.g., T-cells) signal smooth muscle cells to migrate from the media to the area of the developing lesion in the intima, which then secrete extracellular matrix components. Over time, this secretion can accumulate to form a complete fibrous cap over the lesion. Moreover, the foam cells undergo cellular death (apoptosis) releasing their lipid contents under the fibrous cap to form an extracellular lipid core in the lesion. The expansion of developing lesions is initially directed outwards toward the adventitia layer. However, as lesions progress, the artery is no longer able to remodel outward and, therefore, begins to protrude into the flow of blood, resulting in a narrowing of arteries.

Calcification also occurs in atherosclerotic lesions, which hardens the blood vessels (Johnson, Leopold & Loscalzo, 2006). Evidence of calcification is detectable only in advanced lesions that have formed a lipid core (Stary et al., 1995). This is due to calcium deposits combining and growing inside the lipid core to form large structures, which can progress until the majority of a lipid core becomes calcified. Because calcium

deposits appear only in advanced lesions, detection of calcium deposits indicates the presence of more advanced atherosclerosis.

The process of subclinical atherosclerosis progresses over many years, during which time individuals are asymptomatic (Libby, 2004). However, subclinical atherosclerosis can have life threatening consequences due to changing physiology. Specifically, the narrowing and hardening of blood vessels (a) impedes blood flow and reduces oxygen supply to tissues and (b) promotes increased velocity and turbulence of blood flow, which can cause lesions to rupture (Arroyo & Lee, 1999). When a lesion ruptures, a blood clot (thrombus) may develop at the site of the rupture (Stary et al., 1995; Zipes, Libby, Bonow, & Braunwald, 2004). Thrombi can dislodge and become emboli, which are carried through the circulation and lodge at distant sites. Both thrombi and emboli can partially or completely block blood flow to regions of the heart or the brain. These processes can result in various clinical events, including heart tissue death (myocardial infarction), brain tissue death (stroke), insufficient blood flow to the heart (cardiac ischemia), and cardiac arrest. The occurrence of one or more of these events signifies the transition from subclinical atherosclerosis to clinical CVD.

Measurement of Subclinical Atherosclerosis

Empirical studies have utilized several measures of CVD, including indicators of clinical CVD (e.g., cardiac events) and subclinical atherosclerosis. A criticism of some cardiovascular behavioral medicine research is the use of "soft" measures (e.g., self-reported CVD events), which lends results susceptible to subjective reporting biases (Steptoe & Whitehead, 2005). In contrast, the current study will examine two markers of

subclinical atherosclerosis: (1) carotid intima-media thickness (CIMT) and (2) coronary artery calcification (CAC). These noninvasive imaging technologies make it possible to detect and quantify early to late states of subclinical atherosclerosis (Santos & Nasir, 2009).

The first marker, CIMT, is a measure of the arterial wall thickening (Sharma, Blaha, Blumenthal, & Musunuru, 2009). In the assessment of CIMT, B-mode ultrasound equipment is used to assess the combined thickness of intima and media layers of the carotid artery, one of two major arteries on each side of the neck that supply blood to the head (Peters, den Ruijter, Bots, & Moons, 2012; Sharma et al., 2009). Although obtained from the carotid artery, CIMT measurements are positively associated with the extent of atherosclerosis in other vascular beds, including the coronary arteries (Mancini, Dahlof, & Diez, 2004). This measurement technique is used to detect early to late stages of subclinical atherosclerosis (Sharma et al., 2009).

The second marker, CAC, quantifies the degree of calcification in the walls of the coronary arteries (Johnson et al., 2006). Although there are multiple ways to measure CAC, multi-detector computerized tomography (MDCT) is one noninvasive imaging method (Budoff et al., 2006). From MDCT images, CAC scores can be obtained by using the standardized Agatston scoring system (Johnson et al., 2006). Because calcification is detectable only in advanced stage lesions, this measurement technique is used to detect late stages of subclinical atherosclerosis.

Both CIMT and CAC are considered to be excellent surrogate indicators of the extent of underlying atherosclerotic burden (Peters et al., 2012). These measures have a graded association with risk of CVD events (Lester, Eleid, Khandheria, & Hurst, 2009).

Moreover, evidence suggests CIMT and CAC predict CVD events, independent of conventional risk factors (Peters et al., 2012). CIMT and CAC also predict CVD events independently of one another (Hurst, Ng, Kendall, BS, & Khandheria, 2007; Santos & Nasir, 2009).

Risk Factors for Cardiovascular Disease

Research has identified non-modifiable and modifiable risk factors for CVD in the biological, psychological, and social domains (Booth-Kewley & Friedman, 1987). Non-modifiable risk factors include age, sex, race/ethnicity, and family history of CVD. The incidence of CVD increases with age (Cardi, Munk, Zanjani, Kruger, Schaie, & Willis, 2010). Additionally, men have a higher risk of CVD than women, although women have a higher risk of stroke (Roger et al., 2012). Regarding race/ethnicity, the incidence of CVD is highest among African Americans, followed by Caucasian Americans and Mexican Americans (Schiller, Lucas, Ward, & Peregoy, 2010). Modifiable risk factors also contribute to CVD, including hyperlipidemia, hypertension, diabetes, obesity, tobacco use, and physical inactivity (Ray, 2005; Everson-Rose & Lewis, 2005). Psychosocial factors, such as SLEs and depression, are emerging modifiable risk factors for CVD (Rozanski, Blumenthal, Davidson, Saab, & Kubzansky, 2005).

Although research has identified several CVD risk factors, these factors are understudied in racial/ethnic minorities (Kurian & Cardarelli, 2007). The available research suggests the prevalence of conventional risk factors (e.g., hypertension, hyperlipidemia, diabetes, and tobacco use) is higher in African Americans than in

Caucasian Americans; however, these risk factors predict CVD similarly in Caucasian and African Americans (Hozawa, Folsom, Sharrett, & Chambless, 2007; Kurian & Cardarelli, 2007). Therefore, it is plausible that the higher CVD risk of African Americans is, in part, attributable to the higher prevalence of conventional risk factors (Hozawa et al., 2007). Similarly, racial differences in prevalence and impact of emerging CVD risk factors (e.g., SLEs and depression) could also partially explain the elevated CVD risk of African Americans.

Stressful Life Events and Cardiovascular Disease

Stressful Life Events

SLEs constitute any set of circumstances that signifies or requires change in a person's life pattern (Holmes & Rahe, 1967). SLEs can be classified into thematic domains, such as changes in marital, occupational, or health status (Oei & Zwart, 1986). SLEs can also be classified according to severity, chronicity, and period. Severity reflects the degree of disruption and distress that the SLE causes (Cohen, Kessler, & Underwood Gordon, 1997). Severity can range from small hassles causing minimal disruption and distress (e.g., traffic) to traumatic experiences causing major disruption and distress (e.g., sexual abuse and natural disasters; Kanner, Coyne, Schaefer, & Lazarus, 1981; Updegraff & Taylor, 2000). Chronicity reflects the persistence or recurrence of SLEs over time (Cohen et al., 1997). The two broad chronicity categories are discrete (isolated, transient SLEs) and chronic (SLEs that persist or recur for a prolonged period; Liu, 2013). Lastly,

period reflects when the SLE occurred. For example, SLEs can occur in childhood (< 18 years old) or adulthood (≥ 18 years old).

The two main methods for measuring SLEs are checklist and interview. Checklist measures ask respondents to identify the events they have experienced during a specific period (e.g., past year) from a standard list of SLEs (Cohen et al., 1997). Interviews use qualitative probes to illicit information about potential SLEs and are typically designed to capture more nuanced information, including severity and chronicity. Trained researchers use this additional information and interview rating guidelines to categorize SLEs on the various dimensions.

Of relevance to the present study, there appears to be differential exposure to SLEs across racial/ethnic groups. In one study of a population-based sample, African Americans reported a greater number of negative life events, exposure to discrimination, and financial strain than Caucasian Americans (Williams et al., 1997). More recent research corroborates these findings (Schetter, Schafer, Lanzi, Clark-Kauffman, Raju, & Hillemeier, 2013). African American parents reported higher rates of everyday racism than Caucasian and Latino American parents. Moreover, chronic stress scores from a qualitative interview assessing demands in three life domains (family, partner, and neighborhood) were higher among African American parents than Caucasian American parents.

Stress Response

SLEs typically induce a stress response. Lazarus and Folkman (1984) formulated a top-down model of the stress response, which proposes that, when people experience

environmental events, they evaluate (1) whether the demands pose a potential threat and (2) whether they have sufficient adaptive capacities to adequately cope (Lovallo, 2005). If the demands are perceived as threatening and their coping resources are deemed inadequate, then the situation will be appraised as stressful. This perceived stressor can produce affective (e.g., negative emotions) and behavioral (e.g., substance use) changes, as well as physiologic changes.

To understand the potential effect of SLEs on health, it is important to review the physiologic processes of the stress response. These physiologic changes include activation of the sympathetic nervous system, HPA axis, and immune system, which are intended to help an organism adapt to the perceived threat (Glaser & Kiecolt-Glaser, 2005). Activation of these systems involves a cascade of physiologic events described below (Gold & Chrousos, 2002).

Activation of the sympathetic nervous system involves the sympathetic–adrenal–medullary (SAM) axis (Lovallo, 2005). This pathway originates in the hypothalamus and brainstem and signals the adrenal medulla to release catecholamines (i.e., epinephrine and norepinephrine), which initiate the fight-or-flight response. This promotes further physiologic changes, including release of fuel stores from adipose tissue and the liver, increases in cardiac output and respiration rate, dilation of peripheral blood vessels, and enhancement of skeletal muscle contraction.

Activation of the HPA axis begins with the release of corticotrophin-releasing factor (CRF) from the hypothalamus. CRF stimulates the release of norepinephrine, which in turn promotes the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary (Gold & Chrousos, 2002). ACTH stimulates the secretion of

glucocorticoids (e.g., cortisol), mineralocorticoids, and androgens from the adrenal cortex. Increased concentrations of cortisol, in turn, increase blood glucose concentrations through gluconeogenesis (formation of glucose from smaller molecules) and glycogenolysis (breakdown of glycogen to form glucose).

Activation of the immune system also occurs in response to stress (Gu et al., 2012; Marslanda, Bachenb, Cohen, Rabind, & Manuck, 2002). Evidence suggests that sympathetic and HPA axis responses to stress are involved in the regulation of the immune system response (Lovallo, 2005). Specifically, norepinephrine secretion promotes the release of several cytokines, which activate the synthesis of acute phase response proteins, cell adhesion molecules, and fibrinogen (Vale, 2005). This culminates in an acute proinflammatory response (Vale, 2005). Cortisol released by the HPA axis, however, down-regulates this proinflammatory response (Vale, 2005).

The acute stress response can be adaptive when allostasis returns these systems back to a balanced state of homeostasis (Chrousos & Gold, 1992). However, if the stress response persists, this results in sustained sympathetic and HPA axis activation (Chrousos & Gold, 1992). Under chronic stress, the proinflammatory effects of sympathetic activation can surpass anti-inflammatory effects of HPA axis activation (Vale, 2005) because immune cells become less sensitive to cortisol over time due to downregulation (Cohen et al., 2012; Black & Garbutt, 2002). This can result in exaggerated and prolonged inflammatory responses, which can ultimately lead to a chronic, low-grade inflammatory state among people experiencing chronic stress (Black & Garbutt, 2002).

Stressful Life Events and Cardiovascular Disease

Empirical evidence suggests that SLEs are involved in the development and progression of CVD. For example, multiple studies have reported that adults with chronic occupational or marital stress have a two to three times higher risk of cardiac events (Thomas, Nelesen, Ziegler, Bardwell, & Dimsdale, 2004; Matthews & Gump, 2002). However, results in this area are inconsistent. A 15-year prospective study of a national representative sample found no associations between accumulated childhood, adulthood, and work SLEs and the onset of CVD (Andersen, Diderichsen, Kornerup, Prescott, & Hulvej Rod, 2011). In another population-based sample, SLEs were associated with an increased risk of stroke but not myocardial infarction (Kornerup, Osler, Boysen, Barefoot, Schnohr, & Prescott, 2010). The mixed findings regarding the relationship between SLEs and CVD could be due to inconsistent measurement of SLEs, including the degree of subjectivity captured by the measure (e.g., event counts verses perceived stress; Everson-Rose & Lewis, 2005) and the type of SLE under investigation (e.g., occupational SLEs versus any SLEs; Bunker et al., 2003).

Other studies have linked SLEs to measures of subclinical atherosclerosis, including CIMT and CAC (Rozanski et al., 2005; Matthews, 2005). Many studies in this area have found that stressful work conditions, characterized by high demand and low decisional latitude, are related to increased CIMT (Everson, Lynch, Chesney, 1997; Kamarck et al., 2004; Muntaner et al., 1998; Nordstrom, Dwyer, Merz, Shircore, & Dwyer, 2001; Rosvall et al., 2002). Discrimination, another form of stress, may also have an impact on subclinical atherosclerosis. Specifically, in a study of African American women, chronic exposure to everyday discrimination was associated with a greater

likelihood of CAC (Lewis et al., 2006). The impact of SLEs on CAC, however, is inconsistent across studies. A prospective study of U.S. Army personnel found that the number and severity of SLEs did not predict the presence of CAC (O'Malley, Jones, Feuerstein, & Taylor, 2000).

Several physiologic and behavioral mechanisms may explain the relationship between SLEs and subclinical atherosclerosis. Stress-related physiologic changes can promote atherosclerosis (Black & Garbutt, 2002). Specifically, the stress hormones released by the sympathetic nervous system and HPA axis increase cardiovascular activity and vasoconstriction, both of which can damage the endothelium (Joynt et al., 2003). Moreover, catecholamines increase coagulation by activating blood clotting factors and platelets, and HPA axis hormones (e.g., cortisol) promote the development of CVD risk factors, including insulin resistance, visceral fat deposition, and hypertension (Gold & Chrousos, 2002; Joynt et al., 2003). Lastly, exaggerated and prolonged inflammatory responses to stress can lead to: (a) increased secretion of inflammatory mediators by vascular endothelium, (b) increased expression of cellular adhesion molecules, (c) increased uptake of lipids into macrophages, (d) decreased cell division, survival, and function, reducing the efficiency of the immune response, and (e) increased activation of vascular smooth muscle cells (Vale, 2005). In addition to physiologic mechanisms, SLEs are associated with worsening health behaviors, including increases in smoking, decreases in exercise (Dimsdale, 2008), and increases in the consumption of energy dense foods, which are high in sugar and fat (Torres, Susan, & Nowson, 2007). However, the relationship between SLEs and atherosclerosis persists after adjustment for

these health behaviors (Brotman, Golden, & Wittstein, 2007). Therefore, it is likely that both physiologic and behavioral mechanisms explain the link between SLEs and CVD (Dimsdale, 2008).

The impact of SLEs on CVD may be particularly pronounced among African Americans. Evidence suggests that African Americans have increased exposure to SLEs (Schetter, et al., 2013; Williams et al., 1997). Furthermore, due to socioeconomic inequalities, African Americans may have fewer resources to effectively cope with SLEs and, thus, be especially vulnerable to their cardiotoxic effects (Geronimus, Hicken, Keene, & Bound, 2006). Supporting this notion, a study comparing African American and Caucasian women revealed that chronic stress scores related to higher CIMT in African Americans only (Troxel, Matthews, Bromberger, & Sutton-Tyrrell, 2003).

Depression and Cardiovascular Disease

Depression

Depressive disorders are common conditions that impact a person's mental and physical functioning (Pratt & Brody, 2008). The lifetime prevalence of major depressive disorder and dysthymic disorder is 16.2% and 6%, respectively (American Psychological Association, 2000; Kessler et al., 2009). Symptoms of depressive disorders are depressed mood, loss of interest/pleasure, appetite or weight changes, sleep disturbances, psychomotor retardation/agitation, feelings of worthlessness or guilt, fatigue, concentrations problems, and suicidal ideation (American Psychological Association, 2000). For a diagnosis of major depressive disorder, five or more of these symptoms are

required. In addition, at least one of the symptoms must be either depressed mood or loss of interest/pleasure, and the symptoms must cause significant distress or impairment nearly every day over a 2-week period.

Depression can be conceptualized as a dichotomous variable (presence/absence of a depressive disorder) or a continuous variable (severity of depressive symptoms). The presence/ absence of a depressive disorder is typically determined through the use of a structured clinical interview, such as the Depression Interview and Structured Hamilton (DISH; Freedland et al., 2002). In contrast, depressive symptom severity is usually assessed by self-report questionnaires, such as the Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff, 1977) and the Beck Depression Inventory (Beck, Ward, Mendelson, Mock & Erbaugh, 1961).

Depression and Cardiovascular Disease

Prospective studies indicate that adults with depressive disorders or elevated depressive symptoms are at increased risk of developing CVD (Matthews, 2005; Joynt, Whellan, & O'Connor, 2003). Of note, the evidence supports a graded relationship (Rosanski, 1999). To illustrate, minor depression is associated with a 1- to 2-fold increase in risk of CVD, and major depression is associated with a 3- to 5-fold increase in risk (Bunker et al., 2003). The risk conferred by major depression is comparable to that of conventional CVD risk factors (Bunker et al., 2003).

Although most studies have examined risk of clinical CVD, there is also considerable research linking depression to subclinical atherosclerosis. In a prospective study of healthy, older adults, higher depressive symptoms predicted greater 3-year

increases in CIMT, even after adjustment for conventional risk factors, medication use, medical conditions, and other correlated negative emotional factors (Stewart, Janicki, Muldoon, Sutton-Tyrrell, & Kamarck, 2007). There is also evidence indicating that depression is associated with CAC or predicts the onset of CAC in generally healthy samples (Haas et al., 2005; Janssen et al., 2011; Matthews, Chang, Sutton-Tyrrell, Edmundowicz, & Bromberger, 2010; Stewart et al., 2012). For instance, Janssen et al. (2011) found that elevated depressive symptom severity at baseline was associated with 2-year progression of CAC in a sample of healthy women.

Depression has been associated with physiologic and behavioral factors that promote atherosclerosis, all of which are mechanisms that may underlie the depression-CVD relationship (Joynt et al., 2003; Grippo & Johnson, 2009). For instance, depression has been linked with metabolic syndrome, HPA axis dysregulation, autonomic nervous system dysfunction, systemic inflammation, and platelet hyperactivation. Depression has also been associated with poor health behaviors, such as smoking, physical inactivity, and noncompliance with medical recommendations intended to prevent CVD (Berntson, K. R. Stewart, Vrany, Khambaty, & J. C. Stewart, 2015).

The impact of depression on CVD may vary by race/ethnicity. For example, Davidson and colleagues (2000) followed 3,340 individuals in the Coronary Artery Risk Development in Young Adults (CARDIA) study. Results indicated that those with elevated CES-D scores (≥16) had a higher incidence of hypertension five years later. The strength of this relationship was the greatest in African Americans. Additional research suggests the relationship between depression and atherosclerosis may be moderated by race. In a study by Lewis et al. (2009), the association between depressive symptoms and

aortic calcification was detected in African American but not Caucasian women. Taken together, these results suggest that African Americans may be particularly vulnerable to the cardiotoxic effects of depression.

Depression and Stressful Life Events

A large body of literature suggests that SLEs play a causal role in many instances of depression (Hammon, 2005). Recently, however, there has been increasing interest in the transactional nature of the SLEs-depression association, with more recent research indicating a bidirectional relationship. Specifically, depression may also create more SLEs. Moreover, the SLEs-depression relationship appears to change over time, as recurrent depressive episodes appear to be more independent of SLEs than first depressive episodes. Further research is needed to elucidate the complex relationship between SLEs and depression. In particular, depressive symptoms have the potential to impact the appraisal of SLEs, as well as the physiologic and behavioral responses to SLEs.

Depression as a Potential Moderator of the Relationship Between Stressful Life Events and Cardiovascular Disease

As previously noted, exposure to SLEs is an emerging risk factor for CVD. However, the magnitude and/or duration of physiologic and behavioral responses elicited by these events may be more pronounced for certain individuals. One potential moderator of the SLE-CVD relationship is depression. Specifically, individuals with depression may

exhibit altered physiologic and behavioral responses to SLEs (Joynt et al., 2003), which may accelerate the development and progression of CVD.

Depression-Related Dysregulation of Physiologic Stress Response Systems

It has been proposed that depressed persons have exaggerated responses (reactivity) to stress and a slower return to baseline (recovery) following stress (Rozanski, Blumenthal, & Kaplan, 1999). This exaggerated reactivity and delayed recovery can manifest across multiple systems, including the sympathetic nervous system, HPA axis, and inflammatory branch of the immune system (Brotman et al., 2007; Gu, Tang & Yang, 2012; Vale, 2005). The following sections summarize research examining whether depression moderates stress-related responses of these systems.

Depression and the Sympathetic Nervous System Response to Stress

Light and colleagues (1998) examined the relationship between BDI scores and norepinephrine and cardiovascular responses to laboratory speech and postural stressors. Women with higher versus lower depressive symptoms had an increased heart rate and norepinephrine response to the speech stressor but not the postural stressor. These findings were extended by Gold and colleagues (2004), who investigated epinephrine responses to a laboratory speech stressor in healthy women. These women were classified into two groups based on a median split of BDI scores. There were no group differences in epinephrine reactivity immediately after the stressor. However, at 15 and 30 minutes post-stressor, the high depression group had elevated epinephrine levels relative to the low depression group. To summarize, the available evidence suggests that depression

may delay sympathetic recovery from stress, and there is mixed evidence as to whether depression increases sympathetic reactivity to stress.

Depression and the Hypothalamic-Pituitary-Adrenal Axis Response to Stress

Burke et al. (2005) conducted a meta-analysis of seven studies examining the association between depression and cortisol responses to psychological laboratory stressors. No difference in cortisol reactivity was detected between depressed and nondepressed participants. However, an analysis of the four studies that included cortisol recovery measures revealed that depressed participants had higher cortisol levels than nondepressed participants during recovery periods (more than 25 minutes after stressor offset). These findings suggest that depressed individuals may exhibit delayed HPA axis recovery from stress but not exaggerated reactivity to stress.

Depression and the Inflammatory Response to Stress

Evidence of the potential moderating effect of depression on inflammatory responses to stressors has been reported in two studies. The first study examined levels of interleukin-6 (IL-6), lymphocyte subsets, and DNA binding of nuclear factor kappa B (a transcription factor in the inflammatory signaling cascade) before and after a laboratory stressor in healthy men (Pace et al., 2006). Half of these participants had current major depressive disorder and increased early life stress (n = 14), and half were not depressed (n = 14). The depressed participants with increased early life stress had greater elevations in inflammatory markers (IL-6 and DNA binding nuclear factor kappa B) in response to a speech stressor than the nondepressed participants. Moreover, these inflammatory

responses were positively correlated with depressive symptom severity but not early life stress. This study suggests that inflammatory reactivity to stress may be exaggerated in depressed men. A second study corroborates these findings in 72 women, half whom met diagnostic criteria for a depressive disorder (Miller, Rohleder, Stetler, & Kirschenbalm, 2005). Inflammatory marker levels (IL-6 and tumor necrosis factor-α) were assessed in blood samples exposed to dexamethasone, a corticosteroid that inhibits production of inflammatory markers. At baseline, women with depression had higher sensitivity to the anti-inflammatory effects of dexamethasone than women without depression. However, after exposure to a job interview stressor, depressed women's sensitivity to dexamethasone declined while the controls' sensitivity increased. These results suggest that, under stress, depression is associated with resistance to hormones that terminate the inflammatory response, which could lead to prolonged inflammatory responses to stressors (i.e., delayed recovery). Altogether, findings from these studies suggest that depressed persons may have exaggerated and prolonged inflammatory responses to stress.

Depression-Related Maladaptive Coping Responses to Stress

In addition to physiologic responses, it is possible that depression alters behavioral responses to stress. For instance, depressed persons are more likely to use avoidance coping strategies in an attempt to deal with stressors than nondepressed persons (Felsten, 1997). Avoidance coping refers to attempts to avoid actively confronting a problem (distraction, denial, social diversion, behavioral disengagement) or to indirectly reduce emotional tension by eating or using substances, including tobacco

and alcohol (Holahan & Moos, 1987; Ingledew & Hardy, 1996). In a recent meta-analysis, depression was found to have a moderate positive association with avoidance coping (r = .48; Aldao, Nolen-Hoeksema, & Schweizer, 2010). Use of avoidance coping strategies may partially explain depressed persons increased baseline levels of tobacco use and consumption of low-nutrient, energy dense foods (Strine, Mokdad, & Dube, 2008). Therefore, during or following stressors, depressed individuals may be more likely to engage in poor health behaviors that could accelerate the development and progression of CVD.

The Present Study

Although both SLEs and depression have been associated with subclinical atherosclerosis and an increased risk of CVD events, most studies in these literatures have examined SLEs and depression in isolation, even though these factors may act together to influence CVD outcomes. Accordingly, the purpose of the present study was to examine whether depressive symptoms moderate the relationships between SLEs in adulthood and subclinical atherosclerosis (CIMT and CAC) in a community sample of African American adults. If it is found that exposure to SLEs is a stronger risk factor for CVD in African Americans with higher depressive symptoms, it would identify this group as one that is particularly vulnerable to the cardiotoxic effect of SLEs.

Figure 1 presents the conceptual model guiding the present study, and Figure 2 shows the hypothesized relationships among the variables examined in this study. To evaluate the model shown in Figure 2, I will test the following hypotheses:

1. SLEs will be positively associated with the degree of subclinical atherosclerosis.
2. Depressive symptom severity will be positively associated with the degree of subclinical atherosclerosis.
3. Depressive symptom severity will moderate the relationship between SLEs and CVD such that SLEs will be more strongly associated with subclinical atherosclerosis among African Americans with elevated depressive symptoms versus those with minimal or no symptoms.

Because measures of SLEs, depression, and subclinical atherosclerosis were obtained from a community sample of African Americans, data from the AAH-Heart study provide a good opportunity to test the aforementioned hypotheses.

METHOD

Study Sample

This thesis used data from AAH-Heart study, which involves a subsample of the AAH parent study. The AAH parent study is a prospective cohort study of 998 African Americans aged 49-65 years living in the St. Louis metropolitan area. The recruitment rate for this study was 76%. Two areas of the city – a poor, inner-city location and a suburban location northwest of the city – were sampled. This AAH cohort underwent seven waves of assessments over nine years from 2000 to 2009.

Between 2009 and 2011, AAH participants still participating as of 2009 (N = 735) were contacted by telephone or e-mail. Of those contacted, 430 (58.5%) did not participate in the AAH-Heart study for the following reasons: declined participation (n = 152); unable to contact (e.g., disconnected or wrong telephone numbers; n = 246); relocated outside the St. Louis metropolitan area, institutionalized, or incarcerated (n = 26); or death since 2009 (n = 6). The remaining 305 (41.5%) were enrolled in the AAH-Heart study. Sampling weights and propensity score re-weighting adjustments for differential participation in the AAH-Heart study allows the cohort to approximate a population sample of the non-institutionalized African Americans from the AAH geographical areas according to the 2000 census. However, these sample weights and

propensity score re-weighting adjustments were not utilized in this current study, as the analyses approach chosen (PROCESS; see Data Analyses section) does not allow for these adjustments.

From the participants enrolled in the AAH-Heart study (N = 305), I removed 3 respondents with known dementia because this condition would likely interfere with the retrospective reporting of SLEs and depressive symptoms. I then excluded respondents with missing data for SLEs (n = 9), 17-item Hamilton Rating Scale for Depression (HAM-D-17) (n = 2), education (n = 1), high density lipoprotein cholesterol (HDL-C) (n =1), and antidepressant use (n = 2), leaving a sample of 287 older adults. From this sample, I removed 13 respondents with missing data for carotid intima-media thickness (CIMT) to create the CIMT cohort (N = 274) and separately removed 8 respondents with missing data for coronary artery calcification (CAC) to create the CAC cohort (N = 279). These two final cohorts had complete data on all variables utilized in primary hypothesis-testing analyses.

For hypothesis-testing analyses utilizing the alternate depression variable (Center for Epidemiologic Studies Depression Scale – Short Form (CES-D-SF)), additional respondents were excluded. For the CIMT cohort, 21 respondents were excluded for missing data for the CES-D-SF, leaving 253 respondents. For the CAC cohort, 22 respondents were excluded for missing CES-D-SF data, leaving 257 respondents.

For exploratory analyses, additional respondents were excluded. For the CIMT cohort, 13 respondents were excluded for missing data for number of fruit and vegetable servings, and 12 were excluded for missing data for C-reactive protein, leaving 249

respondents. For the CAC cohort, 14 respondents were excluded for missing fruits/vegetable servings data, and 12 were excluded for missing C-reactive protein data, leaving 253 respondents.

The AAH-Heart study was a collaborative endeavor between three institutions: Washington University School of Medicine, Saint Louis University School of Medicine, and Indiana University School of Medicine. AAH-Heart was approved by ethics committees at all three institutions, and written informed consent was obtained from all participants.

Measures

Independent variable

Life Events Calendar (LEC)

To assess SLEs, the AAH-Heart investigators created the LEC by combining several standardized approaches to life events interviewing. The rationale for creating a new instrument was that all existing interviews and self-report inventories lacked comprehensiveness, as determined following a review of available materials. These investigators attempted to address this limitation by creating a more comprehensive measure. The LEC is a structured interview comprised of open-ended questions which gather data related to past stressful life experiences. Participants were questioned about recent SLEs (past 6 months), other SLEs in adulthood, and then SLEs in childhood. During all phases of inquiry, domains of SLEs were used as cues to recall stressful

experiences (e.g., Any stressful changes in your living situation?). Based on predetermined criteria (see Appendix), interviewers rated the reported events in terms of severity (1 = somewhat stressful, 2 = very stressful, 3 = extremely stressful or traumatic), chronicity (chronic = stressor lasted months or years, discrete = stressor lasted no more than a few hours, days, or weeks), period (adulthood = event occurred during or after age 18, childhood = event occurred before age 18, recent = event occurred within the past 6 months), and domain (76 category codes within the following domains: medical illnesses, injuries, or medical care; stressful changes in living arrangement; financial, work, or school-related problems; non-family relationship problems; marital relationships; family relationships; violence or trauma; and childhood).

For this study, a SLE score was computed for each participant as the count of all events (across all domains) that had codes of 2-3 on severity, chronic or discrete for chronicity, and adulthood for period. Events with severity ratings of 1 were excluded so that the SLE score was not driven by more minor events (Monroe, 2008). Recent SLEs were excluded because these stressors may not have had enough time to promote atherosclerosis. Childhood SLEs were excluded, given that responses to these events are less likely to be moderated by depression because they are more likely to precede depressive symptom onset. Psychometric information (such as interrater reliability and construct validity) is not available for the LEC because it was created for this study. However, interview-based methods are the current gold standard for assessing SLEs (Monroe, 2008).

Dependent variables

Carotid Intima-Media Thickness (CIMT)

To obtain measures of the thickness of the intima and media layers of the carotid artery, bilateral ultrasound imaging was performed using a 9-MHz linear array transducer of the extracranial carotid artery at the common carotid artery, approximately 1 cm proximal to the carotid bifurcation. Procedural details are described elsewhere (Stein et al., 2008). CIMT was measured with an automated edge detection system (AMS; Wendelhag, Liang, Gustavsson, & Wikstrand, 1997). This system derived a continuous CIMT variable: the average intima-media thickness of the far wall of the right and left common carotid arteries, while excluding raised lesions and plaques.

Coronary Artery Calcification (CAC)

To obtain measures of coronary, carotid, and thoracic aorta calcification, participants were examined using a 64-slice dual-source multi-detector computerized tomography (MDCT) scanner (Somatom Sensation 64, Siemens, Forchheim, Germany). Scan parameters included: 24×1.2 mm collimation, 1.5 mm slice thickness, 0.37 second rotation time, spiral mode, 120 kilovoltage, and 80 mAs. Cardiac-pulsing imaging reduced radiation exposure and cardiac motion. Scans were acquired during a single breath-hold at the end of expiration (~5-15 second duration). Images derived from the MDCT were then analyzed for coronary calcium scores/volume. Intra- and inter-reader intraclass correlation coefficients for coronary calcium scores/volumes were ≥ 0.82 and ≥ 0.97, respectively, in the laboratory used for this analysis. Coronary calcium scores were

quantified by standard Agatston scoring, determined by the density and area of identified calcified plaques, which is described in detail elsewhere (Budoff et al., 2006). For the present study's CAC variable, total Agatston scores were dichotomized into the presence (total Agatston score > 0) or absence (total Agatston score = 0) of calcification.

Moderator variables

17-item Hamilton Rating Scale for Depression (HAM-D-17)

A semi-structured interview, the Depression Interview and Structured Hamilton (DISH), was used to diagnose depressive disorders according to DSM-IV criteria and assess depressive symptom severity (Freedland et al., 2002). The DISH is comprised of three sections: *optional opening questions* to build rapport, *current depression symptoms* to aid in diagnosis and severity ratings of depression and depressive subtypes as well as comorbid anxiety disorders (generalized anxiety and panic disorders), and *psychiatric history* to capture lifetime and family history information. A DISH form, the DSM-IV Diagnosis Guide, enables the interviewer to quickly determine whether the diagnostic criteria are met for major depression, minor depression, and/or dysthymia. In a validation study, the DISH had 88% diagnostic overlap with a major depressive disorder diagnosis according to the Structured Clinical Interview for DSM-IV, which is the current gold standard of diagnostic interviews (Freedland et al., 2002). Additionally, in the Enhancing Recovery in Coronary Heart Disease (ENRICHD) study, clinicians' diagnoses, made by listening to tapes of DISH interviews, agreed with 93% of research nurse's diagnoses made using the DISH (Freedland et al., 2002).

Depressive symptom severity was determined from the embedded 17-item Hamilton Rating Scale for Depression (HAM-D-17; Hamilton, 1960) using the Structured Interview Guide for the Hamilton Depression scale (SIGH-D; Williams, 1988). This guide was created to increase the reliability of the HAM-D-17 when used by lay interviewers. The symptoms are defined by anchor-point descriptions, and raters consider both the intensity and frequency of a symptom when assigning it a value of 0-2, 0-3, or 0-4. The scale yields a total score ranging from 0 to 52, with higher scores indicating more severe symptoms of depression. The SIGN-D version, which was used in the AAH-Heart study, has demonstrated good inter-rater reliability (r = 0.81; Williams, 1988). The primary depression variable for this study was this HAM-D-17 score.

Center for Epidemiologic Studies Depression Scale – Short Form (CES-D-SF)

An 11-item self-report measure, the short form of the CES-D, was also used to assess the severity of depressive symptoms (Kohout, Berkman, Evans, & Cornoni-Huntley, 1993). For each item of the CES-D-SF, participants indicated how often they experienced various symptoms during the last week using a scale ranging from 0 (rarely or none of the time) to 3 (most or all of the time). Total scores can range from 0 to 33, with higher scores indicating greater depressive symptom severity. The CES-D-SF has demonstrated good internal consistency (Cronbach's α = .76-.81), as well as strong correlations with clinician ratings and other self-report measures of depression (Radloff, 1977; Weissman, Sholomskas, Pottenger, Prusoff, & Locke, 1977).

Covariates

Given their associations with SLEs, depression, and atherosclerosis, a number of potential confounders were included in the models as covariates. First, the following self-reported demographic factors were included: age, sex, and years of education. Second, the biomedical factors that were included are self-reported diabetes (yes = 1, no = 0) assessed through a self-report index of medical comorbidities (Charlson Comorbidity Index; Charlson, Pompei, Ales, & MacKenzie, 1987); echocardiography derived mean arterial pressure; fasting low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), and hemoglobin A1c (HbA1c); measured body mass index (BMI; Huxley, Mendis, Zheleznyakov, Reddy, & Chan, 2010; Takami et al., 2001); and self-reported current use of antihypertensive medications, lipid-lowering medications, diabetes medications, and antidepressants (yes = 1, no = 0).

Potential Mediators

Given that a number of physiologic and behavioral factors may mediate the SLEs to atherosclerosis relationship moderated by depression, I identified a number of these potential mediators which were used in exploratory moderated mediation analyses. Potential mediators measured are current tobacco use (0 = no, 1 = yes), number of daily fruit and vegetable servings (CDC Questionnaire – 6 items; Center for Disease Control and Prevention, 2011), physical activity (International Physical Activity Questionnaire Short Form [IPAQ-SF] - 9 items; Lee, Macfarlane, Lam, & Stewart, 2011), and a biomarker for inflammation (C - reactive protein [mg/L]).

Procedure

Participants in the AAH-Heart study attended data collection visits between June 2009 and November 2011. During these visits, the assessments of SLEs, CIMT, CAC, depressive disorders and symptoms, demographic factors, biomedical factors, and potential mediator variables described above were performed. Additional assessments to measure factors not part of the present study were also completed (Bruchas et al., 2013). All assessment components were conducted and interpreted by trained personnel under the supervision of the study investigators.

Data Analyses

Data Cleaning

Initial data cleaning procedures assessed for missing data, outliers, and normality for each variable.

To check for systematic missingness in the dataset, age, sex, and education were examined as predictors of missing data. This check was completed by creating a dichotomous missingness variable for each variable (0 = no missing, 1 = missing). Then, age, sex and education were entered simultaneously into logistic regressions models predicting each missingness variable. I observed only one relationship: as age increased so did the likelihood of missingness on the CES-D-SF variable (*OR* = 1.14, 95% *CI:* 1.01-1.28, $p = 0.04$). Because the CES-D-SF was not the primary depressive symptom severity measure, analytic procedures proceeded as planned.

To identify out-of-range values, I examined variable frequencies, and all variables were found to be within the plausible range. All outliers for continuous variables (z scores ≥ 3.3) in the data set were identified. The number of outliers for each variable was as follows: SLEs (n = 4), HAM-D-17 (n = 1), CES-D-SF (n = 1), education (n = 2), HDL-C (n = 3), HbA1c (n = 4). The four outliers for the SLE variable were no longer outliers after winsorizing this distribution to address kurtosis (described below). All other outliers were not altered or deleted for three reasons: (1) these cases did not result in non-normal distributions, (2) some z scores ≥ 3.3 are expected when sample sizes are large, and (3) these cases are likely legitimate cases of the sample population (Tabachnick & Fidell, 2001).

Determining normality of variables included assessments of skewness (< 3.0) and kurtosis (< 10.0) (Kline, 1998). Because the distribution for SLEs violated the normality assumption (kurtosis = 15.3), I visually inspected it, which revealed positive skew and a number of outliers near the upper end of the distribution. Because these values are likely true values, I decided to winsorize this variable at the upper end by setting the top 5% of the values equal to the value corresponding to the 95th percentile. The HbA1c distribution also violated normality assumptions (skewness = 3.7, kurtosis = 20.3). This variable was log transformed, which normalized the distribution (skewness = 2.7, kurtosis = 9.0). After making these changes to the SLEs and HbA1c variables, deviations from normality across variables were insubstantial.

Software

All analyses were conducted using SPSS statistical software (Version 20). I used SPSS linear and logistic regression to test the main effects models for Hypotheses 1 and 2, and I used the SPSS Macros called PROCESS (Hayes, 2013) to test the moderation model for Hypothesis 3, as well as the exploratory mediation and moderated mediation models. PROCESS estimates the coefficients of a model using ordinary least squares regression for continuous outcomes or maximum likelihood logistic regression for dichotomous outcomes. Importantly, PROCESS uses bootstrapping, which is a nonparametiric approach to effect size estimation that uses resampling (MacKinnon, Lockwood, & Williams, 2004). Subsamples are selected from the original sample, with replacement, and the effect within each subsample is computed. This process is repeated thousands of times to estimate a sampling distribution for the effect of interest. From this distribution, upper and lower estimates of the effect can be identified, and a confidence interval can be computed. When this confidence interval does not contain zero, it can be concluded that the effect is statistically significant. Using this approach, PROCESS generates direct and indirect effects for mediation and mediated moderation models, conditional effects for moderation models, and conditional indirect effects for moderated mediation models. For the current study, effect size estimates are based on biased-corrected 95% bootstrap confidence intervals with 10,000 bootstrap resamples.

PROCESS bootstrapping is appropriate to use in the present study for three reasons. First, it does not require that the sampling distribution be normally distributed, which allows for testing moderation and mediation in cases where there is asymmetry in the distribution (Hayes, 2013; MacKinnon et al., 2004). Second, it has greater statistical

power than some approaches (e.g., Sobel test), while also minimizing the Type I error rate (Hayes, 2013; MacKinnon et al., 2004). Third, PROCESS bootstrapping has the ability to estimate the conditional effects in complex moderated mediation models, which are exploratory analyses in the present study (Preacher, Rucker, & Hayes, 2007).

Regression Models

For hypothesis-testing and exploratory analyses, a series of linear regression models (when CIMT was the dependent variable) and logistic regression models (when CAC was the dependent variable) were conducted. The first set of models was adjusted for the demographic factors (demographic-adjusted models), and the second set was further adjusted for the biomedical factors (fully-adjusted models).

Test of Hypotheses

To test Hypothesis 1, the SLEs measure was entered as the independent variable into models predicting CIMT or CAC. To test Hypothesis 2, one of the depressive symptom severity measures (HAM-D-17 or CES-D-SF) was entered as the independent variable into models predicting CIMT or CAC. The depressive symptom severity measures were examined in separate models.

To test hypothesis 3, I used Model 1 in the PROCESS Macro for SPSS to conduct moderated multiple regressions (Hayes, 2013). This model was constructed to test the conditional effect of SLEs on subclinical atherosclerosis based on depressive symptom severity. For these models, SLEs was entered as the independent variable (X) and CIMT

or CAC as the outcome variable (Y). One of the depressive symptom severity measures was entered as the moderator variable (W) in separate models.

Exploratory Analyses

Moderated Mediation

In exploratory analyses, I planned to explore several candidate mechanisms (i.e., tobacco use, fruit and vegetable consumption, physical activity, and C-reactive protein) of the moderation effect of Hypothesis 3. Two of these potential mediators could not be analyzed and were excluded from these analyses. First, physical activity was excluded because a majority (n = 171) of the sample did not complete key components of the questionnaire (e.g., frequency or duration) required to calculate activity levels. Second, the dichotomous measure of tobacco use was excluded because PROCESS macros does not currently allow for categorical mediator variables (Hayes, 2013). Therefore, in this exploratory analysis, I tested whether number of daily fruit and vegetable servings and C-reactive protein partially mediate the SLE by depressive symptom severity interaction predicting subclinical atherosclerosis. This moderated mediation is also called conditional process modeling (Preacher et al., 2007). I conducted these conditional process models using Model 7 of the PROCESS macro for SPSS (Hayes, 2013). Model 7 allows the indirect effect of an independent variable (X: SLEs) on a dependent variable (Y: CIMT or CAC) through mediators (M: fruit and vegetable consumption and C-reactive protein) to be moderated (W: HAM-D-17 or CES-D-SF). Both mediators were included in models simultaneously. In this moderated mediation model, the indirect effect through the

mediator is constructed as the product of the X → M effect, which is conditional on W, and the M → Y effect. In this Model 7, the "index of moderated mediation" is an inference about whether the indirect effect is moderated. The effects from initial models utilizing CIMT as the Y variable were smaller than the number of decimal places provided in the PROCESS outputs. Therefore, for these moderated mediation analyses, the units of the CIMT variable were converted from millimeters to micrometers.

Alternative Mediation Model

I also tested an alternative mediation model, which examined whether depression mediates the relationship between SLEs and subclinical atherosclerosis. I used Model 4 in the PROCESS Macro for SPSS to conduct mediation multiple regressions (Hayes, 2013). This model tests whether the indirect effect of SLEs on subclinical atherosclerosis (CIMT or CAC) through depressive symptoms severity (HAM-D-17 or CES-D-SF) is significant. For these models, SLEs was entered as the independent variable (X) and CIMT or CAC as the outcome variable (Y). One of the depressive symptom severity measures (HAM-D-17 or CES-D-SF) was entered as the mediator variable (M).

Sensitivity Analyses

For significant relationships, I had planned to rerun all analyses after excluding AAH-Heart participants with clinical (i.e., physician diagnosed) CVD to minimize concerns regarding reverse causality (i.e., clinical CVD leading to increased reports of SLEs and depressive symptoms). Because no significant relationships were detected, none of these sensitivity analyses was performed.

RESULTS

Characteristics of Participants

Descriptive statistics for the final cohorts (CIMT *N*= 274 and CAC *N*=279) are presented in Table 1. Participants' ages ranged from 59-75 years, with a mean age of 66 years. The cohorts were predominantly female, and the mean education level was 13 years.

In both cohorts, 17.5% of participants had a mean arterial pressure that is indicative of hypertension (≥ 107 mmHg; Carlsson, Johansson, Theobald, & Wändell, 2013), and over 70% reported taking an antihypertensive medication. Concerning cholesterol variables, 7.3-7.9% of the participants had high LDL cholesterol (≥ 160 mg/dL; National Institutes of Health, 1998), 4.7% had low HDL cholesterol (< 35 mg/dL), and approximately 40% reported taking a lipid lowering medication. A total of 30% reported a diabetes diagnosis, 28% had HbA1c values indicative of diabetes (≥ 6.5%; World Health Organization, 2011), and 27% reported taking a diabetes medication. The mean BMI fell in the obese range (BMI ≥ 30 kg/m^2). The average number of daily fruit and vegetable servings was 3.9-4.0, and the average C-reactive protein level was 12.7-13.0 mg/L.

The range for the number of SLEs reported was 0 to 11, with a mean of 4.3-4.4. Mean HAM-D-17 and CES-D-SF scores fell in the no depression ranges; however, 22% had a HAM-D-17 score ≥ 8, and 18% had a CES-D-SF score ≥ 8, which are indicative of clinically relevant depression (Levine, 2013; Zimmerman, Martinez, Young, Chelminski, & Dalrymple, 2013). Additionally, 11-12% of the participants reported taking an antidepressant medication. Concerning indicators of subclinical atherosclerosis, mean CIMT was 0.83 mm, and 70% of participants had CAC.

Zero Order Correlations

Pearson's *r (r)* zero order correlations between predictor (SLEs), moderator (HAM-D-17 and CES-D-SF), and outcome variables (CIMT and CAC) were computed in SPSS and are presented in Table 2. As would be expected, I found a strong positive association between the two depressive symptom measures (r = .75 for HAM-D-17 and CES-D-SF). These depressive symptom measures had weak to moderate positive relationships with SLEs (r = .35 [CIMT Cohort] and r = .34 [CAC Cohort] for HAM-D-17 and SLEs; r = .25 for CES-D-SF and SLEs). There was a weak but significant relationship between measures of subclinical atherosclerosis (r = .75 for CIMT and CAC). Lastly, there were no significant zero order associations of psychosocial factors (SLEs, HAM-D-17, or CES-D-SF) with measures of subclinical atherosclerosis (CIMT or CAC).

Primary Results

Tests of Hypotheses 1 and 2

Regression models testing main effects of SLEs and depressive symptoms on CIMT or CAC revealed no significant effects (see Table 3). In demographic-adjusted models, number of SLEs was not associated with CIMT ($p = 0.73$) or CAC ($p = 0.23$). HAM-D-17 score was also not associated with CIMT ($p = 0.30$) or CAC ($p = 0.39$). As is shown in Table 3, a similar pattern emerged when substituting the secondary depressive symptom measure (CES-D-SF) for the HAM-D-17 in the models ($p = 0.61$ for CIMT and p = 0.21 for CAC). Finally, in fully-adjusted models, number of SLEs ($p = 0.98$ for CIMT and $p = 0.16$ for CAC), HAM-D-17 ($p = 0.35$ for CIMT and $p = 0.77$ for CAC), and CES-D-SF ($p = 0.71$ for CIMT and $p = 0.34$ for CAC) remained unrelated to CIMT and CAC. Thus, the results did not support Hypothesis 1 or 2.

Test of Hypothesis 3

Regression models testing the number of SLEs by depressive symptom interactions for CIMT or CAC revealed no significant effects (see Table 4). In demographic-models, the number of SLEs by HAM-D-17 interaction was not associated with CIMT ($p = 0.69$) or CAC ($p = 0.50$). This pattern of results remained the same in fully-adjusted models ($p = 0.89$ for CIMT and $p = 0.69$ for CAC) and in a parallel set of analyses testing the number SLEs by CES-D-SF interaction (demographic-adjusted models: $p = 0.72$ for CIMT and $p = 0.25$ for CAC; fully-adjusted models: $p = 0.83$ for CIMT and $p = 0.38$ for CAC). Therefore, the results did not support Hypothesis 3.

Exploratory Results

Moderated Mediation Results

In the moderated mediation models, I tested whether number of daily fruit and vegetable servings and C-reactive protein partially mediated the hypothesized interaction between SLEs and depressive symptom severity (HAM-D-17 or CES-D-SF) for CIMT and CAC. Across all models, there was no evidence of moderated mediation as determined by the index of moderated mediation, an inference about whether indirect effects are moderated by the depressive symptom measures. In demographic-adjusted models (N = 249), the index of moderated mediation for number of daily fruit and vegetable servings (Index = .0553, SE = .0636, 95% CI: -.0342 to .2257) and CRP (Index = -.0008, SE = .0627, 95% CI: -0.1410 to 0.1261) was not significant for CIMT (μm). The index of moderated mediation for number of daily fruit and vegetable servings (Index = -.0003, SE = .0007, 95% CI: -.0029 to .0006) and CRP (Index = .0000, SE = .0014, 95% CI: -.0027 to .0036) was also not significant for CAC (N = 253). In fully-adjusted models and a parallel set of analyses substituting the CES-D-SF for the HAM-D-17, all 95% confidence intervals for the index of moderation mediation contained zero, indicating that potential indirect effects were not moderated by the depression symptom measures.

Alternative Mediation Model Results

Regression models testing depressive symptom severity as a potential mediator of the SLE-subclinical atherosclerosis relationship revealed no significant indirect effects.

Number of SLEs was positively associated with HAM-D-17 (*B* = 0.6719, *SE* = 0.1087, 95% *CI* = 0.4580 to 0.8859, *p* < .0001), which in turn was unrelated to CIMT (*B* = .0021, *SE* = .0017, 95% *CI* = -.0012 to .0054, *p* = 0.22). Number of SLEs was not indirectly related to CIMT through HAM-D-17 (point estimate of indirect effect = .0014, *SE* = .0012, 95% *CI* = -.0010 to .0040).

Results were similar in models examining CAC. Once again, number of SLEs was positively associated with HAM-D-17 (*B* = 0.6602, *SE* = 0.1106, 95% *CI* = 0.4424 to 0.8781, *p* <.0001), HAM-D-17 was not related to CAC (*B* = .0351, *SE* = .0509, 95% CI = -0.1797 to .0198 *p* = 0.19), and number of SLEs was not indirectly related to CAC through HAM-D-17 (point estimate of indirect effect = .0232, *SE* = .0186, 95% *CI* = -.0097 to .0636). In fully-adjusted models and a parallel set of analyses substituting the CES-D-SF for the HAM-D-17, no significant indirect effects were observed.

DISCUSSION

Summary of Findings

The present study sought to determine whether depressive symptoms moderate the relationships between SLEs in adulthood and subclinical atherosclerosis in a community sample of older, African American adults. Three hypotheses were tested. The hypothesis (Hypothesis 1) that SLEs would be positively associated with the degree of subclinical atherosclerosis was not supported, as there were no significant relationships between number of SLEs and CIMT or CAC. In addition, the hypothesis (Hypothesis 2) that depressive symptom severity would be positively associated with the degree of subclinical atherosclerosis was not supported, given that no significant associations of HAM-D-17 or CES-D-SF with CIMT or CAC were observed. Lastly, the hypothesis (Hypothesis 3) that depressive symptom severity would moderate the relationship between SLEs and subclinical atherosclerosis was also not supported. Models testing the number of SLEs by depressive symptoms (HAM-D-17 or CES-D-SF) interactions revealed no significant effects for CIMT or CAC.

Fit with Prior Literature

Regarding the first hypothesis, the absence of an association between SLEs and subclinical atherosclerosis in African Americans adds to the existing mixed literature on

this relationship. My results are consistent with those of by O'Malley and colleagues (2000), in which it was found that the number and severity of SLEs was not associated with CAC in U.S. Army personnel. However, my results conflict with a study by Troxel et al. (2003) that found that chronic stress scores were related to greater CIMT in African American women but not Caucasian women. Considering that (a) only two previous studies have examined a composite measure of SLEs in relation to subclinical atherosclerosis and (b) the findings of the study that examined racial/ethnic differences conflict with my results, it remains unclear as to the relationship between SLEs and subclinical atherosclerosis in African Americans. Notably, the previous study that observed a relationship in African Americans only used a female sample, whereas the present sample consisted of both men and women. In addition, the types of cumulative SLEs captured differed across measures in the current and previous studies, which may account for the inconsistent results (McQuaid et al., 1992). Specific types of stress (e.g., work stress and racial discrimination) have been found to be related to increased CIMT (Everson, Lynch, Chesney, 1997; Kamarck et al., 2004; Lewis et al., 2006; Muntaner et al., 1998; Nordstrom, Dwyer, Merz, Shircore, & Dwyer, 2001; Rosvall et al., 2002), suggesting that some types of SLEs may be more cardiotoxic than others.

Concerning the second hypothesis, the absence of an association between depressive symptom severity and subclinical atherosclerosis conflicts with previous results. Findings from most studies in this literature support a positive prospective relationship between depressive symptoms and subclinical atherosclerosis, with increased depressive symptom severity predicting longitudinal increases in CIMT (Stewart et al., 2007) and CAC (Haas et al., 2005; Janssen et al., 2011; Matthews, Chang, Sutton-Tyrrell,

Edmundowicz, & Bromberger, 2010; Stewart et al., 2012). Only one study, which was cross-sectional, did not detect such an association (O'Malley, Jones, Feuerstein, & Taylor, 2000). Although none of these investigations examined African American-only samples, studies have found (a) that relationships between depressive symptoms and subclinical atherosclerosis did not differ by race/ethnicity (Janssen et al., 2011; Stewart et al., 2012) and (b) that depressive symptom severity was related to CAC in African Americans but not Caucasians (Lewis et al., 2009).

With respect to the third hypothesis, the lack of SLEs by depressive symptoms interaction effects is inconsistent with results from one of my previous studies utilizing data from 28,583 adults from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) (Berntson & Stewart, 2014). In that study, a significant SLEs by depressive disorder interaction was found (*OR* = 1.20, 95% *CI*: 1.06-1.35, $p < 0.01$). Stratified analyses revealed that number of SLEs was a stronger predictor of incident CVD in adults with a lifetime depressive disorder (*OR* = 1.18, 95% *CI*: 1.10-1.27) than in adults without a lifetime depressive disorder (*OR* = 1.10, 95% *CI*: 1.07-1.14). Although it is presently unclear, several methodological differences may have contributed to these discrepant findings, including the study design (current study: cross-sectional; previous study: prospective), the study samples (current study: a local older, African American sample; previous study: a large sample representative of the U.S. population), the depression measures (current study: continuous symptom severity; previous study: dichotomous depressive disorder status), and the CVD measures (current study: CIMT and CAC; previous study: self-reported incident myocardial infarction, angina, or

arteriosclerosis). To my knowledge, no other studies have examined depressive symptom severity as a potential moderator of the SLE-CVD relationship.

Possible Explanations for Null Findings

The null findings of the present study (a) may reflect the true state of nature or (b) may be due to methodological issues preventing me from detecting the true state of nature (Kazdin, 2002). With respect to explanation (a), SLEs, depressive symptoms, and the SLEs by depressive symptoms interaction may be truly unrelated to subclinical atherosclerosis in African Americans. However, because the present results conflict with those of past studies (Hypothesis 1, 2 and 3; see preceding section) and there is a paucity of studies (Hypothesis 1 and 3), it is unclear if my null results reflect the true state of nature. In regards to explanation (b), a number of methodological issues (i.e., limitations) could also explain the null results.

First, inappropriate study design could explain inconsistencies with prior literature (Kazdin, 2002). The present study was a cross-sectional examination of temporal hypotheses. I assumed that current depressive symptom severity, in part, reflects a stable trait that precedes SLEs and downstream subclinical atherosclerotic progression. However, this may not be the case. Rather, if SLEs occurred prior to the onset of depressive symptoms, then I would have missed the hypothesized moderation effect. Therefore, a prospective study design is needed to best evaluate my temporal hypotheses.

Secondly, biased selection method could also explain inconsistencies with prior literature. Selection bias for the current study likely contributed to a relatively stable sample of participants (246/735 potential participants were unable to be contacted;

33.5%) with the time to participate (152/735 potential participants declined participation; 20.7%). This stability and time to participate may reflect a relatively low-stress sample which may have restricted range on both SLEs and depressive symptoms measures. This theory is consistent with descriptive statistics of my sample: low number of SLEs reported (CIMT Cohort Mean = 4.4; CAC Cohort Mean = 4.3) and low levels on HAM-D-17 (CIMT Cohort Mean = 5.2; CAC Cohort Mean = 5.2) and CES-D-SF (CIMT Cohort Mean = 4.7; CAC Cohort Mean = 4.7) depression measures. Therefore, the current study's sample characteristics could have restricted range in the independent (SLEs) and moderating (depressive symptoms) variables which may have contributed to null results.

Another methodological issue was that I was likely unable to capture some relevant SLEs with the current study's SLEs measurement method. The interview-based method of assessing all lifetime SLEs likely captured only major SLEs which occur infrequently, whereas this method is less likely to have captured relevant daily hassles. Because the type of SLEs likely captured occur less frequent than daily hassles they also are likely to produce a less frequent impact on CVD. Effects may have been detected if frequent stressful events in daily life were the target of measurement. Consistent with this notion, research on types of stress which tend to occur frequently (e.g., work stress and racial discrimination) have been found to be related to increased CIMT (Everson, Lynch, Chesney, 1997; Kamarck et al., 2004; Lewis et al., 2006; Muntaner et al., 1998; Nordstrom, Dwyer, Merz, Shircore, & Dwyer, 2001; Rosvall et al., 2002).

Another relevant methodological issue is possible error variance in the independent variable (Kazdin, 2002). The interview-based method used to assess SLEs

could introduce error variance through biased recall. First, the negative mood likely experienced by participants with depressive symptoms at the time of recall could have led to inflated reports of negative SLEs (Cohen, Towbes, & Flocco, 1988). Second, depression-related cognitive deficits may have reduced the accuracy of SLEs recall in participants with depressive symptoms (Brand, Jolles, & Gispen-de Wied, 1992).

Another methodological limitation that may have contributed to null results is a restricted range in the dependent variables. Age is a strong predictor of subclinical atherosclerotic progression. Therefore, the older age of the current sample (mean age = 66 years) may have restricted the range of the outcome variables, thereby making it more difficult to detect the hypothesized associations. Consistent with this idea, the degree of subclinical atherosclerosis in this sample (68.8% with CAC and mean CIMT of 0.83 mm) was higher than in previous studies utilizing younger samples [e.g., 58.8% with CAC (Lewis et al., 2009) and mean CIMT of 0.62 mm (Troxel et al., 2003) in CVD free African Americans].

As a last methodological limitation, the present study was likely underpowered, especially for tests of Hypothesis 3, due to its small sample relative to traditional epidemiologic studies. Thus, I may have made a type II error. This seems less likely, however, because I utilized bootstrapping analyses that maximized power through re-sampling and because no nonsignificant trends in the hypothesized directions were observed.

While the present study does have important limitations, it also has several strengths. Notable strengths include: (1) a sample of African Americans, (2) an interview-

based method of assessing SLEs, (3) multiple measures of depressive symptom severity and subclinical atherosclerosis, and (4) bootstrapping analyses that maximize statistical power.

Recommendations for Future Research

Although none of the hypothesized effects was detected, replication is needed before definitive evidence of absence can be claimed. This future research should include: (1) a prospective design to determine directionality of any observed relationships, (2) a good representation of African Americans and women to explore moderation by race/ethnicity and gender, (3) a larger middle-aged sample to ensure adequate power and maximize variability in measures of subclinical atherosclerosis, (4) assessments of multiple SLEs indicators (e.g. interview event counts and daily hassles) and depressive symptoms to examine their interactive effect, (5) assessments of multiple CVD outcomes, such as subclinical atherosclerosis and CVD events, to evaluate whether relationships change across the stages of the atherosclerotic process. Investigators should also consider performing separate analyses for men and women, given that there are gender differences in responses to stress (Matthews, Gump, & Owens, 2001), and for different types of SLEs, given that some SLEs may be more cardiotoxic than others (Bunker et al., 2003). Lastly, if effects are detected, investigators should examine mechanistic pathways that may underlie the interactive effect of SLEs and depressive symptoms on CVD outcomes (see Figure 1).

Conclusions

In summary, results of this cross-sectional study utilizing data from the AAH-Heart study suggest that SLEs, depressive symptoms, and their interaction are not associated with measures of subclinical atherosclerosis among older, African Americans adults. Because the current results are inconsistent with some past findings and there is a paucity of studies utilizing African American samples, future research is needed to examine the independent and interactive effects of SLEs and depressive symptoms on subclinical atherosclerosis and other CVD outcomes in this racial group. If my results are repeatedly replicated in studies with stronger methodology (see preceding section), it would suggest that SLEs, depressive symptoms, and their interactive effect do not promote atherosclerotic progression and clinical CVD among African American adults.

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TABLES

Table 1

Participant Characteristics for the CIMT and CAC Cohorts

Characteristic	CIMT Group (*n* = 274)	CAC Group (*n* = 279)
Age, years	65.6 (4.2)	65.6 (4.1)
Female, %	67.5	67.0
Education Level (range: 1-25 years)	13.4 (2.9)	13.4 (2.9)
Mean Arterial Pressure, mmHg	98.0 (11.1)	98.1 (11.0)
Low Density Lipoprotein Cholesterol, mg/dL	108.6 (36.5)	109.5 (36.8)
High Density Lipoprotein Cholesterol, mg/dL	59.4 (18.3)	59.5 (18.1)
HbA1c, mmol/mol	6.4 (1.2)	6.4 (1.2)
Diabetes, %	29.6	29.4
Body Mass Index, kg/m^2	32.1 (7.2)	32.0 (7.2)
Antihypertensive Medication, %	70.4	71.0
Lipid Lowering Medication, %	43.5	43.4
Diabetes Medication, %	27.4	27.2
Antidepressant Medication, %	11.3	11.8
†Number of Daily Fruit and Vegetable Servings (range: 0-6)	4.0 (2.6)	3.9 (2.3)
†C-Reactive Protein, mg/L	13.0 (17.3)	12.7 (16.6)
Number of SLEs (possible range: 0-11)	4.4 (2.9)	4.3 (2.9)
HAM-D-17 (possible range: 0-52)	5.2 (5.4)	5.2 (5.5)
‡CES-D-SF (possible range: 0-33)	4.7 (5.3)	4.7 (5.4)
CIMT, mm	.83 (.14)	-
CAC, %	-	68.8

Note. Continuous variables are presented as mean (standard deviation), and categorical variables are presented as percentage. HbA1c = hemoglobin A1c. SLEs = stressful life events. HAM-D-17 = 17-item Hamilton Rating Scale for Depression. CES-D-SF = Center for Epidemiologic Studies Depression Scale – Short Form. CIMT = Carotid Intima-Media Thickness. CAC = Coronary Artery Calcification.

† Number of daily fruit and vegetable servings and C-reactive protein are based on reduced exploratory analysis samples: CIMT cohort *N* = 249 and CAC cohort *N* = 253.

‡CES-D-SF scores are based on reduced sensitivity analysis samples: CIMT cohort *N* = 253 and CAC cohort *N* = 257.

Table 2

Zero Order Correlations between Stressful Life Events, Depressive Symptoms and Subclinical Atherosclerosis

Variable	1	2	3	4	5
1. Number of SLEs	-	**.34**	**.25**	..	-.09
2. HAM-D-17	**.35**	-	**.75**	..	.04
3. † CES-D-SF	**.25**	**.75**	-	..	.07
4. CIMT, mm	-.05	.06	.04	-	**.15**
5. CAC, %	..	..	..	**.15**	-

Note. Bolded coefficients are significant at $p < .05$ level. SLEs = stressful life events. HAM-D-17 = 17-item Hamilton Rating Scale for Depression. CES-D-SF = Center for Epidemiologic Studies Depression Scale – Short Form. CIMT = Carotid Intima-Media Thickness. CAC = Coronary Artery Calcification.

Coefficients in the non-shaded area are based on the CIMT cohort ($N = 274$) and coefficients in the shaded area are based on the CAC cohort ($N = 279$).

† Correlations with the CES-D-SF variable are based on reduced sensitivity analysis samples: non-shaded area CIMT cohort $N = 253$ and shaded area CAC cohort $N = 257$.

Table 3

Results of Regression Models Testing Main Effects of Number of Stressful Life Events (SLEs) and Depressive Symptoms on Carotid Intima-Media Thickness (CIMT) Coronary Artery Calcification (CAC)

	CIMT (*N* = 274)		CAC (*N* = 279)	
	Demographic-adjusted models†	Fully-adjusted models‡	Demographic-adjusted models†	Fully-adjusted models‡
	B (*SEB*)	*B* (*SEB*)	*B* (*SEB*)	*B* (*SEB*)
Number of SLEs	-.0011 (.0031)	.0001 (.0031)	-.0578 (.0478)	-.0752 (.0528)
HAM-D-17	.0016 (.0016)	.0016 (.0017)	.0217 (.0251)	.0082 (.0280)
CES-D-SF◊	.0008 (.0017)	.0007 (.0018)	.0354 (.0283)	.0303 (.0316)

Note. B = unstandardized regression coefficient. *SEB* = standard error of *B*. HAM-D-17 = 17-item Hamilton Rating Scale for Depression. CES-D-SF = Center for Epidemiologic Studies Depression Scale – Short Form.

†Adjusted for demographic factors (age, sex, and education).

‡Adjusted for demographic factors (age, sex, and education), cardiovascular risk factors (mean arterial pressure, low-density lipoprotein, high-density lipoprotein, log transformed HbA1c, body mass index, and diabetes), and medication use (antihypertensive, lipid-lowering, diabetes, and antidepressant medication use).

◊Models with CES-D-SF score utilized reduced sensitivity analysis samples: CIMT cohort *N* = 253 and CAC cohort *N* = 257.

Table 4

Results of Regression Models Testing the Stressful Life Events (SLEs) by Depressive Symptoms Interactions for Carotid Intima-Media Thickness (CIMT) and Coronary Artery Calcification (CAC)

	CIMT (*N* = 274)		CAC (*N* = 279)	
	Demographic-adjusted models†	Fully-adjusted models‡	Demographic-adjusted models†	Fully-adjusted models‡
	B (*SEB*)	*B* (*SEB*)	*B* (*SEB*)	*B* (*SEB*)
SLEs by HAM-D-17 Interaction	.0002 (.0005)	.0001 (.0005)	-.0057 (.0085)	-.0036 (.0090)
SLEs by CES-D-SF Interaction◊	.0002 (.0006)	.0001 (.0006)	-.0099 (.0105)	-.0077 (.0110)

Note. B = unstandardized regression coefficient. *SEB* = standard error of *B*. HAM-D-17 = 17-item Hamilton Rating Scale for Depression. CES-D-SF = Center for Epidemiologic Studies Depression Scale – Short Form.

†Adjusted for demographic factors (age, sex, and education).

‡Adjusted for demographic factors (age, sex, and education), cardiovascular risk factors (mean arterial pressure, low-density lipoprotein, high-density lipoprotein, log transformed HbA1c, body mass index, and diabetes), and medication use (antihypertensive, lipid-lowering, diabetes, and antidepressant medication use).

◊Models with CES-D-SF score utilized reduced sensitivity analysis samples: CIMT n = 253 and CAC n = 257.

FIGURES

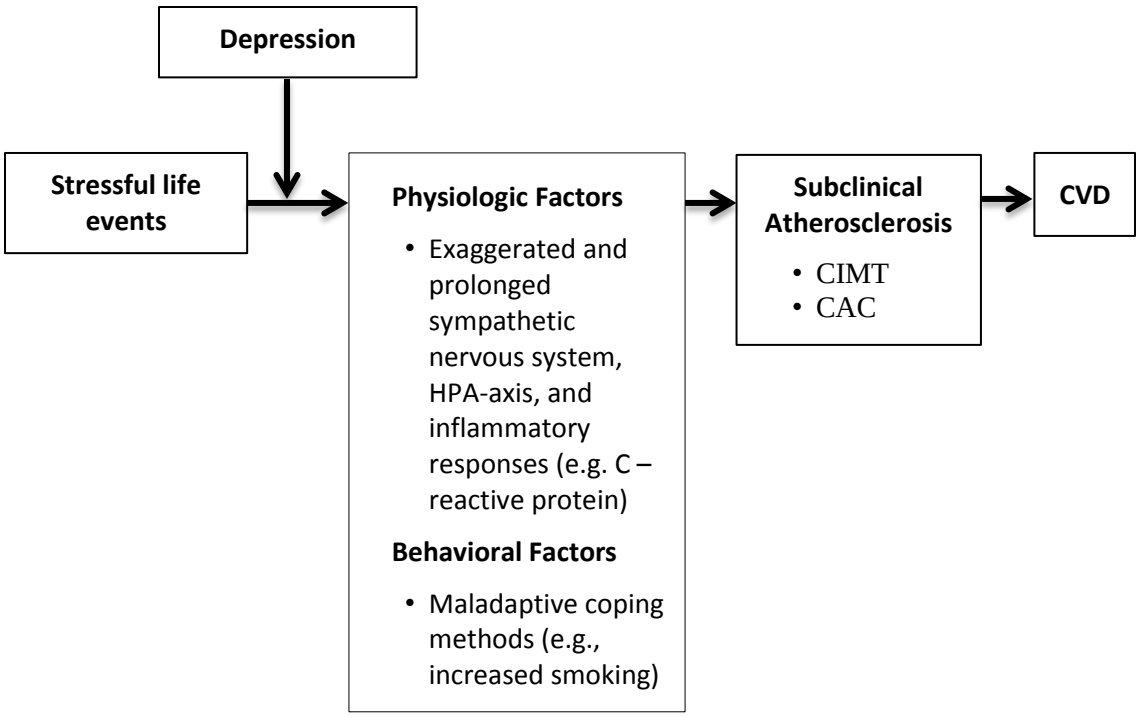

Figure 1. Conceptual model depicting potential relationships among stressful life events, depression, and cardiovascular disease. CIMT = carotid intima-media thickness. CAC = coronary artery calcification. CVD = cardiovascular disease.

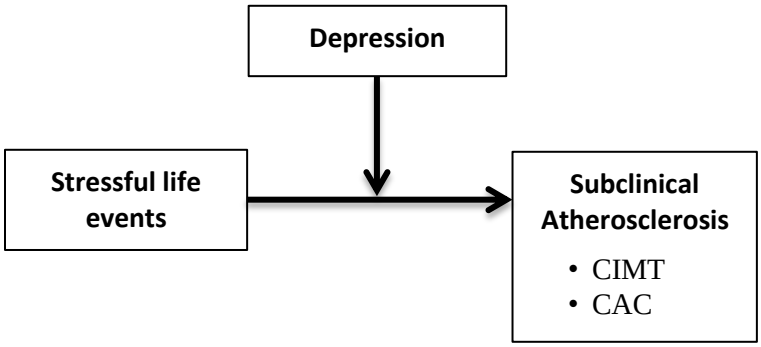

Figure 2. Conceptual model depicting hypothesized relationships among the variables examined in the present study. CIMT = carotid intima-media thickness. CAC = coronary artery calcification.

APPENDIX

APPENDIX

Life Events Interview

Instructions: Use this form to guide the life events interview and to take notes. Use the Life Events Record (LER) form to record data based on this interview.

Severity Rating Scale:
1 = Somewhat stressful: unpleasant, difficult, but not too serious.
NOTE: Do not record discrete Level 1 events on the LER form, but do code chronic Level 1 events.
2 = Very stressful: e.g., caused significant loss or harm; created a lot of pressure; was difficult to cope with; provoked a strong negative emotional reaction such fear, anxiety, anger, or discouragement; etc.
3 = Extremely stressful or traumatic: e.g., caused severe loss or harm; was a terrible, devastating,
catastrophic experience; produced an intense or overwhelming emotional reaction; etc.

Chronicity: *Code the duration of the stressor, not the duration of its emotional or other effects on the patient.*
C = Chronic: stressful event or situation that lasted more than a few weeks; lasted months or years.
D = Discrete: stressful event that lasted no more than a few hours, days, or weeks.

Period:
A = Adulthood; a stressful event or situation that occurred when patient was at least 18 years old.
C = Childhood; a stressful event or situation occurred before patient was 18 years old.
R = Recent; a stressful event or situation that occurred within the past 6 months.

Carving Up Multifaceted Events: A single event or situation might fit multiple categories. For example, the initiating (triggering) event may represent one kind of stressors, and the aftermath may represent several different kinds of stressors. E.g., a car crash might be coded as a serious injury, the months of rehab that followed might be coded as a stressful medical treatment, and the job loss due to accident-related disability might be coded as a financial or work-related problem. Thus, it might take several different codes to describe a car crash and its aftermath.

In such cases, count the entire, complex situation as a single stressful life event if at all possible. This means that you should try to code it on a single row of the LER form. Code as many categories as applies to the event. Within each category, pick the most stressful item that applies. E.g., for the car crash example above, you would enter 1 in column A if the injury itself was the

most stressful aspect of the medical situation. If, on the other hand, the rehab was more stressful than the crash, you would enter 5 (rather than 1) in column A. Since the crash also resulted in job loss due to disability, you would enter 4 in column C. If a friend was entered in the same crash, you might enter a 5 in column D for the same event.

Some aspects of a complex event might be more stressful than others; pick the severity rating corresponding to the worst level of stress that applies to the event. E.g., if the crash was "extremely traumatic" but losing the job because of accident-related disability was "very stressful", the event would be coded as a level 3. Similarly, some aspects of the event may happen quickly (e.g., the crash), whereas others may unfold over a longer period of time (e.g., the rehab or the unemployment that followed). If any part of the event is long-lasting, choose C for the chronicity code. If none of it took longer than a few weeks to resolve, choose D.

Instructions for the Patient

This interview is about the stressful experiences you've had during your lifetime. I'm going to ask you about a variety of different kinds of stressful events and situations. I'm going to start by asking you about any stressful experiences you might have had in the past 6 months. Next, we'll talk about ones you've had during any other time in your adult life. Finally, we'll talk about any serious stressful or traumatic experiences you might have had when you were a child or a teenager. Please let me know if there are any stressful or traumatic events that you don't want to talk about, please let me know.

Have you had any very stressful experiences or problems in the past 6 months? *If the participant brings up a recent SLE, probe for details so that you can code it in terms of categories, severity, and chronicity. (The period will be Recent). Whether or not the participant brings up an event (or more than one event), briefly review categories A through G. Adapt your questions so they fit with what the participant has already told you.*

Example: **Besides the problem you just told me about, have you had any other stressful experiences in the past month? How about any stressful medical problems or injuries? Any stressful changes in your living situation? How about in your work or finances? etc.**

Let's think about other times in your adult life, before the last 6 months. You're in your *(e.g., 70's)* now. How about in your 50's or 60's – did you have any very stressful experiences back then? Like a very stressful medical problem, financial problem, or family problem, for instance?

How about earlier in your adult life – when you were in your 30's or 40's? Or when you were a young adult, in your 20's?

Now let's talk about when you were a teenager – what were the most stressful things that happened to you back then?

How about when you were a child?

Review the list and ask: ***Can you think of anything else? Any serious losses, any really stressful or traumatic experiences, anything that was hard to handle or hard to cope with?***

Notes

#	Description	
1		Categories:
		Severity: 1 2 3
		Chronicity: Chronic Discrete
		Period: Child Adult Recent
2		Categories:
		Severity: 1 2 3
		Chronicity: Chronic Discrete
		Period: Child Adult Recent
3		Categories:
		Severity: 1 2 3
		Chronicity: Chronic Discrete
		Period: Child Adult Recent
4		Categories:
		Severity: 1 2 3
		Chronicity: Chronic Discrete
		Period: Child Adult Recent

Event Categories and Codes

A. Medical Illnesses, Injuries, Medical Care	**B. Stressful Changes in Living Arrangement**
A1.Serious illness or injury A2. Hospitalized for serious illness A3. Hospitalized for serious injury A4. Major surgery A5. Stressful medical treatment A6. Other stressful medical event or situation A7. Multiple events in this category	B1. Relocation to nursing home | other care facility B2. Lost home to fire, flood, or other disaster B3. Lost home for financial or other reasons B4. Became homeless B5. Incarcerated in jail, prison, or other institution B6. Other stressful change in living arrangement B7. Multiple events in this category
C. Financial, Work, or School-Related Problems	**D. Non-Family Relationship Problems**
C1. Serious financial crisis C2. Laid off of job C3. Fired from job C4. Lost job due to disability C5. Lost job for other reason C6. Had to change job or career C7. Had to quit school C8. Failed out of school C9. Other stressful financial, work, or school problem C10. Multiple events in this category	D1. Break-up of romantic relationship D2. Serious illness of boyfriend | girlfriend | partner D3. Death of boyfriend | girlfriend | partner D4. Estrangement | separation from friend | confidant D5. Serious injury or illness of friend | confidant D6. Death of close friend | confidant D7. Social isolation or rejection D8. Other relationship crisis | loss D9. Multiple events in this category
E. Marital Relationships	**F. Family Relationships**
E1. Separation, divorce, or break-up E2. Serious injury or illness of current spouse E3. Death of current spouse E4. Serious injury or illness of former spouse E5. Death of former spouse E6. Serious injury or illness of my child's other parent E7. Death of my child's other parent E8. Other marital crisis or loss E9. Multiple events in this category	F1. Birth or adoption of a child F2. Stillbirth, miscarriage, or abortion F3. Serious injury or illness of a minor child F4. Death of a minor child F5. Serious injury or illness of an adult child F6. Death of an adult child F7. Serious injury or illness of parent F8. Death of parent F9. Serious injury or illness of other family member F10. Death of other family member F11. Family member victim of crime F12. Family member victim of disaster F13. Other family crisis or loss F14. Multiple events in this category

G. Violence or Trauma	H. Childhood
G1. Victim of serious nonviolent crime G2. Victim of violent crime G3. Victim of sexual assault G4. Victim of sexual abuse G5. Victim of physical abuse G6. Victim of emotional abuse G7. Victim of neglect or abandonment G8. Victim of natural disaster G9. Victim of man-made accident or disaster G10. Victim of terrorism, riot, or other violent event G11. Witnessed violent crime or traumatic event G12. Military deployment to a war or disaster zone G13. Participation in military combat G14. Other violent or traumatic event in adulthood G15. Multiple events in this category	H1. Parents separated or divorced H2. Moved to foster home or care facility H3. Moved to other place away from home H4. Other childhood problem H5. Multiple events in this category