Graduate School ETD Form 9
(Revised 12/07)

PURDUE UNIVERSITY
GRADUATE SCHOOL
Thesis/Dissertation Acceptance

This is to certify that the thesis/dissertation prepared

By Stephanie Case

Entitled
Is Depression a Stronger Risk Factor for Cardiovascular Disease among Individuals with a History of Adverse Childhood Experiences?

For the degree of Master of Science

Is approved by the final examining committee:

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Head of the Graduate Program Date

IS DEPRESSION A STRONGER RISK FACTOR FOR CARDIOVASCULAR DISEASE AMONG INDIVIDUALS WITH A HISTORY OF ADVERSE CHILDHOOD EXPERIENCES?

A Thesis

Submitted to the Faculty

of

Purdue University

by

Stephanie M. Case

In Partial Fulfillment of the

Requirements for the Degree

of

Master of Science

December 2013

Purdue University

Indianapolis, Indiana

For my son, who reminds me everyday to “Just keep swimming”.

ACKNOWLEDGMENTS

Thank you, Dr. Jesse Stewart, for your guidance as a mentor, expertise, and assistance at every stage of this process. Additionally, my sincere gratitude to my committee members, Dr. Melissa Cyders and Dr. Adam Hirsh, for their invaluable expertise and feedback.

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ABSTRACT

Case, Stephanie M., M.S., Purdue University, December 2013. Is Depression a Stronger Risk Factor for Cardiovascular Disease Among Individuals with a History of Adverse Childhood Experiences? Major Professor: Jesse C. Stewart.

Epidemiologic studies suggest that depression is an independent risk factor for cardiovascular disease (CVD). Although several possible mediators of this association have been proposed, few studies have examined the role of moderators. Accordingly, I examined adverse childhood experiences (ACE) as a potential moderator of the depression-CVD association, given that individuals with a history of ACE show a greater inflammatory response to depression, and inflammation plays a role in the development of CVD. Data from Waves 1 and 2 of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) were analyzed. Participants were 29,282 adults (58% female, 42% non–white) aged 18–97 years, free of CVD diagnoses at baseline. Lifetime depressive disorder (LDD) was assessed by the Alcohol Use Disorder and Associated Disabilities Interview Schedule–IV (AUDADIS–IV), and adverse childhood experiences (abuse, neglect, and household dysfunction), and CVD were assessed during separate interviews. The primary outcome was incident CVD (n = 1,255), defined as nonfatal arteriosclerosis, angina pectoris, myocardial infarction, and/or stroke reported during the Wave 2 interviews. All analyses were adjusted for demographic and traditional CVD risk

factors. Logistic regression models revealed that both LDD (*OR* = 1.44, 95% *CI*: 1.28–1.62, $p < .001$) and any ACE (*OR* = 1.25, 95% *CI*: 1.16–1.35, $p < .001$) were independent predictors of incident CVD. Interactions between LDD x any ACE ($p = .024$), LDD x neglect ($p = .003$), and LDD x household dysfunction ($p < .001$), but not LDD x abuse ($p = 0.16$), were detected. Analyses stratified by the ACE variables revealed that LDD was a predictor of incident CVD among adults with a history of (1) any ACE (*OR* = 1.51, 95% *CI*: 1.32–1.73, $p < .001$), but not among those without a history (*OR* = 1.15, 95% *CI*: 0.87–1.50, $p = .332$); (2) neglect (*OR* = 1.59, 95% *CI*: 1.36–1.87, $p < .001$) and among those without a history (*OR* = 1.25, 95% *CI*: 1.07–1.62, $p = .005$); (3) household dysfunction (*OR* = 1.73, 95% *CI*: 1.46–2.04, $p < .001$), but not among those without a history (*OR* = 1.18, 95% *CI*: 0.96–1.43, $p = .11$). Overall, the present findings suggest that depression may be a stronger risk factor for CVD among adults with a history of ACE, especially neglect and household dysfunction, than among adults who did not have these experiences.

INTRODUCTION

Cardiovascular disease (CVD) is one of the most costly and prevalent conditions in the United States, accounting for almost $300 billion in healthcare costs and causing one of every three deaths (Roger et al., 2012). Depression, which is also highly prevalent, has been found to be a predictor of future CVD, even after adjustment for traditional CVD risk factors (Van der Kooy et al., 2007). Several candidate mechanisms underlying the depression-CVD relationship have been proposed, including increased systemic inflammation (Raedler, 2011).

To date, few studies have examined moderators of the depression-CVD relationship. One potential moderator is a history of adverse childhood experiences (ACE). These experiences are thought to over-activate the stress response and disrupt the normal functioning of homeostatic regulatory systems, including the inflammatory response (Danese & McEwen, 2012). Evidence of an exaggerated inflammatory response in individuals with a history of ACE provides a rationale for why the depression-CVD relationship may be stronger in these individuals. The current study seeks to address the following question: Is a lifetime depressive disorder a stronger risk factor for CVD among individuals with a history of ACE versus those who have not had such experiences?

Before describing the methodology of the proposed study, several topics will be discussed. First, CVD will be reviewed along with traditional and emerging risk factors for CVD. Second, the depression-CVD relationship will be discussed. Third, the topic of ACE will be introduced, followed by the rationale for why ACE may moderate the depression-CVD relationship. Finally, the conceptual and tested models for the proposed study are presented, including the associated hypotheses.

Cardiovascular Disease

CVD refers to a wide variety of conditions that affect the circulatory system. In this study, however, I will focus on the type of CVD that arises from atherosclerosis (Epstein & Ross, 1999). Atherosclerosis, a subtype of arteriosclerosis, is characterized by the thickening and hardening of the blood vessels due to the accumulation of deposits of modified cholesterol and fatty acids in the vessel walls over several decades. For the purposes of this study, CVD will refer to atherosclerotic CVD for the remainder of the document.

Pathophysiology of Atherosclerosis

Atherosclerosis is a progressive condition that is thought to be the consequence of several physiological and behavioral factors. The most likely mechanism of atherosclerosis involves an inflammatory response to natural circulatory products, which begins with cholesterol (Epstein & Ross, 1999). Cholesterol is obtained from the diet and

is manufactured by the liver. Cholesterol is an integral protein in the cellular membrane that aids in moving materials into and out of the cell to maintain proper function. To be effective in this cellular process, cholesterol must be transported to cells in need of it. The transport and removal of excess cholesterol is maintained by low–density lipoproteins (LDLs) and high–density lipoproteins (HDLs). HDLs are efficiently able to transport cholesterol from the blood vessel to the target cells. However, cholesterol transport by LDLs is less efficient, and these complexes have the potential to become trapped in the innermost wall of vessels, resulting in thickening.

The process of the vessel thickening is not achieved by LDL–cholesterol deposition alone; it is a complex process that involves an inflammatory response by the immune system. When LDL–cholesterol complexes remain lodged in the vessels, they become oxidized. The oxidation process prompts an attempt to clear these complexes by signaling the immune system. The cell signaling can be accomplished by a variety of proteins or peptides. One important signaling molecule in this process is called a cytokine. Macrophages, one of the first responders to the foreign agents, engulf the LDL–cholesterol complexes and expand to become foam cells. Once these foam cells form, they are not able to be removed and thus become permanently embedded in the vessel wall. The accumulation of this type of cellular debris causes a thickening of the inner wall that initially expands toward the most outer elastic layer of the vessel. At this stage, the vessel can be classified as having a fatty streak. These increasing large foreign bodies further signal the immune system to activate a response utilizing T lymphocytes. This process promotes the recruitment of smooth muscle cells to the site of buildup, further expanding the vessel by developing a fibrous capsule on the inner wall.

Eventually, this buildup causes a complete fibrous encapsulation of the foam cells, which becomes an atherosclerotic plaque. Calcium can also be deposited into the plaque, making the vessel hard and inflexible. One consequence of atherosclerosis is a narrowing diameter of the vessel, which decreases the amount of oxygenated blood that is delivered to tissues. However, a more severe consequence is the rapid flowing blood, which can rupture an atherosclerotic plaque. The broken–off plaque, or its debris, can then travel to other areas of the body and occlude blood flow completely, resulting in tissue death.

Atherosclerosis can occur in vessels throughout the body; however, when it occurs in the arteries of the heart or brain, severe consequences may result. When atherosclerosis occurs in the vessels of the heart, coronary artery disease (CAD) may develop. Nearly 90% of CVD cases are classified as CAD, and it accounts for about half of all CVD deaths (Roger et al., 2012). The consequences of CAD include three clinical syndromes: angina pectoris, myocardial infarction (MI), and sudden cardiac death. Angina pectoris is defined as insufficient blood flow to the heart muscle, which physically manifests as chest pain. An MI occurs when a lack of blood supply to the heart, due to an occlusion, causes death of heart muscle. Similarly, when atherosclerosis occurs in vessels of (or that immediately lead to) the brain, plaque rupture (hemorrhage) or an obstruction (thrombosis if clots formed locally or embolism if clots formed elsewhere) can restrict blood flow to areas of the brain, which may result in a stroke (Labarthe, 2010). Damage in non-vital areas of the brain can result in permanent loss of function and damage in vital areas (e.g., the brainstem) may result in death. In the proposed study, new diagnoses of arteriosclerosis, angina, nonfatal MI, and nonfatal stroke will be counted as incident CVD.

Risk Factors of Cardiovascular Disease

While some CVD risk factors are modifiable, others are not, such as age, sex, and race/ethnicity. The incidence of CVD increases with age and is accelerated in the presence of tobacco use, physical inactivity, and obesity (Cardi et al., 2010). Additionally, males have a higher incidence of CAD compared to females; however, women have a higher incidence of stroke (Roger et al., 2012). There is also evidence that African Americans have the highest incidence of CVD, followed by Caucasian and Mexican Americans (Schiller, Lucas, Ward, & Peregoy, 2010).

Several CVD risk factors that can be altered or eliminated have been identified over the past several decades (Lopez, Mathers, Ezzati, Jamison, & Murray, 2006). First, adults with hypertension, defined as a blood pressure greater than 140/90 mmHg, have more than twice the risk of developing CVD compared to those without hypertension (Kannel, 1996). Second, evidence from cross–sectional and longitudinal cohort studies supports the association between high cholesterol levels (> 200 mg/dL) and incident CVD (Ridker & Libby, 2005). Third, socioeconomic status is an associated risk factor for developing CVD. Although socioeconomic status can be defined by income, occupation, and/or education level, Winkleby et al. (1992) observed the strongest association between CVD and education level alone. Fourth, results of a recent meta–analysis indicate that individuals with diabetes have more than twice the risk of CVD than those without the condition (Seshasai et al., 2011). Fifth, as body mass index (BMI) increases, so does the risk of CVD (Wormser et al., 2011). Finally, tobacco use is often associated with an increased risk of future CVD (Kim et al., 2012; Libby & Theroux,

2005). Furthermore, studies suggest atherosclerosis and its consequences can be reduced by implementing smoking cessation programs (Pipe, Papadakis, & Reid, 2010). All of the aforementioned risk factors for CVD will be included as covariates in the analyses for the current study.

Depression-Cardiovascular Disease Relationship

Because traditional risk factors do not fully account for the development of CVD (Van der Kooy et al., 2007), the search for other risk factors continues. Among the emerging risk factors for CVD are depressive disorders and elevated depressive symptoms (Van der Kooy et al., 2007). Symptoms of depression include depressed mood, anhedonia, appetite disturbance, sleep disturbance, psychomotor retardation/agitation, fatigue, feelings of worthlessness, concentration problems, and suicidal ideation. To meet the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM–IV), criteria for major depressive disorder (MDD), an individual must have five or more depressive symptoms and at least one symptom must be either depressed mood or anhedonia. Additionally, the symptoms must be a cause of significant impairment or distress nearly every day, for at least two weeks (American Psychological Association, 2000). MDD has a lifetime prevalence of 17% (Fava & Cassano, 2004) and 20%–25% of these individuals will experience repeated episodes (Mueller & Leon, 1996).

Dysthymic disorder is another depressive disorder with symptoms similar to MDD, although the course and severity of the symptoms differ. The DSM–IV

characterizes dysthymic disorder as a depressed mood for most of the day, for more days than not, in addition to at least two of the depressive symptoms described above, with the exception of suicidality. The symptoms must last over a period of at least two years and, during this period, individuals cannot be symptom free for more than two months. The final criteria for a dysthymic disorder diagnosis is that during the first two years following onset, there can be no discernible episodes of MDD (APA, 2000). The lifetime prevalence of dysthymic disorder is 1.5% globally (Vos et al., 2012).

Research over three decades indicates that depression predicts the development of CVD, even after adjustment for traditional risk factors. Considerable evidence suggests that depression is an independent risk factor for atherosclerotic CVD, including CAD (*RR* = 2.34, *95% CI*: 1.54–3.56) and cerebrovascular disease (*RR* = 1.23, *95% CI*: 0.87–1.75) (Van der Kooy et al., 2007). Additionally, research from Rugulies and colleagues (2002) suggest a dose response in the depression-CVD relationship such that clinical depression is a stronger predictor of incident CVD (*RR* = 2.69, *95% CI*: 1.63–4.43) than elevated depressive symptoms (*RR* = 1.49, 95% *CI*: 1.16–1.92) (Rugulies, 2002). Furthermore, the depression-CVD relationship is consistent among different age groups, genders, and racial/ethnic groups (Rosengren et al., 2004; Suls & Bunde, 2005; Yusuf et al., 2004).

Several potential mechanisms underlying the depression-CVD relationship have been proposed, including behavioral and biological mechanisms. The candidate behavioral mechanisms include engaging in negative health behaviors and poor adherence to medications (Goldston & Baillie, 2008). Patten and colleagues (2009) found that individuals experiencing a major depressive episode are more likely to transition from an active to an inactive pattern of physical activity (Patten, Williams,

Lavorato, & Eliasziw, 2009). There is also evidence that individuals with depression engage in other poor health behaviors, such as tobacco use and consuming high–fat diets. For example, a 21–year study observed an increased incidence of daily smoking among individuals with versus without MDD (Fergusson, Goodwin, & Horwood, 2003). Moreover, individuals with MDD are less successful with tobacco cessation programs (Glassman et al., 1990). Poor diet has also been associated with depression, particularly poor diets that have a high fat content (Sánchez-Villegas et al., 2012). Finally, a meta–analysis found that individuals with depression were three times more likely to be noncompliant with medical treatment recommendations (DiMatteo, Lepper, & Croghan, 2000).

Candidate biological mechanisms that may underlie the depression-CVD relationship include dysfunction of the hypothalamic–pituitary–adrenal axis (Musselman & Nemeroff, 1996; Troxler, Sprague, Albanese, Fuchs, & Thompson, 1977), dysfunction of the autonomic nervous system (Berntson et al., 1997; Huikuri et al., 1999), altered platelet function (Markovitz & Matthews, 1991; Musselman et al., 1996), and increased systemic inflammation (Raedler, 2011). As before, I will describe the inflammatory process, as it relates to the current study.

Circulating markers of systemic inflammation are consistently elevated in both depression and CVD (Howren, Lamkin, & Suls, 2009; Pearson et al., 2003). Depressed individuals, versus nondepressed people, have been found to have higher levels of the proinflammatory cytokines, tumor necrosis factor alpha (TNF–α), interleukin (IL)–6, and IL–1 (Licinio & Wong, 1999; Raison, Capuron, & Miller, 2006). C–reactive protein (CRP), another inflammatory marker secreted from the liver in response to IL–6, is also

associated with depression (Pikhart et al., 2009). Moreover, elevations inflammatory markers, in depressed persons, persist even when depression is in remission (Cizza et al., 2008), suggesting chronic systemic inflammation. Similarly, patients with a history of angina, myocardial infarction, or stroke also have elevated CRP levels (Casas, Shah, Hingorani, Danesh, & Pepys, 2008). Finally, there is evidence that depression predicts elevations in inflammatory markers over time (Stewart, Rand, Muldoon, & Kamarck, 2009) and that CRP and IL-6predicts incident CVD (Pearson et al., 2003).

A History of Adverse Childhood Experiences is a Candidate Moderator of the Depression-Cardiovascular Disease Relationship

In contrast to the attention given to mediation of the depression-CVD association, few studies have examined potential moderators of this relationship. Two recent meta–analyses, Nicholson et al. (2006) involving 54 studies and Van der Kooy et al. (2007) involving 28 studies, observed significant heterogeneity across studies, suggesting that moderators may be present. To my knowledge, a history of ACE has not been examined as a potential moderator of the depression-CVD relationship. Nonetheless, evidence suggests that persons exposed to ACE exhibit an exaggerated inflammatory response, which in turn may increase their risk of CVD.

Adverse Childhood Experiences

According to data from a nationally representative sample, the prevalence of any form of childhood maltreatment is approximately 10.2%, over a 12–month period, and 18.6% over a lifetime in the United States (Finkelhor et al., 2009). Childhood maltreatment has been defined as physical/emotional mistreatment, sexual abuse, or neglect that results in the actual or potential harm to a minor by someone who is in the role of a caregiver or a position of power (Child Abuse Prevention Treatment Act of 1974). In a study published in 1998, Felitti and colleagues (1998) broadened the definition of maltreatment by creating three categories, which collectively define ACE. The categories created by this group were abuse, neglect, and household dysfunction. Abuse can be physical (e.g., intentional use of force including biting, kicking, hitting, or shaking), sexual (e.g., fondling or rape), or psychological (e.g., inappropriate blaming, threatening, frightening, or hostile treatment). Alternatively, neglect involves the failure to provide basic needs and can occur in the following domains: physical (e.g., failure to provide nutrition, clothing, hygiene, or shelter), emotional (e.g., denying, ignoring, or restricting emotional responsiveness), medical (e.g., failure to provide access to medical, visual, or dental care), or educational (e.g., failure to enroll in school). Finally, household dysfunction includes forms of indirect abuse or neglect that often result when children are not provided with adequate supervision or safety. For example, this can occur when a caregiver leaves a minor with someone who does not have the capacity to fully respond to the minor's needs (e.g., an adult who is incapacitated due to alcohol intoxication or a severe mental illness). Household dysfunction also includes exposing

children to violent environments (e.g., witnessing abuse among family members) (Butchart, Phinney Harvey, Mian, Fürniss, & Kahane, 2006).

Adverse Childhood Experiences and the Inflammatory Response

ACE have the potential to produce long-term physiological consequences. These traumatic experiences are thought to activate a chronic stress response, which over time may result in the abnormal functioning of homeostatic mechanisms of the nervous, endocrine, and immune systems (Danese & McEwen, 2012; De Young, Kenardy, & Cobham, 2011). Evidence also suggests when these stressors occur during a critical developmental period, they may disrupt the proper development of these regulatory systems (Coe & Lubach, 2003; Langley-Evans & McMullen, 2010). In particular, altered immune system development and/or functioning in individuals with a history of ACE could result in exaggerated inflammatory responses to proinflammatory stimuli (Surtees et al., 2003).

Consistent with this idea, research suggests that individuals with a history of ACE exhibit evidence of a hyper-responsive inflammatory system. Both cross-sectional and longitudinal studies have found that adults with a history of ACE have elevated levels of circulating inflammatory markers. First, a cross-sectional study of 482 middle-aged twins found that those exposed to ACE had 22% higher CRP and 13% higher IL-6 levels than those who were not exposed to ACE. Next, a longitudinal study, conducted over 32 years, found that childhood maltreatment predicted elevated CRP levels 20 years later (Danese, Pariante, Caspi, Taylor, & Poulton, 2007). In addition, adults with a history of

ACE show exaggerated inflammatory responses to laboratory stressors when compared to adults without a history of ACE (Carpenter et al., 2010). Using a standardized laboratory stress protocol, Carpenter et al. (2010) observed greater stress-related increases in IL-6in those with versus without a history of ACE.

Adverse Childhood Experiences May Moderate the Inflammatory Response to Depression

It is well established that depression is accompanied by an increase in systemic inflammation (Howren et al., 2009), and some evidence suggests that depression predicts future elevations in inflammatory markers (Stewart et al., 2009). Therefore, it is reasonable to conceptualize depression itself as a proinflammatory stimulus. Similar to other proinflammatory stimuli, emerging evidence suggests that individuals exposed to ACE exhibit exaggerated inflammatory responses to depression. In a 32-year study, Danese et al. (2008) found that individuals who were both depressed and maltreated had higher serum CRP levels compared to those who were depressed only, maltreated only, or neither depressed nor maltreated (control group). The observed effect sizes, versus controls, were $d = 0.12$ for the depressed only group, $d = 0.29$ for the maltreated only group, and $d = 0.48$ for the depressed and maltreated group. Furthermore, when controlling for CVD risk factors, analyses revealed that clinically significant levels of inflammation were two times more likely in those who were depressed and maltreated than in controls (Danese et al., 2008).

A second study to support the depression-inflammation relationship in maltreated individuals was conducted by Miller and Cole (2012). This two-year study included six assessments and involved individuals who did not meet the criteria for depression at baseline, but had a family history of the disorder. Each of the six assessments included blood draws to monitor serum CRP and questionnaires assessing childhood adversity and psychiatric disorders. Following data collection, participants were categorized into three groups based on the recency of a depressive episode during the study: (1) no depressive episode, (2) no recent depressive episode, or (3) recent depressive episode. Participants were further divided into three categories according to level of childhood adversity: (1) none, (2) one adversity, or (3) two or more adversities. Their findings suggested that participants who had a recent depressive episode and a history of childhood adversity consistently exhibited higher levels of CRP than those who had a recent depressive episode, but did not have a history of childhood adversity. Additionally, individuals with a history of childhood adversity had higher CRP levels during recent depressive episodes compared to periods when they did not have a depressive episode. Furthermore, those who reported the highest levels of childhood adversity were more than three times more likely to have a CRP level ≥ 3 mg/L six months following a depressive episode. Finally, elevated CRP levels were observed for longer periods during recent depressive episodes for individuals who reported the highest level of maltreatment when compared to all other groups.

Taken together, the findings of these two studies suggest that ACE may moderate the depression-inflammation relationship such that individuals with a history of ACE show a greater inflammatory response to depression. This exaggerated inflammatory

response could result in depression being a stronger risk factor for CVD among individuals with a history of ACE, given that inflammation is thought to play a role in all stages of atherosclerosis and is a predictor of future CVD events (Libby, Ridker, & Maseri, 2002; Pearson et al., 2003). If it is found that depression is a stronger risk factor for CVD among adults with ACE, it could partially explain the higher CVD risk for those with ACE and account for some heterogeneity in the depression-CVD relationship observed in meta-analyses (Batten, Aslan, Maciejewski, & Mazure, 2004; Felitti et al., 1998; Slopen, Koenen, & Kubzansky, 2012).

The Current Study

The overall objective of the proposed study is to examine whether a lifetime depressive disorder is a stronger risk factor for incident CVD among individuals with, versus without, a history of ACE, defined as abuse, neglect, or household dysfunction. To achieve this objective, I examined data from the National Epidemiological Survey on Alcohol and Related Conditions (NESARC). Although the primary purpose of the NESARC data collection was to examine alcohol-related disorders, data were also collected regarding a history of mood disorders, ACE, and various medical conditions, including CVD. In this project, the following hypotheses were tested (see Figure 1 for the conceptual model and Figure 2 for tested model):

Hypothesis 1: Any ACE (i.e., abuse, neglect, or household dysfunction) will moderate the depression-CVD relationship such that a lifetime depressive disorder will be a stronger predictor of incident CVD among individuals with versus without a history of any ACE.

Hypothesis 1: A history of any ACE will moderate the depression-CVD relationship such that a lifetime depressive disorder will be a stronger predictor of incident CVD among individuals with versus without a history of abuse.

Hypothesis 2: Abuse will moderate the depression-CVD relationship such that a lifetime depressive disorder will be a stronger predictor of incident CVD among individuals with versus without a history of abuse.

Hypothesis 3: Neglect will moderate the depression-CVD relationship such that a lifetime depressive disorder will be a stronger predictor of incident CVD among individuals with versus without a history of neglect.

Hypothesis 4: Household dysfunction will moderate the depression-CVD relationship such that a lifetime depressive disorder will be a stronger predictor of incident CVD among individuals with versus without a history of household dysfunction.

METHODS

Sample and Procedures

NESARC is a prospective cohort study with two waves of data collection – Wave 1 (2001–2002) and Wave 2 (2004–2005) - that was designed to determine the prevalence of alcohol use disorders and their associated disabilities in the United States population. The original Wave 1 sample consisted of 43,093 respondents (Grant & Dawson, 2005; Grant et al., 2004). Participants for the NESARC sample were chosen by the method outlined below.

First, the 2000/2001 Census Supplementary Survey was used to determine the sampling frame for interview selection. Next, potential households were stratified within each state by sociodemographic characteristics. Finally, within stratification, households were systematically selected, and one adult respondent (age 18 or older) was selected at random from each household. The total response rate for Wave 1 was 81.0%. NESARC oversampled African American and Hispanic households, as well as young adults (18–24 years). Complete details regarding the sample selection can be found on the NESARC website (http://aspe.hhs.gov/hsp/06/catalog–ai–an–na/nesarc.htm).

All potential respondents were informed in writing about the objective and design of the survey, the potential uses of the data, the voluntary nature of their participation, and the federal laws pertaining to confidentiality. Respondents who provided written

consent underwent face-to-face, computer-assisted interviews conducted in their homes. The Wave 1 interview included questions assessing sociodemographic factors, lifetime alcohol use, tobacco use, use of other medications and drugs, psychiatric disorders, gambling, medical conditions, and victimization. The Wave 2 interview included questions assessing psychiatric disorders, medical conditions, adverse childhood experiences, sexual orientation, social integration, acculturation, and perceived experiences of discrimination. The research protocol, including informed consent procedures, received full ethical review and approval from the United States Census Bureau and the United States Office of Management and Budget.

A total of 34,653 (80.4%) of the Wave 1 participants completed the Wave 2 assessments. There were 39,959 participants eligible for Wave 2 interviews, as 3,314 of the Wave 1 respondents either refused, provided an incorrect telephone number, or were unable to be located. Of those eligible, 5,306 did not complete the Wave 2 assessments because they were institutionalized, were mentally/physically impaired, were on active duty in the armed forces, had been deported, or had died.

Seven inclusion/exclusion criteria were applied to determine the final sample for the proposed study. First, I excluded those who participated in Wave 1, but not Wave 2 interviews (n = 8,440). Of the 34,653 participants who completed the Wave 2 interview, participants were excluded if baseline (Wave 1) CVD status could not be determined due to missing data (n = 1,719) or if they were coded as having CVD at baseline (n = 1,742; see Baseline Cardiovascular Disease section below for details). Participants whose CVD status at Wave 2 (incident cardiovascular disease) could not be determined due to missing data were also excluded (n = 1,074). Additionally, those with missing data on the

demographic variables were excluded (n = 176). Finally, participants missing data for CVD traditional risk factors (i.e., diabetes, high blood pressure, high cholesterol, and tobacco use) were excluded after imputing BMI for 726 cases with missing BMI data (n = 660). Instead of excluding those with missing BMI data, I imputed values using the average BMI in the sample for men and women separately. Data points for BMI were imputed, rather than excluded, because of the large missing data (n = 726). However, a sensitivity analysis excluding those participants with missing BMI values did not change the pattern of results (data not shown). Therefore, the final sample consisted of 29,282 adults.

Measures

Lifetime Depressive Disorder

The presence of lifetime MDD and dysthymia was determined by the Alcohol Use Disorder and Associated Disabilities Interview Schedule–IV (AUDADIS–IV). The AUDADIS–IV is a fully structured diagnostic interview designed to assess alcohol, drug, and mental disorders according to DSM–IV diagnostic criteria in both clinical and general populations (Ruan et al., 2008). This instrument was specifically designed for experienced lay interviewers and was developed to advance measurement of substance use disorders and other mental disorders in large-scale surveys. In the NESARC Wave 1 dataset, dichotomous (yes/no) variables for MDD and dysthymia were provided for the past 12 months and for prior to the past 12 months, with illness-induced and alcohol-

induced depressive disorders included or excluded. The independent diagnoses for MDD and dysthymia for all individuals were coded "yes" or "no" by NESARC personnel if they met the criteria defined by the DSM–IV for MDD and/or dysthymia in the past year, prior to the past year, and illness-induced and alcohol-induced conditions were ruled out. Illness-induced depressive disorders were defined as those episodes that began when the respondent was physically ill or recovering from physical illness, and a health professional confirmed relationship between the psychiatric episode and the illness. Substance–induced depressive disorders were defined as episodes that began after alcohol/drug intoxication or withdrawal, and either (1) were not associated with a period of at least one month of abstinence or (2) did not persist for more than one month after the cessation of alcohol or drug intoxication or withdrawal. Finally, all MDD diagnoses ruled out bereavement (Grant & Dawson, 2005).

The reliability of the AUDADIS–IV was determined by administering the measure to a random sample of 400 adults selected from the 43,093 respondents from Wave 1. The reliability associated with lifetime depressive diagnoses for MDD past year (kappa = 0.59), MDD lifetime (kappa = 0.65), and dysthymia lifetime (kappa = 0.58) were in the fair to good range (Grant et al., 2003).

In the current study, if individuals have a code of "yes" to MDD or dysthymia in past 12 months (illness-induced and substance-induced ruled out), MDD or dysthymia prior to the past 12 months (illness-induced and substance-induced ruled out), or both, they will be coded as "yes" for lifetime depressive disorder. If they have a code of "no" to both MDD and dysthymia in the past 12 months and prior to the past 12 months, they will be coded "no" for lifetime depressive disorder.

Cardiovascular Disease

Baseline Cardiovascular Disease

A dichotomous baseline CVD variable (i.e., arteriosclerosis, angina, or myocardial infarction at Wave 1) was computed from three two-part questions (see Table 1) from the Wave 1 Medical Conditions/Victimization (Section 13) questionnaire. Part A asked if an individual had a cardiovascular condition in the past 12 months (e.g., "Had hardening of the arteries or arteriosclerosis in the past 12 months?") and Part B asked if the condition was confirmed by a medical professional (i.e., "Did a doctor or health professional confirm the diagnosis?"). Response options were yes, no, and don't know. Participants were coded as having no baseline CVD if they answered "no" to Part A of all three CVD questions. Participants were coded as having baseline CVD if they answered "yes" to both Part A and Part B for at least one of the CVD questions. Participants were coded as "unknown" if they answered, "I don't know" to either Part A or Part B for one or more of the CVD questions and did not answer "yes" to both Part A and Part B for at least one question.

Incident Cardiovascular Disease

A dichotomous incident CVD variable (i.e., arteriosclerosis, angina, myocardial infarction, or stroke at Wave 2) was computed from four two-part questions (see Table 1) from the Wave Medical Conditions and Practices (Section 14) questionnaire. As in Wave 1, Part A asked if an individual had a cardiovascular condition in the past year, and Part

B asked if the condition was confirmed by a medical professional. Responses options were yes, no, and don't know. Participants were coded as having no incident CVD if they answered "no" to Part A of all four CVD questions. Participants were coded as having incident CVD if they answered "yes" to both Part A and Part B for at least one of the CVD questions. Participants were coded as "unknown" if they answered, "I don't know" to either Part A or Part B for one or more of the CVD questions and did not answer "yes" to both Part A and Part B for at least one question.

The assessment of baseline and incident CVD has some weaknesses. First, participants reported their medical conditions during the interviews. However, other studies have shown good agreement between self-reported medical history of diabetes, hypertension, myocardial infarction, stroke (Okura, Urban, Mahoney, Jacobsen, & Rodeheffer, 2004), and angina pectoris (Lampe, Walker, Lennon, Whincup, & Ebrahim, 1999) when compared to medical records. In addition, one study found that obtaining self-reported data from an interview was more reliable than obtaining self-reported data from a questionnaire when medical records are not available (Bergmann, Jacobs, Hoffmann, & Boeing, 2004). Second, the questions used to compute baseline and incident CVD assessed these conditions for the past 12 months only. Therefore, data regarding the onset of CVD before these periods are not available. As a result, some individuals with baseline CVD may have been included in the cohort, and the onset of CVD during the follow-up period may have been missed for some participants. Third, because stroke was not included in Wave 1 questions, some participants with a history of stroke (and not the other cardiovascular conditions assessed) may have also been included in the cohort. Fourth, the data only accounts for nonfatal CVD events.

Therefore, fatal CVD events were missed because those who were deceased at the time of the Wave 2 interview were excluded from data collection; information for cause of death for was not available. Despite the limitations presented, the strengths of the NESARC study, including the use of a structured diagnostic interview and ACE data from a large sample representative of the U.S. population, may offset the assessment weaknesses.

Adverse Childhood Experiences

The moderator variables of the proposed study are any ACE and the three ACE categories identified by Felitti and colleagues (1998) – i.e., abuse, neglect, and household dysfunction. These three categories were assessed in items from the Wave 2 interview Background Questions III (Section 13) questionnaire. The questions were adapted from the Adverse Childhood Experiences Study (Dong et al., 2004; Dube et al., 2003), the Conflict Tactics Scale (Straus, 1979; Straus & Gelles, 1990), and the Childhood Trauma Questionnaire (Bernstein et al., 1994; Wyatt, 1985). All questions referred to the period before the age of 18.

The first ACE category is abuse and included physical abuse, emotional abuse, and sexual abuse (see Table 2 for questions). The physical abuse assessment included two items regarding the frequency and severity of physical abuse. The emotional abuse assessment included three items pertaining to physical threats, intimidation, and verbal abuse. The sexual abuse assessment included four items adapted from Wyatt (1985) regarding inappropriate or unwanted sexual contact from adults. There were six response

options (1 = “never”, 2 = “almost never”, 3 = “sometimes”, 4 = “fairly often” 5 = “very often”, 9 = “unknown”) for these items.

Two steps were completed to compute a dichotomous abuse variable. In the first step, participants who responded “never” to all questions related to abuse type were coded as having no history of abuse for each category. Participants who responded “almost never”, “sometimes”, “fairly often”, or “very often”, to at least one question in each type of abuse were coded as having a history of abuse. Finally, participants who answered “unknown” for any of the abuse type questions were coded as unknown history of abuse. This step resulted in three variables, one for each types of abuse (0 = no history, 1 = history of abuse, 9 = unknown history). In the second step, participants with no history of abuse for all three types were coded as having no history of abuse (Total Abuse = 0). Participants with a history of abuse for at least one of the abuse types were coded as having a history of abuse (Total Abuse = 1). Finally, participants with an unknown history for all three types of abuse were excluded from the abuse variable (Total Abuse = 9, which was set to missing).

The second ACE category is neglect and included physical neglect and emotional neglect (see Table 2 for questions). The physical neglect assessment included five items regarding lack of supervision, resources, nutrition, medical attention, and dangerous demands. There were six different possible responses for the physical type of neglect (1 = “never”, 2 = “almost never”, 3 = “sometimes”, 4 = “fairly often” 5 = “very often”, 9 = “unknown”). The emotional neglect assessment included five items regarding the frequency and type of support from caregivers before the age of 18. There were six different possible responses for the emotional type of neglect, which were reversed coded

compared to the physical type of neglect responses (1 = “never true”, 2 = “rarely true”, 3 = “sometimes true”, 4 = “fairly often true” 5 = “very often true”, 9 = “unknown”).

Two steps were completed to compute a dichotomous neglect variable. In the first step, participants who responded “never” to all of the physical neglect questions and “very often true” to all of the emotional neglect questions were coded as having no history of that neglect type. Participants who responded “almost never”, “sometimes”, “fairly often”, or “very often” to at least one of the physical neglect questions or “never true”, “rarely true”, “sometimes true”, or “fairly often true” to at least one emotional neglect question were coded as having a history of that neglect type. Finally, participants who answered “unknown” for any of the neglect type questions were coded as unknown history of neglect. This step resulted in two variables, one for each type of neglect (0 = no history, 1 = history of neglect, 9 = unknown history). In the second step, participants with no history of both types of neglect were coded as having no history of neglect (Total Neglect = 0). Participants with a history of at least one of the neglect types were coded as having a history of neglect (Total Neglect = 1). Finally, participants with an unknown history for both types of neglect were excluded from the neglect variable (Total Neglect = 9, which was set to missing).

The third ACE category is *household dysfunction* and included witnessing abuse toward a caregiver (indirect abuse) and caregiver instability (indirect neglect) (see Table 2 for questions). The indirect abuse assessment included four items regarding the severity and frequency of witnessing abuse of a caregiver. There were six response options (1 = “never”, 2 = “almost never”, 3 = “sometimes”, 4 = “fairly often” 5 = “very often”, 9 = “unknown”). The indirect neglect assessment included a total of six items

that assessed the presence and type of caregiver instability. There were three response options (1 = "yes", 2 = "no", or 9 = "unknown").

Two steps were completed to compute a dichotomous household dysfunction variable. In the first step, participants who responded "never" to all questions related to indirect abuse type and "no" to all questions related to indirect neglect type were coded as having no history of that household dysfunction type. Participants who responded "almost never", "sometimes", "fairly often", or "very often" to at least one indirect abuse question or "yes" to at least one indirect neglect question were coded as having a history of that household dysfunction type. Finally, participants who answered "unknown" for any of the household dysfunction type questions were coded as unknown history of that household dysfunction type. This step resulted in two variables, one for each types of household dysfunction (0 = no history, 1 = history of household dysfunction, 9 = unknown history). In the second step, participants with no history of household dysfunction for both types were coded as having no history of household dysfunction (Total Household Dysfunction = 0). Participants with a history of household dysfunction for at least one household dysfunction type were coded as having a history of household dysfunction (Total Household Dysfunction = 1). Finally, participants with an unknown history for both types of household dysfunction were excluded from the household dysfunction variable (Total Household Dysfunction = 9, which was set to missing).

Finally, I computed an Any ACE variable, which combined all three ACE categories in a similar manner. If participants were coded as "no history" of abuse, neglect, and household dysfunction, they were considered to have no history of any ACE (Any ACE = 0). In contrast, if participants were coded as "history" for at least one, and

up to three, of the three ACE categories, they were considered to have a history of any ACE (Any ACE = 1). Finally, participants with an unknown history of all three of the ACE categories above (e.g. abuse, neglect, and/or household dysfunction) were excluded from the Any ACE variable (Any ACE = 9, which was set to missing).

The primary weakness of the ACE variables is that they are based on retrospective self–reports. However, there is conflicting evidence regarding the validity of retrospective reporting for a history of maltreatment. One study assessed self-reported maltreatment and found a 60% accuracy rate between actual past events (reported by first degree relatives) and reported past events (self-reported) for those who were abused, and a 95% accuracy rate from those who do not report abuse (Hardt & Rutter, 2004). In contrast, other studies with larger samples determined that there was no reporting bias among those with a history of maltreatment and that the retrospective reporting of events was accurate in participants aged 19–78 years old (Dube, Williamson, Thompson, Felitti, & Anda, 2004).

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Other Variables

The following variables will be included as covariates in one or more of the logistic regression models: age (years), sex (0 = male, 1 = female), race/ethnicity, education level, diabetes, high blood pressure, high cholesterol, current tobacco use, and BMI. Demographic data, including participants' age, gender, race/ethnicity, and education level, were acquired via self-report during the Wave 1 home interviews. Race/ethnicity was transformed from the original response options (1 = White, 2 = Black, 3 = American Indian/Alaskan native, 4 = Asian/native Hawaiian, 5 = Hispanic or Latino) into a four–level variable (0 = Caucasian, 1 = African American, 2 = Hispanic or Latino, 3 = Other). The Other category combined the American Indian/Alaskan native and Asian/native Hawaiian categories into one group due to the lower number of respondents in these categories. This four-level race/ethnicity variable was then converted into three dummy coded variables that compared African American (d1), Hispanic or Latino (d2), and Other (d3) groups to the Caucasian group. Education level was assessed by the question, "Highest grade or year of school completed?" Response options ranged from "no formal schooling" to "completed graduate or professional degree." From this variable, I created a 4-level education variable coded as follows: 0 = less than high school, 1 = high school or equivalent, 2 = some college or Associate's degree, 3 = Bachelor's degree or higher. Finally, these variables were transformed into three dummy coded variables that compared high school or equivalent (d1), some college or Associate's degree (d2), and Bachelor's degree or higher (d3) to less than high school. There were no missing cases for demographic variables.

Traditional CVD risk factors were also assessed during the home interviews. The variables assessed at baseline (Wave 1) were high blood pressure, current tobacco use, and BMI [kg/m2]. High blood pressure was self-reported during the Wave 1 home interview. A person was considered to have high blood pressure if they answered "yes" to "Had high blood pressure or hypertension in the last 12 months?" and "yes" to "Did doctor or other health professional confirm diagnosis?" In contrast, if they answered "no" to the first question they were considered free of high blood pressure. If participants answered either "unknown" to the first or second question or to both questions, they were excluded from the analysis. Next, current tobacco use was determined by from the Tobacco Use Status question with possible responses of: 1 = Current user, 2 = Ex–user, 3 = Lifetime nonsmoker. For this study, the Ex–user and Lifetime nonsmoker categories were combined to create a Not Current User category (0). The Current User category (1) remained unchanged. BMI was calculated from self-reported height and weight. There were a total of 726 missing variables for BMI (142 men and 584 women). These missing values were imputed for men and women separately using the average BMI for men (27.29 kg/m2) and women (26.76 kg/m2). Given diabetes and high cholesterol were not collected in Wave 1 interviews, but are also traditional CVD risk factors (Helfand et al., 2009; Roger et al., 2012), I used data collected from Wave 2 to compute these variables. Both variables were determined by the same method as described above for high blood pressure, but were related to either diabetes ("Had diabetes or sugar diabetes in the past year?") or high cholesterol ("Had high cholesterol in the past year?").

RESULTS

Descriptive Statistics

Characteristics of Participants

After the NESARC data set was obtained and the cohort was established, descriptive statistics for covariates were computed. The final sample consisted of 29,282 adults (see Table 3 for participant characteristics). Participant ages ranged from 18 to 97 years at baseline with a mean of 45 years, and there were a larger percentage of women than men. The majority of individuals were Caucasian, and the median education level was some college or Associate's degree. Approximately 8% of the participants had a diagnosis of diabetes, 18% had a diagnosis of high blood pressure, 19% had a diagnosis of high cholesterol, and 25% were current tobacco users. Finally, mean BMI for both men (M = 27.3, SD = 4.8) and women (M = 26.8, SD = 6.1) fell in the overweight category (National Heart, Lung, and Blood Institute).

Lifetime Depressive Disorder, Incident Cardiovascular Disease, and Adverse Childhood Experiences

In addition to covariates, descriptive statistics for depressive disorder, ACE, and incident CVD variables were computed. Approximately 17% of the participants in the

sample met the diagnosis criteria for a lifetime depressive disorder. Table 4 displays the percentages for each depressive disorder, both for the total sample and stratified by the four ACE variables. Chi-square tests revealed that each ACE group had higher prevalence of lifetime depressive disorder (all *p*s < .001), dysthymia only (all *p*s < .001), MDD only (all *p*s < .001), and double depression (MDD superimposed on dysthymia; all *p*s < .001) than the corresponding group without that ACE type.

Descriptive statistics for ACE variables are presented in Figure 3. A total of 19,200 individuals (66%) reported a history of any ACE. More specifically, 14,110 (48%) reported having experienced any type of abuse (physical, emotional, or sexual), 10,216 (35%) reported having experienced any neglect (physical or emotional), and 9,535 (33%) reported having experienced a history of any household dysfunction (indirect abuse or indirect neglect). As is shown in Figure 3, comorbidity rates among the ACE categories was substantial; they were 41% for abuse and neglect, 41% for abuse and household dysfunction, and 34% for neglect and household dysfunction. Of those who experienced any ACE, 22% reported abuse, neglect, and household dysfunction.

During the follow-up period, there were 1,255 cases of incident CVD, including 363 arteriosclerosis cases, 776 angina cases, 176 MIs, and 181 strokes. Of note, 203 participants reported the onset of multiple cardiovascular conditions. For example, 57 participants reported both angina and an MI at follow-up.

Preliminary Analyses

Prior to testing the study hypotheses, the lifetime depressive disorder and ACE variables were examined as predictors of incident CVD in two types of logistic regression models, individual and simultaneous. The individual models included demographic factors, traditional CVD risk factors, and either the lifetime depressive disorder variable or one of the ACE variables. The simultaneous models included the same covariates and both the lifetime depressive disorder variable and one of the ACE variables. All analyses were conducted using SAS 9.3 statistical software, which accounted for the complex survey design of the NESARC.

As shown in Table 5, the results of Model 1 indicated that lifetime depressive disorder was a predictor of incident CVD. Specifically, adults with a lifetime depressive disorder had a 49% greater odds of incident CVD than those without such a history. Of the covariates, age (*OR* = 1.039, 95% *CI*: 1.036–1.039, $p < .001$), sex (*OR* = 0.85, 95% *CI*: 0.78–0.93, $p < .001$), education (d1: *OR* = 0.75, 95% *CI*: 0.66–0.85, $p < .001$; d2: *OR* = 0.80, 95% *CI*: 0.69–0.92, $p = .002$; d3: *OR* = 0.62, 95% *CI*: = 0.54–0.72, $p < .001$), diabetes (*OR* = 1.81, 95% *CI*: 1.62–2.02, $p < .001$), hypertension (*OR* = 1.51, 95% *CI*: 1.41–1.63, $p < .001$), high cholesterol (*OR* = 2.50, 95% *CI*: 2.29–2.73, $p < .001$), and current tobacco use (*OR* = 1.35, 95% *CI*: 1.20–1.52, $p < .001$) were predictors of incident CVD. In contrast, race/ethnicity (d1: *OR* = 1.07, 95% *CI*: 0.99–1.15, $p = .09$; d2: *OR* = 1.00, 95% *CI*: 0.90–1.10, $p = .92$; d3: *OR* = 1.12, 95% *CI*: 0.88–1.42, $p = .37$) and BMI (*OR* = 1.00, 95% *CI*: 0.99–1.01, $p = .99$) were not predictors of incident CVD.

The results of Model 2 revealed that a history of any ACE was a predictor of incident CVD. Specifically, adults with a history of any ACE had a 29% greater odds of incident CVD than those without such a history. The results of Model 3, the first simultaneous model, showed that lifetime depressive disorder and any ACE were independent predictors of incident CVD after adjusting for demographic and traditional CVD risk factors. The pattern of results of the covariates in Models 2 and 3 were similar to the values reported in Model 1.

The individual and simultaneous logistic regression models were repeated for the three ACE categories of abuse, neglect, and household dysfunction (see Table 5). Briefly, all three ACE category variables predicted incident CVD, both in the individual and simultaneous models. Of note, the odds ratios for neglect and household dysfunction were numerically higher than the abuse category.

Primary Analyses

To test the current hypotheses, analyses were conducted in two stages. In the first stage, the interaction terms between lifetime depressive disorder and a history of each ACE category (any ACE, abuse, neglect, and household dysfunction) were tested in four separate logistic regression models. In addition to the interaction terms, these models included demographic factors, traditional CVD risk factors, and main effects for lifetime depressive disorder and the selected ACE variable. A simultaneous model was also constructed, which included the following variables: demographic factors; traditional CVD risk factors; main effects for lifetime depressive disorder, abuse, neglect, and

household dysfunction; and the lifetime depressive disorder x abuse, lifetime depressive disorder x neglect, and lifetime depressive disorder x household dysfunction interaction terms. In the second stage, to illustrate the form of any significant interactions, the sample was stratified by the ACE categories or subcategories. Next, separate logistic regression models were constructed for each ACE group (e.g., no history of any ACE versus a history of any ACE) that included demographic factors, traditional CVD risk factors, and the main effect for lifetime depressive disorder. All analyses described above were conducted using SAS 9.3 statistical software, which accounted for the complex survey design of the NESARC.

Test of Interaction Terms

As is shown in Table 6 (Model 1), a lifetime depressive disorder x any ACE interaction was detected ($B = 0.36$, $SEB = 0.16$, $p = .02$). Additionally, a lifetime depressive disorder x any neglect interaction ($B = 0.32$, $SEB = 0.11$, $p = .003$) and a lifetime depressive disorder x any household dysfunction interaction ($B = 0.46$, $SEB = 0.14$, $p < .001$), but not a lifetime depressive disorder x any abuse interaction ($B = 0.20$, $SEB = 0.14$, $p = .16$), were detected (see Table 6; Models 2, 3, and 4). The simultaneous model revealed that the lifetime depressive disorder x any household dysfunction interaction was significant ($B = 0.42$, $SEB = 0.14$, $p = .002$), while the lifetime depressive disorder x any abuse interaction ($B = -0.06$, $SEB = 0.15$, $p = .69$) and the lifetime depressive disorder x any neglect interaction ($B = 0.22$, $SEB = 0.14$, $p = .12$) were not.

Stratified Analyses

Given that the tests of the interaction terms generally indicated that a history of ACE moderates the depression-CVD relationship, I constructed logistic regression models examining lifetime depressive disorder as a predictor of incident CVD stratified by the ACE categories and subcategories as described above.

Total Adverse Childhood Experiences

Analyses stratified by the any ACE variable (see Model 1 in Table 7) revealed that lifetime depressive disorder was a predictor of incident CVD among adults with a history of any ACE ($B = 0.41$, $SEB = 0.07$, $p < .001$), but not among those without a history ($B = 0.14$, $SEB = 0.14$, $p = .33$). Among those with a history of any ACE, adults with a lifetime depressive disorder had a 51% greater odds of incident CVD than those without a lifetime depressive disorder history. In contrast, among those with a no history of any ACE, adults with a lifetime depressive disorder had only a 15% greater odds of incident CVD.

Abuse

Analyses stratified by the abuse variable (see Model 2 in Table 7) revealed that lifetime depressive disorder was a predictor of incident CVD among adults with a history of abuse ($B = 0.38$, $SEB = 0.06$, $p < .001$) and without such a history ($B = 0.30$, $SEB = 0.13$, $p =$

.02). As is indicated by the nonsignificant lifetime depressive disorder x abuse interaction terms, depression was not a stronger predictor of incident CVD among adults with versus without a history of abuse. Analyses further stratified by the abuse subcategories yielded similar results. As shown in Table 7 (Models 3–5), lifetime depressive disorder was a predictor of incident CVD among adults with and without a history of physical abuse, emotional abuse, or sexual abuse.

Neglect

Analyses stratified by the neglect variable (see Model 6 in Table 7) indicated that lifetime depressive disorder predicted incident CVD among adults with a history of neglect ($B = 0.47$, $SEB = 0.08$, $p < .001$) and without a history ($B = 0.22$, $SEB = 0.08$, $p = .005$), although it was a significantly stronger predictor among those with a neglect history. Among those with a history of neglect, adults with a lifetime depressive disorder had a 59% greater odds of incident CVD than those without a depression history. Among those with no history of neglect, adults with a lifetime depressive disorder had only a 25% greater odds of incident CVD. Analyses were further stratified by the neglect subcategories provided comparable results (Models 7 and 8 in Table 7). Logistic regression models revealed that lifetime depressive disorder was a predictor of incident CVD among adults with and without a history of physical neglect or emotional neglect.

Household dysfunction

Analyses stratified by the household dysfunction variable (see Model 9 in Table 7) indicated that lifetime depressive disorder was a predictor of incident CVD among adults with a history of household dysfunction ($B = 0.55$, $SEB = 0.09$, $p < .001$), but not for those without a history ($B = 0.16$, $SEB = 0.10$, $p = .11$). Among those with a history of household dysfunction, adults with a lifetime depressive disorder had a 73% greater odds of incident CVD than those without a lifetime depressive disorder history. Conversely, among those without a history of household dysfunction, adults with a lifetime depressive disorder had only a 18% greater odds of incident CVD. Analyses, further stratified by the household dysfunction subcategories, yielded similar results (Models 10 and 11 in Table 7). Logistic regression models showed that lifetime depressive disorder was predictive of incident CVD among adults with and without a history of indirect abuse or indirect neglect.

DISCUSSION

The overall objective of the present study was to examine whether depression is a stronger risk factor for CVD among individuals with, versus without, a history of ACE. To achieve this objective, NESARC data from 29,282 men and women who did not report CVD at baseline were examined. Preliminary analyses showed that lifetime depressive disorder and a history of ACE (any ACE, abuse, neglect, or household dysfunction) were independent predictors of incident CVD. Results of logistic regression models adjusted for demographic factors and traditional CVD risk factors supported Hypotheses 1, 3, and 4. The lifetime depressive disorder x any ACE, lifetime depressive disorder x neglect, and lifetime depressive disorder x household dysfunction interactions were all significant. Follow-up models stratified by the ACE variables indicated that the odds ratios were 1.51, 1.59, and 1.73 for lifetime depressive disorder among adults with a history of any ACE, neglect, and household dysfunction versus 1.15, 1.25, and 1.18 among those without these experiences respectively. Hypothesis 2, however, was not supported. The lifetime depressive disorder x abuse interaction was not significant, and the odds ratio was 1.46 for lifetime depressive disorder among adults with a history of abuse versus 1.35 among those without an abuse history. A simultaneous model that included interactions between lifetime depressive disorder and the three ACE categories

(Abuse, Neglect, and Household dysfunction) revealed that only the lifetime depressive disorder x household dysfunction interaction was significant.

Taken together, these findings suggest that depression may be a stronger risk factor for CVD among adults who experienced neglect or household dysfunction during childhood than among adults who did not have these experiences. Furthermore, results of the stratified models and the simultaneous model suggest that having a lifetime depressive disorder may be a stronger risk factor, particularly among those with a history of the ACE category household dysfunction.

Fit with Existing Literature

To my knowledge, this is the first study to examine a history of ACE as a moderator of the depression-CVD relationship. Despite the lack of investigations, a small number of studies do provide evidence that indirectly supports this moderation effect, by showing the depression-inflammation relationship is moderated by childhood maltreatment/adversity. These studies suggest that the inflammatory response that often accompanies depression is larger and lasts longer among individuals with a history of childhood maltreatment/adversity. Danese et al. (2008) found evidence of a correlation between higher systemic CRP and individuals who were both depressed and maltreated, but did not find this association in those who were only depressed. In addition, Miller and Cole (2012) provided evidence of a directional relationship between depressive episodes and inflammation that was moderated by a history of adversity in childhood. Participants who had a recent depressive episode and a history of childhood adversity

exhibited higher and clinically significant CRP levels, that were sustained over longer periods, than those who only had a recent depressive episode, but no history of childhood adversity. This exaggerated inflammatory response could result in depression being a stronger risk factor for CVD among individuals with a history of ACE, given that inflammation is thought to play a role in all stages of atherosclerosis and that inflammatory markers (e.g., IL-6and CRP) predict future CVD events (Libby et al., 2002; Pearson et al., 2003).

While these two studies provide indirect support for the idea that a history of ACE may moderate the depression-CVD relationship, there is a lack of evidence regarding the influence of specific ACE types. For example, Danese et al. (2008) defined childhood maltreatment as maternal rejection, harsh discipline, disruptive caregiver changes, physical abuse, or sexual abuse occurring during the first decade of life. This definition overlaps with the abuse, neglect, and household dysfunction variables in the present study. Additionally, Miller and Cole (2012) included the following experiences in their definition of childhood adversity: birth to a teenage mother, familial disruption before the age of 15, an affective illness in a parent or guardian, parent's education level less than or equal to high school, and renting a home. Of note, Miller and Cole (2012) did not include physical, emotional, or sexual abuse in their definition of childhood adversity. Therefore, this definition has the most overlap with the household dysfunction variable, although several of these experiences were not included in the ACE variable definitions of the present study.

Although history of neglect and household dysfunction were moderators of the depression-CVD relationship, the current study did not find evidence of moderation for a

history of abuse. In contrast to the present evidence, Danese et al. (2011) provided evidence that the depression-inflammation relationship is moderated by a history of physical maltreatment. Although this group showed individuals with a co-occurrence of current depression and a history of maltreatment exhibited the highest inflammatory levels, (compared to those neither depressed nor maltreated, only depressed, or only maltreated) the study did not compare physical maltreatment to other types of maltreatment or adversities (Danese et al., 2011). The current study's null findings may be explained by several reasons. First, the current study and the Danese et al. (2008) study used different methods to assess abuse. For example, Danese et al. (2008) measured physical maltreatment exclusively in the first decade of life. In contrast, the current study's abuse timeframe was broader (any time before the age of 18). Additionally, the ACE questionnaire does not specify the duration nor the types of abuse, which may confer different levels of damage to influence the inflammatory response. Therefore, considering the abuse measurements were a limitation of the current study, the conclusion that a history of abuse does not moderate the depression-CVD relationship may be premature.

Preliminary analyses in the current study provided evidence that lifetime depressive disorder, any ACE, abuse, neglect, and/or household dysfunction were independent predictors of incident CVD. This is consistent with current evidence that supports both the relationships between a history of ACE and CVD (Dong et al., 2004; Felitti et al., 1998) and the association between depression and CVD (Nicholson et al., 2006; Van der Kooy et al., 2007). To my knowledge, no study has examined the concurrent nature of lifetime depressive disorder and a history ACE to predict

atherosclerotic CVD. However, many maltreatment studies control for some aspect of psychological disorder (e.g., low mood, anxiety, high stress level) that are often comorbid. For example, Dong et al. (2004) observed that a history of ACE predicts ischemic heart disease after controlling for depressed affect.

Alternative Explanations

In addition to an exaggerated inflammatory response to depression, other factors may account for lifetime depressive disorder being a stronger risk factor for CVD among adults with versus without a history of ACE. For instance, a meta-analysis that included 16 epidemiologic studies and 10 clinical trials indicates that childhood maltreatment predicts an unfavorable course of depression and treatment outcome (Nanni, Uher, & Danese, 2012). Specifically, individuals with, versus without a history of maltreatment were twice as likely to develop recurrent and persistent depressive episodes. Maltreated individuals were also less likely to respond to depression treatment. As an example, in Miniati et al.'s (2010) clinical trial, individuals with depression and a history of ACE required treatment augmentation (i.e., SSRIs combined with interpersonal therapy) to achieve a response. In contrast, those with depression, but no history of ACE, tended to respond to a single treatment. Also of relevance, individuals with treatment-resistant depression have been found to have higher inflammatory markers (Lanquillon, Krieg, Bening-Abu-Shach, & Vedder, 2000).

A history of ACE has also been linked with an earlier age of depression onset (Bernet & Stein, 1999). Shanahan and colleagues (2011) observed a relationship between

period when maltreatment occurred, and the age of depression onset. Individuals with maltreatment during childhood had a nine times greater odds of developing childhood-onset depression and those with adolescent maltreatment had a seven times greater odds of developing adolescent-onset depression, while those with early adulthood maltreatment only, did not have a greater odds of developing young adult-onset depression than individuals who were never depressed (Shanahan, Copeland, Costello, & Angold, 2011). Therefore, adults with a history of ACE may be more likely to have recurrent, treatment-resistant depression with an earlier age of onset. This increased exposure to depression across a lifetime could explain why depression is a stronger CVD risk factor in this population. Importantly, the lifetime depressive disorder variable in the present study did not take into account the age of onset, number of depressive episodes, or depression treatment history.

Another factor may be the subtype of lifetime depressive disorder experienced by this population. MDD can be classified by the subtypes: nonatypical and atypical depression. Atypical depression is described by reversed vegetative symptoms such as increased appetite/weight gain and hypersomnia, while nonatypical depression includes decreased appetite/weight loss and insomnia (Matza, Revicki, Davidson, & Stewart, 2003; Quitkin, 2002). In addition, patients with atypical depression versus nonatypical depression have more severe depressive symptoms, a more chronic course, and have an earlier age of onset, (Matza et al., 2003; Quitkin, 2002; Singh & Williams, 2006). Accordingly, individuals with a history of maltreatment report more depressive moods and appetite disturbances consistent with atypical depression (Miniati et al., 2010). Additionally, current evidence supports an association between individuals with

traumatic childhood experiences and the atypical subtype of depression (Withers, Tarasoff, & Stewart, 2013). Moreover, atypical MDD has been found to be more strongly associated with inflammatory markers predictive of future CVD than nonatypical depression (Hickman, Khambaty, & Stewart, 2013).

Finally, it is possible that experiencing stressful life events in childhood, including but not limited to ACE, could alter immune system development and/or functioning, resulting in exaggerated inflammatory responses to proinflammatory stimuli (Surtees et al., 2003). However, it may be that the physiologic impact of childhood stressful events is driven more by duration than type of experience. For instance, Shonkoff and colleagues (2012) define tolerable stress as occurring within a time–limited period, after which the body's stress-response systems are efficiently brought back to baseline. One example of a tolerable stressor is a natural disaster. While such an event may be traumatic, it is typically time limited, and the duration of the stress response may not be long enough to permanently influence the development and/or functioning of physiologic systems. In contrast, these authors defined toxic stress as that which produces strong, frequent, and/or prolonged activation of stress-response system and lacks a buffering protection, such as adult support (Shonkoff & Garner, 2012). ACE and its components fall in the category of toxic stress and, therefore, may have a more lasting negative effect on immune system development and/or functioning. However, additional studies are needed to compare the impact of short-term versus longer-term childhood stressors on inflammatory marker levels and responses to proinflammatory stimuli.

Limitations and Future Directions

The current study attempted to provide evidence that ACE moderates the depression-CVD relationship longitudinally, such that lifetime depressive disorders occurred prior to incident CVD. Although the present study has strengths (i.e., longitudinal design, large representative sample, and structured interview measures of depressive disorders), other measured variables also have important limitations. First, the assessment of baseline and incident CVD has some weaknesses. One limitation is that participants reported their medical conditions during the interviews; medical records were not consulted. However, medical conditions utilized in this study have been reported to have good agreement between self-reported measures and medical records (Bergmann et al., 2004; Lampe et al., 1999; Okura et al., 2004). Next, CVD conditions were assessed for the past 12 months only and only account for non-fatal incident CVD. Due to the nature of the interview design, some individuals with baseline CVD may have been included in the cohort. Additionally, incident CVD during the follow-up period may have been missed for participants who suffered a fatal CVD event as participants who were deceased at the time of Wave 2 interviews were excluded. Third, because stroke was not included in Wave 1 questions, some participants with a history of stroke (and not the other cardiovascular conditions assessed) may have also been included in the cohort. However, according to The American Heart Association 77% of stroke cases reported annually are incident, not recurrent stroke (Roger, 2012) which may lessen this possibility. Although it is not clear if this would change the conclusions of this study, future studies that exclude adults with a lifetime history of CVD at baseline and that

assess both nonfatal and fatal CVD events (ideally confirmed with medical records) over the follow-up period would more accurately characterize the prospective relationship between depression and CVD.

Another key limitation is the lack of reliability and validity information for the ACE questionnaire. A related issue for which there is conflicting evidence in the literature is the validity of retrospective reports of childhood maltreatment. One study found a 60% accuracy rate between actual past events (reported by first degree relatives) and self-reported events for those who were abused and a 95% accuracy rate from those who do not report abuse (Hardt & Rutter, 2004). In contrast, other studies involving larger samples suggest that there is no reporting bias among maltreated individuals and retrospective reports of childhood events were accurately characterized up to the age of 78 years (Dube et al., 2004). Therefore, future studies are needed to create a gold standard of assessing ACE that includes establishing the measure's reliability and validity.

Finally, despite the heavy emphasis on the increased systemic inflammation as a potential mechanism, inflammatory markers were not assessed in the NESARC study. Therefore, the conceptual model (see Figure 1) could not be fully evaluated. It is unclear if increased inflammation or another mechanism(s) accounts for depression being a stronger risk factor for CVD among adults with a history of ACE. However, given the evidence from previous studies suggesting that ACE is a moderator of the depression-inflammation relationship, future studies should measure inflammatory markers predictive of CVD (e.g., IL-6 and CRP) to determine whether they explain why depression may be a stronger CVD risk factor among those with a history of ACE.

Implications and Conclusions

Overall, the present findings suggest that depression may be a stronger risk factor for CVD among adults with a history of ACE, especially neglect and household dysfunction, than among adults who did not have these experiences. This line of research could have important study and clinical implications. First, the higher CVD risk of individuals with ACE could be partially explained by depression being a stronger risk factor in this population. Among adults with a history of ACE, depression may be a potent proinflammatory stimulus, and the higher levels of and longer duration of exposure to inflammatory markers may accelerate the onset of CVD. Second, taking history of ACE into consideration may account for some heterogeneity in the depression-CVD relationship observed in previous meta–analyses (Nicholson et al., 2006; Van der Kooy et al., 2007). One explanation for the results explained in these meta-analyses is that included studies may have had a low percentage of individuals with a history of ACE resulting in smaller effect sizes. In contrast, inclusion of studies with higher percentages of individuals with a history of ACE may have resulted in larger effect sizes. The present results suggest that individuals with a history of ACE may be driving the overall depression-CVD relationship. Third, because depressed adults with a history of ACE may be a subpopulation at particularly elevated CVD risk, increased screening for both depressive disorders and ACE in clinical settings, such as primary care clinics, should be considered. In addition, once these high-risk cases are identified, more aggressive management of traditional CVD risk factors, as well as delivering evidence-based

depression treatments, may be warranted to address these patients' psychiatric needs and to delay the onset of atherosclerotic cardiovascular disease.

REFERENCES

REFERENCES

American Psychiatric Assoiciation. (2000). *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR)* 4th ed., text revision ed. Washington, D.C.: American Psychiatric Association.

Batten, S. V., Aslan, M., Maciejewski, P. K., & Mazure, C. M. (2004). Childhood maltreatment as a risk factor for adult cardiovascular disease and depression. *Journal of Clinical Psychiatry, 65*(2), 249-254.

Bergmann, M., Jacobs, E., Hoffmann, K., & Boeing, H. (2004). Agreement of Self-Reported Medical History: Comparison of an In-Person Interview with a Self-Administered Questionnaire. *European Journal of Epidemiology, 19*(5), 411-416. doi: 10.1023/b:ejep.0000027350.85974.47

Bernet, C. Z., & Stein, M. B. (1999). Relationship of childhood maltreatment to the onset and course of major depression in adulthood. *Depression and Anxiety, 9*(4), 169-174.

Bernstein, D. P., Fink, L., Handelsman, L., Foote, J., Lovejoy, M., Wenzel, K., . . . Ruggiero, J. (1994). Initial reliability and validity of a new retrospective measure of child abuse and neglect. *The American Journal of Psychiatry, 151*(8), 1132-1136.

Berntson, G. G., Bigger, J. T., Jr., Eckberg, D. L., Grossman, P., Kaufmann, P. G., Malik, M., . . . van der Molen, M. W. (1997). Heart rate variability: origins, methods, and interpretive caveats. *Psychophysiology, 34*(6), 623-648.

Butchart, A., Phinney Harvey, A., Mian, M., Fürniss, T., & Kahane, T. (2006). *Preventing child maltreatment: a guide to taking action and generating evidence*: World Health Organization.

Cardi, M., Munk, N., Zanjani, F., Kruger, T., Schaie, K. W., & Willis, S. L. (2010). Health Behavior Risk Factors Across Age as Predictors of Cardiovascular Disease Diagnosis. *Journal of Aging and Health, 22*(5), 759-775.

Carpenter, L. L., Gawuga, C. E., Tyrka, A. R., Lee, J. K., Anderson, G. M., & Price, L. H. (2010). Association between Plasma IL-6 Response to Acute Stress and Early-Life Adversity in Healthy Adults. *Neuropsychopharmacology, 35*(13), 2617-2623. doi: 10.1038/npp.2010.159

Casas, J. P., Shah, T., Hingorani, A. D., Danesh, J., & Pepys, M. B. (2008). C-reactive protein and coronary heart disease: a critical review. *Journal of Internal Medicine, 264*(4), 295-314.

Child Abuse Prevention and Treatment Act of 1974. Pub. L. 93-247, 88 Stat. 4, codified as amended at 42 USC §§5101–5106.

Cizza, G., Marques, A. H., Eskandari, F., Christie, I. C., Torvik, S., Silverman, M. N., . . . Sternberg, E. M. (2008). Elevated neuroimmune biomarkers in sweat patches and plasma of premenopausal women with major depressive disorder in remission: the POWER study. *Biological Psychiatry, 64*(10), 907-911.

Coe, C. L., & Lubach, G. R. (2003). Critical periods of special health relevance for psychoneuroimmunology. *Brain, Behavior, and Immunity, 17*(1), 3-12.

Danese, A., Caspi, A., Williams, B., Ambler, A., Sugden, K., Mika, J., . . . Arseneault, L. (2011). Biological embedding of stress through inflammation processes in childhood. *Molecular Psychiatry, 16*(3), 244-246. doi: 10.1038/mp.2010.5

Danese, A., & McEwen, B. S. (2012). Adverse childhood experiences, allostasis, allostatic load, and age-related disease. *Physiology & Behavior, 106*(1), 29-39.

Danese, A., Moffitt, T. E., Pariante, C. M., Ambler, A., Poulton, R., & Caspi, A. (2008). Elevated inflammation levels in depressed adults with a history of childhood maltreatment. *Archives of General Psychiatry, 65*(4), 409-415.

Danese, A., Pariante, C. M., Caspi, A., Taylor, A., & Poulton, R. (2007). Childhood maltreatment predicts adult inflammation in a life-course study. *Proceedings of the National Academy of Sciences of the United States of America, 104*(4), 1319-1324. doi: 10.1073/pnas.0610362104

De Young, A. C., Kenardy, J. A., & Cobham, V. E. (2011). Trauma in early childhood: a neglected population. *Clinical Child and Family Psychology Review, 14*(3), 231-250.

DiMatteo, M. R., Lepper, H. S., & Croghan, T. W. (2000). Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. *Archives of Internal Medicine, 160*(14), 2101-2107.

Dong, M., Giles, W. H., Felitti, V. J., Dube, S. R., Williams, J. E., Chapman, D. P., & Anda, R. F. (2004). Insights into causal pathways for ischemic heart disease: adverse childhood experiences study. *Circulation, 110*(13), 1761-1766.

Dube, S. R., Felitti, V. J., Dong, M., Chapman, D. P., Giles, W. H., & Anda, R. F. (2003). Childhood abuse, neglect, and household dysfunction and the risk of illicit drug use: the adverse childhood experiences study. *Pediatrics, 111*(3), 564-572.

Dube, S. R., Williamson, D. F., Thompson, T., Felitti, V. J., & Anda, R. F. (2004). Assessing the reliability of retrospective reports of adverse childhood experiences among adult HMO members attending a primary care clinic. *Child Abuse & Neglect, 28*(7), 729-737. doi: 10.1016/j.chiabu.2003.08.009

Epstein, F. H., & Ross, R. (1999). Atherosclerosis—an inflammatory disease. *New England Journal of Medicine, 340*(2), 115-126.

Fava, M., & Cassano, P. (2004). Mood disorders: Major depressive disorder and dysthymic disorder. . In R. J. Stern TA, Fava M, Biederman J, Rauch SL (Ed.), *Massachusetts General Hospital handbook of general hospital psychiatry*. Philadelphia: Mosby New York.

Felitti, V. J., Anda, R. F., Nordenberg, D., Williamson, D. F., Spitz, A. M., Edwards, V., . . . Marks, J. S. (1998). Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. *American Journal of Preventive Medicine, 14*(4), 245-258.

Fergusson, D. M., Goodwin, R. D., & Horwood, L. J. (2003). Major depression and cigarette smoking: results of a 21-year longitudinal study. *Psychological Medicine, 33*(8), 1357-1367.

Finkelhor, D., Turner, H., Ormrod, R., & Hamby, S. L. (2009). Violence, abuse, and crime exposure in a national sample of children and youth. *Pediatrics, 124*(5), 1411-1423.

Glassman, A. H., Helzer, J. E., Covey, L. S., Cottler, L. B., Stetner, F., Tipp, J. E., & Johnson, J. (1990). Smoking, smoking cessation, and major depression. *JAMA: The Journal of the American Medical Association, 264*(12), 1546-1549.

Goldston, K., & Baillie, A. J. (2008). Depression and coronary heart disease: a review of the epidemiological evidence, explanatory mechanisms and management approaches. *Clinical Psychology Review, 28*(2), 288-306.

Grant, B. F., & Dawson, D. A. (2005). Introduction to the national epidemiologic survey on alcohol and related conditions. *Alcohol Research and Health, 29*(2), 74.

Grant, B. F., Dawson, D. A., Stinson, F. S., Chou, P. S., Kay, W., & Pickering, R. (2003). The Alcohol Use Disorder and Associated Disabilities Interview Schedule-IV (AUDADIS-IV): reliability of alcohol consumption, tobacco use, family history of depression and psychiatric diagnostic modules in a general population sample. *Drug and Alcohol Dependence, 71*(1), 7-16. doi: http://dx.doi.org/10.1016/S0376-8716(03)00070-X

Grant, B. F., Stinson, F. S., Dawson, D. A., Chou, S. P., Dufour, M. C., Compton, W., . . . Kaplan, K. (2004). Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Archives of General Psychiatry, 61*(8), 807-816.

Hardt, J., & Rutter, M. (2004). Validity of adult retrospective reports of adverse childhood experiences: review of the evidence. *Journal of Child Psychology and Psychiatry, 45*(2), 260-273. doi: 10.1111/j.1469-7610.2004.00218.x

Helfand, M., Buckley, D. I., Freeman, M., Fu, R., Rogers, K., Fleming, C., & Humphrey, L. L. (2009). Emerging risk factors for coronary heart disease: a summary of systematic reviews conducted for the U.S. Preventive Services Task Force. *Annals of Internal Medicine, 151*(7), 496-507.

Hickman, R. J., Khambaty, T., & Stewart, J. C. (2013). C-reactive protein is elevated in atypical but not nonatypical depression: data from the National Health and Nutrition Examination Survey (NHANES) 1999-2004. *Journal of Behavioral Medicine*.

Howren, M. B., Lamkin, D. M., & Suls, J. (2009). Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. *Psychosomatic Medicine, 71*(2), 171-186.

Huikuri, H. V., Jokinen, V., Syvänne, M., Nieminen, M. S., Airaksinen, K. E., Ikäheimo, M. J., . . . Frick, M. H. (1999). Heart rate variability and progression of coronary atherosclerosis. *Arteriosclerosis, Thrombosis, and Vascular Biology, 19*(8), 1979-1985.

Jaffee, S. R., Moffitt, T. E., Caspi, A., Fombonne, E., Poulton, R., & Martin, J. (2002). Differences in early childhood risk factors for juvenile-onset and adult-onset depression. *Archives of General Psychiatry, 59*(3), 215.

Kannel, W. B. (1996). Blood pressure as a cardiovascular risk factor: Prevention and treatment. *JAMA: The Journal of the American Medical Association, 275*(20), 1571-1576. doi: 10.1001/jama.1996.03530440051036

Kapornai, K., & Vetró, A. (2008). Depression in children. *Current Opinion in Psychiatry, 21*(1), 1-7.

Kim, D.-E., Lee, K.-B., Jang, I.-M., Roh, H., Ahn, M.-Y., & Lee, J. (2012). Associations of cigarette smoking with intracranial atherosclerosis in the patients with acute ischemic stroke. *Clinical Neurology and Neurosurgery, 114*(9), 1243-1247. doi: 10.1016/j.clineuro.2012.03.012

Labarthe, D. R. (2010). Epidemiology and prevention of cardiovascular diseases: a global challenge: Jones & Bartlett Learning.

Lampe, F. C., Walker, M., Lennon, L. T., Whincup, P. H., & Ebrahim, S. (1999). Validity of a self-reported history of doctor-diagnosed angina. *Journal of Clinical Epidemiology, 52*(1), 73-81.

Langley-Evans, S. C., & McMullen, S. (2010). Developmental origins of adult disease. *Medical Principles And Practice: International Journal of the Kuwait University, Health Science Centre, 19*(2), 87-98.

Lanquillon, S., Krieg, J. C., Bening-Abu-Shach, U., & Vedder, H. (2000). Cytokine production and treatment response in major depressive disorder. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology, 22*(4), 370-379.

Libby, P., Ridker, P. M., & Maseri, A. (2002). Inflammation and Atherosclerosis. *Circulation, 105*(9), 1135-1143. doi: 10.1161/hc0902.104353

Libby, P., & Theroux, P. (2005). Pathophysiology of coronary artery disease. *Circulation, 111*(25), 3481-3488.

Licinio, J., & Wong, M. L. (1999). The role of inflammatory mediators in the biology of major depression: central nervous system cytokines modulate the biological substrate of depressive symptoms, regulate stress-responsive systems, and contribute to neurotoxicity and neuroprotection. *Molecular Psychiatry, 4*(4), 317-327.

Markovitz, J. H., & Matthews, K. A. (1991). Platelets and coronary heart disease: potential psychophysiologic mechanisms. *Psychosomatic Medicine, 53*(6), 643-668.

Miller, G. E., & Cole, S. W. (2012). Clustering of depression and inflammation in adolescents previously exposed to childhood adversity. *Biological Psychiatry, 72*(1), 34-40.

Miniati, M., Rucci, P., Benvenuti, A., Frank, E., Buttenfield, J., Giorgi, G., & Cassano, G. B. (2010). Clinical characteristics and treatment outcome of depression in patients with and without a history of emotional and physical abuse. *Journal of Psychiatric Research, 44*(5), 302-309.

Mueller, T. I., & Leon, A. C. (1996). Recovery, chronicity, and levels of psychopathology in major depression. *The Psychiatric Clinics of North America, 19*(1), 85-102.

Musselman, D. L., & Nemeroff, C. B. (1996). Depression and endocrine disorders: focus on the thyroid and adrenal system. *The British Journal of Psychiatry. Supplement*(30), 123-128.

Musselman, D. L., Tomer, A., Manatunga, A. K., Knight, B. T., Porter, M. R., Kasey, S., . . . Nemeroff, C. B. (1996). Exaggerated platelet reactivity in major depression. *The American Journal of Psychiatry, 153*(10), 1313-1317.

Nanni, V., Uher, R., & Danese, A. (2012). Childhood maltreatment predicts unfavorable course of illness and treatment outcome in depression: a meta-analysis. *The American Journal of Psychiatry, 169*(2), 141-151.

National Heart, Lung, and Blood Institute. (1998). Executive Summary of the Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. *Archives of Internal Medicine, 158*(17), 1855.

Nicholson, A., Kuper, H., & Hemingway, H. (2006). Depression as an aetiologic and prognostic factor in coronary heart disease: a meta-analysis of 6362 events among 146 538 participants in 54 observational studies. *European Heart Journal, 27*(23), 2763-2774.

Okura, Y., Urban, L. H., Mahoney, D. W., Jacobsen, S. J., & Rodeheffer, R. J. (2004). Agreement between self-report questionnaires and medical record data was substantial for diabetes, hypertension, myocardial infarction and stroke but not for heart failure. *Journal of Clinical Epidemiology, 57*(10), 1096-1103.

Patten, S. B., Williams, J. V. A., Lavorato, D. H., & Eliasziw, M. (2009). A longitudinal community study of major depression and physical activity. *General Hospital Psychiatry, 31*(6), 571-575. doi: http://dx.doi.org/10.1016/j.genhosppsych.2009.08.001

Pearson, T. A., Mensah, G. A., Alexander, R. W., Anderson, J. L., Cannon, R. O., Criqui, M., . . . Vinicor, F. (2003). Markers of Inflammation and Cardiovascular Disease. *Circulation, 107*(3), 499-511. doi: 10.1161/01.cir.0000052939.59093.45

Pikhart, H., Hubacek, J. A., Kubinova, R., Nicholson, A., Peasey, A., Capkova, N., . . . Bobak, M. (2009). Depressive symptoms and levels of C-reactive protein. *Social Psychiatry and Psychiatric Epidemiology, 44*(3), 217-222. doi: 10.1007/s00127-008-0422-1

Pipe, A., Papadakis, S., & Reid, R. (2010). The Role of Smoking Cessation in the Prevention of Coronary Artery Disease. *Current Atherosclerosis Reports, 12*(2), 145-150. doi: 10.1007/s11883-010-0105-8

Raedler, T. J. (2011). Inflammatory mechanisms in major depressive disorder. *Current Opinion in Psychiatry, 24*(6), 519-525.

Raison, C. L., Capuron, L., & Miller, A. H. (2006). Cytokines sing the blues: inflammation and the pathogenesis of depression. *Trends in Immunology, 27*(1), 24-31.

Ridker, P. M., & Libby, P. (2005). Risk factors for atherothrombotic disease. In E. Braunwald, D. Zipes, P. Libby & R. Bonow (Eds.), *Braunwald's heart disease: a textbook of cardiovascular medicine* (pp. 939-958). Philadelphia, PA:: Elsevier Saunders.

Roger, V. L., Go, A. S., Lloyd-Jones, D. M., Benjamin, E. J., Berry, J. D., Borden, W. B., . . . Turner, M. B. (2012). Executive summary: heart disease and stroke statistics--2012 update: a report from the American Heart Association. *Circulation, 125*(1), 188-197.

Rosengren, A., Hawken, S., Ounpuu, S., Sliwa, K., Zubaid, M., Almahmeed, W. A., . . . Yusuf, S. (2004). Association of psychosocial risk factors with risk of acute myocardial infarction in 11119 cases and 13648 controls from 52 countries (the INTERHEART study): case-control study. *Lancet, 364*(9438), 953-962.

Ruan, W. J., Goldstein, R. B., Chou, S. P., Smith, S. M., Saha, T. D., Pickering, R. P., . . . Grant, B. F. (2008). The alcohol use disorder and associated disabilities interview schedule-IV (AUDADIS-IV): reliability of new psychiatric diagnostic modules and risk factors in a general population sample. *Drug and Alcohol Dependence, 92*(1-3), 27-36.

Rugulies, R. (2002). Depression as a predictor for coronary heart disease: a review and meta-analysis. *American Journal of Preventive Medicine, 23*(1), 51-61. doi: 10.1016/s0749-3797(02)00439-7

Sánchez-Villegas, A., Toledo, E., de Irala, J., Ruiz-Canela, M., Pla-Vidal, J., & Martínez-González, M. A. (2012). Fast-food and commercial baked goods consumption and the risk of depression. *Public Health Nutrition, 15*(3), 424-432. doi: 10.1017/s1368980011001856

Schiller, J., Lucas, J., Ward, B., & Peregoy, J. (2010). Summary health statistics for U.S. adults: National Health Interview Survey, 2010. (Vol. 10). Hyattsville, MD: National Center for Health Statistics.

Seshasai, S. R., Kaptoge, S., Thompson, A., Di Angelantonio, E., Gao, P., Sarwar, N., . . . Danesh, J. (2011). Diabetes Mellitus, Fasting Glucose, and Risk of Cause-Specific Death. *New England Journal of Medicine, 364*(9), 829-841. doi: doi:10.1056/NEJMoa1008862

Shanahan, L., Copeland, W. E., Costello, E. J., & Angold, A. (2011). Child-, adolescent- and young adult-onset depressions: differential risk factors in development? *Psychological Medicine, 41*(11), 2265-2274.

Shonkoff, J. P., & Garner, A. S. (2012). The lifelong effects of early childhood adversity and toxic stress. *Pediatrics, 129*(1), e232-e246.

Slopen, N., Koenen, K. C., & Kubzansky, L. D. (2012). Childhood adversity and immune and inflammatory biomarkers associated with cardiovascular risk in youth: a systematic review. *Brain, Behavior, and Immunity, 26*(2), 239-250.

Stewart, J. C., Rand, K. L., Muldoon, M. F., & Kamarck, T. W. (2009). A prospective evaluation of the directionality of the depression-inflammation relationship. *Brain, Behavior, and Immunity, 23*(7), 936-944.

Straus, M. A. (1979). Measuring Intrafamily Conflict and Violence: The Conflict Tactics (CT) Scales. *Journal of Marriage and Family, 41*(1), 75-88.

Straus, M. A., & Gelles, R. J. (1990). Physical violence in American families. *New Brunswick, NJ: Transaction Publishers*.

Suls, J., & Bunde, J. (2005). Anger, anxiety, and depression as risk factors for cardiovascular disease: the problems and implications of overlapping affective dispositions. *Psychological Bulletin, 131*(2), 260-300.

Surtees, P., Wainwright, N., Day, N., Brayne, C., Luben, R., & Kay-Tee, K. (2003). Adverse Experience in Childhood as a Developmental Risk Factor for Altered Immune Status in Adulthood. *International Journal of Behavioral Medicine, 10*(3), 251.

Troxler, R. G., Sprague, E. A., Albanese, R. A., Fuchs, R., & Thompson, A. J. (1977). The association of elevated plasma cortisol and early atherosclerosis as demonstrated by coronary angiography. *Atherosclerosis, 26*(2), 151-162.

Van der Kooy, K., van Hout, H., Marwijk, H., Marten, H., Stehouwer, C., & Beekman, A. (2007). Depression and the risk for cardiovascular diseases: systematic review and meta analysis. *International Journal of Geriatric Psychiatry, 22*(7), 613-626. doi: 10.1002/gps.1723

Vos, T., Flaxman, A. D., Naghavi, M., Lozano, R., Michaud, C., Ezzati, M., . . . Memish, Z. A. (2012). Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet, 380*(9859), 2163-2196. doi: 10.1016/s0140-6736(12)61729-2

Wiersma, J. E., Hovens, J. G. F. M., van Oppen, P., Giltay, E. J., van Schaik, D. J. F., Beekman, A. T. F., & Penninx, B. W. J. H. (2009). The importance of childhood trauma and childhood life events for chronicity of depression in adults. *The Journal of Clinical Psychiatry, 70*(7), 983-989.

Winkleby, M. A., Jatulis, D. E., Frank, E., & Fortmann, S. P. (1992). Socioeconomic status and health: how education, income, and occupation contribute to risk factors for cardiovascular disease. *American Journal of Public Health, 82*(6), 816-820.

Wormser, D., Kaptoge, S., Di Angelantonio, E., Wood, A. M., Pennells, L., Thompson, A., . . . Danesh, J. (2011). Separate and combined associations of body-mass index and abdominal adiposity with cardiovascular disease: collaborative analysis of 58 prospective studies. *Lancet, 377*(9771), 1085-1095.

Wyatt, G. E. (1985). The sexual abuse of Afro-American and white-American women in childhood. *Child Abuse and Neglect, 9*(4), 507-519.

Yusuf, S., Hawken, S., Ounpuu, S., Dans, T., Avezum, A., Lanas, F., . . . Lisheng, L. (2004). Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet, 364*(9438), 937-952.

TABLES

Table 1: *Cardiovascular Disease (CVD) Interview Items*

Variable	CVD Condition	Wave	Question
Baseline CVD	Arteriosclerosis	1	"Had hardening of arteries or arteriosclerosis in last 12 months?"
	Confirmation of Arteriosclerosis	1	"Did doctor or other health professional confirm diagnosis?"
	Angina	1	"Had chest pain or angina pectoris in last 12 months?"
	Confirmation of Angina	1	"Did doctor or other health professional confirm diagnosis?"
	Myocardial Infarction	1	"Had heart attack or myocardial infarction in last 12 months"
	Confirmation of Myocardial Infarction	1	"Did doctor or other health professional confirm diagnosis?"
Incident CVD	Arteriosclerosis	2	"Had hardening of the arteries or arteriosclerosis in the past year?"
	Confirmation of Arteriosclerosis	2	"Did doctor or other health professional confirm diagnosis?"
	Angina	2	"Had chest pain or angina pectoris in the past year?"
	Confirmation of Angina	2	"Did doctor or other health professional confirm diagnosis?"
	Myocardial Infarction	2	"Had a heart attack or myocardial infarction in the past year?"
	Confirmation of Myocardial Infarction	2	"Did doctor or other health professional confirm diagnosis?"
	Stroke	2	"Had a stroke in the past year"
	Confirmation of Stroke	2	"Did doctor or other health professional confirm diagnosis?"

Note: Response options for all items above were 1 = Yes: 2 = No: 9 = Unknown. Baseline CVD items were assessed at Wave 1. Incident CVD items were assessed at Wave 2.

Table 2: *Adverse Childhood Experiences Interview Items*

ACE Category	ACE Subcategory	Question
Abuse	Physical Abuse	"Before age 18, how often did parent/caregiver push, grab, shove, slap or hit you?"
		"Before age 18, how often did parent/caregiver hit you so hard that you had marks or bruises or were injured?"
	Emotional Abuse	"Before age 18, how often did parent/caregiver swear, insult, or say hurtful things to you?"
		"Before age 18, how often did parent/caregiver threaten to hit you or throw something at you?"
		"Before age 18, how often did parent/caregiver make you fear that you would be physically hurt or injured?"
	Sexual Abuse	"Before age 18, how often did adult/other person fondle/touch you in sexual say when you didn't want this/were too young to know what was happening?"
		"Before age 18, how often did adult/other person have you touch them in sexual way when you didn't want this/were too young to know what was happening?"
		Before age 18, how often did adult/other person attempt sexual intercourse with you when you didn't want this/were too young to know what was happening?"
		Before age 18, how often did adult/other person have sexual intercourse with you when you didn't want this/were too young to know what was happening?"
Neglect	Physical Neglect	"Before age 18, how often did parent/caregiver make you do chores that were too difficult or dangerous for someone your age?"

Table 2: *Adverse Childhood Experiences Interview Items (Continued)*

ACE Category	ACE Category	ACE Category
	Emotional Neglect	"Before age 18, How often did parent/caregiver leave you alone or unsupervised before 10 years old?"
		"Before age 18, how often did you go without things you needed because a parent/caregiver spent the money on themselves?"
		"Before age 18, how often did parent/caregiver make you go hungry or not prepare regular meals?"
		"Before age 18, how often did parent/caregiver ignore/fail to get you treatment when you were sick?"
		"Before age 18, felt there was someone in family that wanted me to be a success?"
		"Before age 18, felt there was someone in family who helped me feel that I was important or special?"
		"Before age 18, felt that my family was a source of strength and support?"
		"Before age 18, felt that I was part of a close-knit family?"
		"Before age 18, felt that someone in my family believed in me?"

Table 2: *Adverse Childhood Experiences Interview Items (Continued)*

ACE Category	ACE Category	ACE Category
Household Dysfunction	Indirect Abuse	"Before age 18, how often did your father/other adult male push, grab, slap or throw something at your mother?"
		"Before age 18, how often did your father/other adult male hit your mother with a fist or with something hard?"
		"Before age 18, how often did your father/other adult male repeatedly hit your mother for at least a few minutes?"
		"Before age 18, how often did your father/other adult male threaten your mother with a knife/gun or use a knife/gun to hurt her?"
	Indirect Neglect	"Before age 18, parent/other adult living in home was problem drinker/alcoholic?"
		"Before age 18, parent/other adult living in home had similar problems with drugs?"
		"Before age 18, parent/other adult living in home went to jail/prison?"
		"Before age 18, parent/other adult living in home treated/hospitalized for mental illness?"
		"Before age 18, parent/other adult living in home attempted suicide?"

Table 2: *Adverse Childhood Experiences Interview Items (Continued)*

ACE Category	ACE Category	ACE Category
		"Before age 18, parent/other adult living in home committed suicide?"

Note. Physical Abuse, Emotional Abuse, Sexual Abuse, Physical Neglect, and Indirect Abuse items had response options:1 = Never; 2 = Almost Never; 3 = Sometimes; 4 = Fairly often; 5 = Very often; 9 = Unknown. Emotional Neglect items had response options: 1 = Never true; 2 = Rarely true; 3 = Sometimes true; 4 = Often true; 5 = Very often true; 9 = Unknown. Indirect Neglect items had response options: 1 = Yes; 2 = No; 9 = Unknown.

Table 3: *Characteristics of Participants (N = 29,282)*

Demographic	Age, years		44.8 (17.1)
	Female, %		58.1
	Race-Ethnicity		
		Caucasian, %	58.1
		African American, %	18.7
		Hispanic or Latino, %	18.6
		Other, %	4.5
	Education		
		Less than High School, %	15.1
		High School or Equivalent, %	28.6
		Some College or Associate's Degree, %	30.7
		Bachelor's Degree or Higher, %	25.7
Cardiovascular	Diabetes, %		8.0
Disease	High Blood Pressure, %		18.2
Risk	High Cholesterol, %		19.3
Factors	Current Tobacco Use, %		25.4
	BMI, kg/m^2		27.0 (5.5)

Note. Continuous variables are presented as mean (standard deviation) and categorical variables as percentage.

Table 4: *Percentages for Depressive Disorder Variables*

	Total Sample	ACE	No ACE	Abuse	No Abuse	Neglect	No Neglect	HD	No HD
Lifetime Depressive Disorder	17.1%	20.4%	10.8%	22.7%	11.8%	21.6%	14.6%	23.8%	13.8%
Dysthymia only	0.8%	0.9%	0.5%	1.0%	0.6%	1.0%	0.6%	1.1%	0.6%
MDD only	13.2%	15.5%	8.8%	17.2%	9.5%	15.9%	11.7%	18.0%	10.9%
MDD + Dysthymia	3.1%	3.9%	1.5%	4.5%	1.7%	4.7%	2.2%	4.7%	2.3%

Note. Chi–square tests revealed that each ACE group had higher prevalence of lifetime depressive disorder (all *p*s < .001), dysthymia only (all *p*s < .001), MDD only (all *p*s < .001), and double depression (MDD superimposed on dysthymia; all *p*s < .001) than the corresponding group without that ACE type. ACE = adverse childhood experience. HD = household dysfunction.

Table 5: *Preliminary Logistic Regression Models Examining Lifetime Depressive Disorder and Adverse Childhood Experiences Variables as Predictors of Incident Cardiovascular Disease*

Model		Predictor	*OR*	*95% CI*	*p*
1	LDD → CVD	LDD	1.49	1.33-1.67	<.001
2	Any ACE → CVD	Any ACE	1.29	1.20-1.39	<.001
3	LDD & Any ACE → CVD	LDD	1.44	1.28-1.62	<.001
		Any ACE	1.25	1.16-1.35	<.001
4	Abuse → CVD	Abuse	1.23	1.14-1.32	<.001
5	LDD & Abuse → CVD	LDD	1.45	1.28-1.63	<.001
		Abuse	1.18	1.10-1.27	<.001
6	Neglect → CVD	Neglect	1.42	1.31-1.54	<.001
7	LDD & Neglect → CVD	LDD	1.43	1.27-1.60	<.001
		Neglect	1.39	1.28-1.50	<.001
8	Household Dysfunction → CVD	Household Dysfunction	1.41	1.28-1.54	<.001
9	LDD & Household Dysfunction → CVD	LDD	1.42	1.26-1.60	<.001
		Household Dysfunction	1.36	1.24-1.49	<.001

Note. Models 1, 2, 4, 6, and 8 are individual models adjusted for demographic factors (age, sex, race–ethnicity, education level) and traditional CVD risk factors (diabetes, high blood pressure, high cholesterol, current tobacco use, and body mass index), whereas Models 3, 5, 7, and 9 are simultaneous models with the same covariates. OR = odds ratio. CI = confidence interval. LDD = lifetime depressive disorder. CVD = cardiovascular disease. ACE = adverse childhood experiences.

Table 6: *Tests of Lifetime Depressive Disorder x Adverse Childhood Experiences Interaction Terms*

	Model	Interaction Terms	*OR*	*95% CI*	*p*
Individual	1	LDD x Any ACE	1.43	1.05-1.95	.024
	2	LDD x Abuse	1.22	0.92-1.62	.164
	3	LDD x Neglect	1.37	1.12-1.69	.003
	4	LDD x Household Dysfunction	1.59	1.21-2.09	<.001
Simultaneous	5	LDD x Abuse	0.94	0.70-1.27	.697
		LDD x Neglect	1.25	0.95-1.64	.117
		LDD x Household Dysfunction	1.53	1.17-2.00	.002

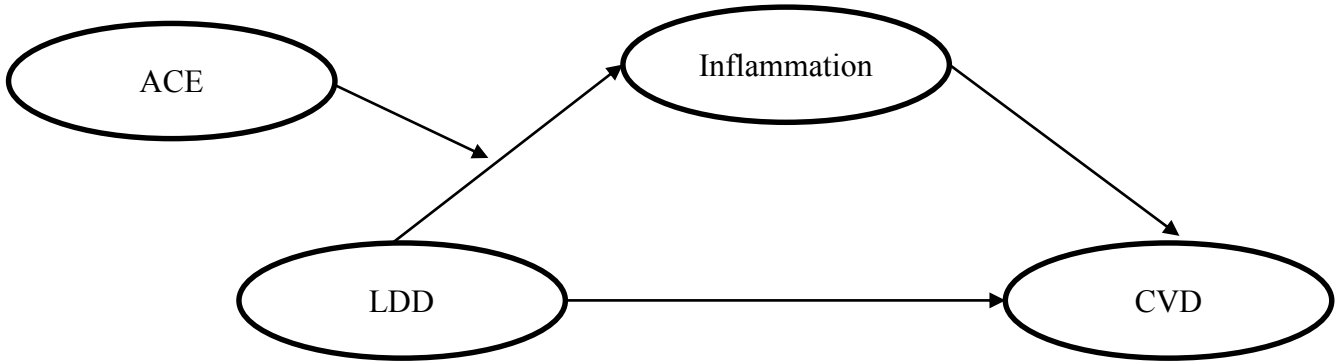
Note. All models were adjusted for demographics (age, sex, race/ethnicity, education) and CVD risk factors (diabetes, high blood pressure, high cholesterol, current tobacco use, BMI). OR = odds ratio. CI = confidence interval. LDD = lifetime depressive disorder. ACE = adverse childhood experiences.

Table 7: *Logistic Regression Models Examining Lifetime Depressive Disorder as a Predictor of Incident Cardiovascular Disease Stratified by Adverse Childhood Experiences Categories and Subcategories*

Model			*OR*	*CI (95%)*	*p*
1	No ACE		1.15	0.87-1.50	.332
	ACE		1.51	1.32-1.73	<.001
2	No Abuse		1.35	1.05-1.74	.021
	Abuse Any		1.46	1.29-1.65	<.001
3		No Physical Abuse	1.44	1.19-1.74	<.001
		Physical Abuse	1.40	1.22-1.60	<.001
4		No Emotional Abuse	1.27	1.01-1.58	.040
		Emotional Abuse	1.50	1.32-1.71	<.001
5		No Sexual Abuse	1.34	1.15-1.55	<.001
		Sexual Abuse	1.49	1.21-1.83	<.001
6	No Neglect		1.25	1.07-1.46	.005
	Neglect Any		1.59	1.36-1.87	<.001
7		No Physical Neglect	1.27	1.11-1.45	.001
		Physical Neglect	1.59	1.34-1.87	<.001
8		No Emotional Neglect	1.43	1.25-1.63	<.001
		Emotional Neglect	1.76	1.43-2.18	<.001
9	No Household Dysfunction		1.18	0.96-1.43	.111
	Household Dysfunction		1.73	1.46-2.04	<.001
10		No Indirect Abuse	1.33	1.15-1.54	<.001
		Indirect Abuse	1.73	1.43-2.08	<.001
11		No Indirect Neglect	1.28	1.08-1.52	.004
		Indirect Neglect	1.71	1.43-2.04	<.001

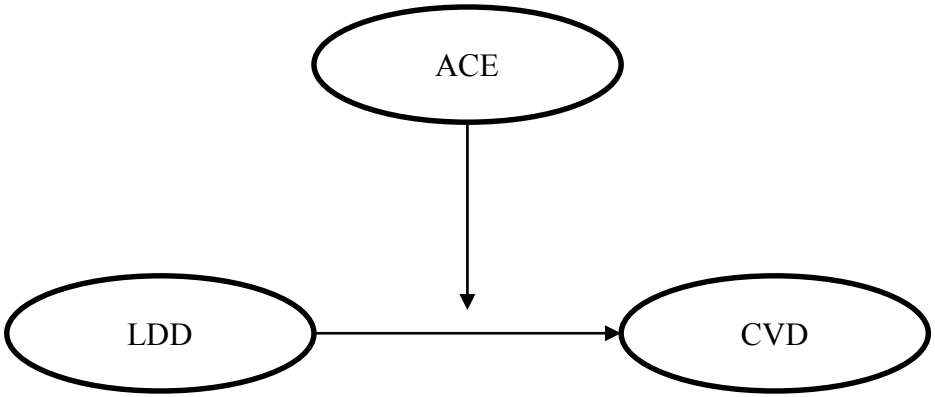
Note. All models were adjusted for demographics (age, sex, race/ethnicity, education) and CVD risk factors (diabetes, high blood pressure, high cholesterol, current tobacco use, BMI). OR = odds ratio. CI = confidence interval. ACE = adverse childhood experiences.

FIGURES



Conceptual Model for the Present Study

Figure 1: Conceptual model for the present study depicting Adverse Childhood Experiences (ACE) as a potential moderator of the longitudinal association between depression and incident cardiovascular disease (CVD) via the inflammation pathway.



Tested Model for the Present Study

Figure 2: Conceptual model for the present study depicting Adverse Childhood Experiences (ACE) as a potential moderator of the longitudinal association between depression and incident cardiovascular disease (CVD) via the inflammation pathway.

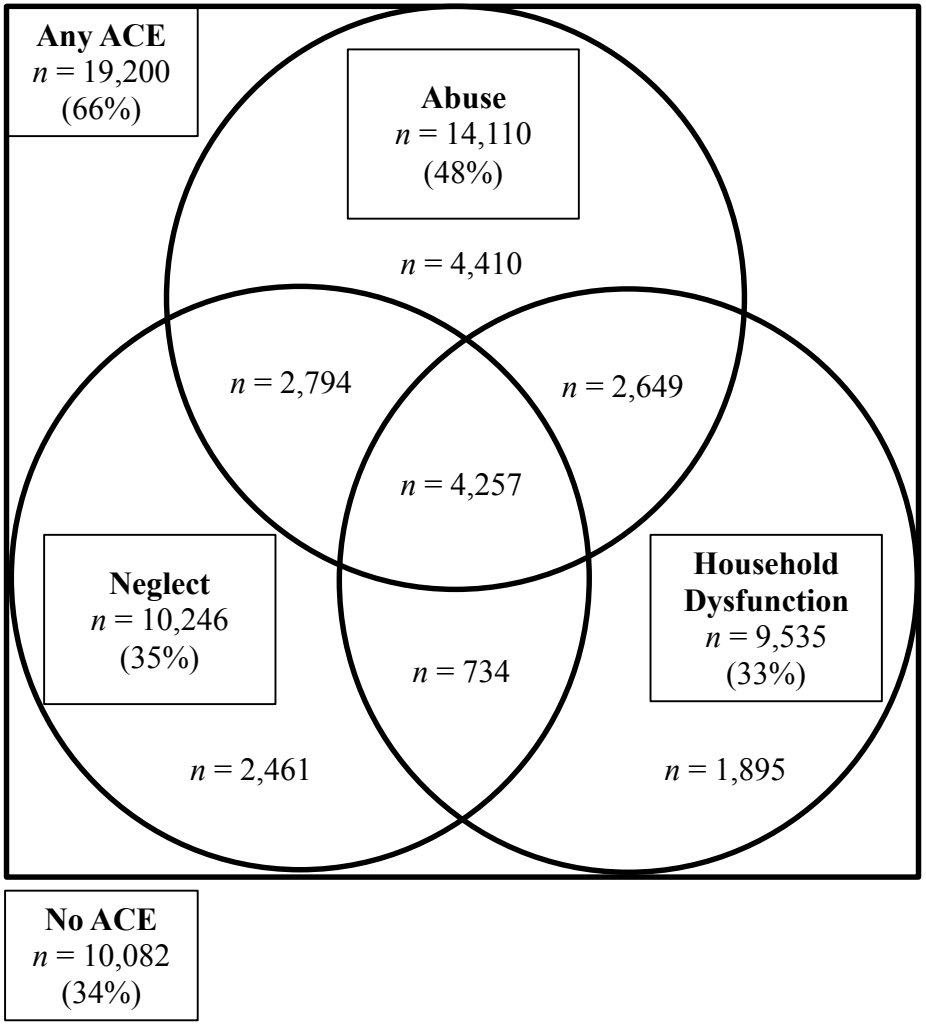


Figure 3: ACE Distribution in the Current Study Sample