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Is Periodontal Disease a Partial Mediator of the Association Between Depressive Symptoms and Cardiovascular Disease?

For the degree of Master of Science

Is approved by the final examining committee:

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IS PERIODONTAL DISEASE A PARTIAL MEDIATOR OF THE ASSOCIATION BETWEEN DEPRESSIVE SYMPTOMS AND CARDIOVASCULAR DISEASE?

A Thesis

Submitted to the Faculty

of

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TABLE OF CONTENTS

Page

LIST OF TABLES

LIST OF FIGURES

ABSTRACT

Khambaty, Tasneem. M.S., Purdue University, December 2011. Is Periodontal Disease a Partial Mediator of the Association Between Depressive Symptoms and Cardiovascular Disease? Major Professor: Jesse C. Stewart.

Epidemiological studies suggest that depression may be an independent risk factor for cardiovascular disease (CVD). Although several possible mediators of this association have been proposed, the precise mechanisms are yet unknown. Accordingly, we examined periodontal disease as a novel mediator of the depression-CVD association, given its separate links with both depression and CVD. Data from the National Health and Nutrition Examination Survey (NHANES) I and its Epidemiologic Follow-up Study (NHEFS) were analyzed. Participants were 3,346 individuals aged 25-74 years free of CVD at baseline (53% female, 16% non-white). Depression was assessed by the, depressed mood subscale of the General Well-Being Schedule Based on the Russell Periodontal Index, periodontal disease (43%) was defined as the presence of four or more periodontal pockets identified by a licensed dentist during an examination. The primary outcome was incident CVD (*n*=727, 22%), defined as nonfatal or fatal coronary artery disease or cerebrovascular disease, identified during the follow-up period by interviews and death certificate records. All analyses were adjusted for demographic and cardiovascular risk factors. Logistic regression analyses revealed no association between the GWBS depressed mood score and periodontal disease (*OR*=1.05, 95% *CI*: 0.96-1.14,

p=.24). Cox proportional hazard models revealed that both periodontal disease (*HR*=1.24, 95% *CI*: 1.06-1.46, *p*=.009) and depressed mood (*HR*=1.08, 95% *CI*: 1.01-1.17, *p*=.03) were significant predictors of incident CVD. However, Sobel analyses found that periodontal disease was not a partial mediator of the depressed mood-incident CVD association (*t*=1.01, *p*=.31). Overall, these mediation results suggest that (a) both periodontal disease and depressed mood are independent predictors of incident CVD and that (b) the effect of depressive symptoms on incident CVD is not mediated by periodontal disease.

INTRODUCTION

Cardiovascular disease (CVD) is currently the leading cause of death in the United States, and depression is the leading cause of disability worldwide. Studies over the past few decades have shown strong evidence that depression is an independent and perhaps causal risk factor for the development of CVD. Multiple pathways by which depression may lead to various cardiovascular outcomes have been suggested in the literature, including autonomic nervous system dysfunction, hypothalamic-pituitary-adrenal (HPA) axis dysregulation, systemic inflammation, and platelet activation. In addition to these potential mechanisms, periodontal disease is a variable that has been associated with both depression and cardiovascular disease, albeit separately. Due to these separate lines of research, one possibility is that periodontal disease is in fact a mediator of the relationship between depression and CVD. Because no study to our knowledge has empirically examined this possibility, the current study is designed to answer the following question: Is periodontal disease a partial mediator of the longitudinal association between depression and CVD?

Several topics will be discussed below in the way of an introduction, to provide background information regarding the variables of interest. First, depression and cardiovascular disease will be reviewed, including their prevalence, incidence, etiology, and known risk and protective factors. Second, the association between depression and

cardiovascular disease will be discussed, with a focus on potential mechanisms underlying this association. Third, the topic of periodontal disease will be introduced, followed by separate discussions of research findings on the association of periodontal disease with depression as well as with cardiovascular disease. After the conceptual framework for the current study is presented, along with the associated hypotheses that were tested, I follow with the current study's methodology, including the study sample, measures and procedures and data analyses. Next, I present the results of these analyses and finally, I discuss alternative explanations, limitations, implications and future directions.

Depression

Depression is a highly debilitating illness that affects both an individual's mental and physical health, and accounts for more disability than any other disorder worldwide (Pratt & Brody, 2008). In addition to causing much suffering, the illness also leads to decreases one's quality of life, impairment in one's social and occupational functioning, not to mention increases in health care costs (Wells et al., 1989). Depression is characterized as both a mood state that is transitory in nature and experienced at least once by most individuals in their lifetime, as well as a clinical syndrome, known as Major Depressive Disorder, or MDD (Fava & Kendler, 2000). MDD consists of the following four symptom clusters: emotional symptoms (e.g., depressed mood and anhedonia), cognitive symptoms (e.g., inappropriate guilt, poor concentration, indecisiveness, feelings of worthlessness, and recurrent thoughts of death or suicide), behavioral symptoms (e.g.,

psychomotor agitation or retardation) and somatic symptoms (e.g., weight loss or gain, sleep disturbances or visible loss of energy) (Fava & Kendler, 2000). According to DSM-IV criteria, five or more of the above symptoms, including depressed mood or anhedonia, must last at for at least two weeks for the diagnosis of MDD. Moreover, these symptoms must be the source of significant distress and impairment in one's daily functioning, and should not be accounted for by substance use or bereavement (American Psychiatric Association, 2000). Dysthymic disorder is a milder, although more chronic form of depression in which symptoms last for two years or more (Blazer, 2009).

The onset of MDD may occur at any stage of life. Data collected in the National Comorbidity Survey Replication indicates the average age of onset of MDD to be the early teen years (Kessler et al., 2003). In early-onset depression, first episodes are experienced in childhood, while late-onset depression is defined as occurring after the age of 60 (Blazer, 2009). In the case of early-onset depression, it is likely that these individuals may experience additional episodes throughout adulthood. In fact, MDD is a life-long episodic disorder for most people (Fava & Kendler, 2000). Although some experience multiple recurrences that are spaced at intervals, approximately 20% to 25% experience a chronic, unremitting course (Mueller & Leon, 1996).

MDD is the most common of the psychiatric disorders and, among "first-world" countries, the most common of all biomedical disorders (Fava & Kendler, 2000). Depression is also one of the most significant risk factors for suicide (Kessler et al., 2003). According to the National Comorbidity Survey, the lifetime prevalence of MDD is approximately 17% (Fava & Kendler, 2000). Moreover, the prevalence of MDD rose markedly in the United States during the decades of 1991-1992 to 2001-2002, from 3.3%

to 7.1% (Lloyd-Jones et al., 2009). Data collected in 2005-2006 through the continuous National Health and Nutrition Examination Survey (NHANES), a cross-sectional survey of the non-institutionalized U.S population, found that in any 2 week period, 5.4% of Americans aged 12 years and over experienced clinical depression and that this rate was highest in women, the non-Hispanic black population, and in individuals between the age of 40 and 59 (Pratt & Brody, 2008). Furthermore, in the age group of 18-59 years, higher rates of depression were found for individuals below the federal poverty line. Despite 80% of people with depression reporting some level of impairment in their daily functioning, only 29% of these individuals reported contacting a mental health professional in the past year.

MDD is diagnosed through clinical assessment whereas depressive symptom severity is measured through a standardized self-report scale such as the Center for Epidemiologic Studies Depression Scale (CES-D) or the Beck Depression Inventory (BDI). These two concepts have been found to be closely related, such that high scores on depressive mood scales are strongly correlated with the presence of MDD (Williams, Pignone, Ramirez, & Perez Stellato, 2002; Goldston & Baillie, 2008). Williams and colleagues (2002) reported a median sensitivity of 85% for major depression and a median specificity of 74%, in their evaluation of 16 different depressive symptom severity scales (including the CES-D and the BDI).

Pathophysiology

The etiology of depression is currently understood to be a gene-environment interaction (Nemeroff, 2008). It is thought that one third of the risk for the development of depression is inherited through genes, while approximately two thirds is environmental (Sullivan, Neale, & Kendler, 2000). Three monoamine systems - serotonin, norepinephrine, and dopamine - have been of primary focus in terms of etiology.

The serotonin hypothesis of depression is one that has gained support over the years. According to the hypothesis, disturbances in the functioning of the serotonergic system play a leading role in the development of depression (Wichers & Maes, 2002). As the serotonergic system has a wide-spread distribution, and enervates virtually all regions of the central nervous system, it is thought to modify multiple behaviors, such as food intake, circadian rhythms, learning, and sexual activity (Wichers & Maes, 2002). Disturbances in this system occur in multiple ways. For example, a reduction in the levels of plasma concentrations of tryptophan, the precursor of serotonin, can lead to reduced production of serotonin. In addition, it is thought that one's genetics control the level of transcriptional activity of the serotonin transporter gene and therefore its function, which is the uptake of serotonin into the presynaptic cleft. Thus, depending on the amount of uptake, more or less serotonin may exist in the synaptic cleft, which in turn, has been associated with anxiety, depression and aggression-related personality traits (Lesch & Mossner, 1998). Lastly, increased 5-HT2 receptor binding and decreased 5-HT1a receptor binding in the frontal cortex among other areas, have been found to exist in depressed individuals, suggesting that these changes in serotonin receptor binding may be involved in the development of depression (Wichers & Maes, 2002).

Another neurotransmitter implicated in the development of depression is norepinephrine (Wichers & Maes, 2002). According to one hypothesis, an increase in norepinephrine release may occur due to impaired negative feedback in the presynamptic neuron. Supporting this theory, studies have shown that depressed individuals have higher plasma norepinephrine levels than non-depressed controls (Maes, Vandewoude, Schotte, Martin, & Blockx, 1990). However, there is great variability in study findings and other competing hypotheses exist (Ressler & Nemeroff, 2000). Overall the data seem most consistent with increased norepinephrine activity, which may be the result of any combination of increased or decreased release of the neurotransmitter, coupled with increased or decreased receptor sensitivity (Ressler & Nemeroff, 2000).

There is also considerable evidence supporting the role of the central nervous system dopaminergic circuits in the etiology of depression (Nemeroff, 2008). The dopamine hypothesis is supported by the fact that one of the primary symptoms of depression is an inability to experience pleasure, which is known to be mediated primarily through the dopamine system (Nemeroff, 2008). Evidence for the involvement of the dopamine circuit also emerges from positron emission tomography imaging studies that show reduced dopamine transporter binding sites, as well as the reduced availability of dopamine in synapses, in individuals with depression (Nemeroff, 2008).

Lastly, some evidence has been found for the role of the HPA axis in the development of depression. The HPA axis is the primary system managing the body's stress response (Nemeroff et al., 1984). The diathesis-stress hypothesis of depression has been posited in response to observations that individuals with depression secrete excess cortisol and other hormones of the HPA axis. The diathesis-stress hypothesis suggests

that individuals with depression have a cognitive vulnerability for depression that is trait-like in nature (Beck, 1967). Only after this diathesis is activated by stressful life events does an individual begin to demonstrate overt depressive symptoms. Support for HPA axis hyperactivity in depressed patients was also found in studies that observed elevated cerebrospinal fluid corticotropin-releasing factor concentrations and plasma cortisol levels in non-medicated individuals with depression (Nemeroff, 1998; Wichers & Maes, 2002).

Risk and Protective Factors

Four risk factors have consistently been discussed in association with MDD. These include female gender, stressful life events, adverse childhood experiences, and certain personality traits (Fava & Kendler, 2000). Multiple studies across varying settings have shown that women are at a greater risk for MDD than men, with a ratio ranging from 1.5 to 2.5. Stressful life events - such as marital difficulties, major health problems, job loss, and loss of a loved one - have all been associated with an increased risk of MDD. Moreover, adverse childhood experiences, including physical or sexual abuse and parental discord or divorce, have also shown to increase this risk. Lastly, the personality trait known as “neuroticism”, which predisposes one to become emotionally upset in reaction to stress, has also been shown to predispose one to developing MDD.

On the other hand, there are some factors that help decrease the risk of MDD by mitigating the impact of known risk factors (Aro, 1994). One study found that young adults from divorced families, with low self-esteem and lacking intimate relationships,

demonstrated the highest prevalence of depression, suggesting that intact families, high self-esteem and intimate relationships provide buffering effects against the risk of depression (Aro, 1994). This study, further examining whether intimate relationships (including steady dating, cohabitation and marriage) served as protective factors against the development of depression, found that young adults were protected from the risk of depression by an intimate relationship, despite the presence of low self-esteem and regardless of family background. Another longitudinal, community-based study traced the development of individuals from age 5 to age 26 and found positive self-appraisals, optimism and good interpersonal relations to be other protective factors against the development of depression in young adulthood (Carbonell et al., 2002).

Cardiovascular Disease

CVD is broadly characterized as disease of the heart and vascular system and includes hypertension, coronary artery disease (CAD), congestive heart failure, congenital heart defects, rheumatic heart disease, peripheral arterial disease (PAD) and stroke (Joshipura et al., 2009). The current study however, is concerned with CVD arising from atherosclerosis. As such, the term, CVD, in the current study, specifically refers to atherosclerotic disease of the arteries of the heart (CAD), the brain (cerebrovascular disease or CBV), or the arms, legs and pelvis (PAD).

CVD is the number one cause of death in the United States (Lloyd-Jones et al., 2009). Its prevalence in the past year was 8.9% among American men and women. Moreover, the cost for CVD in 2010, both direct and indirect, is estimated to be $503.2

billion (Lloyd-Jones et al., 2010). By the year 2020, the number of annual CVD related deaths is predicted to be 25 million (Gaziano, 2005). Despite declining mortality rates for cardiovascular disease, approximately 17 million adults (7.6%) currently have CAD, which accounts for more than half of all cardiovascular events (e.g., myocardial infarction or MI) among individuals under the age of 75 in the United States (Rosamond et al., 2007). In the onset of CAD, women usually lag behind men by about 10 years, yet have a higher likelihood of not surviving a cardiovascular incident (Rosamond et al., 2007).

According to National Center for Health Statistics, the prevalence of stroke in Americans aged 20 years and older during 2003 to 2006 was 2.9% (Llyod-Jones et al., 2009). Females have greater prevalence (3.2%) of strokes than males (2.5%). Additionally, according to 2008 data from the National Health Interview Survey, African Americans have a higher prevalence (3.6%) than Caucasians (2.7%) (Pleis, Lucas, & Ward, 2009). Moreover, the incidence rate of stroke is higher for men compared to women at younger ages, but is the reverse at older ages. The male-to-female incidence ratio among those 55 to 64 years is 1.25(National Heart, Lung, and Blood Institute, 2006). The prevalence of PAD increases considerably with age, such that for American aged 65 years and older, the prevalence is between 12% and 20% (Ostechega, Paulose-Ram, Dillon, Gu, & Hughes, 2007; Selvin, & Erlinger, 2004). In addition, this rate is higher in African Americans compared to other ethnicities. Due to the high prevalence and incidence rates, considerable effort has been spent examining the pathophysiology of and risk factors for CVD.

Pathophysiology

Atherosclerosis has been described as a process more than a disease in and of itself (Ross, 1993). It was initially thought of as a "straight plumbing problem" (pp. 48), in which plaque developed on the surface of artery walls and eventually blocked the arteries. In the last two decades however, atherosclerosis has been re-characterized such that inflammation is thought to play the most crucial role in its development and progression (Libby, 2003). Low-density lipoprotein (LDL) tends to cause the greatest amount of harm to the endothelium, which is a layer of flat cells that line the cavities of blood vessels. While transporting cholesterol from the liver to other organs, large amounts of LDL may become trapped in the arterial wall closest to the blood stream. The LDL particles, once trapped, undergo oxidation and are internalized by macrophages (white blood cells that ingest foreign substances), eventually leading to the formation of foam cells (Ross, 1999). The 'fatty streak' occurs when lipid-rich macrophages and T-lymphocytes aggregate within the intima (the innermost artery wall layer). These fatty streaks are then followed by intermediate lesions, which in turn develop into fibrous plaques – i.e., more advanced, occlusive lesions (Ross, 1993). Previously, these plaque deposits were thought to reduce blood flow to a pinpoint, hence starving the tissues of the heart. It is now known that the buildup of atherosclerotic plaques, although progressively narrowing the arteries and decreasing blood flow to the heart muscle, rarely leads to total occlusion of the artery. Instead the cap of the plaque can rupture suddenly, leading to the formation of a thrombus (blood clot) that completely blocks the artery (Hansson, 2005).

The atherosclerotic process is usually seen in the elastic and muscular arteries, both large and medium-sized, and can result in ischemia of the heart, brain, or peripheral

limbs (Belgg, 2004; Ross, 1999). This, in turn, can lead to infarction (muscle death due to deprivation of blood) in the heart, brain, or limbs. In the heart, atherosclerosis tends to lead to three clinical syndromes. In order of severity, these are angina pectoris, myocardial infarction (MI), and sudden cardiac death. Atherosclerosis in the brain often leads to stroke or another CBV event. When this occurs, blood flow to the brain is typically blocked by a clot, resulting in a cerebral thrombosis or embolism. As a consequence, loss of function and permanent death of brain tissue may occur (Bellg, 2004). Additionally, a subarachnoid or cerebral hemorrhage is caused by a burst blood vessel, otherwise known as an aneurysm. In this case however, the effect may be temporary, as brain function may return once the pressure on the brain is relieved. Finally, PAD occurs when atherosclerosis leads to the obstruction of blood circulation to the upper and lower extremities such that metabolic demand is often not met (Creager & Libby, 2005).

Risk and Protective Factors

Traditional risk factors for CAD can be categorized into modifiable and non-modifiable risk factors. Non-modifiable factors include age, male gender, and a positive family history, while modifiable factors include smoking, hypertension, hyperlipidemia, diabetes mellitus, obesity, and a sedentary lifestyle (Bellg, 2004). Cigarette smoking remains the most significant modifiable risk factor for CAD (Ridker & Libby, 2005). Ever since the first studies reporting positive associations between smoking and CAD emerged in the early 1950's, this association has been consistently reported. In addition,

the effects of smoke exposure are dependent on the dose, such that while smoking 1-4 cigarettes a day significantly increases CAD risk, smoking 20 or more cigarettes a day increases CAD risk two to three times, and even passive smoking can result in endothelial dysfunction and elevate CAD risk (He et al., 1999; Ridker & Libby, 2005). Hypertension, with a prevalence of greater than 20%, is another risk factor for the development of CAD (Nabel, 2003). Individuals with hypertension, defined as resting blood pressure greater than 140/90 mmHg, have been found to be at a two to three-fold greater risk of CAD compared to their normotensive counterparts (Kannel, 1996)

The role of cholesterol in atherosclerosis and subsequent CAD is now generally accepted (Ridker & Libby, 2005). In addition to cross-sectional studies, large scale longitudinal cohort studies such as the Multiple Risk Factor Intervention Trial (MRFIT) and the Atherosclerosis Risk in Communities (ARIC) study have substantiated the finding that high cholesterol levels are associated with coronary death.

Abnormal glucose tolerance, when combined with obesity greatly increases the risk of diabetes. This in turn has been found to increase the risk of a CAD event two-to-eight fold, as compared to non-diabetic individuals matched on age and ethnicity (Howard et al., 2002). Additionally, 75% of all deaths among diabetic individuals are due to CAD (Gu, Cowie, & Harris, 1998).

The risk factors for CVD and PAD are similar, though not identical to those for CAD, and some may confer higher risk for one condition compared to another (Lloyd-Jones et al., 2009). For instance, a transient ischemic attack-temporary neurologic dysfunction due to reduced blood flow to the brain, spinal cord, or retina-increases stroke risk substantially in the short term (Lloyd-Jones et al., 2009). Furthermore, blood

pressure, diabetes, age > 60 years, and female gender are particularly important risk factors for stroke. Women aged 45 to54 years have twice the likelihood of having suffered a stroke compared to men. In a similar fashion, diabetes and smoking confer stronger risk for PAD than CAD (Hirsch et al., 2006).

Conversely, high density lipoprotein (HDL) has been classified as a protective factor for CVD. Both cross-sectional and prospective studies have found an inverse correlation between HDL cholesterol and CVD risk (Ridker & Libby, 2005). It is hypothesized that HDL may carry cholesterol away from the artery wall, and aid in its break down, thus lowering cholesterol levels and decreasing CVD risk. Another protective factor for CVD is regular physical exercise, which has been found to lower the risk of developing the disease (Ridker & Libby, 2005). Regular exercise, such as walking briskly for 30 minutes a day, may lower blood pressure, decrease risk of obesity and diabetes and improve dyslipidemia and vascular inflammation (Thompson et al., 2003). Prospective studies consistently show the benefits of exercise in reducing cardiovascular morbidity, and all-cause mortality. Furthermore, there appears to be an inverse dose-response relationship between the level of exercise and the risk of a coronary event (Ridker & Libby, 2005).

Depression-Cardiovascular Disease Relationship

In the past few decades, compelling evidence for an association between depression and CVD has been reported (Goldston & Baillie, 2008; Rugulies, 2002; Wulsin & Singal, 2003). Countless reviews, meta-analyses and prospective studies have

found support for the role of depression in the pathogenesis of CVD, showing that depression contributes an independent risk for new CVD events (Wulsin & Singal, 2003). Case in point is a meta-analysis conducted by Rugulies and colleagues (2002), who analyzed 11 prospective studies investigating whether depression (either clinical depression or elevated depressive symptom severity) predicted the development of CVD (defined as myocardial infarction or coronary death) in initially healthy individuals. The overall risk ratio for the association between depression and CVD development was found to be 1.64, indicating that depressed individuals have a 64% greater risk of CVD than those with lower or no depressive symptoms. Of note, clinical depression (*RR*=2.69) was found to be a stronger predictor of future CVD than elevated depressive symptoms (*RR*=1.49), suggesting that a dose-response relationship that extends into the subclinical range exists between the two factors (Rozanski, Blumenthal, Davidson, Saab, & Kubzansky, 2005). Studies have also found that the depression-CVD association persists even after the adjustment for traditional CVD risk factors, such as smoking, diabetes, and hypertension (Rugulies, 2002; Wulsin & Singal, 2003).This relationship has been observed in both men and women, across different age and racial/ethnic groups (Rosengren et al., 2004; Suls & Bunde, 2005). Finally, the strength of the association between depression and CVD is similar to that between traditional risk factors and CVD (Goldston & Baillie, 2008; Rozanski et al., 2005).

A few prospective studies further buttress the depression-CVD association. These studies are particularly noteworthy because they all examine data from the First National Health and Nutrition Examination Survey (NHANES I), which is the dataset analyzed in the current study. NHANES I is a nationally representative longitudinal cohort study

conducted by the Centers for Disease Control and Preventions (CDC) in the years 1971 through 1975.

Ferketich and colleagues (2000) examined the depression-CVD association separately in men and women and reported that depression was significantly associated with CVD incidence in both genders. The study analyzed data from 5,007 men and 2,886 women, who were followed for 10 years, beginning in 1982 when they completed the CES-D. When depressive symptom severity was examined as a predictor of CVD incidence, similar risk ratios were observed for both men (*RR*=1.73) and women (*RR*=1.73).

Anda and coworkers (1993) studied 2,832 adults (aged 45-77 years) from the same cohort with a relatively longer follow-up period (mean of 12.4 years). Additionally, they used the General Well-Being Schedule (GWBS) to assess depressive symptoms, as opposed to the CES-D. Data for their outcome variable, namely ischemic heart disease, was obtained through proxy interviews and the National Death Index (NDI). Results, adjusted for demographic and risk factors, showed that depressive symptom severity predicted fatal (*RR*=1.5) and non-fatal (*RR*=1.4) ischemic heart disease.

A more recent study reported positive associations between depression and CVD in individuals with and without diabetes (Egede, Nietert, & Zheng, 2005). A total of 10,025 individuals from the NHANES I cohort were followed for 8 years, with participants categorized by the presence of depressive symptoms (measured by the CES-D) and self-reported diabetes. Mortality information was obtained through proxy interviews and the NDI. The investigators found significant risk for CVD mortality for individuals with comorbid diabetes and depression (*RR*=2.43).

Lastly, Jonas and Mussolino (2000) studied the association between depressive symptoms and stroke in 6,095 individuals from the NHANES I cohort, aged 25 to 74 years at baseline (1971-1975). Depressive symptoms were assessed at baseline with the GWBS. After an average of 16 years of follow-up, hospital records and death certificates were obtained to identify incident cases of stroke. Demographic and risk factor adjusted analyses revealed that depressive symptoms were predictive of stroke incidence in White and African-American individuals of both sexes (RR: 1.73, 95% CI=1.30-2.31). Taken together, these studies support the idea of a prospective association between depressive symptoms and various forms of CVD.

Mechanisms

Given that depression appears to play an important role in the onset of CVD, researchers have spent considerable effort examining the mechanisms by which this may occur. In addition, although many mechanisms have been posited, they are not well understood, thus necessitating further inquiry (Goldston & Baillie, 2008). Overall, these mechanisms fall into two broad categories: biological and behavioral.

Biological Mechanisms

The biological mechanisms implicated in the depression-CVD association include autonomic nervous system (ANS) dysfunction, hypothalamic-pituitary-adrenal axis (HPA) dysregulation, augmented systemic inflammation, and altered platelet function (Lett et al., 2004). Each of these is briefly discussed in the following paragraphs.

ANS dysfunction appears to exist in both depressed patients and CVD patients, leading some to suggest its role as a mechanism linking the two conditions. ANS function is assessed noninvasively through heart rate variability (HRV), referring to periodic fluctuations in heart rate (Bernston et al., 1997). Decreased HRV, which is indicative of ANS dysregulation, has been found in both subclinically depressed individuals, and individuals with MDD. Furthermore, decreased HRV has been associated with atherosclerosis and has been found to predict CVD incidence and mortality in prospective studies (Huikuri et al., 1999; Tsuji et al., 1996).

The HPA axis, which is part of the neuroendocrine system regulates the body's response to stress (Lovallo & Thomas, 2000). Hyperactivity of the HPA axis has been seen in depressed individuals, which can result in increased circulating cortisol and catecholamine levels, as well as increased heart rate and blood pressure peaks. In turn, these increases can escalate the risk of plaques rupturing within arteries, leading to a CVD incidence (Musselman & Nemeroff, 1996). Moreover, HPA axis hyperactivity has been associated with greater CVD risk, as evidenced by a greater prevalence of CVD risk factors including hypertension, dyslipidemia and diabetes (Troxler, Sprague, Albanese, Fuchs, & Thompson, 1977).

Acute phase proteins (e.g., C-reactive protein) and proinflammatory cytokines (e.g., interleukin-6) are markers of systemic inflammatory processes (Maes, 1995). Research indicates that both clinically depressed individuals and those with subclinical symptoms exhibit evidence of immune system activation, such as higher circulating levels of these inflammatory markers (Kop et al., 2002; Suarez, Krishnan, & Lewis, 2003). Importantly, a growing body of evidence indicates that C-reactive protein,

interleukin-6 and other inflammatory markers are predictive of CVD incidence and mortality (Joynt, Whellen, & O'Connor, 2003; Lett et al., 2004; Luc et al., 2003; Pearson et al., 2003).

The last biological mechanism of the depression-CVD association relates to abnormalities in platelet function (Guyton & Hall, 2000). Research shows that major depression is associated with increased platelet activation, as indicated by greater concentrations of platelet byproducts in the plasma of individuals with depression (Musselman et al., 1996). Enhanced platelet activation has also been shown to contribute to the development of atherosclerosis, perhaps by recruiting immune cells to sites of endothelium damage or by increasing the uptake of low density lipoproteins by macrophages (Appels et al., 2000; Lett et al., 2004; Markovitz & Matthews, 1991). One prospective study followed initially healthy men for 13 years and found that those with higher platelet activation had significantly higher rates of CVD mortality (Thaulow, Erikssen, Sandvik, Stormorken, & Cohn, 1991). Another study reported that CVD patients have enhanced platelet activation, which in turn predicts CVD mortality in these individuals (Markovitz & Matthews, 1991).

Behavioral Mechanisms

The chief culprits in terms of behavioral mechanisms include poor health behaviors, physical inactivity, and non-adherence to treatments (Goldston & Baillie, 2008). For example, studies report that depressed individuals engage in negative health behaviors to a greater degree than their non-depressed counterparts, including smoking,

consuming more alcohol, and following poor diets (Everson-Rose, House, & Mero, 2004). In addition, depressed individuals are also likely to be less physically active (Lin et al., 2004). Finally, reports such as those from the Heart and Soul study indicate that depressed individuals are less likely to take their medication and more likely to forget or skip their medication (Gehi, Haas, Pipkin, & Whooley, 2005). In turn, these behaviors have been shown to increase CVD risk.

The mechanisms by which depressive symptoms may lead to CVD have only begun to be explored. Although multiple plausible candidates have been identified, they are poorly understood. It is also possible that other mechanisms that may underlie the depression-CVD relationship have yet to be identified (Mattila et al., 1989; Rugulies, 2002). The present study seeks to examine periodontal disease as a candidate mediator, which is both reasonable and prudent due to two separate lines of research. The first line of research suggests that there is a positive association between depression and periodontal disease. The second line has established a compelling directional relationship between periodontal disease and future CVD. Given these, it is possible that periodontal disease may be a mediator of the depression-CVD relationships (See Figure 1). To date, no study has evaluated this notion. The nature of the depression-periodontal disease and the periodontal disease-CVD relationships are described below, preceded by a brief discussion of the classification and assessment of periodontal disease.

Periodontal Disease

Periodontal disease is defined as any disease that involves the tissues surrounding or supporting the teeth, known as the periodontium, and is usually classified according to the severity of inflammation and infection present (Pihlstrom, Michalowicz, & Johnson, 2005). Most periodontal diseases initiate with the accumulation of plaque either above or below the gum line. When this plaque calcifies, calculus or tartar forms (Coventry, Griffiths, Scully, & Tonetti, 2000). Further accumulation of plaque on the calcification results in an inflammatory reaction which may eventually lead to permanent tooth loss (Coventry et al., 2000). The two major stages of periodontal disease are gingivitis and periodontitis. Gingivitis is a milder, reversible form of the disease, characterized by inflammation of the gum (also known as gingiva). Although prognosis is good if further development of the disease is halted through regular care and treatment, when gingivitis remains untreated, a more chronic inflammatory state may evolve. This is the beginning of the second, more severe stage of the disease known as periodontitis (Rosania, Low, McCormick, & Rosania, 2009). Periodontitis manifests through inflammation of the gingiva and periodontal membranes, which are fibrous tissues that connect the teeth. This may cause loss of supporting tissue as the gingiva detaches from the teeth (Pihlstrom et al., 2005). Indeed, these two manifestations of periodontal disease are also distinguished by whether any attachment loss has occurred (Armitage, 2003). With gingivitis, there is no loss of attachment of the supporting tissue, whereas with periodontitis, the connective tissue detaches from the tooth and creates crevices. Without aggressive treatment, periodontitis eventually leads to permanent loss of the tooth

It has only recently been understood that periodontal disease is initiated by bacterial microorganisms within dental plaque, even though the role of the bacteria is unclear (Van Dyke, 2009). The pathogenesis of the disease is thought to be due to inflammation (Van Dyke, 2009). Without regular cleanings, the dental plaque can mature and elicit an inflammatory response, which can eventually lead to a destruction of the periodontium (Nguyen & Martin, 2008). As a result of periodontitis, soft tissue pockets or deepened crevices between tooth and gum usually form (Coventry et al., 2000; Pihlstrom et al., 2005).

There are multiple methods of diagnosing periodontal disease currently in use. These methods are generally categorized into (a) approaches that assess various agents that cause periodontal disease, such as the oral hygiene index, plaque index, and calculus index (measures the amount of bacteria and other debris accumulated on the tooth surface), and (b) approaches that assess the extent of tissue damage already incurred, including the periodontal disease index, the gingival index (measures the extent of gum inflammation), and the bleeding index (Van Dyke & Tohme, 2000).

Periodontal probes – which are instruments that quantify the extent of loss of attachment between the gingiva and tooth, the amount of dental plaque and gingival inflammation, and the overall progression of periodontal disease – have been in use since the mid 1920's (Listgarten, 1980). Two important measurements obtained through probes are probing pocket depth (PPD) and clinical attachment level (CAL), both of which assess prior rather than current periodontal destruction (*American Academy of Periodontology*, 2003; see Figures 2 and 3 for graphic representations of CAL and PPD). PPD measures the distance (in millimeters) from the gum line to the base of the existing

crevice, thus assessing of the depth of the periodontal pocket. This assessment is generally considered crucial in any periodontal examination. CAL, on the other hand, measures the distance (in millimeters) from the junction of the crown and root (called the cemento-enamel junction) to the base of the existing crevice. Although this assessment is more difficult to measure accurately than probing depth, it provides a superior evaluation of the extent of damage incurred by the periodontium (*American Academy of Periodontology*, 2003). Two other commonly utilized periodontal assessments are recession and bleeding on probing (BOP). Recession assesses (in millimeters) the degree to which the gum line has receded below the junction of the root and the crown of the tooth (Beck, 1999). BOP is a measure of gingivitis, where the tendency of the decaying periodontal tissues to bleed upon probing is assessed in order to identify tooth sites with active disease (Lang, Joss, Orsanic, Gusberti, & Siegrist, 1986).

According to NHANES III, the prevalence of gingivitis is 48% and the prevalence of periodontitis is 15% for Americans aged 30 years and older (Nguyen, 2008). Moreover, it has been estimated that over 90% of the population may be affected by chronic gingivitis at some point in their lives (Coventry et al., 2000).

Both genetic and environmental risk factors for periodontal disease have been identified. It is known that smoking accounts for about half the risk of developing periodontal disease in the United States (Pihlstrom et al., 2005). Cross-sectional and prospective studies have also consistently shown that individuals with poorly controlled Type 1 and Type 2 diabetes have a higher incidence of periodontal disease than those without diabetes (Pihlstrom et al., 2005). Furthermore, data from NHANES III indicate that attachment loss of greater than 3mm, suggesting greater severity of periodontal

disease, was more prevalent in men (58.73%) than women (48%) and in African American (65%) and Mexican-American (56%) populations than Caucasian American (51%) populations (Albandar et al., 1999). Other risk factors include infection with specific periodontal pathogens, such as *Bacteroides forsythus*, Human Immunodeficiency Virus and various systemic diseases, such as leukemia, thrombocytopenia and leucocyte disorders (Pihlstrom et al., 2005).

Depression-Periodontal Disease Relationship

The association between depression and periodontal disease has received increased attention of late. Cross-sectional studies have reported a positive correlation between depression and periodontal disease. For instance, one study examined 100 patients with periodontitis and 50 patients with no periodontal disease (Monteiro da Silva, Oakley, Newman, Nohl, & Lloyd, 1996). In that study, various psychological variables, including depressive symptoms, anxiety and loneliness were assessed using standard questionnaires, and periodontal disease was determined via dental examinations. The authors reported that patients with periodontitis had significantly higher depression and loneliness ratings, but not anxiety ratings than patients with no periodontal disease.

In another cross-sectional study of 1000 Chinese individuals, Ng and colleagues (2006) reported similar findings. Their study examined the association of depressive symptoms, anxious symptoms, and problem-focused and emotion-focused coping with CAL, calculus, BOP, and PPD. It was found that individuals with higher scores on depressive symptoms, anxiety symptoms, and emotion-focused coping measures had

higher odds of severe CAL, while problem-focused coping was associated with lower odds of CAL. Other investigations, utilizing diverse depression measures and assessments of periodontal disease, have corroborated the depression – periodontal disease association (Rosania et al., 2009; Saletu et al., 1996).

Despite these studies, there is a dearth of prospective studies examining this association. Therefore, the temporal relationship between the two variables has not adequately been addressed. Elter and colleagues (2002) conducted one of the few studies that have explored the directionality of this association by gathering 1-year data on 697 health maintenance organization patients, aged 30 to 65 years. These patients underwent an initial periodontal examination and were found to have more than 3 sites with PPD greater than 5mm. Computerized mental health records were abstracted for the same year as the periodontal examination to assess depression status for the cohort, where depression was operationalized as any Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) code for depression in the patient record. Over the next year, each patient underwent various periodontal treatments. The researchers measured the reduction in the numbers of teeth with PPD greater than 5mm at the 1-year follow-up as an indication of poor periodontal treatment outcome. They reported that patients with clinical depression had over twice the odds of poor periodontal treatment outcome (*OR*=2.16). The researchers concluded that depression may negatively influence periodontal treatment outcome.

It is worth noting that the positive association observed in studies such as those discussed above is not a universal finding. For instance, in a case-control study of 165 individuals, Castro and colleagues (2006) were unable to show an association between

depression, as measured by the Beck Depression Inventory (BDI), and periodontal disease, indicated by CAL. Nonetheless, a recent review has shown that study findings of positive correlations between depression and poor oral health outnumber negative study findings by a ratio of 4:1 (Peruzzo et al., 2007). The primary question addressed by this review was whether depression and other psychosocial factors could be considered risk factors for periodontal disease. These authors identified fourteen articles, including seven case-control studies, six cross-sectional studies and one prospective clinical trial, many of which analyzed multiple psychosocial factors (e.g., coping, life events, cortisol levels, anxiety, and depressive symptoms). CAL and PPD were still the outcome variables in most of the studies. Eight studies (57%) found positive outcomes between psychosocial factors and periodontal disease, while another four (28%) reported positive outcomes between a few of the psychosocial factors studied. Two studies (14%) reported negative outcomes between psychosocial factors and periodontal disease. In conclusion, although prospective studies are sorely needed, existing evidence suggests that depression may be predictor of periodontal disease.

Mechanisms

The mechanisms underlying the depression-periodontal disease association are not well understood; however, multiple biological and behavioral mechanisms have been hypothesized.

Biological Mechanisms

Bacteria and immune system dysfunction have been emphasized as the primary biological pathways underlying the depression-periodontal disease association (Elter et al., 2002; Iacopino, 2009; Rosania et al., 2009). Bacteria, although well established causal agents of periodontal disease, do not suffice in promoting advanced tissue destruction (Peruzzo et al., 2007). Therefore, researchers have looked towards the immune system as a co-conspirator. It has been suggested that stress and depression may down-regulate immune system function, which in turn is thought to facilitate chronic inflammation (Rosania et al., 2009). With an impaired immune system, pathogenic bacteria may have greater influence, aiding in the collapse of the periodontal attachment mechanism. These effects may be mediated through the HPA axis and the production of cortisol (Iacopino, 2009). An increased stress response is transmitted to the HPA axis, which promotes the release cortisol by the adrenal cortex (Peruzzo et al., 2007, Rosania et al., 2009). Cortisol, in the short term has the ability reduce inflammation; however, continued release of cortisol inhibits immunoglobin A and immunoglobin G, and thus reduces immunocompetency. As a result, invasion of the connective tissue of the mouth, perhaps by periodontal bacteria, may not be prevented. Additionally, with chronic elevations of cortisol, its ability to inhibit inflammatory responses of the immune system may be lost, and continuous inflammatory destruction of the periodontium may persist, ending in severe destructive periodontitis (Glassman & Miller, 2007).

Behavioral Mechanisms

Poor adherence to oral hygiene or treatment recommendations, and greater engagement in risk behaviors are the two main behavioral mechanisms hypothesized to underlie the depression-periodontal disease association (Iacopino, 2009). It is possible that depressed individuals may neglect oral hygiene – i.e., may not brush or floss on a regular basis and may not keep a healthy diet (Genco et al., 1998). Moreover, they may frequently engage in risk behaviors, such as smoking and drinking (Monteiro da Silva, Newman, Oakley, & O'Leary, 1998). These factors may result in decreased resistance of the periodontium to inflammation and aid in the development of periodontal disease (Iacopino, 2009).

Periodontal Disease-Cardiovascular Disease Relationship

Atherosclerosis

In the last few decades, both cross-sectional and prospective cohort studies have provided intriguing evidence of an association between periodontal disease and various forms of CVD. These studies suggest that periodontal disease may play a role in the development of CVD (Beck et al., 2005; Demmer & Desvarieux, 2006; Hung et al., 2003; Joshipura, Hung, Rimm, Willett, & Ascherio, 2003). Although the precise mechanisms underlying this relationship remain elusive, many researchers postulate that inflammation may be the most credible candidate (Dave & Van Dyke, 2008; Demmer & Desvarieux, 2006). Specifically, it has been shown that individuals with periodontal disease have elevated circulating levels of C-reactive protein and other systemic inflammatory markers,

perhaps triggered by bacteremias or bacterial byproducts associated with periodontal disease (Loos, Craandijk , Hoek , Wertheim-van Dillen, & van der Velden, 2000; Slade, Offenbacher, Beck, Heiss, & Pankow, 2000). Additionally, a decrease in systemic inflammation has been observed in these patients after periodontal disease treatment (D'Aiuto et al., 2004). This systemic inflammation has been shown to contribute to the atherosclerotic process, ultimately leading to CAD, CBV or PAD (Demmer & Desvarieux, 2006; Mattilla, Valle, Nieminen, Valtonen, & Hietaniemi, 1993; Scannapieco, Bush, & Puju, 2003).

Systematic reviews published on the periodontal disease-CVD relationship state that although conclusive evidence, in the form of randomized control trials, is still necessary, existing data show a moderate positive association between these two variables. For instance, a meta-analysis conducted by Janket et al. (2003) reported a relative risk of developing CVD of 1.19 for patients with periodontitis, compared to patients without periodontal disease. They further reported that when stroke was the only outcome, patients with periodontitis had substantially higher relative risk of 2.85. They analyzed eight prospective cohort studies and one retrospective cohort study, all conducted between the years of 1980 and 2001. Included within the definition of periodontal disease were both gingivitis and periodontitis, while their outcome variable included CVD events such as fatal and nonfatal MI, nonhemorrhagic stroke, or admission to a hospital with any CVD diagnosis.

In a more recent meta-analysis examining the periodontal disease-CVD association, Bahekar and colleagues (2007) analyzed separately five cross-sectional, five case-control and five prospective cohort studies (with follow-up times greater than 6

years). Despite small sample sizes in each of these categories as well as varied methodologies for the assessment of periodontal disease, it was found that individuals with periodontal disease versus controls had a 1.14, 2.22, and 1.59 times greater risk of CVD, in prospective cohort, case-control and cross-sectional studies, respectively. As with Jenket et al.'s meta-analysis, CVD encompassed both CAD and CBV, while periodontal disease incorporated both periodontitis and gingivitis.

Finally, a recent review summarizing 31 studies examining the relationship between periodontal disease and atherosclerosis found similar results (Scannapieco, Bush, & Puju, 2003). Of the 5 case-control studies, 4 reported positive relations between measures of poor oral health and atherosclerosis. In addition, 11 of the 15 cross-sectional studies found a positive periodontal disease-CVD association, after controlling for cardiovascular risk factors, such as smoking. Moreover, 3 cross-sectional studies and 1 prospective study reported a positive relationship between periodontal disease and stroke, and one other cross-sectional study detected a positive association between periodontal disease and PAD. Although data from a few studies did not support the connection between periodontal disease and CVD, the authors stated that the heterogeneity in the assessment of periodontal disease may have contributed to this pattern of results.

The following sections review key individual studies that have examined the periodontal disease-CVD relationship. Discussion is organized by the CVD category examined in the studies. Therefore, the periodontal disease-CAD association is discussed first, followed by the periodontal disease-CBV association and the periodontal-disease-PAD disease association.

Coronary Artery Disease

The first case-control study examining the association between periodontal disease and CAD was conducted by Mattila et al. (1989). These investigators examined 100 patients admitted to hospitals with MI and compared them to 102 controls selected randomly from the community (matched on age and sex). Both groups were systematically examined by dentists and the number of caries, periodontitis status, and the number of pockets was assessed. A total dental index was formulated for each participant based on the arithmetic sum of scores given for each of the above categories. The authors found that the men and women with MI had significantly worse total dental index scores then the controls. They further found that the association between periodontitis and MI was significant after the adjustment for traditional CVD risk factors.

Since this preliminary research, evidence for this relationship has continued to accumulate. Studies now support a dose-response relationship, such that with increasing severity of periodontal disease, the odds of a cardiovascular event also increase (Arbes, Slade, & Beck, 1999). A randomized controlled trial conducted by D'Aiuto and colleagues (2006) compellingly indicates that periodontal disease may be causal risk factor for CVD. In that study, 40 patients with periodontitis were randomized to either a standard course of periodontal therapy, including subgingival scaling and root planning, or to an intensive therapy, which included antimicrobial intensive periodontal therapy (IPT). Compared to the standard group, the IPT demonstrated significant reductions in inflammatory markers, total cholesterol, and systolic blood pressure at one and two months following therapy, as well as reduced cardiovascular risk at six months (as indicated by reduced cardiovascular risk factor scores).

Various prospective studies conducted with diverse populations have demonstrated that periodontal disease precedes and predicts cardiovascular events (Morrison, Ellison, & Taylor, 1999). For instance, the Nutrition Canada Survey (NCS), conducted from 1970 to 1972, tracked mortality data for men and women (aged 35-84 years) who were free of cardiovascular disease at baseline (Morrison et al., 1999). With 21 years of follow-up, analyses revealed a significant relationship between severe gingivitis and the risk of CAD death (*RR*=2.15).

DeStefano et al. (1993) examined data from NHANES I, in which participants aged 25-74 at baseline were followed for 13 years. Via a standardized dental examination, the total number of permanent decayed teeth, a periodontal classification, an oral hygiene index and a periodontal index were calculated. They further ascertained CAD mortality using National Death Index (NDI) data. The investigators reported that either periodontitis or having no remaining permanent teeth increased the risk of CAD mortality by 25%, and the risk of all-cause mortality by 50% during follow-up. Interestingly, they also noted that the degree of dental debris and calculus was more predictive of CAD incidence than the severity of periodontal disease.

Although the studies discussed above suggest that there is a prospective association between periodontal disease and various forms of CVD, other researchers have found either no associations or non-significant positive trends between periodontal disease and CVD (Beck et al., 2005). Among these are Hujoel and colleagues (2000), who examined the association between gingivitis and periodontitis and incident CAD in the NHANES I data. They however concluded that neither gingivitis (HR=1.05) nor periodontitis (HR=1.21) was associated with a CAD event after the adjustment for

confounders and the sampling design. Other researchers have raised some concern that Hujoel et al. (2000) may have over-adjusted for these confounders and could also have misclassified participants over the follow-up period, which may have contributed to their null findings (Genco et al., 2002).

While Joshipura et al. (1996) also reported no overall association between periodontal disease and CAD incidence over 6 years (RR=1.04), it is possible that because participants responded to a 'yes' or 'no' question in order to diagnose periodontal disease, substantial error may have been introduced through misclassification (Genco, Offenbacher, & Beck, 2002). Taken together, the extant data demonstrate a significant, though modest association between periodontal disease and CAD.

Cerebrovascular Disease

Recent studies have also linked periodontal disease to CBV, particularly stroke. Joshipura and colleagues' (2002) review the literature found two case-control and five longitudinal studies that have specifically explored this association. They reported that, despite diverse outcomes, ranging from fatal stroke to ischemic stroke and diverse samples, including German and Finnish samples and health professionals, five of the seven studies indicated and increased risk for CBV conferred by periodontal disease (*RR* ranges=1.22 to 2.90). A few of the key studies are summarized below.

One case-control study evaluated ischemic stroke and its relation to various periodontal measures, including a total dental index, a 14 point scale with scores increasing with the amount of caries and the severity of periodontitis (Grau, Buggle, &

Ziegler, 1997). Participants were 166 patients with acute cerebrovascular ischemia, and 166 controls, matched on age and sex. Higher total dental index scores were found to be significantly associated with cerebrovascular ischemia (*OR*: 2.6), after adjustment for age, sex, social status, diabetes, smoking status and previous vascular disease.

Joshipura and coworkers (2003) conducted a prospective study of 41,380 males participating in the Health Professionals' Follow-Up Study. These men, free of cardiovascular disease and diabetes at baseline, were mailed questionnaires to assess periodontal disease history. Stroke incidence was then accessed via medical history and medical records during the 12 years of follow-up. After controlling for a host of factors, including smoking, obesity, family history of CVD, alcohol use and exercise, Joshipura et al. (2003) observed a significant, though modest association between baseline periodontal disease and ischemic stroke (*HR*: 1.33).

It is possible that adjusting for a large number of factors may have attenuated the *HR* observed by Joshipura et al. (2003). In addition, the use of questionnaires to assess periodontal status could also attenuate the *HR*, as they are more likely to lead to misclassification. In a comparatively better designed study, Wu et al. (2000) followed 9,962 adults from the NHANES I cohort from 1971 through 1992. Periodontal examinations were conducted by trained examiners at baseline (1971-1975). Incident CBV was ascertained by the Health Care Facility Stay data, which was collected at each of the four follow-up interviews conducted in 1982, 1985, 1986, and 1992. This data provided death certificates and dates of hospitalizations or nursing home admissions. The investigators categorized participants into four groups: those with no periodontal disease, those with gingivitis, those with periodontitis, and those with no teeth on either arch or

for whom all teeth were roots. Their results showed that periodontitis significantly predicted total CBV incidence (*RR*=1.66), particularly nonhemorrhagic stroke (*RR*=2.11), when compared to no periodontitis, while gingivitis did not significantly predict either CBV incidence (*RR*=1.02) or nonhemorrhagic stroke (*RR*=1.24). Lastly, having no teeth on either arch was not a significant risk for CBV (*RR*=1.23) or nonhemorrhagic stroke (*RR*=1.41). Collectively, the aforementioned studies support the notion of that periodontal disease precedes and predicts CBV.

Peripheral Arterial Disease

The association between periodontal disease and PAD specifically has also been explored. Prospective studies not only provide evidence of a link, but also suggest that periodontal disease precedes PAD and therefore may be a risk factor for PAD.

Hung and colleagues (2002) followed 45,136 men participating in the Health Professionals Follow-up Study, aged 40 to 75 years and free of cardiovascular disease at baseline. Participants were asked to report number of teeth at baseline, as well as the subsequent loss of teeth over the follow-up period through mailed questionnaires. PAD incidence was obtained through both self-report questionnaires and medical records during the 12 year follow-up period. Analyses revealed that, compared to men without tooth loss, those with any tooth loss since baseline had a 51% greater risk of PAD, even after adjustment for age and smoking. The relative risk remained significant after adjusting for traditional CVD risk factors (*RR*=1.39). In addition, a history of periodontal disease at baseline also predicted PAD incidence (*RR*=1.32), with the association

between tooth loss and PAD risk increased for those with a history of periodontal disease (*RR*=1.88). However, because both periodontal disease and PAD were assessed via self-report in this study, these results should be interpreted with some caution.

Another study with better variable measurements, however, found similar results. In the Veteran Affairs Dental Longitudinal Study (Mendez et al., 1998), oral examinations for 1,110 men were conducted at baseline, and mean bone loss was calculated as a measure of periodontal disease. These men were also given comprehensive physical examinations at baseline and at each triennial follow-up visit, with the International Classification of Diseases, 8th revision (ICD-8) codes used to diagnose PAD. After 25 to 30 years of follow-up, the authors reported that individuals with clinical periodontal disease at baseline had a relative risk of 2.25 for the development of PAD, controlling for age, body mass index (BMI), and family history of heart disease.

Mechanisms

One possible mechanism through which periodontal disease may increase risk of CVD is chronic, low-level bacteremia (Hujoel, Drangsholt, Spiekerman, & DeRouen, 2000). Certain dental procedures have been shown to increase bacteria in the blood-stream, otherwise known as bacteremias (Demmer & Desvarieux, 2006; Kinane, Riggio,Walker, MacKenzie, & Shearer, 2005). Other studies have also found periodontal pathogens in arterial plaques, suggesting that these bacteria are able to gain systemic access via the circulatory system (Haraszthy, Zambon, Trevisan, Zeid, & Genco, 2000).

Once in the bloodstream, these bacteremias are able to initiate or exacerbate atherosclerotic development and hypercoagulability, as evidenced by the ability of certain strains of *P.gingivalis* (a periodontal bacteremia) to infect macrophages and enhance foam cell formation in the arterial wall (Demmer & Desvarieux, 2006; Giacona et al., 2004). Additionally, Herzberg and Meyer (1996) found that *P.gingivalis* and Sterptococcus sanguis can induce platelet aggregation and hypercoagulability, thus promoting thrombosis and eventual ischemic cardiovascular events. Furthermore, in response to the bacteremia, an elevation in inflammatory mediators (e.g., C-reactive protein, prostaglandins, interleukin-1, and tumor necrosis factor) has been shown to occur, which also contribute to the atherosclerotic process (Slade, Offenbacher, Beck, Heiss, &, Pankow, 2000).

Current Study

Extant literature provides preliminary evidence for the association between depressive symptoms and CVD (see path 'c' in Figure 1), the association between depressive symptoms and periodontal disease (see path 'a' in Figure 1), and the association between periodontal disease and CVD (see path 'b' in Figure 1). In doing so, this literature lends support to the examination of periodontal disease as a mediator of the relationship between depressive symptoms and CVD. To the author's knowledge, no studies to date have examined periodontal disease in this light.

Two of the three paths – namely, paths 'b' and 'c' – have been previously examined in the NHANES I cohort, which is the sample for the current study. In addition

to testing whether periodontal disease mediates the depression-CVD relationship, the current investigation extends previous evidence by expanding the cardiovascular outcome variable, which includes incident CAD, CBV, and PAD. The existing NHANES I studies, beginning with those that examined path 'c' and followed by those studies that examined path 'b', are summarized below.

NHANES I studies investigating the depressive symptoms-CVD association all differed with respect to the duration of follow-up, the scale used to assess depressive symptom severity, and the cardiovascular outcome. With a follow-up period of 12 years, Anda et al. (1993) found GWBS scores to be modestly predictive of ischemic heart disease, both fatal and non-fatal. With a follow-up of 10 years, Ferketich and colleagues (2000) analyzed data for men and women separately and reported that CES-D scores predicted CAD incidence (obtained through hospital discharge records) in both genders, but CAD mortality (data obtained through the National Death Index and proxy interviews) only in men. A more recent study examined a much larger subsample of the NHANES I cohort (10,025 individuals) with and without diabetes, over an 8-year period (Egede, Nietert & Zheng, 2005). Compared to individuals without diabetes or depressive symptoms, individuals with both depressive symptoms (indicated by CES-D scores) and diabetes (data obtained through self-reports) had a 2.4-fold increased risk of CAD mortality. Moreover, individuals with depression but not diabetes had a 1.3-fold increased risk of CAD mortality, and individuals with diabetes but no depression had a 2.3-fold increased risk of CAD mortality. Lastly, analyses by Jonas and Mussolino (2000) revealed a significant longitudinal association between scores from the general well-being schedule (GWBS) and stroke incidence in White and African-American individuals

of both sexes who were followed for an average of 16 years. The relationship between depressive symptoms and PAD incidence or mortality has not been examined in the NHANES I cohort.

Fewer studies have utilized data from NHANES I to examine the periodontal disease-CVD association. Nonetheless, DeStefano et al. (1993) reported that periodontitis or having no permanent teeth increased the risk of CAD by 25% and the risk of CAD mortality by 50% during a follow-up of 13 years. With an 11-year follow-up period, Wu and Colleagues (2000) also reported that periodontitis increased CBV risk. The relationship between periodontitis and PAD incidence or mortality has not been examined in the NHANES I cohort.

Primary Objectives

The overall aim of the current study was to examine whether periodontal disease partially explains the longitudinal relationship between depression and CVD (see Figure 1). In order to do so, the following four specific hypotheses were tested:

Hypothesis 1: Periodontal disease is a partial mediator of the relationship between depression and CVD incidence, defined as incident CAD, CBV, or PAD.

Hypothesis 2: Periodontal disease is a partial mediator of the relationship between depression and incident CAD.

Hypothesis 3: Periodontal disease is a partial mediator of the relationship between depression and incidence CBV.

Hypothesis 4: Periodontal disease is a partial mediator of the relationship between depression and incident PAD.

METHODS

Study Sample

Data from NHANES I was analyzed to test the hypotheses of the present study. NHANES I is a survey conducted by the National Center for Health Statistics (NCHS) between the years of 1971 and 1975. The primary purpose of this cross-sectional survey was to collect health-related information in a probability sample of civilian non-institutionalized individuals in the contiguous United States (National Center for Health Statistics [NCHS], 1965). As such, the health and nutrition status of children and adults aged 1 through 74 years was assessed. Population groups who were at a higher risk of malnutrition, such as women of childbearing age, low-income groups, preschool children, and the elderly, were oversampled.

For this survey, the contiguous United States were divided into 1,900 geographic areas, and then collapsed into 25 strata based on population density and geographic region (NCHS, 1965). From each stratum, two geographic areas were then chosen, with each area further divided into 6 segments. Systematic sampling was conducted from each of these segments, and households within the segment boundaries were contacted. Once age, sex and other demographic data of each member were verified, systematic random sampling was conducted for each age-sex group. A total of 31,973 individuals participated in NHANES I. Prior to these interviews, a general news release was

distributed to local news media outlining the survey program. Individual post-cards were also sent to each selected household describing the survey and informing members that a NHANES interviewer would be arriving in the next few days.

Upon arriving, the NHANES interviewer obtained written consent as well as authorization to obtain physician, dentist, and hospital records (National Center for Health Statistics [NCHS], 1977). A few other questionnaires, including a medical history questionnaire, were also administered as this time. Lastly, the participant scheduled an appointment for the examination component of the survey, conducted at three specially equipped trailers, collectively known as the mobile Health Examination Center (MEC). A general medical examination; a dental, dermatological, and ophthalmological examination; anthropometric measurements; and hand-wrist x-rays were performed in the MEC. In addition, blood samples were obtained, and various assays were performed.

A subset of the NHANES I participants, aged 25-74 years, was given a more detailed health examination, for which data collection continued until October 1975 (National Center for Health Statistics [NCHS], 1978). This subsample of 6,913 participants, representative of the U.S population during the time of data collection, was randomly selected from the original NHANES cohort and was not over-sampled in any manner. Although the operation of the survey proceeded as before, some additions were made to the content and design of the examination. Specifically, participants in the detailed survey component received a medical history supplement, additional questionnaires regarding arthritis, respiratory and cardiovascular conditions, a health care needs questionnaire, and a general well-being questionnaire (the GWBS). Additional examination components included an extended medical evaluation, audiometry,

electrocardiography, goniometry, spriometry, various x-rays, pulmonary diffusion, and tuberculin tests.

Of the total NHANES I sample (*N*=31,973), 23,808 individuals were given a medical exam. Of these, 6,913 individuals (3,172 men and 3,741 women) participated in the detailed survey component and completed the GWBS, which includes a depression subscale. Moreover, of the participants with depressive symptom data, 3,854 had periodontal disease data (i.e., underwent the dental examination) and incident CVD data. A total of 424 of these individuals with existing cardiovascular conditions were excluded from analyses because periodontal disease is being explored as a potential mediator of the depression-CVD relationship and for the mediator to precede the outcome, all existing CVD conditions must be excluded. CVD at baseline was defined via both self-report questions ("Has a doctor ever told you that you have heart failure", "Has a doctor ever told you that you have had a heart attack", or "Has a doctor ever told you that you have had a stroke?") from the Medical History Questionnaire and assessments conducted by physicians during the MEC examinations. The physicians reported the results of the examination by listing International Classification of Diseases, ninth revision (ICD-9) codes in each individual's record, with codes 410-414, 420-429, 430-438, and 440-448 denoting the presence of a cardiovascular condition. Of the resulting 3,430 individuals, 84 additional participants were excluded due to missing data on covariates. Consequently, 3,346 individuals comprised the final sample.

Measures and Procedures

Depressive Symptoms

During NHANES I data collection, depressive symptoms were measured with the GWBS (Dupuy, 1977). The GWBS was administered to individuals in the detailed survey component (aged 25-74 years) by designated personnel at the MEC. The GWBS consists of six subscales, the items of which were designed to assess six major constructs of psychological well-being, namely 1) Freedom from Health Worry, Concern, 2) Energy Level, 3) Satisfying, Interesting Life, 4) Cheerful vs. Depressed Mood, 5) Relaxed vs. Tense, Anxious, and 6) Emotional-Behavioral Control. These individual scales arithmetically combine to form a total general well-being score, for which scores may range from 0 to 110 (with higher scores indicating better psychological well-being). Each of the 33 items of the scale inquires as to how one has been feeling in the past month. Four of the 33 items in the GWBS comprise the depressed mood subscale (Cheerful vs. Depressed Mood subscale; see Appendix). Scores for this subscale range from 0 to 25, with lower values representing increased depressive symptoms. Of note, these raw scores were converted to z-scores [(score – mean)/standard deviation] and further inverted by multiplying by -1 so that higher scores would be indicative of higher depressive symptom severity. As a result, odds and hazard ratios for the depressed mood variable reflect the change in risk associated with a 1-SD increase in depressed mood. In the NHANES I sample, the subscale has shown adequate internal consistency (r=.77). Costa et al. (1987) report adequate 9-year test-retest reliability (r=.48) for the GWBS. Moreover, in a college

student sample, a three-month test-retest reliability coefficient of .85 was reported by Fazio (1977). Lastly, of the depressed mood subscale demonstrates validity through its correlations with other depressive symptom scales, such as the CES-D (r=0.71) and the Zung Depression Scale (r=0.62) (Dupuy, 1977; Fazio, 1977).

Periodontal Disease

Oral health data was collected through standard dental examinations (Kelly & Harvey, 1979; NCHS, 1977). Written guidelines for all procedures were followed by trained dental examiners, and steps were taken to eliminate possible sources of systematic bias. During the examinations, a trained health technician recorded the condition of each tooth, as dictated by the dentist. Teeth could be classified as sound, filled, decayed, filled-defective, and non-functional. Moreover, missing permanent teeth could be classified as unerupted, carious, extraction, accidental loss, and orthodontic extraction. The primary periodontal disease variable was a periodontal classification made by the attending dentist. Each tooth was scored based on the degree of gingival inflammation, the presence of periodontal pockets, and how firmly a tooth was situated. Teeth were classified as (1) no periodontal disease – no overt gingival inflammation or loss of function observed, (2) gingivitis – area of overt inflammation observed, (3) pockets – epithelial attachment loss observed, forming a pocket, (4) four pockets or more– observed teeth loose in their sockets, (5) inconsistent data for both arches (Because no cases were reported, this category is not used for coding purposes) and (6) no teeth. For the present study, categories 1 and 2 were combined to indicate absence of periodontal disease, while

categories 3, 4 and 6 were combined to indicate the presence of periodontal disease. This dichotomization was chosen after examination of other NHANES I studies, which show that periodontal disease (represented by categories 3, 4, and 6), but not gingivitis (category 2), is associated with elevated CVD risk (Wu et al., 2000). Additionally, after careful review and consultation with a periodontal researcher on campus (Dr. Michael Kowolik), the sixth category ('no teeth') was not excluded from analyses, as it has been suggested that tooth loss is the final step of the periodontal disease process. As a result, the absence of any teeth is likely indicative of severe periodontal disease.

Cardiovascular Disease

Incident CVD, defined as nonfatal CVD events or CVD mortality, is the primary outcome of this study. Deaths were identified either during interviews that were part of the NHANES I follow-up (conducted in 1982-84, 1986, 1987, and 1992), or through probabilistic matching between NHANES I and National Death Index (NDI) death certificate records. The NDI (http://www.cdc.gov/nchs/ndi.htm) is a centralized database that electronically indexes death record information in the state vital statistics offices.

Nonfatal CVD events, consisting of CAD, CBV, or PAD events were identified from the Health Care Facility Stay records collected by the NHANES team during each of the follow-up interviews. These records include information on overnight stays in hospitals and non-hospital health care facilities, such as nursing homes and mental health care facilities. While the participants themselves reported overnight stays during the interview, the facilities were later contacted to corroborate this information by reviewing

the participant's medical records and providing exact dates of admission and discharge, as well as diagnoses.

Both fatal and nonfatal events obtained via the aforementioned processes were coded according to the ICD-9. In the present study, codes 410-414 and 429.2 were used to identify CAD, codes 430-434 and 436-438 were used to identify CBV, and codes 440.2 and 443.9 were used to identify PAD. As multiple nonfatal events could potentially be reported for each participant, after all CAD incidence data was obtained and sorted by participant ID, all reports for a single participant were manually examined and the earliest nonfatal CAD event and its accompanying date were retained. This record was then compared to the participant's fatal CAD event, if one was present, and the earlier of the two was chosen as the first combined CAD event. Therefore, if a nonfatal event occurred before a fatal event, the latter was not examined for that participant. A similar process was used to identify the first CBV and PAD events for each individual. In order to conduct survival analyses, time to first event for each individual was calculated by subtracting the date of their NHANES I baseline examination from the date of their first fatal or nonfatal event. In addition, a dichotomous '0' and '1' coding was employed to identify whether a CVD, CAD, CBV or PAD event was reported for each participant.

Two modifications to the original study proposal are worthy of mention. First, because only two PAD events were identified in our cohort, PAD was not examined as a separate outcome but instead incorporated into the global CVD outcome. And second, although mortality for all participants who completed the medical examination is available from the date of their NHANES I participation (1971-1975) through December 31, 2006, the last 14 years of data have been deemed 'limited access' by the NHANES I

team, and therefore are not available to researchers without charge. Specifically, any follow-up data of individuals originally participating in NHANES I after July 17th, 1993 (last day of follow-up for the 1992 interview) must be purchased through the NHANES Research Data Center. Due to the lack of funding to acquire this last decade of mortality data, the follow-up period for the current study was limited to between 18 and 22 years, as opposed to the 35-year follow-up originally proposed.

Other Variables

Sociodemographic data, including participants' age, gender, race/ethnicity, and education level were acquired during the initial home interviews conducted by NHANES personnel. In addition, data on traditional risk factors for CVD were also obtained during the subsequent MEC examinations. These variables, which were all assessed at baseline (1971-1975), were blood pressure (mmHg), BMI (kg/m^2), total serum cholesterol levels, smoking status, and diabetes history. Systolic and diastolic blood pressures were obtained by a physician during the medical examination. After this, measurements of height and weight (which were used to calculate BMI) were made by laboratory and health technicians. Serum cholesterol levels were measured during the nutritional biochemistry section of the medical exam. Participants were also asked questions regarding the number of cigarettes smoked per day and history of diabetes in the medical history questionnaire and the general medical history supplement (NCHS, 1977).

Data Analyses

Once data sets containing all variables of interest were downloaded from the NCHS website (http://www.cdc.gov/nchs/) and combined, the following analyses were conducted to test the four hypotheses of this study. To determine whether periodontal disease is a partial mediator of the relationship between depressed mood and incident CVD (Hypothesis 1), the strength of the association between depressed mood and periodontal disease (path 'a' in Figure 1), between periodontal disease and incident CVD (path 'b' in Figure 1), and between depressed mood and incident CVD (path 'c' in Figure 1) were quantified. For path 'a', logistic regression analyses were conducted to analyze whether baseline depressive symptoms are significantly associated with baseline periodontal disease. For path 'b', Cox proportional hazards analyses were conducted to examine whether baseline periodontal disease predicts incident CVD during the 22-year follow-up period. Cox models were utilized here because they take into account the differing times to event and, therefore, are preferred over logistic regression models (Jonas & Mussolino, 2000). Path 'c' was tested in a similar fashion with Cox models. Mediation was tested by conducting Sobel tests (Aroian version), with $p > .05$ determining statistical significance. A significant Sobel test would indicate that periodontal disease is a mediator of the relationship between depressive symptoms and incident CVD. The equation $(B_{mediator} - B_{fully\text{-}adjusted}) / B_{fully\text{-}adjusted} \times 100$ was used to quantify the change in the effect size of the depressed mood-incident CVD relationship after the inclusion of periodontal disease in the model. In the equation, $B_{mediator}$ refers to the unstandardized beta coefficient for the depressed mood measure from the model including demographic factors, CVD risk factors and periodontal disease, while $B_{fully\text{-}}$

$_{adjusted}$ refers to the unstandardized beta coefficient for the depressed mood measure from the model including demographic and CVD risk factors.

Parallel sets of analyses were conducted to test Hypotheses 2 (incident CAD) and 3 (incident CBV) as separate CVD outcomes. Furthermore, in order to account for potential confounding factors, the above analyses were repeated (a) adjusting for demographic factors (age, sex, race/ethnicity, and education) and (b) adjusting for CVD risk factors (smoking, hypertension, BMI, cholesterol, and diabetes) in addition to demographic factors. All data analyses were conducted with SPSS Statistics 18.0 statistical software.

RESULTS

Characteristics of Participants

As was previously mentioned, the final sample consisted of 3,346 individuals (see Table 1 for the participant characteristics). There was a roughly equal number of men and women in the sample, and participant ages' ranged from 35 years to 63 years at baseline, with a mean of 49 years. Most individuals were Caucasian, and the mean education level was 10.8 years (less than a high school diploma). Almost half of the participants were current tobacco users, while only 4% reported ever been told they had diabetes by their physician. Lastly, mean arterial pressure fell in the normal category, mean total serum cholesterol fell in the borderline high category, and mean BMI fell in the overweight category.

Descriptive statistics for the psychological, dental, and cardiovascular variables of interest for the final sample are presented in Table 2. Although the mean GWBS depressed mood subscale score fell in the subclinical range, 314 individuals (9.4%) endorsed clinically significant levels of depressed mood (scores ≤ 12; Carnethon, Kinder, Fair, Stafford, & Fortmann, 2003). At NHANES I baseline, a total of 1,558 individuals met the present study's definition of periodontal disease. During the 18- to 22-year follow-up period, there were 727 CVD events, which included 505 nonfatal events and 222 deaths. Included in this total number were 537 CAD events (354 nonfatal events and

183 deaths) and 190 CBV events (151 nonfatal events and 39 deaths). The average time to first CVD event was 16.8 years, and the average time to first CAD and CBV event was 17.0 and 18.4 years, respectively.

Path 'a': Association of Depressed Mood with Periodontal Disease

As is shown in Table 3, the unadjusted logistic regression analyses revealed that the association between the GWBS depressed mood score and periodontal disease fell short of statistical significance (p=.06). The demographic-adjusted (p=.09) and the fully-adjusted models (p=.24) also did not show an association. Of the control variables, age (*OR*=1.06, 95% *CI*: 1.05-1.07, $p < .001$), race (*OR*=1.33, 95% *CI*: 1.06-1.66, p=.01), education (*OR*=0.87, 95% *CI*: 0.85-0.89, $p < .0001$), BMI (*OR*=1.02, 95% *CI*: 1.00-1.04, p=.04), and current tobacco use (*OR*=1.87, 95% *CI*: 1.57-2.19, $p < .001$) were related to periodontal disease in the fully-adjusted model, while sex (*OR*=0.95, 95% *CI*: 0.81-1.12, p=.54) , mean arterial pressure (*OR*=1.00, 95% *CI*: 0.10-1.01, p=.22), total cholesterol (*OR*=0.99, 95% *CI*: 0.99-1.00, p=.50), and diabetes (*OR*=1.05, 95% *CI*: 0.71-1.54, p=.80) were not associated with periodontal disease. In short, path 'a' was found to be nonsignificant in both unadjusted and adjusted models. However, smoking increased the risk of periodontal disease almost two-fold, and African Americans had a 33% greater risk of developing periodontal disease compared to Caucasians.

Path 'b': Association of Periodontal Disease with Incident Cardiovascular Disease

Cox proportional hazards analyses were conducted to determine if periodontal disease predicted incident CVD over the follow-up period (see Table 4). The unadjusted model demonstrated that this was in fact the case ($p < .001$). This effect was attenuated with adjustment for demographic factors but remained significant ($p=.003$). In the fully-adjusted model, the depressive symptoms-incident CVD relationship was similar to that observed in the demographics-adjusted model ($p=.009$). Specifically, individuals with periodontal disease at baseline had a 24% greater risk of a CVD event over the 18-22 years of follow-up than those who did not have baseline periodontal disease. Consistent with existing evidence (Ridker & Libby, 2005), other independent predictors of incident CVD were age (*HR*=1.07, 95% *CI*: 1.06-1.08, $p <.001$), sex (*HR*=0.58, 95% *CI*: 0.50-0.68, $p<.001$), mean arterial pressure (*HR*=1.01, 95% *CI*: 1.01-1.02, $p <.001$), total cholesterol (*HR*=1.003, 95% *CI*: 1.001-1.004, $p <.001$), current tobacco use (*HR*=1.48, 95% *CI*: 1.27-1.74, $p <.001$), and diabetes (*HR*=2.24, 95% *CI*: 1.74-2.89, $p <.001$). As seen here, being female engendered a protective effect against CVD, while diabetes more than doubled the risk of CVD. Conversely, race (*HR*=0.87, 95% *CI*: 0.71-1.07, $p=.20$), education, (*HR*=0.99, 95% *CI*: 0.97-1.02, $p=.60$), and BMI (*HR*=0.01, 95% *CI*: 0.99-1.02, $p=.41$) were not predictive of incident CVD in the fully-adjusted model.

Parallel analyses with incident CAD as the outcome revealed a similar pattern of results. Periodontal disease was a predictor of incident CAD in unadjusted ($p < .001$), demographics adjusted ($p=.004$), and fully-adjusted ($p=.01$) models. In this set of analyses, age (*HR*=1.06, 95% *CI*: 1.06-1.07, $p < .001$), sex (*HR*=0.53, 95% *CI*: 0.44-0.63, $p<.001$), race (*HR*=0.71, 95% *CI*: 0.55-0.91, $p=.007$), mean arterial pressure (*HR*=1.02,

95% *CI*: 1.00-1.02, *p*<.001), total cholesterol (*HR*=1.003, 95% *CI*: 1.002-1.005, *p* <.001), current tobacco use (*HR*=1.49, 95% *CI*: 1.25-1.78, *p*<.001), and diabetes (*HR*=2.36, 95% *CI*: 1.78-3.14, *p*<.001) all independently predicted incident CAD. Here too, males were at a greater risk of incident CAD compared to women, current tobacco users were at a 50% greater risk of CAD, and diabetes more than doubled CAD risk. Education (*HR*=0.99, 95% *CI*: 0.97-1.01, *p*=.37) and BMI (*HR*=1.01, 95% *CI*: 1.00-1.03, *p*=.10), on the other hand, were not related to incident CAD in the fully-adjusted model.

Lastly, as is shown in Table 4, results of the periodontal disease-incident CBV analyses demonstrated that the magnitude of the effect size for this association was similar to that observed for incident CAD in the unadjusted analyses (*p* <.001). This effect, however, was substantially attenuated in the demographic-adjusted (*p*=.31) and fully-adjusted (*p*=.44) models to the point that periodontal disease was no longer a predictor of incident CBV. Of the included covariates in the fully-adjusted model, age (*HR*=1.09, 95% *CI*: 1.07-1.11, *p*<.001), race (*HR*=0.67, 95% *CI*: 0.48-0.94, *p*=0.02), current tobacco use (*HR*=1.42, 95% *CI*: 1.06-1.90, *p*=.02), and mean arterial pressure (*HR*=1.02, 95% *CI*: 1.01-1.03, *p*=.0003) were predictors of incident CBV, whereas sex (*HR*=0.82, 95% *CI*: 0.62-1.09, *p*=.18), education (*HR*=1.006, 95% *CI*: 0.97-1.05, *p*=.75), diabetes (*HR*=1.50, 95% *CI*: 0.94-2.42, *p*=.09), BMI (*HR*=1.002, 95% *CI*: 0.97-1.03, *p*=.90), and total cholesterol (*HR*=1.001, 95% *CI*: 0.99-1.004, *p*=.58) were not related. Given the similarity between the CAD and CVD results and the fact that periodontal disease appears to be an independent predictor of CAD but not CBV, it can be argued that the overall CVD results primarily reflect CAD events and not CBV events. This is

reasonable considering that CAD events comprise the majority (roughly 75%) of all CVD events.

Path 'c': Association of Depressed Mood with Incident Cardiovascular Disease

Table 5 shows the results of the Cox models examining the GWBS depressed mood score as a predictor of incident CVD. These analyses indicated that although depressed mood was not a predictor of incident CVD in the unadjusted model (p=.61), it became a significant predictor in the demographic-adjusted ($p < .001$) and fully-adjusted (p=.03) models. In fully-adjusted analyses, 1-SD increase in the depressed mood score was associated with an 8% increase in the likelihood of incident CVD during the 18- to 22-year follow-up period. In the presence of the GWBS depressed mood score, age, sex, mean arterial pressure, total cholesterol, current tobacco use, and diabetes predicted incident CVD, with similar effect sizes to those reported in the path 'b' section.

Parallel analyses for CAD showed that, once again, depressed mood score was not predictive of incident CAD in unadjusted analyses (p=.83), but became a predictor in the demographic-adjusted analyses (p=.007). The depressed mood score, however, fell just short of significance (p=.07) in the fully-adjusted model, although the magnitude of this effect was identical to that observed for the incident CVD outcome. Apart from education and BMI, all other covariates were independent predictors of incident CAD with effect sizes similar to those reported for path 'b' above. The depressed mood score was not predictive of incident CBV in unadjusted (p=.99), demographic-adjusted (p=.31) or fully-

adjusted models (p=.55). Similar to the path 'b' analyses, age, race, current tobacco use and mean arterial pressure predicted incidence CBV.

Mediation Analyses

Sobel tests were conducted to test the three hypotheses proposing periodontal disease as a partial mediator of the longitudinal association between depressed mood and the three cardiovascular outcomes. As can be seen in Table 6, for incident CVD, periodontal disease was not a partial mediator of the observed association in unadjusted (t=1.86, p=.06), demographic-adjusted (t=1.41, p=.16) or fully-adjusted analyses (t=1.01, p=.31). Considering these results, Hypothesis 1 was not supported. Results of the corresponding Sobel tests for incident CAD were similar to those for incident CVD. Specifically, there was no evidence of statistical mediation in unadjusted (t=1.85, p=.06), demographic-adjusted (t=1.38, p=.16) or fully-adjusted (t=1.003, p=.31) models. In sum, Hypothesis 2 was not supported by these results. Finally, evidence that periodontal disease is a mediator of the depressed mood-CBV relationship was not observed in the unadjusted (t=1.80, p=.07), demographic adjusted (t=.76, p=.45), or fully-adjusted (t=.52, p=.60) models, resulting in a lack of support for Hypothesis 3.

In the fully-adjusted model predicting incident CVD that included both the GWBS depressed mood score and periodontal disease, the hazard ratio for depressed mood (HR=1.09, 95% CI: 1.01-1.17, p=.02) did not substantially change (2.4% increase) from the path 'c' fully-adjusted analysis. The corresponding percent change for the depressed mood-incident CAD association was an 1.3% increase and 0.0% change for the

depressed mood-incident CBV association. These descriptive results provide further support for the Sobel test results in that there is no evidence of mediation. Also of note, in the presence of GWBS depressed mood score, the hazard ratio for periodontal disease (*HR*=1.25, 95% *CI*: 1.06-1.47, *p*=.008) predicting CVD increased by 13.8% in the path 'b' fully-adjusted analyses. Overall, these mediation results suggest that (a) both periodontal disease and depressed mood are independent predictors of incident CVD and that (b) the effect of depressive symptoms on incident CVD is not mediated by periodontal disease.

DISCUSSION

The principal question addressed by the present study is whether periodontal disease is a partial mediator of the prospective relationship between depressed mood and CVD. In an effort to answer this question, associations between depressed mood and periodontal disease (path 'a'), periodontal disease and incident CVD (path 'b'), and depressed mood and incident CVD (path 'c') were examined. Logistic regression analyses indicated that depressed mood is not related to periodontal disease. Cox proportional hazards models revealed that, over the 18- to 22-year follow-up period, depressed mood and periodontal disease were independent predictors of incident CVD and CAD, but not CBV. However, the hypotheses that periodontal disease would be a mediator of the depressed mood-incident CVD relationship (Hypothesis 1), depressed mood-incident CAD relationship (Hypothesis 2), and depressed mood-indent CBV relationship (Hypothesis 3) were not supported by Sobel tests. Therefore, the answer to the primary question of the present study is that, in this sample of healthy adults representative of the United States population, periodontal disease is not a partial mediator.

Fit with Existing Literature

To my knowledge, this is the first study to examine periodontal disease as a mediator of the depression-CVD relationship. Additionally, this study reports the association between depressed mood and periodontal disease, which has not previously been evaluated with NHANES I data. However, other researchers have examined path 'a', with Ng et al. (2006), Monteiro da Silva et al. (1996), Saletu et al. (2005), and Rosania et al. (2009) demonstrating a positive relationship between these two variables. Our null findings are in line with those of Elter et al. (2002), Castro et al. (2006), Solis et al. (2004), and Moss et al. (1996), all of whom were unable to demonstrate a depression-periodontal disease relationship. For instance, Castro et al. (2006) reported that BDI scores were not related to clinical attachment loss in a community sample of 165 Brazilian individuals. Elter et al. (2002) also did not find any differences in the prevalence or extent of periodontal disease between depressed and nondepressed patients. Upon reflection, some emerging patterns within these studies are worthy of mention. First, all previous investigations of the depression-periodontal disease relationship, including the present study, have been cross-sectional in design. Second, inconsistent criteria have been used across studies to determine periodontal and psychological factors, making comparisons across studies more difficult. Lastly, with an equal number of studies providing evidence for and against path 'a' thus far, the present study tips the scales towards the notion that perhaps depressive symptoms are not related to periodontal disease. However, a major limitation of the current study, namely the measurement of depressive symptoms, suggests that this conclusion may be premature. It is possible that

the low content validity of the depression assessment may explain the lack of agreement with reports that show of a positive depression-periodontal disease association.

The path 'b' results of the present study effectively replicate those reported by DeStefano et al. (1993), who also examined the periodontal disease-incident CAD link in the NHANES I dataset. The similarity in the magnitude of the effect sizes found in these two studies (*HR*=1.25 in their study compared to *HR*=1.27 in this study) supports this conclusion. Moreover, the hazard ratio for path 'b' in the current study is also comparable to the overall hazard ratios calculated by Janket et al. (2003) and Bahekar et al. (2007) in their meta-analyses of the periodontal disease-incident CVD association (*RR*=1.19 and *RR*=1.14, respectively). As has been mentioned by other researchers, one reason why the investigation of the NHANES I data by Hujoel and colleagues (2000) found no association between periodontal disease and incident CAD, contrary to the current study's results and other published reports, may be due to their extensive adjustment for confounders, such as marital state, poverty index, physical activity and history of nervous breakdown (Genco et al., 2002). In terms of CBV, a key difference between the present study and past investigations that have detected a periodontal disease-CBV association (Joshipura et al., 2003; Wu et al., 2000) is that those studies had larger sample sizes and higher event rates. Compared to our sample size of 3,346 individuals (190 incident CBV events), Wu and colleagues (2000) analyzed a sample 9,962 individuals (803 incident CBV events), and Joshipura et al. (2003) had an even larger sample of 41,380 individuals (349 incident CBV events). Therefore, the previous studies had greater statistical power than the present one.

Finally, the observed association between depressed mood and CVD (path 'c') is not only consistent with other NHANES I investigations, but is also in line with the primary reviews and meta-analytic results in the area, which report relative risk ratios between 1.5 and 2.7 (Rugulies, 2002; Wulsin & Singal, 2003). While the present study's observed hazard ratio of 1.08 in the fully adjusted model falls below this range, this could be attributable to the depression assessment, as is discussed in depth below. Given that Anda et al. (1993) examined the depressed mood-incident CVD association in the same dataset using the same measures, it is not surprising that the present study's findings parallel theirs. Importantly, the present study extends the findings of Anda et al. (1993) by increasing the length of follow-up from 12.4 years to 22 years. Similar to the path 'b' results, it is likely that low power prevented us from detecting the longitudinal association between GWBS depressed mood and incident CBV that was found by Jonas and Mussolino (2000) in their examination of the NHANES I data. Specifically, the 583 stroke cases (total sample of 6,095) reported by Jonas and Mussolino (2000) far exceed the 190 CBV cases in the current sample.

To summarize, although the present study's findings do not lend support to role of periodontal disease as a mediator of the depression-CVD relationship, the path 'b' and path 'c' results are mostly consistent with existing evidence. Additionally, while our evaluation of the depression-periodontal disease connection (path 'a') suggests no association, it may be that this association depends on methodological factors, such as the measure used to assess depression. To my knowledge, evidence that depression and periodontal disease are independent predictors of incident CVD, as observed in the present study, has not been reported previously.

Alternative Explanations

According to Kazdin (2000), two possible explanations for null findings are (a) the presence of methodological issues that hinder detection of relationships existing in the population and (b) the true inexistence of the relationships in nature. One important concern in the present study is the content validity of the depression measure. Factor analyses of multiple depression measures have shown that depression is a multidimensional construct consisting of cognitive (e.g., worthlessness and concentration difficulties), affective (e.g., depressed mood and anhedonia), behavioral (e.g., psychomotor agitation or retardation), and somatic (e.g., sleep and appetite disturbances) symptom clusters (Campbell, Burgess, & Finch, 1984). Different depression measures capture these symptom clusters to varying degrees. Examination of the four items of the GWBS depressed mood subscale (see Appendix) reveals that, while the affective component of depression appears to be well assessed, the cognitive, behavioral, and somatic components are largely ignored. A potential consequence of this narrow scope is that the GWBS depressed mood subscale is able to detect only a fraction of the true depression-periodontal disease signal. Thus, the utilization of a depressive symptom measure with better content validity (e.g., the BDI) may have resulted in a stronger relationship between depression and periodontal disease. A second, related concern is the possibility that one symptom cluster of depression may have a stronger association with periodontal disease than another. If, for currently unidentified reasons, the cognitive, behavioral or somatic depression clusters, and not the affective symptom cluster, accounts for greater variance in periodontal disease, this may explain why the GWBS depressed mood subscale was not predictive of periodontal disease. In either case, a

similar outcome ensues. Path 'a' becomes weaker, and when multiplied by path 'b', produces a weaker 'ab' cross-product, which in turn contributes to a nonsignificant test of statistical mediation.

A second scenario worth consideration is that perhaps it is depression that mediates the longitudinal periodontal disease-CVD relationship. This notion of reverse causality warrants particular discussion because depressed mood and periodontal disease were both assessed at baseline, precluding our ability to ascertain whether depressed mood or periodontal disease occurred first. A periodontal disease to depressive symptoms association is plausible in that individuals with chronic periodontal disease are likely to experience halitosis, tooth loss, difficulty chewing, and ongoing pain. As a result of halitosis and tooth loss, one could experience social anxiety or social isolation, which are known correlates of depressive symptoms (Kaplan, Roberts, Camacho, & Coyne, 1987). Pain has also been shown to predict increases in depressive symptoms (Korff & Simon, 1996; Bair, Robinson, Katon, & Kroenke, 2003). Higher levels of depressive symptoms have been shown to predict incident CVD, possibly via both biological and behavioral mechanisms (Suls & Bunde, 2005). In an effort to test this possibility, mediation analyses similar to those reported in the results section above were conducted. It was found that in this sample, depressed mood was not a mediator of the longitudinal periodontal disease-CVD association (t=1.01, p=.31). Nonetheless, investigations in which the independent variable precedes and longitudinally predicts the mediator would offer a more ideal context to evaluate such mediation.

The second explanation for nonsignificant results proposed by Kazdin (2000) is that the findings reflect a true inexistence of the relationship in the population. Given that

the present study involved a large sample of adults representative of the U.S. population and contained a strong operationalization of the mediator and dependent variable, it is likely that periodontal disease is not, in fact a partial mediator of the depression-CVD relationship among American adults. Nonetheless, methodological shortcomings preclude one from drawing a definitive conclusion based on these data alone. Future studies in which (a) multiple assessments of depressive symptoms and periodontal disease status are obtained over time (to establish temporal order) and (b) a broader measure of depressive symptom severity is administered may have better capability to evaluate the present hypotheses.

Limitations and Future Directions

Although the current study and the NHANES I data has key strengths (e.g., a large representative sample, a long follow-up period, CVD incidence and mortality data), there are some important limitations as well. The main limitations, which have been discussed above, include the narrow scope of the depression measure and the cross-sectional nature of path 'a'. A third weakness of the NHANES I study is that depression and periodontal disease were measured simultaneously only one time during the 22-year study. While another depression measurement was made using the CES-D in the 1982 follow-up, periodontal disease was not assessed. This reflects the overall low focus on assessing psychological and dental variables in the NHANES I study. The fact that these two variables were assessed on a much smaller subset of the total sample further supports this impression. Finally, the external validity of findings derived from the NHANES I

data may be in question, given that the sample was representative of the U.S. population at the time that the data was collected (i.e., 1971-1975). As the demographics of the country have changed since the early 1970's, results from the NHANES I data may not necessarily apply to the current U.S. population (Hobbs & Stoops, 2002). Bearing in mind these limitations, the present research design would be substantially improved by (a) examining the association between depression and periodontal disease prospectively, (b) employing a broader depression scale, and (c) measuring psychological and dental variables at more than one point. These future directions are detailed below.

The majority of extant studies of the depression-periodontal disease association hypothesize that depression and other psychosocial variables precede and predict periodontal disease; however, most of these study designs have also been cross-sectional. Therefore, the directionality of path 'a' is unknown, highlighting the need for more prospective studies in this area. An ideal study scenario would include the assessment of the independent and mediator variables at a minimum of two points. This would allow one to test both directions of the relationship (depression → periodontal disease versus periodontal disease → depression), as well as examine the two mediation models discussed above (depression → periodontal disease → CVD versus periodontal disease → depression → CVD). Short-term manipulations of periodontal disease (e.g., by preventing individuals from engaging in daily oral hygiene) may also be useful in determining the directionality of this relationship. Moreover, studies evaluating whether treatment of periodontal disease reduces depressive symptoms or whether treatment of depression reduces the risk of periodontal disease would be make similar contributions to the literature.

Implications and Conclusions

CVD is the leading cause of death in the United States, and depression is the foremost cause of disability. Together, these two conditions amount to billions of dollars in health- and work-related expenditures. Yet, after several years of research, the mechanisms that underlie the prospective link between depression and CVD remain elusive. Due to the gravity of both these conditions, there is an urgent need to examine novel candidate mediators that may help explain this association, as identifying the mediators could lead to the development of novel treatment approaches to prevent CVD. Accordingly, the aim of present study was to examine whether periodontal disease is a potential mediator of the depression-CVD association. The main finding is that periodontal disease does not appear to mediate this relationship in a large sample of adults representative of the U.S. population. In fact, the present results suggest that depressive symptoms and periodontal disease may be independent predictors of incident CVD.

A misinformed conclusion of this study would be to disregard completely the potential role of periodontal disease in the depression-CVD relationship. As previously mentioned, other investigations that replicate our findings are needed before periodontal disease is conclusively ruled out as a candidate mediator. Other types of relationships among these three variables are also plausible. For instance, depression may moderate the degree of CVD risk conferred by periodontal disease. In summary, while the hypotheses were not supported, the present study has raised awareness of periodontal disease as a candidate mediator of the depression-CVD relationship, which may stimulate further research on this currently understudied cardiovascular risk factor.

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LIST OF REFERENCES

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TABLES

Table 1

Characteristics of Participants

Age, years	49.2 (14.0)
Female, %	53.2
Non-white, %	16.1
Education, years	10.8 (3.5)
Mean Arterial Pressure, mmHg	101.0 (14.8)
Total Serum Cholesterol, mg/100ml	222.7 (46.8)
Body Mass Index, kg/m^2	25.8 (5.01)
Current Tobacco Use, %	44.9
Ever had Diabetes, %	4.3

Note. N=3346. Continuous data are presented as mean±SD, and categorical data are presented as percentages.

Table 2

Descriptive Statistics for Depressed Mood, Periodontal Disease, and Cardiovascular Disease (CVD)

	N	*%*
GWBS depressed mood subscale ≤ 12, %	314	9.4
Periodontitis, %	1,558	46.2
Total CVD events, %	727	21.7
CAD events, %	537	16.0
CBV events, %	190	5.7

Note. N=3346. GWBS=General Well-Being Scale. CAD=coronary artery disease. CBV=cerebrovascular disease.

Table 3

Path a: Logistic Regression Analyses Predicting Periodontal Disease with the GWBS Depressed Mood Subscale

	Model	*OR* (95% *CI*)
GWBS depressed mood subscale	Unadjusted	1.07 (0.99-1.14)
	Demographics	1.07 (0.99-1.16)
	Fully-Adjusted	1.05 (0.96-1.14)

Note: N=3346. GWBS=General Well-Being Scale. Hazard ratios from the demographics model are adjusted for age, sex, race, and education, while the fully-adjusted model also includes mean arterial pressure, cholesterol, diabetes, current tobacco use, and body mass index as covariates

Table 4

Path b: Cox Proportional Hazard Models Predicting Incident Cardiovascular Disease (CVD) with Baseline Periodontal Disease

	Model	Incident CVD *HR* (95% *CI*)	Incident CAD *HR* (95% *CI*)	Incident CBV *HR* (95% *CI*)
Periodontal disease	Unadjusted	2.60* (2.24-3.04)	2.56* (2.16-3.04)	2.63* (1.98-3.48)
	Demographics	1.28* (1.09-1.51)	1.31* (1.09-1.57)	1.17 (0.86-1.57)
	Fully-adjusted	1.24* (1.06-1.46)	1.27* (1.06-1.53)	1.12 (0.83-1.52)

Note: N=3346. CAD=coronary artery disease. CBV=cerebrovascular disease. Hazard ratios from the demographics model are adjusted for age, sex, race, and education, while the fully-adjusted model also includes mean arterial pressure, cholesterol, diabetes, current tobacco use, and body mass index as covariates.

*$p < .05$

Table 5

Path c: Cox Proportional Hazard Models Predicting Incident Cardiovascular Disease (CVD) with Baseline Depressed Mood

	Model	Incident CVD *HR* (95% *CI*)	Incident CAD *HR* (95% *CI*)	Incident CBV *HR* (95% *CI*)
GWBS depressed mood subscale	Unadjusted	1.02 (0.95-1.10)	1.01 (0.93-1.10)	1.00 (0.87-1.14)
	Demographics	1.12* (1.05-1.21)	1.12* (1.03-1.22)	1.07 (0.94-1.22)
	Fully-adjusted	1.08* (1.01-1.17)	1.08 (0.99-1.17)	1.04 (0.91-1.19)

Note: N=3346. CAD=coronary artery disease. CBV=cerebrovascular disease. Hazard ratios from the demographics model are adjusted for age, sex, race, and education, while the fully-adjusted model also includes mean arterial pressure, cholesterol, diabetes, current tobacco use, and body mass index as covariates.

*$p < .05$

Table 6

Summary of Sobel Analyses Testing Periodontal Disease as a Mediator of the Relationship Between Depressed Mood and Incident Cardiovascular Disease (CVD)

Dependent Variable	Model	*t*	*p*
Incident CVD	Unadjusted	1.86	.06
	Demographics	1.41	.16
	Fully-adjusted	1.01	.31
Incident CAD	Unadjusted	1.85	.06
	Demographics	1.38	.16
	Fully-adjusted	1.00	.31
Incident CBV	Unadjusted	1.80	.07
	Demographics	0.76	.45
	Fully-adjusted	0.52	.60

Note: N=3346. CAD=coronary artery disease. CBV=cerebrovascular disease. Hazard ratios from the demographics model are adjusted for age, sex, race, and education, while the fully-adjusted model also includes mean arterial pressure, cholesterol, diabetes, current tobacco use, and body mass index as covariates.

FIGURES

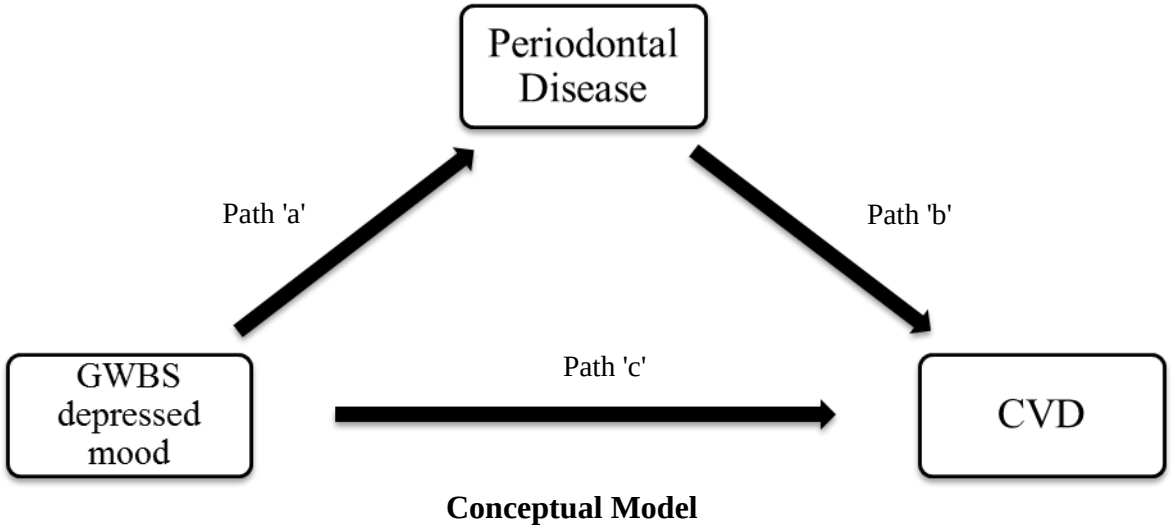
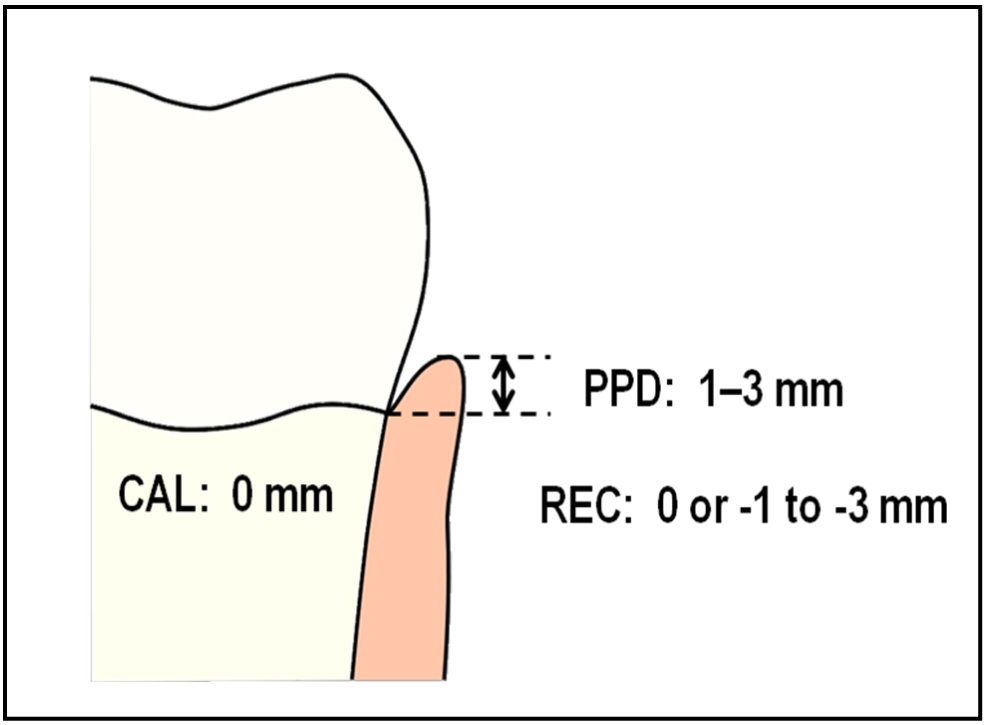


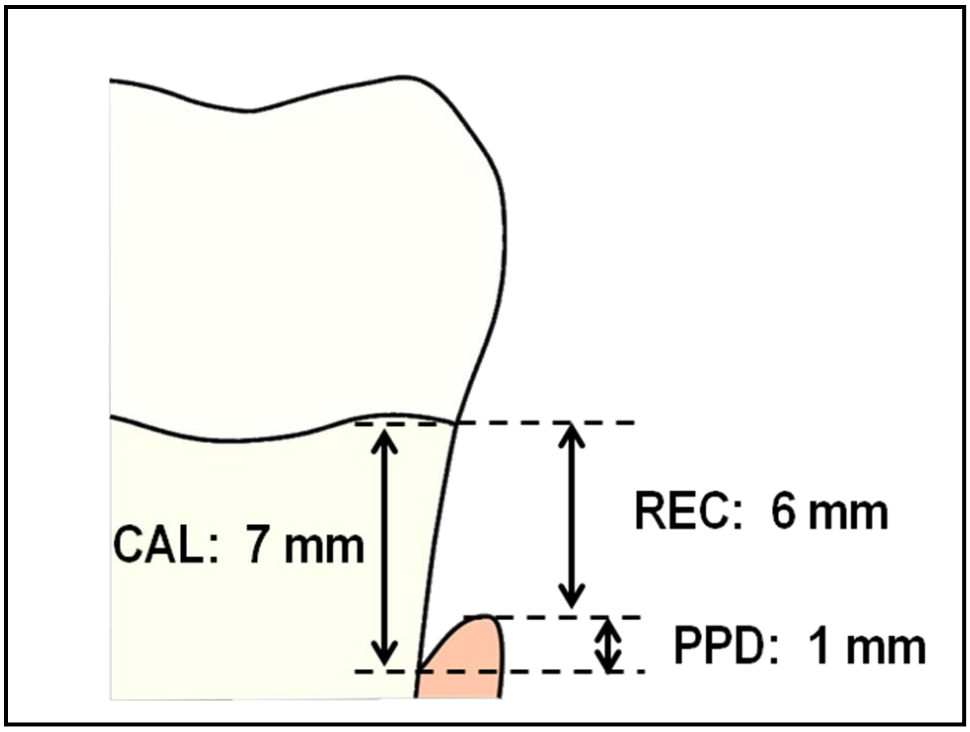
Figure 1. Conceptual model for the present study depicting periodontal disease as a potential mediator of the longitudinal association between depressive symptoms and incident cardiovascular disease (CVD).

GWBS=General Well-Being Scale.



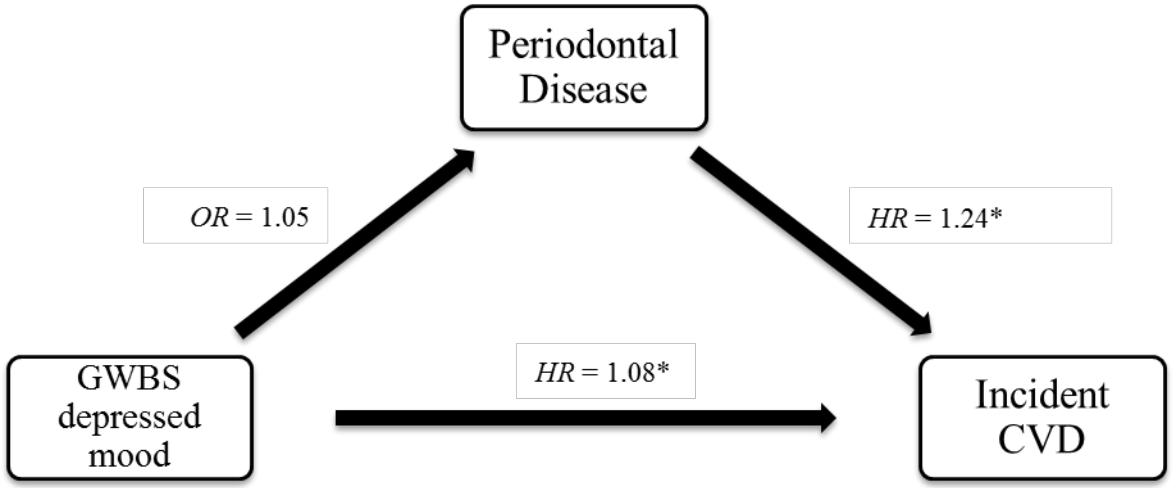
Tooth with No Periodontal Disease

Figure 2. Graphical representation of clinical attachment loss (CAL) and probing pocket depth (PPD) in a tooth with no periodontal disease. PPD, as seen above, measures the distance from the gum line to the base of the existing crevice, whereas CAL measures the distance from the cemento-enamel junction to the base of the existing crevice. Reprinted with permission of Micheal J. Kowolik, BDS, Ph.D.



Tooth with Severe Periodontal Disease

Figure 3. Graphical representation of clinical attachment loss (CAL) and probing pocket depth (PPD) in a tooth with severe periodontal disease. PPD, as seen above, measures the distance from the gum line to the base of the existing crevice whereas CAL measures the distance from the cemento-enamel junction to the base of the existing crevice. Reprinted with permission of Micheal J. Kowolik, BDS, Ph.D.



Odds and Hazard Ratios for Paths 'a', 'b', and 'c'

Figure 4. Odds and hazard ratios for paths 'a', 'b', and 'c' in the fully-adjusted model with incident cardiovascular disease (CVD) as the cardiovascular outcome.

GWBS=General Well-Being Scale.

*p < .05

APPENDIX

APPENDIX

General Well-Being Schedule – Depression subscale

Instructions: This section is concerned with how you feel and how things have been going with you. For each question, mark (X) the answer which best applies to you.

1. Have you felt down-hearted and blue? (during the past month)

    a. All the time
    b. Most of the time
    c. A good bit of the time
    d. Some of the time
    e. A little of the time
    f. None of the time

2. How have you been feeling in general? (during the past month)

    a. In excellent spirits
    b. In very good spirits
    c. In good spirits mostly
    d. I have been up and down in spirits a lot
    e. In low spirits mostly
    f. In very low spirits

3. Have you felt so sad, discouraged, hopeless, or had so many problems that you wondered if anything was worthwhile? (during the past month)

    a. Extremely so – to the point that I have just about given up
    b. Very much so
    c. Quite a bit
    d. Some – enough to bother me
    e. A little bit
    f. Not at all

4. How depressed or cheerful have you been? (during the past month)