

**ASSOCIATIONS BETWEEN AFFECTIVE TRAITS AND
ENDOTHELIAL FUNCTION IN DEPRESSED ADULTS**

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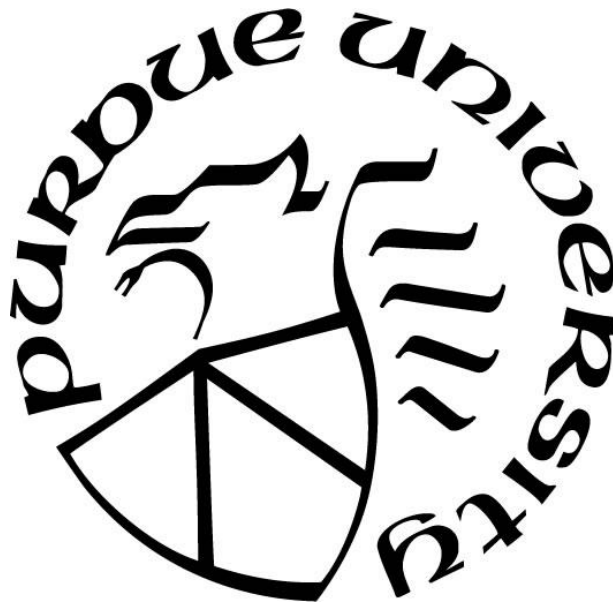
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ABSTRACT

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Depressed adults are at increased risk of developing atherosclerotic cardiovascular disease (CVD). However, heterogeneity in the depressed population engenders a key question: Are there subgroups of depressed adults at greater risk of developing CVD? Because other affective traits – i.e., anxiety, hostility/anger, and low trait positive affect – have also been associated with increased CVD risk, depressed adults with higher levels of these co-occurring affective traits may have an elevated risk of developing CVD. Consequently, the present study's first aim was to examine, in depressed adults, which affective traits (depression, anxiety, hostility/anger, or low positive affect) are associated with endothelial function, a marker of cumulative CVD risk. In addition, because the other affective traits overlap with depressive symptom severity, this study's second aim was to investigate which components of pairs of affective traits (shared versus unique) are related to endothelial function. Finally, given that the mechanisms underlying affective trait-endothelial function relationships in depressed adults are unknown, this study's third aim was to explore traditional CVD risk status as a candidate mediator of observed relationships. To achieve these aims, I combined pre-treatment, cross-sectional data from three randomized controlled trials involving 138 depressed primary care patients with no history of clinical CVD. Assessments included validated self-report questionnaires for affective traits, brachial artery flow-mediated dilation (FMD) for endothelial function, and 10-year Framingham risk score for traditional CVD risk status. I conducted structural equation modeling (SEM) with confirmatory factor analysis to examine the

relationships of interest after adjusting for age, sex, race/ethnicity, education, and baseline arterial diameter. Although the shared variance between each affective trait pair could not be modeled due to poor fit, adequate fitting models revealed that hostility/anger and the unique components of hostility/anger were associated with poorer endothelial function (standardized coefficients = $-.18$ and $-.22$, respectively). All of the other affective traits and their components (depression, anxiety, positive affect, unique depression, unique anxiety, and unique positive affect) were not related to endothelial function (all p s $> .08$). Traditional CVD risk status did not partially explain the relationship between the unique components of hostility/anger and endothelial function (standardized coefficient for the indirect effect = $.00$; $p = .89$). If my results are supported by future findings, it would suggest that depressed adults with hostility/anger (a) may be a subgroup of the depressed population at greater risk of developing CVD and (b) may be in need of earlier, more intense, and/or different CVD primary prevention efforts. Future studies are needed to confirm this relationship and identify underlying mechanisms.

INTRODUCTION

Cardiovascular Disease

Epidemiology of Cardiovascular Disease

Cardiovascular disease (CVD), which refers to disorders of the heart and the vascular system, is highly prevalent, deadly, and costly (Mozaffarian et al., 2015). Approximately one in three American adults has at least one type of CVD. In 2011, CVD accounted for 31% of all deaths in the U.S., making it the leading cause of mortality. In addition, the cost of CVD exceeds that of any other health condition. The estimated annual cost of CVD in 2011 was \$320 billion. Due to the high prevalence and costs of CVD, the need for primary prevention efforts is greater now than ever before. Among the preventive strategies recommended by the American Heart Association, and of relevance to the present study, is the early detection and management of CVD risk factors (Heidenreich et al., 2011).

Pathophysiology of Atherosclerotic Cardiovascular Disease

Although CVD encompasses a variety of conditions, the present study will focus on atherosclerotic CVD, a progressive systemic disease involving the thickening and hardening of blood vessels in the heart, brain, and peripheral circulation (Santos & Nasir, 2009). Injury to endothelium – the single layer of cells lining the blood vessels – instigates the process of atherosclerosis by increasing the adhesiveness and permeability of the vessel walls (Santos & Nasir, 2009). As a result, lipids flowing in the bloodstream begin to accumulate as deposits (Santos & Nasir, 2009). Chemical modifications to these lipid deposits result in endothelial dysfunction, a state of the endothelium characterized by decreased production/availability of

vasodilators (particularly nitric oxide) and/or increased production/availability of vasoconstrictors (Hadi, Carr, & Suwaidi, 2005). This imbalance leads to a reduced ability of the vascular lining to maintain normal homeostasis – namely, impairment of endothelium-dependent vasodilation (Corretti et al., 2002). In addition to impairment in endothelium-dependent vasodilation, the proinflammatory, proliferative, and procoagulatory state of endothelial dysfunction acts to promote downstream atherosclerotic processes, including structural changes in vascular walls (lesion formation and calcification) that narrow and harden blood vessels (Davignon, & Ganz, 2004; Hadi et al., 2005). These structural changes can (a) impede blood flow and reduce oxygen supply to tissues and (b) promote increased velocity and turbulence of blood flow, which can cause lesions to rupture (Zipes, Libby, Bonow, & Braunwald, 2004). A blood clot (thrombus) may develop at the site of ruptured lesions (Zipes et al., 2004). Thrombi or dislodged thrombi that travel through the circulation (emboli) can partially or completely block blood flow to regions of the heart or the brain (Zipes et al., 2004).

Atherosclerosis can progress asymptotically for decades (subclinical atherosclerosis) but can eventually result in fatal and nonfatal CVD events, including heart tissue death (myocardial infarction; MI), brain tissue death (stroke), insufficient blood flow to the heart and chest pain (cardiac ischemia and angina pectoris), and sudden cessation of heartbeat and cardiac function (cardiac arrest; Libby, 2004). The first occurrence of one or more of these clinical events signifies the onset of clinical CVD. Notably, the current study sample is comprised of adults free of clinical CVD.

Assessment of Atherosclerotic Cardiovascular Disease

Empirical studies have utilized several measures of CVD, including indicators of clinical CVD and subclinical atherosclerosis. The vast majority of cardiovascular behavioral medicine

research has examined whether psychosocial factors predict future CVD events (Matthews, 2005). However, it is possible that psychosocial factors exert a stronger cardiotoxic effect earlier in the atherosclerotic process (Matthews, 2005). To examine the earlier stages of CVD, noninvasive imaging technologies can be utilized to measure early to late stages of subclinical atherosclerosis (Santos & Nasir, 2009). These technologies can measure structural or functional characteristics of subclinical atherosclerosis (Bisoendial et al., 2002).

The present study examines a functional measure of subclinical atherosclerosis: endothelial function assessed by flow-mediated dilation (FMD) of the brachial artery. This measure quantifies the degree of impairment in endothelium-dependent vasodilation (Corretti et al., 2002). Examining endothelial function in the current study is advantageous for several reasons. One, endothelial dysfunction is detectable early in the development of subclinical atherosclerosis yet also promotes progression of subclinical atherosclerosis across all stages of the disease (Hadi et al., 2005). Two, endothelial dysfunction is thought to be the final common pathway through which CVD risk factors promote subclinical atherosclerosis (Frick & Weidinger, 2007; Vita & Keaney, 2002) and, accordingly, is considered a marker of cumulative CVD risk (Hadi et al., 2005). Three, endothelial dysfunction (a) has been observed in adults with CVD risk factors but no detectable disease (Celermajer et al., 1992) and (b) is an independent predictor of CVD events among initially healthy persons (Schindler et al., 2003; Yeboah et al., 2009) and among those with elevated CVD risk (Perticone et al., 2001; Rossi, Nuzzo, Origliani, & Modena, 2008).

Endothelial function can be assessed in the coronary and peripheral arteries (Hadi et al., 2005). The gold standard test for the evaluation of endothelial function requires invasive infusions of endothelium-dependent vasodilators (e.g., acetylcholine) into the coronary arteries

(Hadi et al., 2005). However, this method is limited due to its invasive nature. Consequently, noninvasive techniques have also been developed to assess endothelial function. While multiple noninvasive measures exist, brachial artery flow-mediated dilation (FMD) is the preferred noninvasive measure of endothelial function (Deanfield et al., 2007). This technique utilizes high-resolution ultrasound to measure the degree to which the brachial artery dilates in response to increased blood flow induced by the release of a blood pressure cuff (Thurston, Rewak, & Kubzansky, 2013).

Traditional Risk Factors for Cardiovascular Disease

A number of CVD risk factors are well established in the literature. Non-modifiable risk factors for CVD are older age, male sex, African American race, and a positive family history of CVD (Mozaffarian et al., 2015). Modifiable CVD risk factors have also been identified in the biological (dyslipidemia, hypertension, diabetes, and obesity) and behavioral (tobacco use, physical inactivity, and poor diet) domains (Yusuf, Reddy, Ôunpuu, & Anand, 2001). However, even when considering all of these traditional CVD risk factors, it is estimated that half of the variance in CVD events remains unexplained (Yusuf et al., 2001). Moreover, cross-sectional evidence suggests that greater than 60% of the variance in subclinical atherosclerosis is unexplained by traditional CVD risk factors (Santos et al., 2015). Consequently, it is crucial to further our understanding of emerging CVD risk factors, such as depression, that may account for a portion of this unexplained variance.

Depression as a Risk Factor for Cardiovascular Disease

Depression

Depressive disorders are common conditions (the lifetime prevalence is 16.5% for major depressive disorder [MDD] and 2.5% for dysthymic disorder; Kessler et al., 2005) that impact a person's affective, cognitive, behavioral, and physiological functioning (Pratt & Brody, 2008). Symptoms of depressive disorders are depressed mood, loss of interest/pleasure, appetite/weight changes, sleep disturbances, psychomotor retardation/agitation, feelings of worthlessness or guilt, fatigue, concentrations problems, and suicidal ideation (American Psychiatric Association, 2013). Depression can be conceptualized and measured as a dichotomous disorder diagnosis or a continuous symptom severity. Of note, depressive symptom severity is relatively stable over time. To illustrate, test-retest correlations for measures of depressive symptom severity indicate stability over one year (r range: 0.61-0.72), two to three years (r range: 0.55 to 0.61), and six years (r range: 0.52-0.55; Brown, 2007; Wetherell, Gatz, & Pedersen, 2001).

Depression and Cardiovascular Disease

A substantial literature supports depression as one emerging risk factor for CVD. For example, a meta-analysis of 11 high-quality prospective studies revealed that, compared to adults without depression, those with a depressive disorder or elevated depressive symptoms are at a 54% increased risk for incident CVD (Van der Kooy et al., 2007) after controlling for traditional CVD risk factors. This depression-CVD relationship has been detected in men and women and in various age and racial/ethnic groups (Brown, Stewart, Stump & Callahan, 2011; Rosengren et al., 2004; Stewart et al., 2012; Van der Kooy et al., 2007). Moreover, the magnitude of the

relationship between depression and CVD is comparable in strength to traditional CVD risk factors (Wilson et al., 1998).

Literature also supports relationships of depressive disorders and depressive symptom severity with subclinical atherosclerosis. Studies have found depressive symptoms to prospectively predict structural measures of subclinical atherosclerosis, such as progression of coronary artery calcification (Janssen et al., 2011; Stewart et al., 2012) and carotid intima-media thickness (Stewart, Janicki, Muldoon, Sutton-Tyrrell, & Kamarck, 2007). Additionally, one study found that, compared to adults without MDD, those with MDD have greater progression of coronary artery calcification (Matthews et al., 2010). Studies also support the relationship between depression and functional measures of subclinical atherosclerosis. Of relevance here, a meta-analysis of 12 studies indicates that depression is related to poorer endothelial function (Cooper, Tomfohr, & Milic, 2011). Specifically, this meta-analysis found a significant relationship between depression (defined as either MDD [$k = 5$] or depressive symptom severity [$k = 7$]) and worse brachial FMD ($r = 0.19$) that was stronger in the six high-quality studies ($r = 0.29$; in this meta-analysis r conveys effect size but not directionality; Cooper et al., 2011).

Variability in the Relationship between Depression and Cardiovascular Disease

There is a high degree of heterogeneity in the depressed population (Fried & Nesse, 2015). For instance, because depression is comprised of affective, cognitive, behavioral, and somatic components, symptom presentation can vary across depressed adults. Those with depression can also vary with regard to severity, chronicity, and subtype of depressive disorder. In addition, the presence or absence of comorbid psychiatric conditions (e.g., anxiety disorders) may also vary across depressed people. Thus, it is possible that the degree of excess CVD risk conferred by depression varies within this heterogeneous population (Davidson, Rieckmann, &

Rapp, 2005). This engenders a key question: Are there subgroups of depressed people at greater risk of developing CVD than others? Initial research in this area has sought to identify which clusters of depressive symptoms (e.g., cognitive-affective versus somatic), what severity and chronicity presentations (e.g., recurrent versus single episode MDD), and which depressive disorder subtypes (e.g., atypical versus nonatypical depression) are associated with the greatest risk of developing CVD.

Evidence suggests that the CVD risk conferred by depression varies across depressive symptom clusters (Pratt & Brody, 2008). For instance, a recent investigation of older adults found that, when all depressive symptom clusters were modeled together, the somatic cluster – but not the depressed affect, interpersonal problems, or (lack of) positive affect clusters – predicted 15-year incidence of coronary artery disease (Hawkins, Callahan, Stump, & Stewart, 2014). Similarly, in another study of older adults, the somatic-vegetative cluster, but not the cognitive-affective cluster, was a predictor of 3-year progression of carotid intima-media thickness (Stewart et al., 2007). In contrast to these previous findings, a study of middle-aged adults revealed that only the depressed affect cluster predicted 5-year incidence of coronary artery calcification (Stewart et al., 2012). In this study, the somatic symptoms, interpersonal problems, and (lack of) positive affect clusters were not associated with coronary artery calcification. These varying results may be due to differences in the age of the study sample (i.e., older adults versus middle-aged adults). Nonetheless, these studies suggest that the depressive symptom clusters may confer differential CVD risk.

Another line of research suggests that the severity and chronicity of depression also influences the degree of CVD risk conferred by depression. First, there appears to be a graded relationship between depression severity and CVD risk (Rugulies, 2002). Supporting this notion,

minor depression is associated with a 1- to 2-fold increase in CVD risk, whereas major depression is associated with a 3- to 5-fold increase in risk (Bunker et al., 2003). Moreover, one study found that moderate/severe depressive symptoms, but not mild symptoms, predicted increases in carotid intima-media thickness over time (Pizzi et al., 2014). Second, greater chronicity also appears to be associated with increased CVD risk. For example, a recent study found that recurrent MDD ($HR = 1.85$, 95% $CI: 1.02-3.36$), but not single episode MDD ($HR = 1.23$, 95% $CI: 0.62-2.43$), predicted 6-year incidence of CVD (Seldenrijk et al., 2015).

Finally, CVD risk may be greatest for certain subtypes of depressive disorders. For instance, one study found that lifetime atypical MDD (MDD with reversed somatic-vegetative symptoms of hyperphagia and hypersomnia; Quitkin, 2002) was associated with a greater risk of incident CVD than lifetime nonatypical MDD, lifetime dysthymic disorder, and no depression history groups (Case, Sawhney, & Stewart, 2018). Results further revealed that double depression (MDD superimposed on dysthymic disorder; Keller & Shapiro, 1982) was associated with a greater risk of incident CVD than MDD only, dysthymic disorder only, and no depression history groups (Case et al., 2018). Therefore, this study suggests that adults with atypical or double depression may be two subgroups at a heightened risk of developing CVD.

To summarize, only recently have investigators begun to examine which depressed adults are at greatest risk of developing CVD. Initial research suggests that symptom presentation, severity, chronicity, and subtype may all influence the degree of CVD risk in depressed adults. Of key interest to the present study are affective traits (anxiety, hostility/anger, and low positive affect) that often co-occur with depression and that may put depressed adults at elevated risk of developing CVD (Suls & Bunde, 2005). In the following section, I will review these affective traits that overlap with depression and their potential to elevate the CVD risk of depressed adults.

Affective Traits that Overlap with Depression and Predict Cardiovascular Disease

In addition to the depression-CVD literature, a growing body of evidence suggests that other affective traits – i.e., anxiety, hostility/anger, and low positive affect – predict the development of CVD. Importantly, adults with depression are likely to experience co-occurring anxiety, hostility/anger, and low positive affect. Therefore, depressed adults with higher levels of these co-occurring affective traits may be at greater risk of developing CVD than those with lower levels of these traits. In this section, I review anxiety, hostility/anger, and low positive affect with respect to (a) their overlap with depression, (b) their relationship with CVD risk in the general population, and (c) their relationship with CVD risk in depressed adults.

Anxiety

Anxiety disorders are common conditions (the lifetime prevalence of any anxiety disorder is 28%; Kessler et al., 2005) that involve symptoms of excessive fear and anxiety as well as related behavioral disturbances (American Psychiatric Association, 2013). Symptoms of anxiety are thought to arise from a perceived sense of future threat or danger (Barlow, 2004). However, anxiety disorders – such as generalized anxiety disorder, panic disorder, and phobias – are each unique regarding the type of objects or situations that induce symptoms (American Psychiatric Association, 2013). Anxiety can be conceptualized and measured as a dichotomous disorder diagnosis or a continuous symptom severity. As is the case with depression, anxiety symptom severity is relatively stable over time. Test-retest correlations for measures of anxiety symptom severity suggest stability over one year (r range: 0.66-0.69), two to three years (r range: 0.58-0.62) and six years (r range: 0.55-0.61; Brown et al., 2007; Wetherell et al., 2001).

Overlap Between Anxiety and Depression

The symptoms of anxiety and depression overlap considerably (Mineka, Watson, & Clark, 1998; Clark & Watson, 1991). Correlations between self-report measures of depression and anxiety symptoms are typically moderate to large (r range: 0.45-0.75; Watson et al., 1995). Moreover, adults with depressive disorders are likely to experience comorbid anxiety disorders (Mineka et al., 1998). For instance, a large cohort study found that, of those with a current depressive disorder, 67% and 75% met criteria for a current and lifetime anxiety disorder, respectively (Lamers et al., 2011). Results of numerous studies indicate that the presence of anxiety in depressed adults is associated with increased depression severity, greater depression chronicity, higher relapse rates, and reduced psychosocial functioning (Mineka et al., 1998).

Anxiety and Cardiovascular Disease Risk in the General Population

Evidence suggests that adults with anxiety disorders or elevated anxiety symptoms are at increased risk of developing CVD (Thurston et al., 2013). A recent meta-analysis of 34 prospective studies revealed that adults with anxiety have a 50% greater risk of incident CVD compared to those without anxiety after adjustment for traditional CVD risk factors (Batelaan, Seldenrijk, Bot, van Balkom, & Penninx, 2016). Additionally, results of this meta-analysis revealed that the prospective effect of anxiety on CVD outcomes did not significantly differ between studies that adjusted for/excluded depression ($k = 14$; pooled $HR = 1.57$, 95% $CI: 1.29-1.90$) and studies that did not ($k = 25$; pooled $HR = 1.47$, 95% $CI: 1.30-1.65$; Batelaan et al., 2016). This suggests that the relationship between anxiety and incident CVD is independent from depression in the general population.

Compared to this anxiety-clinical CVD literature, fewer studies have investigated the relationship between anxiety and measures of subclinical atherosclerosis, and the findings have been mixed. For instance, of the two longitudinal studies in this literature, one found that higher anxiety symptom severity predicts 4-year progression of carotid intima-media thickness (but not coronary artery calcification) in both men and women and more plaque formation in men only (Paterniti et al., 2001). The other study found no relationship between anxiety symptom severity and 3-year progression of carotid intima-media thickness both before and after controlling for depressive symptom severity (Stewart et al., 2007). Cross-sectional relationships between anxiety and arterial stiffness are also weakly supported. While two studies found that anxiety is associated with increased arterial stiffness (Cicek et al., 2012; Seldenrijk, van Hout, van Marwijk, de Groot, & Gort, 2011), two other studies observed no relationship (Lewis et al., 2010; Nomura, Nakao, Karita, Nishikitani, & Yano, 2005). Overall, relationships between anxiety and structural measures of subclinical atherosclerosis are inconsistent.

The relationship between anxiety and functional measures of subclinical atherosclerosis have also been inconsistent (Thurston et al., 2013). Although two studies did not detect an association between anxiety and endothelial function (Routledge et al., 2017; Schott, Kamarck, Matthews, Brockwell, & Sutton-Tyrrell, 2009), three other investigations have found that anxiety symptom severity was associated with poorer endothelial function (Cooper et al., 2010; Harris, Matthews, Sutton-Tyrrell, & Kuller, 2003; Narita et al., 2007). Another study found that post-traumatic stress disorder, a condition which often includes severe anxiety, was associated with worse endothelial function in veterans (Grenon et al., 2016). Overall, the relationship between anxiety and subclinical atherosclerosis has been most consistent for endothelial function.

However, none of these studies accounted for the potential of depressive symptom severity to confound anxiety-endothelial function relationships.

Anxiety and Cardiovascular Disease in Depressed Adults

Two investigations have examined the influence of anxiety on incident CVD in depressed adults. The first of these studies, a longitudinal case-control study of patients with and without panic disorder (Gomez-Caminero et al., 2005), found that panic disorder was related to incident CVD to a greater degree in depressed adults ($HR = 2.61$, 95% CI : 2.32-2.95) than in nondepressed adults ($HR = 1.86$, 95% CI : 1.82-1.89). A second study found that panic disorder ($HR = 1.22$, 95% CI : 1.07-1.39) and anxiety disorder unspecified ($HR = 1.11$, 95% CI : 1.03-1.20) – but not generalized anxiety disorder, social phobia, or post-traumatic stress disorder – predicted incident CVD in depressed veterans (Scherrer et al., 2010). These studies suggest that some types of anxiety disorders, but perhaps not others, increase CVD risk in depressed adults. However, neither accounted for the potential confounder of depressive symptom severity.

Other studies have examined the relationship between comorbid depressive and anxiety disorders, depressive disorder only, anxiety disorder only, and neither disorder (reference category) with CVD outcomes. Four of these studies have examined incident CVD outcomes (Berecki-Gisolf, McKenzie, Dobson, McFarlane, & McLaughlin, 2013; Garfield et al., 2014; Phillips et al., 2009; Seldenrijk et al., 2015). In all four studies, the magnitude of CVD risk was greatest for the adults with comorbid depression and anxiety. Moreover, in two of these studies, only adults with comorbid depressive and anxiety disorders were at increased CVD risk (Berecki-Gisolf et al., 2013; Phillips et al., 2009).

Two other studies have also examined the cross-sectional relationship between comorbid depression and anxiety and measures of subclinical atherosclerosis. One study found that adults

with comorbid depressive and anxiety disorders, but not those with a depressive or anxiety disorder only, had greater arterial stiffness than adults without depressive or anxiety disorders (Seldenrijk et al., 2011). In contrast, another study found that ankle-brachial index (the ratio of ankle to arm blood pressure, where lower scores indicate peripheral artery disease) was comparable across those with current depressive disorder only, current anxiety disorder only, and comorbid depressive and anxiety disorders. Specifically, all three groups had a 2-3 fold increased risk of low ankle-brachial index compared to the group with no depressive or anxiety disorders (Seldenrijk et al., 2010).

Taken together, the majority of this evidence has found a *numerically* greater degree of CVD risk in depressed adults with versus without comorbid anxiety. Of note, I use the word “numerically” because those with comorbid depressive and anxiety disorders are never directly compared to those with depressive disorder only. Rather, both of these groups are compared to the reference group with neither depression nor anxiety. Another limitation is that these studies fail to account for depressive symptom severity, which is problematic because those with psychiatric comorbidities tend to have more severe symptoms (Kessler et al, 2005).

Potential Mechanisms of the Anxiety-Cardiovascular Disease Relationship in Depressed Adults

To my knowledge, no study has examined mechanisms that may underlie anxiety-CVD relationships in depressed adults. However, an emerging literature suggests that depressed adults with anxiety disorders or increased anxiety symptom severity may have more severe levels of CVD risk factors than depressed adults without anxiety. First, one study found that, in depressed adults, anxiety symptom severity was associated with higher total cholesterol levels (Fava et al., 1996). Another study of middle-aged men found that adults with comorbid depressive and

anxiety disorders ($OR = 1.85$, 95% CI : 1.29-2.64), but not those with a depressive or anxiety disorder only, had a greater odds of having hypertension than adults without depressive or anxiety disorders (Carroll, Phillips, Gale, & Batty, 2010). A final study involving adults free of CVD examined associations of MDD (all cases) and MDD with comorbid generalized anxiety disorder with diminished high-frequency heart rate variability, a marker of parasympathetic nervous system function and an emerging CVD risk factor (Kemp, Quintana, Felmingham, Matthews, & Jelinek, 2012). Results of this study revealed that, while MDD was associated with lower high-frequency heart rate variability (a medium effect size), MDD with generalized anxiety disorder was associated with greater reductions in this factor (a large effect size; Kemp et al., 2012). Overall, this small literature suggests that anxiety may be associated with increased levels of CVD risk factors in depressed adults. Consequently, it is plausible that anxiety may increase CVD risk in depressed adults through these CVD risk factors.

Hostility/Anger

Hostility is a tendency to view the world in a negative and cynical fashion involving a negative attitude toward others, enmity, denigration, and ill will (Smith, Glazer, Ruiz, & Gallo, 2004). Hostility is typically grouped with and accompanied by anger, a negative emotion ranging in intensity from irritation or annoyance to fury or rage that is usually elicited by perceived injustice (Torquato, de Souza, Iosifescu, & Fraguas, 2012). Moreover, hostility/anger can be expressed behaviorally as verbal and/or physical aggression (Smith et al., 2004). Consequently, as an affective trait, hostility/anger is the tendency to experience hostile attitudes, angry emotion, and/or aggression (Buss & Perry, 1992). Hostility/anger is typically measured as a continuous construct (Torquato et al., 2012), although an example of a dichotomous measure is the presence/absence of anger attacks (Cassidello-Robbins & Barlow, 2016). In adults, hostility/anger

has high stability over time, as indicated by high test-retest correlations over one to three years (r range: 0.84-0.85), six years (r range: 0.61-0.66), and 30 years ($r = 0.39$; Barefoot, Dahlstrom, & Williams, 1983; Shekelle, Gale, Ostfeld, & Paul, 1983; Siegler et al., 1990; Stewart, Fitzgerald, & Kamarck, 2010).

Overlap Between Hostility/Anger and Depression

Like anxiety, hostility/anger overlaps with depression (Suls & Bunde, 2005). Correlations between self-report measures of depression and hostility/anger range from 0.22 to 0.44 (Mook, Van Der Ploeg, & Chr. Kleijn, 1990; Newman, Fuqua, Gray, & Simpson, 2006). Moreover, those with depressive disorders experience greater levels of hostility/anger compared to healthy controls (Cassidello-Robbins & Barlow, 2016). To illustrate, recent evidence suggests that over 50% of MDD patients experience clinical levels of overt anger/irritability (Judd, Schettler, Coryell, Akiskal, & Fiedorowicz, 2013). It has also been estimated that 33-44% of MDD patients experience anger attacks (Cassidello-Robbins & Barlow, 2016). This common hostility/anger comorbidity in depressed adults is also associated with more severe, chronic, and complex depressive disorders (i.e., poorer prognosis, reduced psychosocial functioning, and a greater likelihood of comorbid psychiatric disorders; Judd et al., 2013).

Hostility/Anger and Cardiovascular Disease in the General Population

Evidence suggests that adults with higher levels of hostility/anger are at increased risk of developing CVD. A meta-analysis of 21 prospective studies revealed that, in initially healthy populations, hostility/anger was associated with a 19% increased risk of incident coronary heart disease (Chida & Steptoe, 2009). However, evidence for this relationship is less robust than for the depression-CVD and anxiety-CVD relationships, considering that the hostility/anger-CVD

relationship fell short of significance after controlling for key covariates, such as smoking, physical activity, body mass index, and socioeconomic status (Chida & Steptoe, 2009).

Nonetheless, some studies have found that the relationship between hostility/anger and incident CVD remains after including depression as a covariate (Boyle, Michalek, & Suarez, 2006; Kubzansky, Cole, Kawachi, Vokonas, & Sparrow, 2006; Newman et al., 2011), suggesting that the hostility/anger-CVD relationship may be independent from depression.

Associations between hostility/anger and incident CVD may, in part, be due to the relationship between hostility/anger and subclinical atherosclerosis. Consistent with this notion, prospective evidence suggests that anger (Räikkönen, Matthews, Sutton-Tyrrell, & Kuller, 2004), as well as cynical distrust and anger control (Julkunen, Salonen, Kaplan, Chesney, & Salonen, 1994), promote the progression of carotid intima-media thickness. Additionally, those with higher levels of cynicism and those with higher levels of cynicism and anger (interaction effect) have greater progression of coronary artery calcification compared to those with lower levels of these characteristics (Low et al., 2011). Of note, in a study that accounted for anxiety and depression, neither hostility nor anger predicted 3-year progression of carotid intima-media thickness (Stewart et al., 2007). However, hostility/anger has consistently been found to relate to poorer endothelial function (Cooper et al., 2010; Harris et al., 2003; Lin et al., 2008; Schott et al., 2009), and one of these studies found that this relationship persisted after accounting for anxiety and depression (Lin et al., 2008). In summary, the majority of literature indicates that hostility/anger is associated with greater subclinical atherosclerosis, and initial evidence suggests that this relationship may persist after controlling for other affective traits.

Hostility/Anger and Cardiovascular Disease in Depressed Adults

Although the evidence suggests that hostility/anger increases CVD risk in the general population, to my knowledge, no studies have examined the relationship between hostility/anger and CVD outcomes in depressed adults. Consequently, it remains unknown whether depressed adults with hostility/anger are at greater CVD risk than depressed adults without hostility/anger.

Potential Mechanisms of the Hostility/Anger-Cardiovascular Disease Relationship in Depressed Adults

Given the preceding section, it is not surprising that no studies have investigated factors that may mediate hostility/anger-CVD risk relationships in depressed adults. Nonetheless, some candidate mediators can be identified by examining which CVD risk factors have been associated with hostility/anger in depressed adults. Compared to depressed adults without anger attacks, depressed adults with anger attacks have higher total cholesterol levels (Fava et al., 1996; Fraguas et al., 2007) and more years of smoking (Fraguas et al., 2007). Two other studies found hostility to be associated with higher levels of inflammatory markers in adults with higher depressive symptoms but not in adults with lower depressive symptoms (Stewart, Janicki-Deverts, Muldoon, & Kamarck, 2008; Suarez, 2003). This small literature suggests hostility/anger may be positively associated with some CVD risk factors in depressed adults. Consequently, it is plausible that hostility/anger may increase CVD risk in depressed adults through these CVD risk factors.

Low Trait Positive Affect

Positive affect is the experience of pleasurable emotions such as joy, happiness, excitement, enthusiasm, and contentment (Tomkins et al., 1963). While these emotions can be transient and reflect current mood state, trait positive affect – the dispositional tendency to experience positive affect – is stable over time (Krueger, McGue, & Iacono, 2001; Watson, 2002). For instance, Watson and Walker (1996) found that undergraduate students have relatively stable trait positive affect over six years ($r = 0.42$). Moreover, trait positive affect shows even stronger stability at later ages. For example, one study found high stability over 25 years of follow-up from age 27 to 52 years ($r = 0.61$; Helson & Klohnen, 1998). The degree of trait positive affect is typically assessed as a continuous construct (Pressman & Cohen, 2005). Also of importance, evidence supports the independence of positive affect from negative affect, meaning that positive and negative affect are not merely bipolar extremes of the same continuum (Diener & Emmons, 1984; Headey, Kelley, & Wearing, 1993; Watson, Clark, & Tellegen, 1988). To illustrate, a person who has a tendency to experience positive affect can also have a co-occurring tendency to experience various forms of negative affect (e.g., depression, anxiety, and hostility/anger).

Overlap Between Low Trait Positive Affect and Depression

Given that low pleasure and interest (i.e., anhedonia) is one core feature of depressive disorders (Pelizza & Ferrari, 2009), it is not surprising that positive affect and depression have been found to be negatively associated. To illustrate, a recent meta-analysis of 59 studies (pooled $N = 24,503$) found a significant cross-sectional correlation between trait positive affect and depression ($r = -0.34$; Khazanov & Ruscio, 2016). Of note, trait positive affect has been found to

related to measures of depressive symptom severity (e.g., Crawford & Henry, 2004; Headey et al., 1993; Watson, Clark, & Tellegen, 1988) and depressive disorders (e.g., Brown, Chorpita, & Barlow, 1998; Watson, Clark, Carey, 1988). Finally, evidence suggests that, compared to depressed adults with lower levels of anhedonia, those with higher levels of anhedonia have more severe depressive symptoms (Pelizza & Ferrari, 2009).

Low Trait Positive Affect and Cardiovascular Disease in the General Population

A relatively small literature has examined the relationship between trait positive affect and CVD risk. This literature suggests that, after adjustment for traditional CVD risk factors, trait positive affect is associated with a lower risk of incident stroke (Ostir, Markides, Peek, & Goodwin, 2001), coronary heart disease (Davidson, Mostofsky, & Whang, 2010; Hawkins et al., 2014; Newman et al., 2011; Yanek et al., 2013), and composite cardiometabolic conditions (i.e., heart problems, hypertension, diabetes, or high cholesterol; Boehm, Chen, Williams, Ryff, & Kubzansky, 2016). Across these studies, trait positive affect was associated with a 12% to 26% reduced risk of the CVD outcomes. Two of these studies retained a positive affect-CVD relationship after controlling for depressive symptoms (Davidson et al., 2010; Newman et al., 2011), and two others did not (Boehm et al., 2016; Hawkins et al., 2014). Of note, two additional studies did not detect a relationship between positive affect and incident CVD (Freak-Poli et al., 2015; Nabi et al., 2008). Nonetheless, the majority of this literature suggests that positive affect is associated with reduced CVD risk; however, it is unclear whether this relationship is independent of negative affective traits.

Only one study has examined the relationship between positive affect and subclinical atherosclerosis (Kroenke, Seeman, Matthews, Adler, & Epel, 2012). Cross-sectional analyses revealed that, compared to people with higher positive affect, those with lower positive affect

(averaged over the course of a day by means of ecological momentary assessment) had an 86% increased likelihood of any coronary artery calcification and twice the likelihood of substantial coronary artery calcification, after adjustment for traditional CVD risk factors and depression. However, positive affect was unrelated to incident coronary artery calcification over the 5-year follow-up period. Of note, no studies have examined the relationship between trait positive affect and endothelial function.

Low Trait Positive Affect and Cardiovascular Disease in Depressed Adults

Because low trait positive affect is related to higher CVD risk in the general population, it is plausible that low positive affect may also elevate CVD risk in the depressed population. However, no studies have examined this relationship in depressed adults. As a result, it remains unknown whether depressed adults with lower trait positive affect are at greater CVD risk than depressed adults with higher trait positive affect.

Potential Mechanisms of the Low Trait Positive Affect-Cardiovascular Disease Relationship in Depressed Adults

Although studies have yet to investigate factors that may mediate a trait positive affect-CVD relationship in depressed adults, a few studies suggest that higher trait positive affect may protect against processes that promote CVD in those with negative affect (Fredrickson, 2001; Pressman & Cohen, 2005). For example, evidence suggests that higher positive affect may accelerate cardiovascular recovery from negative emotional arousal (Fredrickson & Levenson, 1998; Tugade, & Fredrickson, 2004). This accelerated cardiovascular recovery may be protective against future cardiovascular risk (Chida & Steptoe, 2010). Additionally, one study found that positive mood was related to higher levels of natural killer cell activity, an immune marker that

is reduced in those with CVD (Camous, Pera, Solana, & Larbi, 2012), only among those who also experienced negative mood over the day (Valdimarsdottir & Bovbjerg, 1997). This small literature suggests that trait positive affect may reduce the degree of CVD risk factors in those with negative affect.

The Present Study

Although substantial evidence suggests that depressed adults are at increased risk of CVD, there may be subgroups in the depressed population at greater risk of developing CVD than others. Because other affective traits – i.e., anxiety, hostility/anger, and low trait positive affect – have been associated with increased CVD risk in the general population, depressed adults with higher levels of these co-occurring affective traits may be at greater risk of developing CVD. However, only the association between anxiety and CVD outcomes has been examined in depressed adults. To my knowledge, *no study has simultaneously examined whether depression, anxiety, hostility/anger, and low trait positive affect are associated with CVD outcomes in depressed adults.*

In the studies examining the relationship between anxiety and CVD outcomes in depressed adults, none has controlled for depressive symptom severity. This is a key limitation for two reasons: (1) depressive symptom severity is positively correlated with other affective traits in depressed adults and (2) depressive symptom severity is positively related to increased CVD risk in depressed adults. Consequently, the observed associations between anxiety and CVD outcomes in depressed adults may be due to greater depressive symptom severity.

One approach to disentangling these overlapping affective traits is to unpack them into mutually exclusive shared and unique components (see Figure 1) and examine how these components relate to CVD outcomes (see Figure 2). Some previous research suggests that unique

anxiety (Batelaan et al., 2016), unique hostility/anger (Boyle et al., 2006; Kubzansky et al., 2006; Newman et al., 2011; Lin et al., 2008), and unique trait positive affect (Davidson et al., 2010; Newman et al., 2011; Kroenke et al., 2012) predict future CVD in the general population. In these investigations, depressive symptom severity was included as a covariate in models examining the relationship between the affective traits and CVD outcomes. Additionally, two previous studies found that the shared variance between depression, anxiety, and hostility/anger predicted incident CVD in initially healthy samples (Boyle et al., 2006; Kubzansky et al., 2006). However, *no study has examined the shared and unique components of these affective traits in relation to CVD outcomes in depressed adults.*

Finally, the evidence reviewed suggests that anxiety and hostility/anger are positively related to various CVD risk factors in depressed adults and that positive affect may reduce the degree of CVD risk factors in those with negative affect. Thus, it is plausible that these CVD risk factors partially mediate affective trait-CVD relationships in depressed adults. However, *no study has examined candidate mediators of affective trait-CVD associations in depressed adults.*

The aims of the present study are designed to begin to address the aforementioned gaps in knowledge. The three aims are as follows:

- 1) To examine which affective traits – depression (depressive symptom severity), anxiety (anxiety symptom severity), hostility/anger, and low trait positive affect – are associated with endothelial function in depressed adults
- 2) To investigate which components of affective traits are associated with endothelial function in depressed adults

- a. To examine which depression and anxiety components (shared variance, unique depression variance, and unique anxiety variance) are associated with endothelial function
 - b. To examine which depression and hostility/anger components (shared variance, unique depression variance, and unique hostility/anger variance) are associated with endothelial function
 - c. To examine which depression and trait positive affect components (shared variance, unique depression variance, and unique positive affect) are associated with endothelial function
- 3) To explore traditional CVD risk factor status as a candidate mediator of any significant relationships observed in the Aim 2 models

To achieve these aims, I combined pre-treatment, cross-sectional data from three randomized controlled trials involving primary care patients with clinically significant depressive symptoms. All three trials were designed to examine whether a depression treatment improved endothelial function as indicated by brachial artery FMD. These data provide a good opportunity to achieve the present study's aims because the pre-treatment assessments for all three trials included measures of the affective traits of interest, endothelial function, and traditional CVD risk factors. Based on the literature reviewed, I hypothesized (1) that all of the affective traits will be negatively associated with endothelial function, (2) that both the shared and unique components of each affective trait will be negatively related to endothelial function, and (3) that traditional CVD risk status would partially mediate observed associations in the Aim 2 models. To test this hypothesis, I utilized a composite measure of traditional CVD risk status: 10-year Framingham risk score (D'Agostino et al., 2008). This risk score uses an algorithm to combine

individual traditional CVD risk factors (age, sex, systolic blood pressure, BMI, taking an antihypertensive medication, diabetes diagnosis, and current smoking status) into a single estimate of traditional CVD risk status that is expressed as the estimated percentage (0-100%) of 10-year CVD onset in adults initially free of CVD (D'Agostino et al., 2008; Greenland et al., 2010).

METHODS

Study Sample

To create the study sample, I combined pre-treatment, cross-sectional data from three randomized controlled trials involving depressed primary care patients from Eskenazi Health: Beating the Blues for Your Heart Trial (BtB-Heart Trial; $n = 29$), Targeting Systemic Inflammation to Concurrently Treat Late-Life Depression and Reduce Coronary Artery Disease Risk (INFLAMED Trial; $n = 17$), and Modernized Collaborative Care to Reduce the Excess CVD Risk of Older Depressed Patients (eIMPACT Trial; $n = 94$). Eskenazi Health is the second largest safety net healthcare system in the U.S providing care to $\approx 20\%$ of the Indianapolis population. Eskenazi Health patients are mostly underinsured/uninsured (90%) and approximately half are non-Hispanic Black. From the combined sample of 142 adults, I excluded three participants with missing values for endothelial function ($n = 1$ from BtB-Heart, $n = 1$ from INFLAMED, and $n = 1$ from eIMPACT) and one participant from BtB-Heart who was missing all questionnaire data. All 138 remaining participants had complete data across demographic factors and FMD. There was $<1\%$ missingness across the affective traits data, which was accounted for when parceling the questionnaire items (see Data Analyses). There were also five missing values (3.6% missingness) for the 10-year Framingham risk score, which was accounted for by utilizing full information maximum likelihood (FIML) estimation in the analysis that utilized this variable. Thus, the present study's sample consisted of 138 depressed primary care patients.

The recruitment approaches and inclusion/exclusion criteria were similar across the three trials. First, the Eskenazi Health electronic medical record was searched in accordance with

HIPAA to generate lists of potentially eligible patients. Next, research assistants from ResNet, Indiana University's primary care practice-based research network, obtained permission to approach these patients. Finally, ResNet assistants conducted in-clinic and telephone screening of identified patients to determine eligibility. For eligible and interested patients, ResNet assistants obtained informed consent and authorization.

Eligible primary care patients were those with no history of clinical CVD (coronary artery disease, cerebrovascular disease, acute MI, percutaneous coronary intervention, or coronary artery bypass graft) and with clinically significant depressive symptoms. Clinically significant depressive symptoms were defined as a score ≥ 10 on the Patient Health Questionnaire-9 (PHQ-9), a cutoff which has a sensitivity of 88% and a specificity of 88% for major depressive disorder (Kroenke, Spitzer, & Williams, 2001). Complete inclusion/exclusion criteria for each of these trials is presented in Appendix A.

Measures

Independent Variables

The questionnaires used to assess the independent variables are presented in Appendix B. Descriptions of these questionnaires are provided below.

Depressive Symptom Severity

Depressive symptom severity was assessed with the 20 depression items from the Symptom Checklist-90 (SCL-20; Derogatis, Lipman, & Covi, 1973). For each item on the SCL-20, participants indicated how often they experienced various depressive symptoms during the last week, with response options of *not at all* (0), *a little bit* (1), *moderately* (2), *quite a bit*

(3), and *extremely* (4). The average score across all items is calculated so that the SCL-20 total score ranges from 0 to 4, with higher scores indicating greater depressive symptom severity. The SCL-20 has demonstrated good internal consistency (Cronbach's $\alpha = .86$) and test-retest reliability (r over one week = .81; Derogatis, Lipman, Rickels, Uhlenhuth, & Covi, 1974) and is strongly related to other validated measures of depressive symptom severity (Dinning & Evans, 1977).

Anxiety Symptom Severity

The Generalized Anxiety Disorder-7 (GAD-7), a seven-item questionnaire, was utilized to assess anxiety symptom severity (Spitzer, Kroenke, Williams, & Löwe, 2006). For each item on the GAD-7, participants were asked to indicate the degree to which they had been bothered by the selected symptom during the last two weeks, with response options of *not at all* (0), *several days* (1), *more than half the days* (2), and *nearly every day* (3). Scores are summed across all items so that the GAD-7 total score ranges from 0 to 21, with higher scores indicating greater anxiety symptom severity. The internal consistency of the GAD-7 is excellent (Cronbach's $\alpha = 0.92$), and its test-retest reliability is good (r over one week = 0.83; Spitzer et al., 2006). It also demonstrates good convergent validity, as indicated by strong correlations with other self-reported measures of anxiety symptom severity (Spitzer et al., 2006).

Hostility/Anger

Hostility/anger was assessed with 29 items from the Buss-Perry Aggression Questionnaire (BPAQ; Buss & Perry, 1992). For each item, participants indicated how uncharacteristic or characteristic statements are in describing them, with response options of *extremely uncharacteristic* (1), *somewhat uncharacteristic* (2), *neither uncharacteristic nor*

characteristic (3), *somewhat characteristic* (4), and *extremely characteristic* (5). The BPAQ consists of the following four subscales: hostility, anger, verbal aggression, and physical aggression. Scores across all items are summed so that the BPAQ total score ranges from 29 to 145, with higher scores indicating greater hostility/anger. The BPAQ has demonstrated adequate to good internal consistency for the subscales (Cronbach's $\alpha = 0.72-0.85$) and the total score (Cronbach's $\alpha = 0.89$; Buss & Perry, 1992). It has also demonstrated adequate test-retest reliability over a 9-week period for each subscale ($r = 0.72-0.80$) and the total score ($r = 0.80$; Buss & Perry, 1992). Convergent validity of the BPAQ has been demonstrated by moderate correlations of the total score with measures of similar personality traits, such as assertiveness, competitiveness, and impulsivity (Buss & Perry, 1992).

Trait Positive Affect

Trait positive affect was assessed using the positive affect (PA) subscale of the Positive and Negative Affect Schedule (PANAS; Watson, Clark, & Tellegen, 1988). Participants were asked to report the extent to which they have experienced ten positive emotions, on average, on a 5-point scale, with response responses of *very slightly or not at all* (1), *a little* (2), *moderately* (3), *quite a bit* (4), or *extremely* (5). Scores are summed across all items so that the PANAS-PA total score ranges from 10 to 50, with higher scores indicating greater trait positive affect. The PANAS-PA has demonstrated good internal consistency (Cronbach's $\alpha = 0.86-0.90$) and is relatively stable over an 8-week period ($r = 0.47-0.68$; Watson & Clark, 1994). The PANAS-PA also relates to peer-reports of trait positive affect and demonstrated good convergent validity with similar constructs, such as vigor (Watson & Clark, 1994).

Dependent Variable

Endothelial Function

Endothelial function was assessed by brachial artery FMD. FMD is a noninvasive technique that uses high-resolution ultrasound to measure changes in brachial artery diameter in response to an induction of increased blood flow (Celermajer et al., 1992). In the assessment of FMD, a blood pressure cuff is inflated around the forearm to occlude the brachial artery for several minutes (Celermajer et al., 1992). Then, the cuff is rapidly released to induce increased blood flow, which increases sheer stress on the vessel wall (Celermajer et al., 1992). High-resolution ultrasound is used to measure the degree to which the brachial artery dilates in response to this increase in sheer stress (Thurston et al., 2013). A healthy artery dilates substantially in response to this stimulus, whereas a compromised artery dilates minimally or may even constrict (Matthews, 2005). Because this response is mediated by the endothelium, a lesser degree of dilation is indicative of greater endothelial dysfunction (Hadi, Carr, & Suwaidi, 2005; Thurston et al., 2013).

In all three trials, patients underwent FMD assessments in accordance with consensus guidelines (Corretti et al., 2002). The vascular ultrasonographer who completed the FMD assessments and the physician who scored the ultrasound images had completed certified training through the University of Wisconsin Brachial Artery Reactivity Testing Symposium. To obtain the brachial artery images, a GE Logiq E ultrasound system with AccessPoint 2011 software was used. After a 10-minute supine rest, high-resolution baseline images of the brachial artery were obtained from three consecutive cardiac cycles. Next, the forearm cuff was inflated to 250 mmHg for five minutes before being rapidly deflated. At 60 and 90 seconds post deflation, images from three consecutive cardiac cycles were acquired. Fifteen minutes post deflation,

baseline images were again obtained. Brachial diameters were measured at peak R wave. FMD values were computed as the percent change in diameter at 60 and 90 seconds post deflation, and the larger of the two values was used.

Covariates

Given their potential associations with both the affective traits and endothelial function, demographic factors (age [years], sex [0 = male, 1 = female], race/ethnicity [0 = not non-Hispanic Black, 1 = non-Hispanic Black], and education [0 = high school graduate/GED or equivalent or more than high school, 1 = less than high school] and baseline arterial diameter (cm) were included as covariates. Participants were asked to indicate their age, sex, race/ethnicity, and highest education level completed. Responses were aggregated into two categories for race/ethnicity and education to effectively merge the slightly differing response options for these factors across the three trails. Finally, baseline arterial diameter was assessed during the FMD assessment.

Traditional Cardiovascular Disease Risk Status Mediator

Many traditional CVD risk factors are candidate mediators of the hypothesized affective trait-endothelial function relationships. Framingham risk scores use algorithms to combine traditional CVD risk factors into a single quantitative estimate of CVD risk expressed as a percentage (Greenland et al., 2010). I chose to calculate the 10-Year Framingham risk score, which estimates risk of CVD onset (coronary death, MI, coronary insufficiency, angina, ischemic stroke, hemorrhagic stroke, transient ischemic attack, peripheral artery disease, and heart failure) over the next 10 years in adults initially free of CVD (D'Agostino et al., 2008). Values range from 0 to 100%, and values greater than 20% are indicative of high CVD risk (Greenland et al.,

2010). The Framingham algorithm incorporates the following traditional CVD risk factors that were assessed across the three trials: age, sex, systolic blood pressure, BMI, taking an antihypertensive medication, diabetes diagnosis, and current smoking status. Three seated blood pressure readings were obtained by a research nurse using a standard sphygmomanometer, and systolic blood pressure was computed as the average of the last two readings. BMI was computed as measured weight (kg) divided by measured height (m) squared. Current smoking status (yes, no) was determined through self-report; participants who reported smoking at least 100 cigarettes during their lifetime and indicated that they now smoke cigarettes every day or some days were classified as current smokers (Nelson et al., 2000). Antihypertensive medication (yes, no) was assessed by asking participants to indicate whether or not they were currently taking medication for high blood pressure. Diabetes diagnosis (yes, no) was assessed by querying participants whether or not they had ever been diagnosed with diabetes by a health professional.

Procedure

As soon as was feasible after enrollment, participants attended a 3-hour pre-treatment visit at the Clinical Research Center of the Indiana Clinical and Translational Sciences Institute. Participants were instructed to fast and to avoid tobacco and exercise for eight hours before their visit. Participants had their height, weight, and blood pressure measured; completed self-report scales via a website on a secure computer; and underwent the FMD assessment and a blood draw. For two of the three trials (BtB-Heart and eIMPACT), participants' heart rate was also monitored for approximately five minutes while resting supine to derive a measure of high-frequency heart rate variability. To end the pre-treatment visits, participants were randomized to one of two groups, and additional study visits were scheduled.

Data Analyses

Parceling Affective Measures

Items of each affective measure were randomly aggregated to create three parcels for each affective trait (Parceling approach recommended by Matsunaga, 2008). For example, items on the SCL-20 were randomly aggregated to create three Depression parcels: SCL-20 Parcel 1, SCL-20 Parcel 2, and SCL-20 Parcel 3. This process was repeated for the GAD-7 items, BPAQ items, and PANAS-PA items to create three parcels for Anxiety, Hostility/Anger, and Positive Affect, respectively. There was <1% missingness across all affective traits data. After parceling, within-parcel missingness ranged from 0.2% to 1.3%. Examination of individual cases revealed two cases with one instance of within-parcel missingness >50% (one case with 6 of the 10 values missing for the BPAQ Parcel 1 items and another case with 2 of the 3 values missing for the PANAS-PA Parcel 2 items). Given the low rates of within-parcel missingness and the few individual cases with instances of >50% within-parcel missingness, I utilized within-parcel mean imputation to account for these missing values. The resulting affective trait parcels with complete data were utilized in the Aim 1-3 models.

Data Cleaning

Initial data cleaning procedures assessed for missing data, outliers, and normality for each variable using SPSS statistical software (Version 20).

Prior to any imputation or FIML procedures to account for missing data, I checked for systematic missingness in the dataset by age, sex, race/ethnicity, and education. To complete this check, I created a dichotomous missingness variable (0 = not missing, 1 = missing) for the 12 affective trait parcels, FMD, baseline arterial diameter, 10-year Framingham risk score, and

individual CVD risk factors included in this risk score. Then, I conducted chi-square tests for sex, race/ethnicity, and education and independent sample t-tests for age with each missingness variable. This check revealed only one relationship: mean age was significantly younger for those with missing data on the BPAQ Parcel 1 ($M = 48$ years, $SD = 3.1$) compared to those with no missing data ($M = 57$ years, $SD = 6.9$; $t(136) = 3.69$, $p < 0.001$). It is likely that the detected relationship is a type 1 error because (a) 80 analyses were performed to check for systematic missingness and (b) age did not relate to missingness on the other BPAQ parcels. Accordingly, analytic procedures proceeded as planned.

To identify out-of-range values, I examined variable frequencies. This examination revealed all values to be within the plausible range. To identify outliers, I examined all continuous variables for z score values ≤ -3.3 or ≥ 3.3 . Amongst all variables in the dataset, only two outliers were detected (z scores = 3.4 and 3.6), which were for the Framingham Risk Score variable. These two outliers were not altered or deleted for three reasons: (1) these cases did not result in non-normal distributions, (2) some z scores ≤ -3.3 or ≥ 3.3 are expected with larger samples, and (3) these cases are likely legitimate cases of the sample population (Tabachnick & Fidell, 2001).

To determine normality, I examined variables for excessive skew (≤ -3 or ≥ 3) and kurtosis (≤ -10 or ≥ 10) (Kline, 1998). Because no variables exhibited excessive skew or kurtosis, deviations from normality in this dataset were insubstantial.

Computing Correlations

Correlation analyses were completed using SPSS statistical software (Version 20). I conducted two sets of correlational analyses: bivariate correlations and partial correlations after controlling for the covariates (age, sex, race/ethnicity, education, and baseline arterial diameter).

These correlational analyses were conducted (a) between all affective trait measures to elucidate the degree of overlap among these factors, (b) between each affective trait measure and the 10-year Framingham risk score to examine associations of affective traits and traditional CVD risk status, (c) between each affective trait measure and FMD to examine the associations of affective traits with endothelial function, and (d) between the 10-year Framingham risk score and FMD to examine the association between traditional CVD risk status and endothelial function.

Primary Analyses

For all primary analyses, I utilized LISREL 8.8 software (Jöreskog & Sörbom, 2008) to conduct structural equation modeling (SEM). These SEM analyses included measurement models that utilized confirmatory factor analysis (CFA) – a statistical, hypothesis-driven approach that examines covariation among observed indicator variables to gather information on a smaller number of latent variables (Brown, 2006). This approach is preferable to exploratory factor analysis because it allows the researcher to specify and test a model based on empirical and/or theoretical literature (Brown, 2006). CFA measurement models were followed by construction of structural models, which examine directional relationships between latent variables (Schreiber, Nora, Stage, Barlow, & King, 2006). I utilized maximum likelihood estimation for the Aim 1 and 2 models and FIML estimation for the Aim 3 model to account for five missing Framingham risk score values. To assess model fit, I examined absolute (model χ^2 statistic and standardized root mean square residual; SRMR), parsimonious (root mean square of approximation; RMSEA), and incremental (comparative fit index; CFI) fit indices (Hu & Bentler, 1999). Values for these fit indices were evaluated using the following common recommendations for acceptable model fit: $< .08$ for SRMR, $< .06$ for RMSEA, and $> .95$ for

CFI (Hu & Bentler, 1999) as well as a low model χ^2 statistic relative to degrees of freedom ($\chi^2/\text{df} < 3:1$ ratio) with an insignificant p value ($p > 0.05$; Kline, 2005).

Latent variables were constructed from the observed indicator variables. The three parcels for each affective trait measure served as indicators loading onto their corresponding affective trait latent variables: Depression, Anxiety, Hostility/Anger, and Positive Affect. In the present study, a parceling approach is preferable to using all of the individual questionnaire items as indicators because model fit can be adversely affected by large sets of indicators (Little, Cunningham, Shahar, & Widaman, 2002). FMD value served as the single indicator loading onto the Endothelial Function latent variable, and the 10-year Framingham risk score served as the single indicator loading onto Traditional CVD Risk Status latent variable. To achieve identification, one of the loadings for each set of three parcels was set to one, the error for FMD was set to zero, and the error for the Framingham risk score was set to zero (Hayduk & Littvav, 2012).

All analyses utilizing the FMD indicator accounted for age, sex, race/ethnicity, education, and baseline arterial diameter by residualizing the FMD indicator for these potential confounders prior to constructing the Endothelial Function latent variable. This residualizing approach was utilized because including these variables in models as covariates would have result in a ratio of participants to estimated parameters below the acceptable lower limit of 5:1 (Kline, 2005). To illustrate, after utilizing this residualizing approach, the most complex model (see Figure 7) had a ratio of participants (138) to estimated parameters (21) of 6.6:1.

RESULTS

Characteristics of Participants

Descriptive statistics for the total sample are presented in Table 1. Participants' ages ranged from 40-74 years, with a mean of 56. The sample was almost 70% women, nearly 40% identified as non-Hispanic Black, and 18% had less than a high school education. Traditional CVD risk factors were highly prevalent, as 32% reported a diabetes diagnosis, 64% had a BMI in the obese range ($\text{BMI} \geq 30 \text{ kg/m}^2$), 59% reported taking antihypertensive medication, 34% had a systolic blood pressure indicative of hypertension ($\geq 140 \text{ mmHg}$), and 43% reported current smoking. The high CVD risk factor burden resulted in mean 10-year Framingham risk score of 23%, which falls in the high CVD risk range ($> 20\%$). Regarding the affective trait measures, the mean SCL-20 score (1.8) was comparable to that observed in other depressed primary care samples (Katon et al., 1996; Williams, Stellato, Cornell, & Barrett, 2004). The mean GAD-7 score (10.4) fell in the moderate anxiety symptom severity range (Spitzer et al., 2006). As was expected, the mean BPAQ score (75.0) was higher and the mean PANAS score (27.2) was lower than that observed in samples of the general adult population (Hawkins, Stewart, Fitzgerald, & Kim, 2011; Suarez & Krishnan, 2006; Watson & Clark, 1994).

Descriptive statistics for each of the three subsamples are also presented in Table 1. Although the participant characteristics were generally similar across the three trials, ANOVAs and chi-square tests revealed some significant differences. Specifically, the BtB-Heart subsample was younger than the eIMPACT and INFLAMED subsamples, likely due to differences in age inclusion criterion (see Appendix A). The eIMPACT subsample was comprised of more women than the BtB-Heart subsample, even though there were no inclusion/exclusion criteria regarding

sex. Concerning traditional CVD risk factors, eIMPACT subsample had a higher diabetes prevalence than the BtB-Heart subsamples, had higher systolic blood pressure than the INFLAMED subsample, had higher antihypertensive medication use than the BtB-Heart and INFLAMED subsamples, and had a higher 10-year Framingham risk score than the BtB-Heart subsample. These differences are likely due to eIMPACT being the only trial with elevated CVD risk as an inclusion criterion. No other differences were detected between subsamples across all remaining variables.

Correlations

Both bivariate and partial correlations revealed depression (SCL-20) was positively related to anxiety (GAD-7; shared variance of 49% [bivariate] and 52% [partial]) and negatively related to positive affect (PANAS-PA; shared variance of 10% [bivariate] and 8% [partial]) but was unrelated to hostility/anger (BPAQ; shared variance of 1% [bivariate] and 3% [partial]) (see Table 2). Bivariate correlations between affective trait measures and FMD revealed no significant relationships. However, a significant and negative partial correlation between hostility/anger (BPAQ) and FMD was detected ($p = 0.02$). All other partial correlations between affective trait measures and FMD were not significant. In addition, both the bivariate and partial correlations between 10-year Framingham risk score and FMD were not significant.

Primary Results

Aim 1 Results

Measurement models were not constructed for Aim 1 hypotheses because they would have been saturated (i.e., the number of estimated parameters would be equivalent to the number of data points), which prevents estimation of fit indices.

To examine which affective traits are associated with endothelial function (Aim 1), four structural models were constructed, one for each affective trait (see Models 1-4 in Figure 3). Each model consisted of one latent variable for the affective trait and one for Endothelial Function. All analyses had a directional path specified from the affective trait to Endothelial Function. In general, all four models showed acceptable fit to the data (see Table 3 for fit indices). The one exception was for the RMSEA score (.07) for Model 4, which fell slightly above the recommended cut-off value (<.06). However, this fit statistic is more likely a function of a small df (2) and low N (138), the combination of which often results in artificially large RMSEA values that falsely indicate a poor model fit (Kenny, Kaniskan, & McCoach, 2015). For this reason, Kenny and colleagues (2015) advised against computing RMSEA for low df models that lack large samples.

As is shown in Figure 3, the paths from Depression, Anxiety, and Positive Affect to Endothelial Function were all not significant ($p = .19, .87, \text{ and } .71$, respectively), and the standardized coefficients were small, ranging from $-.03$ to $.11$. In contrast, the path from Hostility/Anger to Endothelial Function was significant ($p = .04$). The standardized coefficient indicated that every 1-standard deviation (SD) increase in Hostility/Anger was associated with a $.18$ - SD decrease in Endothelial Function.

Aim 2 Results

To evaluate model fit for pairs of affective traits, measurement models were constructed, two sets for each affective trait pair. In the first set, both affective traits were specified as first-order latent variables freed to correlate. As is detailed in Table 3, Models 5.1 (Depression, Anxiety) and 7.1 (Depression, Positive Affect) showed acceptable fit to the data; however, Model 6.1a (Depression, Hostility/Anger) showed poor fit. Modification indices suggested that the error of two pairs of indicators be correlated to improve model fit: SCL-20 Parcel 2 error correlated with BPAQ Parcel 2 error and SCL-20 Parcel 3 error correlated with BPAQ Parcel 3. I correlated these errors in Model 6.1b, which resulted in generally acceptable fit to the data (see Table 3). The one exception was for the RMSEA score (.07) that fell slightly above the recommended cut-off value (<.06), which may be a function of a small df (6) and low N (138) (Kenny et al, 2015).

In the second set of measurement models, a second-order latent variable (Shared Variance), representing overlapping aspects of each affective trait pair (Brown, 2006), was added to Models 5.1, 6.1b, and 7.1 to construct Models 5.2, 6.2, and 7.2. As is shown in Table 3, all of the models with the Shared Variance latent variable showed poor fit to the data. For each poor fitting model, suggested modifications indices were too numerous to be feasibly implemented. Altogether, these results do not support modeling the Shared Variance between each affective trait pair.

Therefore, I proceeded to investigate which unique components of affective traits are associated with endothelial function in depressed adults (Aim 2) by constructing three structural models (see Figures 4, 5, and 6). Of note, these models (Models 8, 9, and 10) build upon the first set of measurement models that achieved acceptable fit (Models 5.1, 6.1b, and 7.1) by adding

Endothelial Function as a latent variable and a directional path from each affective trait to Endothelial Function. All three of these Aim 2 Structural Models showed acceptable fit to the data (see Table 3).

The paths from Depression and Anxiety ($p = .12$ and $.31$; Figure 4) and from Depression and Positive Affect ($p = .21$ and $.92$; Figure 6) to Endothelial Function were all not significant. Similarly, in Figure 5, the path from Depression to Endothelial Function was again not significant ($p = .08$); however, the path from Hostility/Anger to Endothelial Function was significant ($p = .02$). The standardized coefficient indicated that every 1-*SD* increase in Hostility/Anger was associated with a .22-*SD* decrease in Endothelial Function. Importantly, while the standardized coefficient between Positive Affect and Endothelial Function was small (.01; Figure 6), other nonsignificant coefficients were of notable magnitude, including paths between Depression and Endothelial Function (standardized coefficients of .22 and .15; Figures 4 and 5, respectively), and the path between Anxiety and Endothelial Function (standardized coefficients = .14; Figure 4).

Aim 3 Results

To explore Traditional CVD Risk Status as a candidate mediator of the significant path from Hostility/Anger to Endothelial Function, I constructed Model 11 presented in Figure 7. This model added the Traditional CVD Risk Status latent variable and directional paths from Hostility/Anger to this variable and from this variable to Endothelial Function to Model 9. Model 11 showed acceptable fit to the data (see Table 3). As seen in Figure 7, the path from Hostility/Anger to Endothelial Function remained significant ($p = .02$). However, the Hostility/Anger to Traditional CVD Risk Status path ($p = .56$) and Traditional CVD Risk Status to Endothelial Function path ($p = .88$) were both not significant. Not surprisingly, the indirect

effect of Hostility/Anger to Endothelial Function through Traditional CVD Risk Status was also not significant (standardized coefficient for the indirect effect = .00; $p = .89$). Consequently, the relationship between the unique components of hostility/anger and endothelial function were not partially explained by traditional CVD risk status.

DISCUSSION

Summary of Findings and Fit with Prior Literature

The present study sought to examine, among depressed adults, (1) whether depression, anxiety, hostility/anger, and low trait positive affect are associated with endothelial function, (2) whether the shared and unique components of these affective traits are related to endothelial function, and (3) whether traditional CVD risk factor status mediates these affective trait-endothelial function associations. To achieve these aims, three hypotheses were tested.

My first hypothesis that all of the affective traits would be negatively associated with endothelial function was, for the most part, unsupported. The associations of depression, anxiety, and positive affect with endothelial function were all not significant and small in magnitude. One exception to these null results was hostility/anger, which had a significant negative association with endothelial function. This finding is in line with a small but consistent literature indicating that hostility/anger is related to poorer endothelial function in the general population (Cooper et al., 2010; Harris et al, 2003; Lin et al., 2008; Schott et al, 2009). My results extend this relationship to depressed adults.

While this is the first study to examine the relationship between depressive symptom severity and endothelial function in depressed adults, my null result conflicts with the majority of previous literature supporting an inverse association between depression and endothelial function in the general population (Cooper et al., 2011; Wu, Sun, Wang, & Ma, 2018). Consequently, our sample comprised of only depressed adults may account for the lack of relationship between depression and endothelial function. Although utilizing a depressed sample did not restrict the range of depression scores ($M = 1.8$, $SD = 0.8$, observed range: 0.0 to 3.7, possible range: 0.0-

4.0), only a small proportion of my sample had low depression scores (only 4 participants had SCL-20 scores ≤ 0.5 ; Dietrich et al., 2004). This clustering of depression scores away from low values could prevent detection of a relationship previously observed in general population samples. Given the significant correlations of depression with anxiety and positive affect (see Table 2), my depressed sample may have similarly influenced, to a lesser degree, the distributions of these affective traits and their associations with endothelial function. Indeed, I observed few mild anxiety scores (14 participants with GAD-7 scores < 5 ; Spitzer et al., 2006) and a higher mean anxiety score (10.4) than that observed in general population samples (4.9; Spitzer et al., 2006). In addition, the mean PANAS score (27.2) was lower than that observed in samples of the general adult population (36.0; Watson & Clark, 1994).

The null result for anxiety adds to a small and inconsistent literature on the anxiety-endothelial function relationship in generally healthy adults. My finding is consistent with two previous studies not detecting an association (Routledge et al., 2017; Schott et al., 2009), which conflict with three other investigations reporting that anxiety symptom severity is associated with poorer endothelial function (Cooper et al., 2010; Harris et al., 2003; Narita et al., 2007). However, to my knowledge, this is the first study to examine this relationship in depressed adults. Moreover, because previous studies suggest that some types of anxiety disorders (e.g., panic disorder), but not others (e.g., generalized anxiety disorder and social phobia), are related to incident CVD in depressed adults (Gomez-Camirero et al., 2005; Scherrer et al., 2010), it may be that the relationship between anxiety and endothelial function in depressed adults also varies by anxiety type. Given that the aforementioned studies examined the relationship between general anxiety measures and endothelial function, moderation by anxiety type remains a potential explanation for the mixed literature.

Finally, although this is the first study to examine the positive affect-endothelial function relationship in any population, my null result adds to a small mixed literature on the relationship between positive affect and CVD outcomes in general. My finding is consistent with the smaller segment of this literature that did not find positive affect to be associated with coronary artery calcification (Kroenke et al., 2012) and incident CVD (Freak-Poli et al., 2015; Nabi et al., 2008). However, given that the majority of previous studies have found positive affect to be negatively related to CVD outcomes (Boehm et al., 2016; Davidson et al., 2010; Hawkins et al., 2014; Kroenke et al., 2012; Newman et al., 2011; Ostir et al., 2001; Yanek et al., 2013), it is more likely that positive affect is not associated with CVD outcomes in depressed adults in particular, although further research is needed to evaluate this possibility.

My second hypothesis that both the shared and unique components of each affective trait would be negatively related to endothelial function was also generally unsupported. First, I was unable to model the shared variance between each affective trait pair because all models failed to achieve acceptable model fit when the second-order latent variable (Shared Variance) was added to them. This outcome is inconsistent with two previous studies that successfully examined the shared variance between affective traits in relation to CVD outcomes (Boyle et al., 2006; Kubzansky et al., 2006). However, those studies did not evaluate model fit, utilized an exploratory rather than a confirmatory factor analytic approach to create their shared variance variables, examined the shared variance between three and four affective traits rather than two traits, and examined general population samples rather than a depressed sample, all of which may have contributed to the differing modeling outcomes.

When I proceeded to investigate which unique components of affective trait pairs are associated with endothelial function in depressed adults, the pattern of results was identical to

that from the Hypothesis 1 models. Specifically, only the unique components of hostility/anger were associated with endothelial function, and this relationship was in the negative direction. Although a previous study did not detect a relationship between hostility and 3-year progression of carotid intima-media thickness after controlling for depression and anxiety (Stewart et al., 2007), the detected relationship is consistent with most of the previous literature, which has found that hostility/anger is associated with worse clinical CVD outcomes (Boyle et al., 2006; Kubzansky et al., 2006; Newman et al., 2011) and poorer endothelial function (Lin et al., 2008) after including depression as a covariate. Importantly, my results extend these findings to the depressed population. Moreover, the magnitude of the observed unique hostility/anger-endothelial function relationship ($r = -.22$ using the Peterson and Brown [2005] conversion method) is comparable to (a) the magnitude of this relationship detected in the one previous study in the general population (i.e., $r = -.23$ between hostility/anger and endothelial function after accounting for depression and anxiety; Lin et al., 2008) and (b) the magnitude of traditional CVD risk factor-endothelial function relationships detected in previous studies, such as that for cigarette smoking ($r = -0.20$), older age ($r = -0.20$), and overall CVD risk factor status ($r = -0.30$) (Celermajer, Sorensen, Bull, Robinson, & Deanfield, 1994). The latter set of results suggests that the detected hostility/anger-endothelial function relationship may be clinically meaningful.

The Hypothesis 2 null results warrant careful consideration. For instance, the magnitude of the detected relationship between unique hostility/anger and endothelial function (standardized coefficient = $-.22$; $p = .02$) was similar to that of the undetected relationship between unique depression and endothelial function when modeled with anxiety (standardized coefficient = $.22$; $p = .12$) or hostility/anger (standardized coefficient = $.15$; $p = .08$). Moreover, the direction of the unique depression-endothelial function relationship was consistent when

depression was modeled alone (standardized coefficient = .11; $p = .19$) or with positive affect (standardized coefficient = .12; $p = .21$). Surprisingly, this relationship was in the opposite direction of that anticipated, as the unique depression components were related to numerically better endothelial function. This observation conflicts with a large prior literature linking depressive symptom severity to worse CVD outcomes in the general population (Bunker et al., 2003; Cooper et al., 2011; Janssen et al., 2011; Pizzi et al., 2014; Stewart et al., 2012; Stewart et al., 2007; Van der Kooy et al., 2007). Confounding by antidepressant medication use, especially selective serotonin reuptake inhibitors (SSRIs) use, could be driving the depression-endothelial function relationship in the unanticipated direction, as the likelihood of being prescribed an antidepressant increases with depressive symptom severity (Dumesnil et al., 2012; Kendrick et al., 2009) and SSRIs, in particular, may have cardiovascular benefits (Belcher, Drake-Holland, & Noble, 2005; Lekakis et al., 2010).

Regarding the other Hypothesis 2 null results, unique anxiety was numerically, though not significantly, related to endothelial function (standardized coefficient = -.14; $p = .31$). The direction of this nonsignificant relationship is consistent with most of the previous literature, including a meta-analysis (Batelaan et al., 2016) revealing that anxiety increases the risk of incident CVD, even in studies that took depression into account. Unique positive affect did not relate to endothelial function (standardized coefficient = .01; $p = .92$), a result that adds to the mixed prior literature. Specifically, prior studies including depression as a covariate have found that either positive affect predicted future CVD outcomes (Davidson et al., 2010; Newman et al., 2011; Kroenke et al., 2012) or was unrelated to CVD outcomes (Boehm et al., 2016; Hawkins et al., 2014; Kroenke et al., 2012).

My third hypothesis that traditional CVD risk status would partially mediate observed associations in the Aim 2 models was not supported, given that the 10-year Framingham risk score accounted for none of the detected relationship between unique hostility/anger and endothelial function. To my knowledge, this is the first study to examine traditional CVD risk status or risk factors as candidate mediators of affective trait-CVD outcome associations in depressed adults. Nonetheless, my null result is inconsistent with (1) the smaller literature involving depressed adults that supports positive associations between hostility/anger and total cholesterol levels (Fava et al., 1996; Fraguas et al., 2007), smoking (Fraguas et al., 2007), and inflammatory markers (Stewart et al., 2008; Suarez, 2003) and (2) the larger literature that supports inverse relationships between CVD risk factors and endothelial function (Hadi et al., 2005). While it was surprising that we did not detect an inverse relationship between traditional CVD risk status and endothelial function, a meta-regression revealed that the relationship between 10-year Framingham risk score and brachial FMD was evident among adults at low CVD risk (<3% risk) but not among adults at medium or high CVD risk (>3% risk; Witte et al., 2005). Importantly, the current study's sample was mostly comprised of eIMPACT Trial participants, for which elevated CVD risk is an inclusion criterion. As a result, my sample had a mean Framingham risk score in the high CVD risk range, which may explain the lack of relationship between traditional CVD risk status and endothelial function.

How Might Hostility/Anger Increase CVD Risk in Depressed Adults?

My findings suggest that the unique hostility/anger components are associated with poorer endothelial function in depressed adults and that this relationship is not mediated by traditional CVD risk status. Given that hostility/anger has been consistently related to endothelial function (Cooper et al., 2010; Harris et al., 2003; Lin et al., 2008; Schott et al., 2009) and less

consistently related to later clinical CVD outcomes (Chida & Steptoe, 2009), this affective trait may be particularly cardiotoxic during the earlier stages of CVD. Additionally, if the hostility/anger-endothelial function relationship is not mediated by traditional CVD risk factors, then other candidate mechanisms should be examined. Emerging CVD risk factors hold promise for future investigations. In particular, systemic inflammation (a) has been found to drive early atherosclerotic progression, even in the absence of traditional risk factors (Libby, 2012), and (b) is associated with higher levels of hostility in adults with higher depressive symptoms but not in adults with lower depressive symptoms (Stewart et al., 2008; Suarez, 2003). Therefore, systemic inflammation is a candidate mediator of the hostility/anger-endothelial function relationship in depressed adults that should be tested in future studies.

Methodological Limitations

The present study's results (a) may reflect the true state of nature or (b) may be due to methodological issues that interfere with my ability to detect the true state of nature (Kazdin, 2002). While the preceding two sections discuss previous literature to elucidate the likelihood of explanation (a), methodological limitations that could have contributed to and methodological strengths that could have protected against explanation (b) are discussed below.

First, suboptimal study design could explain inconsistencies with prior literature (Kazdin, 2002). Because the present study was a cross-sectional examination of temporal hypotheses, the observed relationship between hostility/anger and endothelial function could be due to confounding, especially by preexisting medical conditions. While this possibility was minimized by excluding participants with clinical CVD, HIV/AIDS, chronic kidney disease, systemic inflammatory disease, or past-year cancer, not all preexisting medical conditions were taken into consideration. Some of these unconsidered medical conditions (e.g., diabetes, arthritis, and

chronic obstructive pulmonary disease) could contribute to both hostility/anger (Harrison, Falvo, Weiss, & Holland, 2017) and worsening cardiovascular health (Candido, Bernardi, & Allen, 2009; Peters et al., 2009; Sin & Man, 2005). Therefore, the potential for confounding prevents me from interpreting my results as indicative of directional or causal relationships.

Second, characteristics of the current sample could have affected measurement of key variables. Importantly, my older adult, higher CVD risk sample may have reduced FMD's validity as a marker of endothelial function. One limitation of FMD is that it estimates endothelial function by presupposing a normal brachial artery structure (Maruhashi et al., 2013). However, blood vessels, including the brachial artery, become progressively stiffer with age and increasing CVD risk factors (Benetos et al., 2002). Increased arterial stiffness, in turn, may compromise the ability of the brachial artery to dilate, even in the presence of a functional endothelium. Consequently, in my sample, FMD may reflect a combination of endothelial function and arterial stiffness. While nitroglycerin-induced vasodilation, an index of endothelium-independent vasodilation, has been used as a control test to rule out this possibility (Corretti et al., 2002), it was not assessed in the present investigation due to safety concerns related to nitroglycerin administration. Therefore, my older adult, higher CVD risk sample may have increased error variance in the endothelial function measure, resulting in underestimation of the magnitude of relationships and an increased likelihood of type II errors.

Third, although my study employed a theory-driven and rigorous analytic approach, there are also some drawbacks. Most notably, when modeling depression and hostility/anger together, LISREL modification indices suggested that the error of two pairs of indicators be correlated to improve model fit. Because I observed some conceptual/grammatical overlap between these pairs when examining questionnaire items, I correlated these errors as suggested. While these

post-hoc modifications enabled the model to achieve acceptable fit, they also inflated the chance of making a type I error (i.e., achieving fit indices that support an incorrect model). Thus, future research is needed to confirm this model and the hostility/anger-endothelial function relationship.

Finally, my study was likely underpowered due to utilizing a sample size smaller than that of past epidemiologic studies examining affective trait-CVD outcome relationships. For example, the two previous studies that examined associations of affective traits' shared variance with CVD outcomes had N 's > 1000 (Boyle et al., 2006; Kubzansky et al., 2006). Limited power likely decreased my ability to detect (a) relationships of interest and (b) well-fitting models. Possibility (a) is especially relevant for unique depression-endothelial function relationships, which appear to be of meaningful magnitude but fell short of significance. However, as previously mentioned, these relationships were in the opposite direction of that anticipated and potentially confounded by SSRI use. Possibility (b) is supported by the wide confidence intervals of the RMSEA estimates (see Table 3), which may reflect imprecision due to low power. A diminished ability to detect well-fitting models is most relevant for my shared variance models, which all failed to achieve acceptable fit. However, all shared variance models had poor fit in at least one index that is less influenced by sample size (i.e., SRMR and/or CFI; Iacobucci, 2010), suggesting that these poor fitting models may reflect true problems with modeling these shared variance constructs in depressed adults.

Recommendations for Future Research

Future research examining relationships between affective traits and CVD outcomes in depressed adults should: (1) use a prospective design to determine directionality of any observed relationships; (2) utilize a larger sample to ensure adequate power; (3) administer validated measures of multiple affective traits; (4) assess multiple CVD outcomes, such as subclinical

atherosclerosis and clinical events, to evaluate whether relationships change across the stages of atherosclerosis; (5) exclude or adjust for all important potential confounders, especially prevalent medical conditions and SSRI use, to rule out confounding as an explanation of any observed relationships; (6) test candidate mechanisms, including systemic inflammation, that may underlie detected relationships; and (7) ensure good variability in age and traditional CVD risk status to allow for examination of moderation by these factors.

Several other recommendations pertain to modeling the shared and unique variance between affective traits in depressed adults. I recommend employing a theory-driven approach, such as SEM with confirmatory factor analysis, rather than exploratory approaches to maximize generalizability of the results beyond the sample. I also recommend investigating the unique and shared variance of various affective trait combinations (e.g., two versus three affective traits) in depressed adults to determine if a shared variance construct emerges only when a sufficient number of traits are examined. Finally, a strategy feasible with larger samples would be to randomly split that data and estimate models twice (Pohlmann, 2004) in order to provide validation for any suggested modification indices and reduce the likelihood of overfitting a model to the sample.

Conclusions

In this cross-sectional study, I found that hostility/anger (all components) and the unique hostility/anger components (those that do not overlap with depression) are both associated with poorer endothelial function in depressed older adults with elevated CVD risk. However, all of the other affective traits – i.e., depression, anxiety, positive affect, unique depression, unique anxiety, and unique positive affect – were not related to endothelial function. Finally, traditional CVD risk status did not mediate the observed relationship between unique hostility/anger and

endothelial function. Because this is the first study to simultaneously examine unique and all variance components of these affective traits in relation to CVD outcomes in depressed adults, future research is needed to replicate and extend my findings.

If my results are supported by future findings, it would suggest that depressed adults with hostility/anger (a) may be a subgroup of the depressed population at greater risk of developing CVD and (b) may be in need of earlier, more intense, and/or different CVD primary prevention efforts. Regarding the latter, hostility/anger interventions have not typically been the focus of treatment for depressed adults but may be beneficial for reducing CVD risk in this group. Some evidence suggests that depressed adults with higher hostility/anger may be difficult to treat, as this group has been found to have greater depression severity and lower depression treatment response rates than depressed adults with low hostility/anger (Fisher et al., 2015). Nonetheless, initial research suggests that SSRIs are effective in reducing hostility/anger in those with (Fava et al., 1993) and without depression (Kamarck et al., 2009). Importantly, the latter study observed a specific treatment effect for the affective but not the behavioral or cognitive components of hostility/anger (Kamarck et al., 2009). Given the prior literature suggesting that depression is related more to attitudinal than motoric hostility/anger (Moreno, Fuhrman, & Selby, 1993), this specific treatment effect may indicate that SSRIs more effectively target the hostility/anger components shared with depression and that components not shared with depression may require additional forms of treatment. Of relevance to this idea, a pilot study reported benefit from adding an anticonvulsant to antidepressant medication for unipolar depressed patients presenting with prominent symptoms of anger, irritability, and hostility (Pasquini et al., 2007). However, additional research is needed to more definitively test this approach and, more generally, to determine how treatment should be optimized for adults with both depression and hostility/anger.

Importantly, treating hostility/anger may concurrently reduce CVD risk. For example, treating adults with hostility/anger with an SSRI appears to improve metabolic risk factors for CVD, such as waist circumference, fasting glucose, high-density lipoprotein cholesterol, and diastolic blood pressure (Kamarck et al., 2011). Despite the potential benefits of SSRI's for depressed adults with hostility/anger, medication is a rare treatment choice for adults presenting with anger in medical settings (Ewigman, 2014). Therefore, if my results are supported by future studies, providers may benefit from screening for hostility/anger in depressed adults and leveraging available treatment options to address their patients' negative affectivity and possibly reduce their patients' CVD risk.

In sum, the present findings advance understanding regarding whether there are subgroups of depressed adults at greatest CVD risk who may be driving the overall depression-CVD relationship and may be in need of earlier, more intense, and/or different CVD primary prevention efforts.

REFERENCES

- American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders (DSM-5®)*. American Psychiatric Pub.
- Barefoot, J. C, Dahlstrom, W G., & Williams, R. B. (1983). Hostility, CHD incidence, and total mortality: A 25-year follow-up study of 255 physicians. *Psychosomatic Medicine*, 45, 59-63.
- Batelaan, N. M., Seldenrijk, A., Bot, M., van Balkom, A. J., & Penninx, B. W. (2016). Anxiety and new onset of cardiovascular disease: critical review and meta-analysis. *The British Journal of Psychiatry*, 208(3), 223-231.
- Barlow, D. H. (2004). *Anxiety and its disorders: The nature and treatment of anxiety and panic*. Guilford press.
- Benetos, A., Waeber, B., Izzo, J., Mitchell, G., Resnick, L., Asmar, R., & Safar, M. (2002). Influence of age, risk factors, and cardiovascular and renal disease on arterial stiffness: clinical applications. *American Journal of Hypertension*, 15(12), 1101-1108. restricted the range of key variables of interest.
- Berecki-Gisolf, J., McKenzie, S. J., Dobson, A. J., McFarlane, A., & McLaughlin, D. (2013). A history of comorbid depression and anxiety predicts new onset of heart disease. *Journal of Behavioral Medicine*, 36(4), 347–53. doi:10.1007/s10865-012-9428-y
- Bisoendial, R. J., Hovingh, G. K., de Groot, E., Kastelein, J. J., Lansberg, P. J., & Stroes, E. S. (2002). Measurement of subclinical atherosclerosis: beyond risk factor assessment. *Current Opinion in Lipidology*, 13(6), 595-603.
- Belcher, P. R., Drake-Holland, A. J., & Noble, M. I. (2005). Serotonin reuptake inhibitors and cardiovascular disease. *Vascular Disease Prevention*, 2(1), 67-76.

- Boehm, J. K., Chen, Y., Williams, D. R., Ryff, C. D., & Kubzansky, L. D. (2016). Subjective well-being and cardiometabolic health: An 8–11 year study of midlife adults. *Journal of Psychosomatic Research, 85*, 1-8.
- Boyle, S. H., Michalek, J. E., & Suarez, E. C. (2006). Covariation of psychological attributes and incident coronary heart disease in US Air Force veterans of the Vietnam war. *Psychosomatic Medicine, 68*(6), 844-850.
- Brown, T. A. (2006). *Confirmatory factor analysis for applied research*. Guilford Publications.
- Brown, T. A. (2007). Temporal course and structural relationships among dimensions of temperament and DSM-IV anxiety and mood disorder constructs. *Journal of Abnormal Psychology, 116*(2), 313.
- Brown, T. A., Chorpita, B. F., & Barlow, D. H. (1998). Structural relationships among dimensions of the DSM-IV anxiety and mood disorders and dimensions of negative affect, positive affect, and autonomic arousal. *Journal of Abnormal Psychology, 107*(2), 179.
- Brown, J. M., Stewart, J. C., Stump, T. E., & Callahan, C. M. (2011). Risk of coronary heart disease events over 15 years among older adults with depressive symptoms. *The American Journal of Geriatric Psychiatry, 19*(8), 721-729.
- Bunker, S. J., Colquhoun, D. M., Esler, M. D., Hickie, I. B., Hunt, D., Jelinek, V. M., ... & Tonkin, A. M. (2003). " Stress" and coronary heart disease: psychosocial risk factors. *The Medical Journal of Australia, 178*(6), 272-276.
- Buss, A. H., & Perry, M. (1992). The aggression questionnaire. *Journal of Personality and Social Psychology, 63*(3), 452.

- Callahan, C. M., Unverzagt, F. W., Hui, S. L., Perkins, A. J., & Hendrie, H. C. (2002). Six-item screener to identify cognitive impairment among potential subjects for clinical research. *Medical Care, 40*(9), 771-781.
- Camous, X., Pera, A., Solana, R., & Larbi, A. (2012). NK cells in healthy aging and age-associated diseases. *BioMed Research International, 2012*.
- Candido, R., Bernardi, S., & Allen, T. J. (2009). Linking diabetes and atherosclerosis. *Expert Review of Endocrinology & Metabolism, 4*(6), 603-624.
- Carroll, D., Phillips, A. C., Gale, C. R., & Batty, G. D. (2010). Generalized anxiety and major depressive disorders, their comorbidity and hypertension in middle-aged men. *Psychosomatic Medicine, 72*(1), 16-19.
- Case, S. M., Sawhney, M., & Stewart, J. C. (2018). Atypical depression and double depression predict new-onset cardiovascular disease in US adults. *Depression and Anxiety, 35*(1), 10-17.
- Cassidello-Robbins, C., & Barlow, D. H. (2016). *Anger: The unrecognized emotion in emotional disorders*. Clinical Psychology: Science and Practice.
- Celermajer, D. S., Sorensen, K. E., Bull, C., Robinson, J., & Deanfield, J. E. (1994). Endothelium-dependent dilation in the systemic arteries of asymptomatic subjects relates to coronary risk factors and their interaction. *Journal of the American College of Cardiology, 24*(6), 1468-1474.
- Celermajer, D. S., Sorensen, K. E., Gooch, V. M., Sullivan, I. D., Lloyd, J. K., Deanfield, J. E., & Spiegelhalter, D. J. (1992). Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. *The Lancet, 340*(8828), 1111-1115.

- Chida, Y., & Steptoe, A. (2009). The association of anger and hostility with future coronary heart disease: a meta-analytic review of prospective evidence. *Journal of the American College of Cardiology*, 53(11), 936-946.
- Chida, Y., & Steptoe, A. (2010). Greater cardiovascular responses to laboratory mental stress are associated with poor subsequent cardiovascular risk status a meta-analysis of prospective evidence. *Hypertension*, 55(4), 1026-1032.
- Cicek, Y., Durakoglugil, M. E., Kocaman, S. A., Guveli, H., Cetin, M., Erdogan, T., ... & Canga, A. (2012). Increased pulse wave velocity in patients with panic disorder: independent vascular influence of panic disorder on arterial stiffness. *Journal of Psychosomatic Research*, 73(2), 145-148.
- Clark, L. A., & Watson, D. (1991). Tripartite model of anxiety and depression: psychometric evidence and taxonomic implications. *Journal of Abnormal Psychology*, 100(3), 316.
- Cohen, B.E., Edmondson, D., & Kronish, I.M. (2015). State of the Art Review: Depression, Stress, Anxiety, and Cardiovascular Disease. *American Journal of Hypertension*, 28(11), 1295-1302.
- Cooper, D. C., Milic, M. S., Tafur, J. R., Mills, P. J., Bardwell, W. A., Ziegler, M. G., & Dimsdale, J. E. (2010). Adverse impact of mood on flow-mediated dilation. *Psychosomatic Medicine*, 72(2), 122.
- Cooper, D. C., Tomfohr, L. M., Milic, M. S., Natarajan, L., Bardwell, W. A., Ziegler, M. G., & Dimsdale, J. E. (2011). Depressed mood and flow-mediated dilation: a systematic review and meta-analysis. *Psychosomatic Medicine*, 73(5), 360.

- Corretti, M. C., Anderson, T. J., Benjamin, E. J., Celermajer, D., Charbonneau, F., Creager, M. A., ... & Vallance, P. (2002). Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force. *Journal of the American College of Cardiology*, *39*(2), 257-265
- Craig, C.L., Marshall, A.L., & Sjostrom, M., et al. (2003). International physical activity questionnaire: 12-country reliability and validity. *Medicine & Science in Sports & Exercise*, *35*(8), 1381-1395.
- Crawford, J. R., & Henry, J. D. (2004). The Positive and Negative Affect Schedule (PANAS): Construct validity, measurement properties and normative data in a large non-clinical sample. *British Journal of Clinical Psychology*, *43*(3), 245-265.
- D'Agostino, R. B., Vasan, R. S., Pencina, M. J., Wolf, P. A., Cobain, M., Massaro, J. M., & Kannel, W. B. (2008). General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation*, *117*(6), 743-753.
- Davidson, K. W., Mostofsky, E., & Whang, W. (2010). Don't worry, be happy: positive affect and reduced 10-year incident coronary heart disease: The Canadian Nova Scotia Health Survey. *European Heart Journal*, ehp603.
- Davidson, K. W., Rieckmann, N., & Rapp, M. A. (2005). Definitions and distinctions among depressive syndromes and symptoms: implications for a better understanding of the depression–cardiovascular disease association. *Psychosomatic medicine*, *67*, S6-S9.
- Davignon, J., & Ganz, P. (2004). Role of endothelial dysfunction in atherosclerosis. *Circulation*, *109*(23 suppl 1), III-27 – III-32.

- Deanfield, J. E., Halcox, J. P., & Rabelink, T. J. (2007). Endothelial function and dysfunction testing and clinical relevance. *Circulation, 115*(10), 1285-1295.
- Derogatis, L.R., Lipman, R.S., & Covi, L. (1973). SCL-90: An outpatient psychiatric rating scale--preliminary report. *Psychopharmacol. Bull, 9*(1), 13-28.
- Derogatis, L. R., Lipman, R. S., Rickels, K., Uhlenhuth, E. H., & Covi, L. (1974). The Hopkins Symptom Checklist (HSCL): A self-report symptom inventory. *Behavioral Science, 19*(1), 1-15.
- Diener, E., & Emmons. R.A. (1984). The independence of positive and negative affect. *J Pers Soc Psychol, 47*, 1105–1117.
- Dietrich, A. J., Oxman, T. E., Williams, J. W., Schulberg, H. C., Bruce, M. L., Lee, P. W., ... & Rost, K. (2004). Re-engineering systems for the treatment of depression in primary care: cluster randomised controlled trial. *Bmj, 329*(7466), 602.
- Dinning, W. D., & Evans, R. G. (1977). Discriminant and convergent validity of the SCL-90 in psychiatric inpatients. *Journal of Personality Assessment, 41*(3), 304-310.
- Dumesnil, H., Cortaredona, S., Verdoux, H., Sebbah, R., Paraponaris, A., & Verger, P. (2012). General practitioners' choices and their determinants when starting treatment for major depression: a cross sectional, randomized case-vignette survey. *PLoS One, 7*(12), e52429.
- Enderle, M. D., Schroeder, S., Ossen, R., Meisner, C., Baumbach, A., Haering, H. U., ... & Pfohl, M. (1998). Comparison of peripheral endothelial dysfunction and intimal media thickness in patients with suspected coronary artery disease. *Heart, 80*(4), 349-354.
- Ewigman, N. L. (2014). *The diagnosis and treatment of anger in outpatient medical settings* (Doctoral dissertation, University of Florida).

- Fava, M., Abraham, M., Pava, J., Shuster, J., & Rosenbaum, J. (1996). Cardiovascular risk factors in depression: the role of anxiety and anger. *Psychosomatics*, 37(1), 31-37.
- Fava, M., Rosenbaum, J. F., Pava, J. A., McCarthy, M. K., Steingard, R. J., & Bouffides, E. (1993). Anger attacks in unipolar depression, Part 1: Clinical correlates and response to fluoxetine treatment. *American Journal of Psychiatry*, 150, 1158-1158.
- Fisher, L. B., Fava, M., Doros, G. D., Alpert, J. E., Henry, M., Huz, I., & Freeman, M. P. (2015). The role of anger/hostility in treatment-resistant depression: A secondary analysis from the ADAPT-A study. *The Journal of Nervous and Mental Disease*, 203(10), 762-768.
- Fraguas, R., Iosifescu, D. V., Bankier, B., Perlis, R., Clementi-Craven, N., Alpert, J., & Fava, M. (2007). Major depressive disorder with anger attacks and cardiovascular risk factors. *The International Journal of Psychiatry in Medicine*, 37(1), 99-111.
- Freak-Poli, R., Mirza, S. S., Franco, O. H., Ikram, M. A., Hofman, A., & Tiemeier, H. (2015). Positive affect is not associated with incidence of cardiovascular disease: A population-based study of older persons. *Preventive Medicine*, 74, 14-20.
- Fredrickson, B. L. (2001). The role of positive emotions in positive psychology: The broaden-and-build theory of positive emotions. *American Psychologist*, 56(3), 218.
- Fredrickson, B., & Levenson, R. W. (1998). Positive emotions speed recovery from the cardiovascular sequelae of negative emotions. *Cognition & Emotion*, 12(2), 191-220.
- Frick, M., & Weidinger, F. (2007). Endothelial function: a surrogate endpoint in cardiovascular studies? *Current Pharmaceutical Design*, 13(17), 1741-1750.
- Fried, E. I., & Nesse, R. M. (2015). Depression is not a consistent syndrome: an investigation of unique symptom patterns in the STAR* D study. *Journal of Affective Disorders*, 172, 96-102.

- Garfield, L. D., Scherrer, J. F., Hauptman, P. J., Freedland, K. E., Chrusciel, T., Balasubramanian, S., Carney, R. M., et al. (2014). Association of anxiety disorders and depression with incident heart failure. *Psychosomatic Medicine*, *76*(2), 128–36.
doi:10.1097/PSY.0000000000000027
- Greenland, P., Alpert, J. S., Beller, G. A., Benjamin, E. J., Budoff, M. J., Fayad, Z. A., et al. (2010). 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*, *122*(25), e584-e636.
- Grenon, S. M., Owens, C. D., Alley, H., Perez, S., Whooley, M. A., Neylan, T. C., ... & Cohen, B. E. (2016). Posttraumatic Stress Disorder Is Associated With Worse Endothelial Function Among Veterans. *Journal of the American Heart Association*, *5*(3), e003010.
- Gomez-Camirero, A., Blumentals, W. A., Russo, L. J., Brown, R. R., & Castilla-Puentes, R. (2005). Does panic disorder increase the risk of coronary heart disease? A cohort study of a national managed care database. *Psychosomatic Medicine*, *67*(5), 688-691.
- Hadi, H. A., Carr, C. S., & Suwaidi, J. A. (2005). Endothelial dysfunction: cardiovascular risk factors, therapy, and outcome. *Vascular Health and Risk Management*, *1*(3), 183.
- Harris, K. F., Matthews, K. A., Sutton-Tyrrell, K., & Kuller, L. H. (2003). Associations between psychological traits and endothelial function in postmenopausal women. *Psychosomatic Medicine*, *65*, 402–409.
- Harrison, C., Falvo, D., Weiss, V., & Holland, B. E. (2017). *Medical and psychosocial aspects of chronic illness and disability*. Jones & Bartlett Learning.

- Hawkins, M. A., Callahan, C. M., Stump, T. E., & Stewart, J. C. (2014). Depressive Symptom Clusters as Predictors of Incident Coronary Artery Disease Events: A 15-Year Prospective Study of Older Adults. *Psychosomatic Medicine*, *76*(1), 38.
- Hawkins, M. A., Stewart, J. C., Fitzgerald, G. J., & Kim, S. (2011). Combined effect of depressive symptoms and hostility on autonomic nervous system function. *International Journal of Psychophysiology*, *81*(3), 317-323.
- Hayduk, L. A., & Littvay, L. (2012). Should researchers use single indicators, best indicators, or multiple indicators in structural equation models?. *BMC Medical Research Methodology*, *12*(1), 159.
- Headey, B., Kelley, J., & Wearing, A. (1993). Dimensions of mental health: life satisfaction, positive affect, anxiety and depression. *Social Indicators Research*, *29*(1), 63-82.
- Heidenreich, P. A, Trogon, J. G., Khavjou, O. A, Butler, J., Dracup, K., Ezekowitz, M. D., Finkelstein, E. A., et al. (2011). Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. *Circulation*, *123*(8), 933–44. doi:10.1161/CIR.0b013e31820a55f5
- Helson, R., & Klohnen, E. C. (1998). Affective coloring of personality from young adulthood to midlife. *Personality and Social Psychology Bulletin*, *24*(3), 241-252.
- Hu, L., & Bentler, P. M. (1999). Cutoff criteria for fit indexes in covariance structure analysis: Conventional criteria versus new alternatives. *Structural Equation Modeling*, *6*, 1–55.
- Iacobucci, D. (2010). Structural equations modeling: Fit indices, sample size, and advanced topics. *Journal of Consumer Psychology*, *20*(1), 90-98.

- Janssen, I., Powell, L. H., Matthews, K. A., Cursio, J. F., Hollenberg, S. M., Sutton-Tyrrell, K., ... & Everson-Rose, S. A. (2011). Depressive symptoms are related to progression of coronary calcium in midlife women: The Study of Women's Health Across the Nation (SWAN) Heart Study. *American Heart Journal*, *161*(6), 1186-1191.
- Jöreskog, K. G., & Sörbom, D. (2008). *LISREL for Windows [Computer software]*. Lincolnwood, IL: Scientific Software International.
- Jöreskog, K. G., & Sorbom, D. (2008). *LISREL (version 8.8)*. Chicago, IL: Scientific Software International.
- Judd, L. L., Schettler, P. J., Coryell, W., Akiskal, H. S., & Fiedorowicz, J. G. (2013). Overt irritability/anger in unipolar major depressive episodes: past and current characteristics and implications for long-term course. *JAMA Psychiatry*, *70*(11), 1171-1180.
- Julkunen, J., Salonen, R., Kaplan, G. A., Chesney, M. A., & Salonen, J. T. (1994). Hostility and the progression of carotid atherosclerosis. *Psychosomatic Medicine*, *56*, 519–525.
- Juonala, M., Viikari, J. S., Laitinen, T., Marniemi, J., Helenius, H., Rönnemaa, T., & Raitakari, O. T. (2004). Interrelations between brachial endothelial function and carotid intima-media thickness in young adults the cardiovascular risk in young finns study. *Circulation*, *110*(18), 2918-2923.
- Kamarck, T. W., Haskett, R. F., Muldoon, M., Flory, J. D., Anderson, B., Bies, R., ... & Manuck, S. B. (2009). Citalopram intervention for hostility: results of a randomized clinical trial. *Journal of Consulting and Clinical Psychology*, *77*(1), 174.

- Kamarck, T. W., Muldoon, M. F., Manuck, S. B., Haskett, R. F., Cheong, J., Flory, J. D., & Vella, E. (2011). Citalopram improves metabolic risk factors among high hostile adults: results of a placebo-controlled intervention. *Psychoneuroendocrinology*, *36*(7), 1070-1079.
- Katon, W., Robinson, P., Von Korff, M., Lin, E., Bush, T., Ludman, E., ... & Walker, E. (1996). A multifaceted intervention to improve treatment of depression in primary care. *Archives of General Psychiatry*, *53*(10), 924-932.
- Kazdin, A. E. (2002). *Research Design in Clinical Psychology*. Needham Heights, MA: Allyn and Bacon Publishing.
- Kendrick, T., Dowrick, C., McBride, A., Howe, A., Clarke, P., Maisey, S., ... & Smith, P. W. (2009). Management of depression in UK general practice in relation to scores on depression severity questionnaires: analysis of medical record data. *Bmj*, *338*, b750.
- Khazanov, G. K., & Ruscio, A. M. (2016). Is Low Positive Emotionality a Specific Risk Factor for Depression? A Meta-Analysis of Longitudinal Studies. *Psychological Bulletin*, *142*(9), 991-1015.
- Keller, M. B. & Shapiro, R. W. (1982). "Double depression": superimposition of acute depressive episodes on chronic depressive disorders. *American Journal of Psychiatry* *139*, 438-42.
- Kemp, A. H., Quintana, D. S., Felmingham, K. L., Matthews, S., & Jelinek, H. F. (2012). Depression, comorbid anxiety disorders, and heart rate variability in physically healthy, unmedicated patients: implications for cardiovascular risk. *PloS One*, *7*(2), e30777.
- Kenny, D. A., Kaniskan, B., & McCoach, D. B. (2015). The performance of RMSEA in models with small degrees of freedom. *Sociological Methods & Research*, *44*(3), 486-507.

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Merikangas, K. R., & Walters, E. E. (2005).

Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry*, 62(6), 593-602.

Kline, R. B. (2005). *Principles and practice of structural equation modeling*. New York: The Guilford Press.

Kroenke, C. H., Seeman, T., Matthews, K., Adler, N., & Epel, E. (2012). Mood patterns based on momentary assessment of positive and negative moods over a day and coronary artery calcification in the CARDIA study. *Psychosomatic Medicine*, 74(5), 526-534.

Kroenke K, Spitzer RL. The PHQ-9: A new depression diagnostic and severity measure. *Psychiatric Annals*. 2002;32(9):509-515.

Kroenke, K., Spitzer, R. L., & Williams, J. B. (2001). The PHQ-9. *Journal of General Internal Medicine*, 16(9), 606-613.

Krueger, R. F., McGue, M., & Iacono, W. G. (2001). The higher-order structure of common DSM mental disorders: Internalization, externalization, and their connections to personality. *Personality and Individual Differences*, 30, 1245–1259.
[http://dx.doi.org/10.1016/S0191-8869\(00\)00106-9](http://dx.doi.org/10.1016/S0191-8869(00)00106-9)

Kubzansky, L. D., Cole, S. R., Kawachi, I., Vokonas, P., & Sparrow, D. (2006). Shared and unique contributions of anger, anxiety, and depression to coronary heart disease: a prospective study in the normative aging study. *Annals of Behavioral Medicine*, 31(1), 21-29.

- Lamers, F., van Oppen, P., Comijs, H. C., Smit, J. H., Spinhoven, P., Van Balkom, A. J., ... & Penninx, B. W. (2011). Comorbidity patterns of anxiety and depressive disorders in a large cohort study: The Netherlands Study of Depression and Anxiety (NESDA). *The Journal of Clinical Psychiatry*, 72(3), 341-348.
- Lekakis, J., Ikonomidis, I., Papoutsis, Z., Moutsatsou, P., Nikolaou, M., Parissis, J., & Kremastinos, D. T. (2010). Selective serotonin re-uptake inhibitors decrease the cytokine-induced endothelial adhesion molecule expression, the endothelial adhesiveness to monocytes and the circulating levels of vascular adhesion molecules. *International Journal of Cardiology*, 139(2), 150-158.
- Lewis, T. T., Sutton-Tyrrell, K., Penninx, B. W., Vogelzangs, N., Harris, T. B., Vaidean, G. D., ... & Newman, A. B. (2010). Race, psychosocial factors, and aortic pulse wave velocity: the Health, Aging, and Body Composition Study. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, 65(10), 1079-1085.
- Libby, P. (2004). The Vascular Biology of Atherosclerosis. In D. P. Zipes, P. Libby, R. Bonow, & Braunwald, E. (Eds.), *Braunwald's Heart Disease: A Textbook of Cardiovascular Disease* (7th ed., pp. 921-938). Philadelphia, PA: WB Saunder.
- Libby, P. (2012). Inflammation in atherosclerosis. *Arteriosclerosis, Thrombosis, and Vascular Biology*, 32(9), 2045-2051.
- Lin, T. K., Weng, C. Y., Wang, W. C., Chen, C. C., Lin, I. M., & Lin, C. L. (2008). Hostility trait and vascular dilatory functions in healthy Taiwanese. *Journal of Behavioral Medicine*, 31(6), 517-524.

- Little, T. D., Cunningham, W. A., Shahar, G., & Widaman, K. F. (2002). To parcel or not to parcel: Exploring the question, weighing the merits. *Structural Equation Modeling, 9*, 151–173.
- Low, C. A., Matthews, K. A., Kuller, L. H., & Edmundowicz, D. (2011). Psychosocial predictors of coronary artery calcification progression in postmenopausal women. *Psychosomatic Medicine, 73*(9), 789.
- Maruhashi, T., Soga, J., Fujimura, N., Idei, N., Mikami, S., Iwamoto, Y., ... & Chayama, K. (2013). Nitroglycerine-Induced Vasodilation for Assessment of Vascular Function Significance: A Comparison With Flow-Mediated Vasodilation. *Arteriosclerosis, Thrombosis, and Vascular Biology, 33*(6), 1401-1408.
- Matsunaga, M. (2008). Item parceling in structural equation modeling: A primer. *Communication Methods and Measures, 2*(4), 260-293.
- Matthews, K. A. (2005). Psychological perspectives on the development of coronary heart disease. *American Psychologist, 60*(8), 783.
- Matthews, K. A., Chang, Y. F., Sutton-Tyrrell, K., Edmundowicz, D., & Bromberger, J. T. (2010). Recurrent major depression predicts progression of coronary calcification in healthy women: Study of Women's Health Across the Nation. *Psychosomatic Medicine, 72*(8), 742.
- Mayfield, D., McLeod, G., & Hall, P. (1974). The CAGE questionnaire: validation of a new alcoholism screening instrument. *American Journal of Psychiatry, 131*(10), 1121-1123.
- Mineka, S., Watson, D., Clark, L. A. (1998). Comorbidity of anxiety and unipolar mood disorders. *Annual Review of Psychology, 49*, 377–412.

- Mook, J., Van Der Ploeg, H. M., & Chr. Kleijn, W. (1990). Anxiety, anger and depression: Relationships at the trait level. *Anxiety Research*, 3(1), 17-31.
- Moreno, J. K., Fuhrman, A., & Selby, M. J. (1993). Measurement of hostility, anger, and depression in depressed and nondepressed subjects. *Journal of Personality Assessment*, 61(3), 511-523.
- Mozaffarian, D., Benjamin, E. J., Go, A. S., Arnett, D. K., Blaha, M. J., Cushman, M., ... & Huffman, M. D. (2015). Heart disease and stroke statistics-2015 update: a report from the American Heart Association. *Circulation*, 131(4), e29.
- Nabi, H., Kivimaki, M., De Vogli, R., Marmot, M. G., & Singh-Manoux, A. (2008). Positive and negative affect and risk of coronary heart disease: Whitehall II prospective cohort study. *BMJ*, 337, a118.
- Narita, K., Murata, T., Hamada, T., Takahashi, T., Omori, M., Suganuma, N., ... & Wada, Y. (2007). Interactions among higher trait anxiety, sympathetic activity, and endothelial function in the elderly. *Journal of Psychiatric Research*, 41(5), 418-427.
- Nelson, D. E., Holtzman, D., Bolen, J., Stanwyck, C. A., & Mack, K. A. (2000). Reliability and validity of measures from the Behavioral Risk Factor Surveillance System (BRFSS). *Sozial-und Praventivmedizin*, 46, S3-42.
- Neunteufl, T., Katzenschlager, R., Hassan, A., Klaar, U., Schwarzacher, S., Glogar, D., ... & Weidinger, F. (1997). Systemic endothelial dysfunction is related to the extent and severity of coronary artery disease. *Atherosclerosis*, 129(1), 111-118.

- Newman, J. D., Davidson, K. W., Shaffer, J. A., Schwartz, J. E., Chaplin, W., Kirkland, S., & Shimbo, D. (2011). Observed hostility and the risk of incident ischemic heart disease: a prospective population study from the 1995 Canadian Nova Scotia Health Survey. *Journal of the American College of Cardiology*, *58*(12), 1222-1228.
- Newman, J. L., Fuqua, D. R., Gray, E. A., & Simpson, D. B. (2006). Gender differences in the relationship of anger and depression in a clinical sample. *Journal of Counseling and Development: JCD*, *84*(2), 157.
- Nomura, K., Nakao, M., Karita, K., Nishikitani, M., & Yano, E. (2005). Association between work-related psychological stress and arterial stiffness measured by brachial-ankle pulse-wave velocity in young Japanese males from an information service company. *Scandinavian Journal of Work, Environment & Health*, 352-359.
- Ostir, G. V., Markides, K. S., Peek, M. K., & Goodwin, J. S. (2001). The association between emotional well-being and the incidence of stroke in older adults. *Psychosomatic Medicine*, *63*(2), 210-215.
- Pasquini, M., Picardi, A., Speca, A., Orlandi, V., Tarsitani, L., Morosini, P., ... & Biondi, M. (2007). Combining an SSRI with an anticonvulsant in depressed patients with dysphoric mood: an open study. *Clinical Practice and Epidemiology in Mental Health*, *3*(1), 3.
- Paterniti, S., Zureik, M., Ducimetière, P., Touboul, P. J., Fève, J. M., & Alperovitch, A. (2001). Sustained anxiety and 4-year progression of carotid atherosclerosis. *Arteriosclerosis, Thrombosis, and Vascular Biology*, *21*(1), 136-141.
- Pelizza, L., & Ferrari, A. (2009). Anhedonia in schizophrenia and major depression: state or trait? *Annals of General Psychiatry*, *8*, 22.

- Perticone, F., Ceravolo, R., Pujia, A., Ventura, G., Iacopino, S., Scozzafava, A., ... & Schillaci, G. (2001). Prognostic significance of endothelial dysfunction in hypertensive patients. *Circulation, 104*(2), 191-196.
- Peters, M. J., Van Halm, V. P., Voskuyl, A. E., Smulders, Y. M., Boers, M., Lems, W. F., ... & Heine, R. (2009). Does rheumatoid arthritis equal diabetes mellitus as an independent risk factor for cardiovascular disease? A prospective study. *Arthritis Care & Research, 61*(11), 1571-1579.
- Peterson, R. A., & Brown, S. P. (2005). On the use of beta coefficients in meta-analysis. *Journal of Applied Psychology, 90*(1), 175.
- Phillips, A. C., Batty, G. D., Gale, C. R., Deary, I. J., Osborn, D., MacIntyre, K., & Carroll, D. (2009). Generalized anxiety disorder, major depressive disorder, and their comorbidity as predictors of all-cause and cardiovascular mortality: the Vietnam experience study. *Psychosomatic Medicine, 71*(4), 395–403. doi:10.1097/PSY.0b013e31819e6706
- Pizzi, C., Costa, G. M., Santarella, L., Flacco, M. E., Capasso, L., Bert, F., & Manzoli, L. (2014). Depression symptoms and the progression of carotid intima–media thickness: A 5-year follow-up study. *Atherosclerosis, 233*(2), 530-536.
- Pohlmann, J. T. (2004). Use and interpretation of factor analysis in The Journal of Educational Research: 1992-2002. *The Journal of Educational Research, 98*(1), 14-23.
- Pratt, L. A., & Brody, D. J. (2008). Depression in the United States Household Population, 2005-2006. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention.
- Pressman, S. D., & Cohen, S. (2005). Does positive affect influence health? *Psychological Bulletin, 131*(6), 925.

- Quitkin, F. M. (2002). Depression With Atypical Features: Diagnostic Validity, Prevalence, and Treatment. *Prim Care Companion J Clin Psychiatry*, 4, 94-99.
- Räikkönen, K., Matthews, K. A., Sutton-Tyrrell, K., & Kuller, L. H. (2004). Trait anger and the metabolic syndrome predict progression of carotid atherosclerosis in healthy middle-aged women. *Psychosomatic Medicine*, 66(6), 903-908.
- Routledge, F. S., Dunbar, S. B., Higgins, M., Rogers, A. E., Feeley, C., Ioachimescu, O., ... & Quyyumi, A. (2017). Insomnia Symptoms Are Associated With Abnormal Endothelial Function. *The Journal of Cardiovascular Nursing*, 32(1), 78-85.
- Rosengren, A., Hawken, S., Ôunpuu, S., Sliwa, K., Zubaid, M., Almahmeed, W. A., ... & INTERHEART investigators. (2004). Association of psychosocial risk factors with risk of acute myocardial infarction in 11 119 cases and 13 648 controls from 52 countries (the INTERHEART study): case-control study. *The Lancet*, 364(9438), 953-962.
- Rossi, R., Nuzzo, A., Origliani, G., & Modena, M. G. (2008). Prognostic role of flow-mediated dilation and cardiac risk factors in post-menopausal women. *Journal of the American College of Cardiology*, 51(10), 997-1002.
- Rugulies, R. (2002). Depression as a predictor for coronary heart disease: a review and meta-analysis. The full text of this article is available via AJPM Online at www.ajpm-online.net. *American Journal of Preventive Medicine*, 23(1), 51-61.
- Santos, I. S., Alencar, A. P., Rundek, T., Goulart, A. C., Barreto, S. M., Pereira, A. C., ... & Lotufo, P. A. (2015). Low impact of traditional risk factors on carotid intima-media thickness the ELSA-Brasil cohort. *Arteriosclerosis, Thrombosis, and Vascular Biology*, 35(9), 2054-2059.

- Santos, R. D., & Nasir, K. (2009). Insights into atherosclerosis from invasive and non-invasive imaging studies: Should we treat subclinical atherosclerosis? *Atherosclerosis*, 205(2), 349–56. doi:10.1016/j.atherosclerosis.2008.12.017
- Scherrer, J. F., Chrusciel, T., Zeringue, A., Garfield, L. D., Hauptman, P. J., Lustman, P. J., ... & True, W. R. (2010). Anxiety disorders increase risk for incident myocardial infarction in depressed and nondepressed Veterans Administration patients. *American Heart Journal*, 159(5), 772-779.
- Schindler, T. H., Hornig, B., Buser, P. T., Olschewski, M., Magosaki, N., Pfisterer, M., ... & Just, H. (2003). Prognostic value of abnormal vasoreactivity of epicardial coronary arteries to sympathetic stimulation in patients with normal coronary angiograms. *Arteriosclerosis, Thrombosis, and Vascular Biology*, 23(3), 495-501.
- Schott, L. L., Kamarck, T. W., Matthews, K. A., Brockwell, S. E., & Sutton-Tyrrell, K. (2009). Is brachial artery flow-mediated dilation associated with negative affect?. *International Journal of Behavioral Medicine*, 16(3), 241-247.
- Schreiber, J. B., Nora, A., Stage, F. K., Barlow, E. A., & King, J. (2006). Reporting structural equation modeling and confirmatory factor analysis results: A review. *The Journal of Educational Research*, 99(6), 323-338.
- Seldenrijk, A., van Hout, H. P., van Marwijk, H. W., de Groot, E., Gort, J., Rustemeijer, C., ... & Penninx, B. W. (2011). Depression, anxiety, and arterial stiffness. *Biological Psychiatry*, 69(8), 795-803.
- Seldenrijk, A., Vogelzangs, N., Batelaan, N. M., Wieman, I., van Schaik, D. J., & Penninx, B. J. (2015). Depression, anxiety and 6-year risk of cardiovascular disease. *Journal of Psychosomatic Research*, 78(2), 123-129.

- Seldenrijk, A., Vogelzangs, N., van Hout, H. P., van Marwijk, H. W., Diamant, M., & Penninx, B. W. (2010). Depressive and anxiety disorders and risk of subclinical atherosclerosis: findings from the Netherlands Study of Depression and Anxiety (NESDA). *Journal of Psychosomatic Research*, *69*(2), 203-210.
- Shekelle, R. B., Gale, M., Ostfeld, A. M., & Paul, O. (1983). Hostility, risk of coronary heart disease, and mortality. *Psychosomatic Medicine*, *45*, 109-114
- Siegler, I. C, Zonderman, A. B., Barefoot, J. C, Williams, R. B., Jr., Costa, P. T, Jr., & McCrae, R. R. (1990). Predicting personality in adulthood from college MMPI scores: Implications for follow-up studies in psychosomatic medicine. *Psychosomatic Medicine*, *52*, 644-652.
- Sin, D. D., & Man, S. P. (2005). Chronic obstructive pulmonary disease as a risk factor for cardiovascular morbidity and mortality. *Proceedings of the American Thoracic Society*, *2*(1), 8-11.
- Smith, T. W., Glazer, K., Ruiz, J. M., & Gallo, L. C. (2004). Hostility, anger, aggressiveness, and coronary heart disease: An interpersonal perspective on personality, emotion, and health. *Journal of Personality*, *72*(6), 1217-1270.
- Spitzer, R. L., Kroenke, K., Williams, J. B., & Löwe, B. (2006). A brief measure for assessing generalized anxiety disorder: the GAD-7. *Archives of Internal Medicine*, *166*(10), 1092-1097.
- Stewart, J. C., Fitzgerald, G. J., & Kamarck, T. W. (2010). Hostility now, depression later? Longitudinal associations among emotional risk factors for coronary artery disease. *Annals of Behavioral Medicine*, *39*(3), 258-266.

- Stewart, J.C., Janicki-Deverts, D., Muldoon, M.F., & Kamarck, T.W. (2008). Depressive symptoms moderate the influence of hostility on serum interleukin-6 and C-reactive protein. *Psychosomatic Medicine*, *70*, 197-204.
- Stewart, J. C., Janicki, D. L., Muldoon, M. F., Sutton-Tyrrell, K., & Kamarck, T. W. (2007). Negative emotions and 3-year progression of subclinical atherosclerosis. *Archives of General Psychiatry*, *64*(2), 225-233.
- Stewart, J. C., Zielke, D. J., Hawkins, M. A., Williams, D. R., Carnethon, M. R., Knox, S. S., & Matthews, K. A. (2012). Depressive symptom clusters and 5-year incidence of coronary artery calcification: the CARDIA study. *Circulation*, CIRCULATIONAHA-112.
- Suarez, E. C. (2003). Joint Effect of Hostility and Severity of Depressive Symptoms on Plasma Interleukin-6 Concentration. *Psychosomatic Medicine*, *65*(4), 523-527.
- Suarez, E., & Krishnan, K. R. R. (2006). The relation of free plasma tryptophan to anger, hostility, and aggression in a nonpatient sample of adult men and women. *Annals of Behavioral Medicine*, *31*(3), 254-260.
- Suls, J., & Bunde, J. (2005). Anger, anxiety, and depression as risk factors for cardiovascular disease: the problems and implications of overlapping affective dispositions. *Psychological Bulletin*, *131*(2), 260.
- Tabachnick, B., & Fidell, L. (2001). *Using multivariate statistics*. New York: Harper-Collins College Publishers.
- Task Force of the European Society of Cardiology. (1996). Heart rate variability standards of measurement, physiological interpretation, and clinical use. *Eur Heart J*, *17*, 354-381.
- Thurston, R. C., Rewak, M., & Kubzansky, L. D. (2013). An anxious heart: anxiety and the onset of cardiovascular diseases. *Progress in Cardiovascular Diseases*, *55*(6), 524-537.

- Torquato Jr, M. A., de Souza, B. P., Iosifescu, D. V., & Fraguas, R. (2012). *Anger, Hostility and Other Forms of Negative Affect: Relation to Cardiovascular Disease*. INTECH Open Access Publisher.
- Tomkins, S.S. (1963). *Affect Imagery Consciousness: The Positive Affects*. New York, NY: Springer Publishing Inc; 1963.
- Tugade, M. M., & Fredrickson, B. L. (2004). Resilient individuals use positive emotions to bounce back from negative emotional experiences. *Journal of Personality and Social Psychology, 86*(2), 320.
- Valdimarsdottir, H. B., & Bovbjerg, D. H. (1997). Positive and negative mood: Association with natural killer cell activity. *Psychology and Health, 12*(3), 319-327.
- Van der Kooy, K., Van Hout, H., Marwijk, H., Marten, H., Stehouwer, C., & Beekman, A. (2007). Depression and the risk for cardiovascular diseases: systematic review and meta analysis. *International Journal of Geriatric Psychiatry, 22*(7), 613-626.
- Vita, J. A., & Keaney, J. F. (2002). Endothelial function a barometer for cardiovascular risk?. *Circulation, 106*(6), 640-642.
- Watson, D. (2002). Positive affectivity. *Handbook of Positive Psychology, 106-119*.
- Watson, D., & Clark, L. A. (1994). The PANAS-X: Manual for the positive and negative affect schedule-expanded form. Ames: University of Iowa.
- Watson, D., Clark, L. A., & Carey, G. (1988). Positive and negative affectivity and their relation to anxiety and depressive disorders. *Journal of Abnormal Psychology, 97*(3), 346.
- Watson, D., Clark, L. A., & Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect: the PANAS scales. *Journal of Personality and Social Psychology, 54*(6), 1063.

- Watson, D., Clark, L. A., Weber, K., Assenheimer, J. S., Strauss, M. E., & McCormick, R. A. (1995). Testing a tripartite model: II. Exploring the symptom structure of anxiety and depression in student, adult, and patient samples. *Journal of Abnormal Psychology, 104*, 15–25.
- Watson, D., & Walker, L. M. (1996). The long-term stability and predictive validity of trait measures of affect. *Journal of Personality and Social Psychology, 70*(3), 567.
- Wetherell, J. L., Gatz, M., & Pedersen, N. L. (2001). A longitudinal analysis of anxiety and depressive symptoms. *Psychology and Aging, 16*(2), 187.
- Williams Jr, J. W., Stellato, C. P., Cornell, J., & Barrett, J. E. (2004). The 13-and 20-item Hopkins Symptom Checklist Depression Scale: psychometric properties in primary care patients with minor depression or dysthymia. *The International Journal of Psychiatry in Medicine, 34*(1), 37-50.
- Wilson, P. W., D'Agostino, R. B., Levy, D., Belanger, A. M., Silbershatz, H., & Kannel, W. B. (1998). Prediction of coronary heart disease using risk factor categories. *Circulation, 97*(18), 1837-1847.
- Witte, D. R., Westerink, J., de Koning, E. J., van der Graaf, Y., Grobbee, D. E., & Bots, M. L. (2005). Is the association between flow-mediated dilation and cardiovascular risk limited to low-risk populations?. *Journal of the American College of Cardiology, 45*(12), 1987-1993.
- Wu, Y., Sun, D., Wang, B., Li, Y., & Ma, Y. (2018). The relationship of depressive symptoms and functional and structural markers of subclinical atherosclerosis: A systematic review and meta-analysis. *European Journal of Preventive Cardiology, 20*47487318764158.

- Wyman, R. A., Keevil, J. G., Busse, K. L., Aeschlimann, S. E., Korcarz, C. E., & Stein, J. H. (2006). Is the ankle-brachial index a useful screening test for subclinical atherosclerosis in asymptomatic, middle-aged adults? *WMJ-MADISON*, *105*(6), 50.
- Yanek, L. R., Kral, B. G., Moy, T. F., Vaidya, D., Lazo, M., Becker, L. C., & Becker, D. M. (2013). Effect of positive well-being on incidence of symptomatic coronary artery disease. *The American Journal of Cardiology*, *112*(8), 1120-1125.
- Yeboah, J., Folsom, A. R., Burke, G. L., Johnson, C., Polak, J. F., Post, W., ... & Herrington, D. M. (2009). Predictive value of brachial flow-mediated dilation for incident cardiovascular events in a population-based study the multi-ethnic study of atherosclerosis. *Circulation*, *120*(6), 502-509.
- Yusuf, S., Reddy, S., Ôunpuu, S., & Anand, S. (2001). Global burden of cardiovascular diseases part I: general considerations, the epidemiologic transition, risk factors, and impact of urbanization. *Circulation*, *104*(22), 2746-2753.
- Zipes, D. P., Libby P., Bonow, R., & Braunwald, E. (Eds.). (2004). *Braunwald's Heart Disease: A Textbook of Cardiovascular Disease* (7th ed.). Philadelphia, PA: WB Saunder.

Table 1

Characteristics of Participants

Characteristic	Total Sample (<i>N</i> = 138)	eIMPACT (<i>n</i> = 94)	INFLAMED (<i>n</i> = 17)	BtB-Heart (<i>n</i> = 27)	ANOVA or 2x3
					Chi-Square <i>P</i> Value
Age, years	56.27 (7.1)	58.5 ^a (5.5)	55.2 ^b (8.1)	49.2 ^{ab} (6.8)	< .001
Female, %	69	76 ^a	65	48 ^a	.02
Non-Hispanic Black, %	38	37	47	41	.67
Less Than High School, %	18	22	6	11	.15
Baseline Arterial Diameter, cm	0.40 (0.07)	0.40 (0.07)	0.39 (0.07)	0.41 (0.06)	.10
Diabetes, % (<i>n</i> = 137)	32	38 ^a	35 ^b	8 ^{ab}	.01
Body Mass Index, kg/m ² (<i>n</i> = 137)	34.2 (10.0)	34.3 (10.0)	35.6 (12.5)	32.8 (8.4)	.65
HTN Meds, % (<i>n</i> = 136)	59	69 ^{ab}	35 ^a	39 ^b	.002
SBP, mmHg (<i>n</i> = 136)	133.7 (19.2)	137.0 ^a (19.2)	124.5 ^a (18.0)	127.5 (17.0)	.01
Current Smoker, %	44	43	59	37	.35
10-Year FRS (<i>n</i> = 133)	23.0 (14.4)	26.1 ^a (14.6)	19.5 (12.7)	13.0 ^a (8.0)	< .001
SCL-20 Score (<i>n</i> = 122)	1.8 (0.8)	1.9 (0.7)	1.7 (0.9)	1.5 (0.8)	.18
GAD-7 Score (<i>n</i> = 130)	10.4 (5.1)	10.5 (4.8)	10.5 (5.4)	10.0 (6.4)	.93
BPAQ Score (<i>n</i> = 113)	75.0 (20.4)	75.6 (20.6)	73.4 (22.1)	73.1 (19.8)	.87
PANAS-PA Score (<i>n</i> = 132)	27.2 (9.0)	27.4 (8.9)	27.1 (10.6)	26.6 (8.9)	.94
Flow-Mediated Dilation, % change	3.2 (2.6)	3.2 (2.3)	3.4 (3.2)	2.9 (3.1)	.07

Note. Continuous variables are presented as *M* (*SD*), and categorical variables are presented as percentage. HTN Meds = antihypertensive medication. SBP = systolic blood pressure. FRS = Framingham risk score. SCL-20 = Symptom Checklist-20. GAD-7 = Generalized Anxiety Disorder 7. BPAQ = Buss-Perry Aggression Questionnaire. PANAS-PA = Positive and Negative Affect Schedule-Positive Affect subscale. Shaded indicates *p* < .05.

^{a,b} Matching letters (e.g., ^a and ^a) indicate a significant difference between values as determined by a Tukey's post-hoc test for continuous variables or 2x2 chi-square for dichotomous variables

Table 2

Correlations among Measures of Affective Traits, 10-Year Framingham Risk Score, and Endothelial Function

Characteristic	SCL-20 Score	GAD-7 Score	BPAQ Score	PANAS Score	10-Year FRS
GAD-7 Score	.70				
GAD-7 Score [Partial]	.72				
BPAQ Score	.10	.23			
BPAQ Score [Partial]	.18	.22			
PANAS-PA Score	-.31	-.26	.03		
PANAS-PA Score [Partial]	-.29	-.22	.04		
10-Year FRS	.07	.13	-.01	.02	
10-Year FRS [Partial]	.13	.19	.15	-.08	
Flow-Mediated Dilation	.09	.01	-.18	-.09	-.09
Flow-Mediated Dilation [Partial]	.10	.00	-.22	-.06	.01

Note. [Partial] = partial correlations controlling for age, sex, race/ethnicity, education, and baseline arterial diameter. SCL-20 = Symptom Checklist-20. GAD-7 = Generalized Anxiety Disorder 7. BPAQ = Buss-Perry Aggression Questionnaire. PANAS-PA = Positive and Negative Affect Schedule-Positive Affect subscale. FRS = Framingham risk score. Shaded indicates $p < .05$.

Table 3

Model Fit Indices

Model	<i>df</i> , <i>N</i>	χ^2 (<i>p</i>)	<i>SRMR</i>	<i>RMSEA</i> (90% <i>CI</i>)	<i>CFI</i>
Aim 1 Structural Models					
Model 1 (DEP – EF)	2, 138	.37 (.83)	.01	.00 (.00, .10)	1.00
Model 2 (ANX – EF)	2, 138	1.08 (.58)	.02	.00 (.00, .14)	1.00
Model 3 (H/A – EF)	2, 138	1.49 (.47)	.02	.00 (.00, .16)	1.00
Model 4 (PA – EF)	2, 138	3.39 (.18)	.02	.07 (.00, .20)	.99
Aim 2 Measurement Models					
Model 5.1 (DEP, ANX)	8, 138	7.86 (.45)	.02	.00 (.00, .10)	1.00
Model 5.2 (DEP, ANX, Shared Variance)	9, 138	20.30 (.02)	.32	.10 (.04, .15)	.98
Model 6.1a (DEP, ANG)	8, 138	26.33 (<.001)	.04	.13 (.08, .19)	.96
Model 6.1b (DEP, ANG [m])	6, 138	10.10 (.12)	.03	.07 (.00, .14)	.99
Model 6.2 (DEP, ANG [m], Shared Variance)	7, 138	39.17 (<.001)	.04	.18 (.13, .24)	.89
Model 7.1 (DEP, PA)	8, 138	3.95 (.86)	.01	.00 (.00, .05)	1.00
Model 7.2 (DEP, PA, Shared Variance)	9, 138	53.50 (<.001)	.55	.19 (.14, .24)	.81
Aim 2 Structural Models					
Model 8 (DEP, ANX – EF)	12, 138	9.58 (.65)	.02	.00 (.00, .07)	1.00
Model 9 (DEP, ANG [m] – EF)	10, 138	11.21 (.34)	.03	.03 (.00, .10)	1.00
Model 10 (DEP, PA – EF)	12, 138	7.77 (.80)	.02	.00 (.00, .06)	1.00
Aim 3 Structural Model					
Model 11 (DEP, ANG [m] – CVD Risk – EF)	15, 138	14.81 (.47)	---	.00 (.00, .08)	---

Note. DEP = Depression. ANX = Anxiety. H/A = Hostility/Anger. PA = Positive Affect. EF = Endothelial Function. CVD risk = Traditional Cardiovascular Disease Risk Status. [m] = with modification indices. *SRMR* = Standardized Root Mean Square Residual. *RMSEA* = Root Mean Square of Approximation. *CI* = confidence interval. *CFI* = Comparative Fit Index. LISREL does not provide *SRMR* and *CFI* estimates for Model 11 because it uses full information maximum likelihood (FIML) estimation.

Bold and shaded = Fit indices outside recommended guidelines for acceptable model fit (i.e., recommended cut-off values close to <.08 for *SRMR*, <.06 for *RMSEA*, and >.95 for *CFI* [Hu & Bentler, 1999] as well as a low model χ^2 -statistic relative to degrees of freedom [$\chi^2/df < 3:1$ ratio] with an insignificant *p* value [$p > 0.05$] [Kline, 2005]).

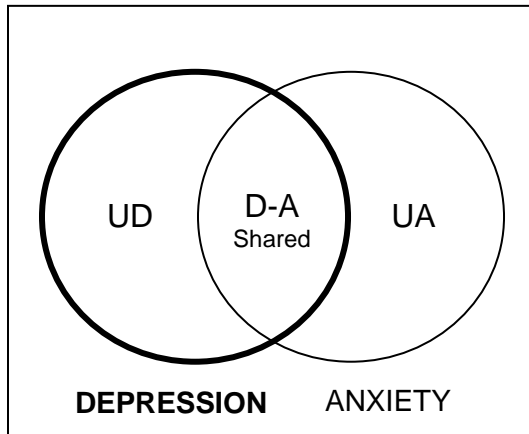
FIGURES

Figure 1. Venn Diagram illustrating the unique depression variance (UD), unique anxiety variance (UA), and shared variance between depression and anxiety (D-A Shared).

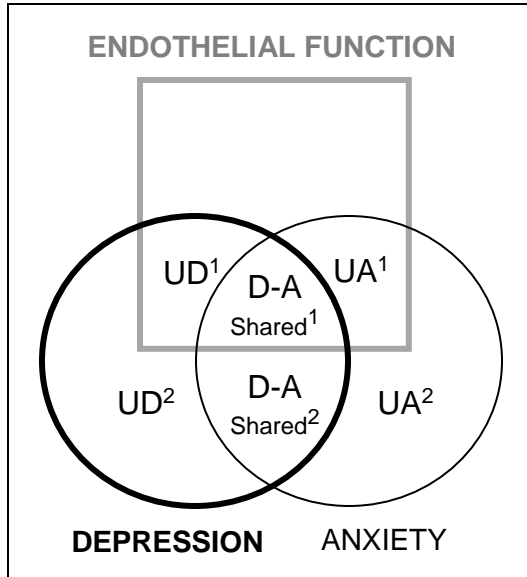


Figure 2. Venn diagram illustrating the potential relationships of unique depression variance (UD), unique anxiety variance (UA), and the shared variance between depression and anxiety (D-A Shared) with endothelial function. UD¹ = unique depression variance shared with endothelial function. UD² = unique depression variance not shared with endothelial function. UA¹ = unique anxiety variance shared with endothelial function. UA² = unique anxiety variance not shared with endothelial function. D-A Shared¹ = shared variance between depression and anxiety shared with endothelial function. D-A Shared² = shared variance between depression and anxiety not shared with endothelial function.

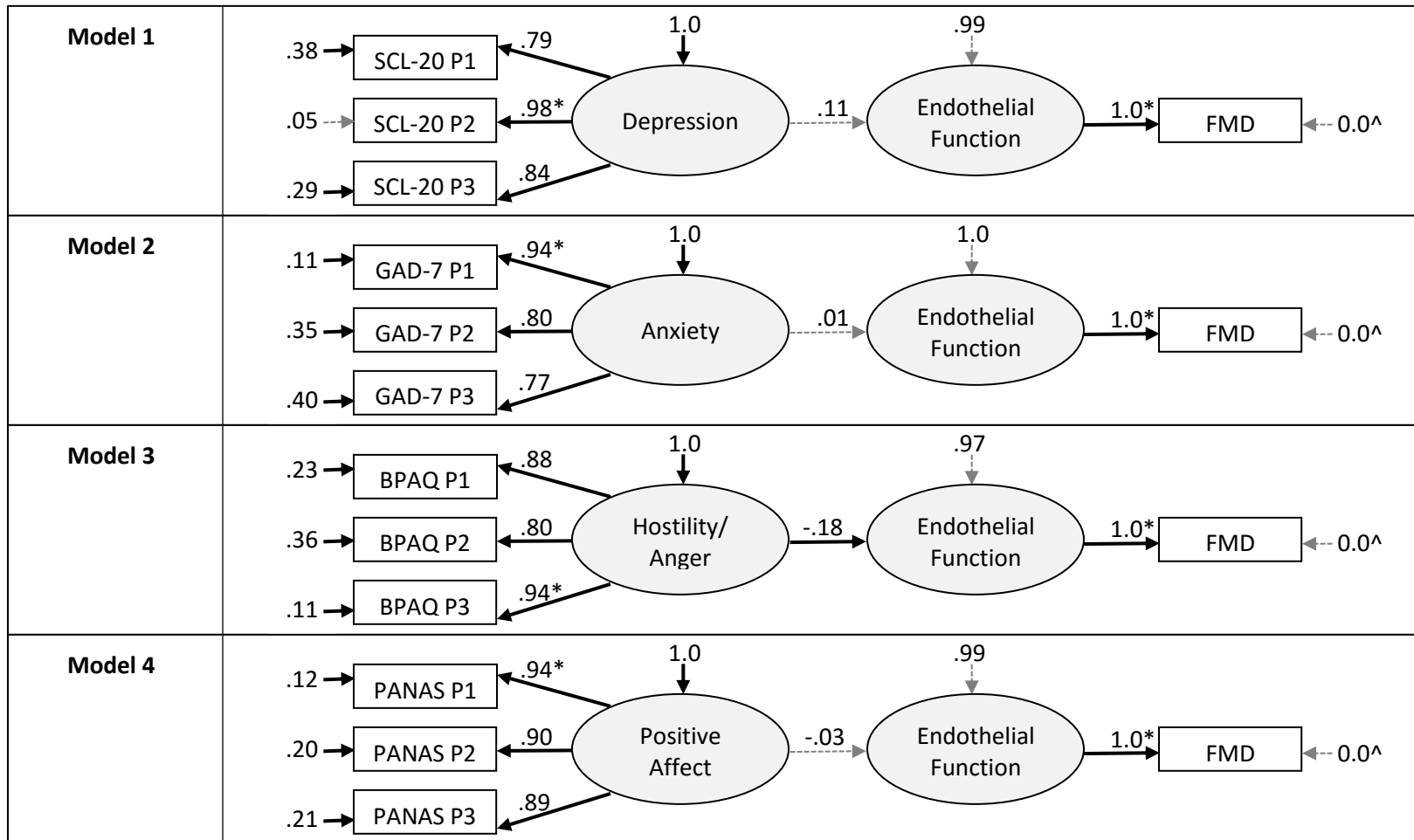


Figure 3. Models of Depression (Model 1), Anxiety (Model 2), Hostility/Anger (Model 3), and Positive Affect (Model 4) as predictors of Endothelial Function. Unidirectional arrows between variables are standardized regression coefficients and unidirectional arrows pointing at a single variable represent error variances. Paths with significant values are solid. Paths with nonsignificant values are dashed. SCL-20 = Symptom Checklist-20. GAD-7 = Generalized Anxiety Disorder 7. BPAQ = Buss-Perry Aggression Questionnaire. PANAS = Positive and Negative Affect Schedule-Positive Affect subscale. P1 = Parcel 1. P2 = Parcel 2. P3 = Parcel 3. FMD = flow-mediated dilation. $N = 138$. *Coefficient fixed to 1.0 prior to standardization. ^Error variance fixed to 0.

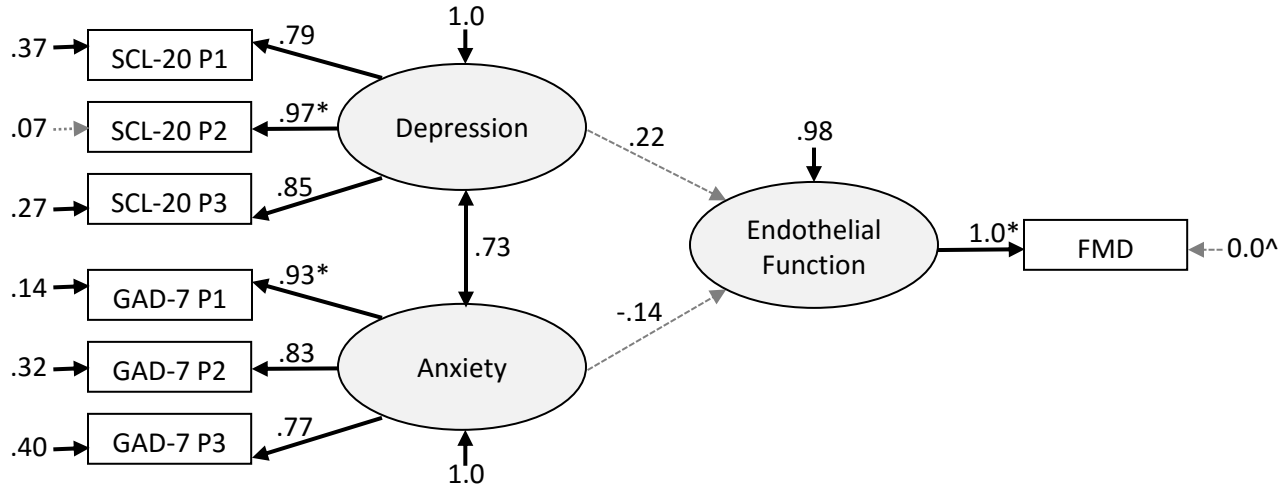


Figure 4. Model 8: Model of Depression and Anxiety as simultaneous predictors of Endothelial Function. Unidirectional arrows between variables are standardized regression coefficients and unidirectional arrows pointing at a single variable represent error variances. Paths with significant values are solid. Paths with nonsignificant values are dashed. SCL-20 = Symptom Checklist-20. GAD-7 = Generalized Anxiety Disorder 7. P1 = Parcel 1. P2 = Parcel 2. P3 = Parcel 3. FMD = flow-mediated dilation. $N = 138$. *Coefficient fixed to 1.0 prior to standardization. ^Error variance fixed to 0.

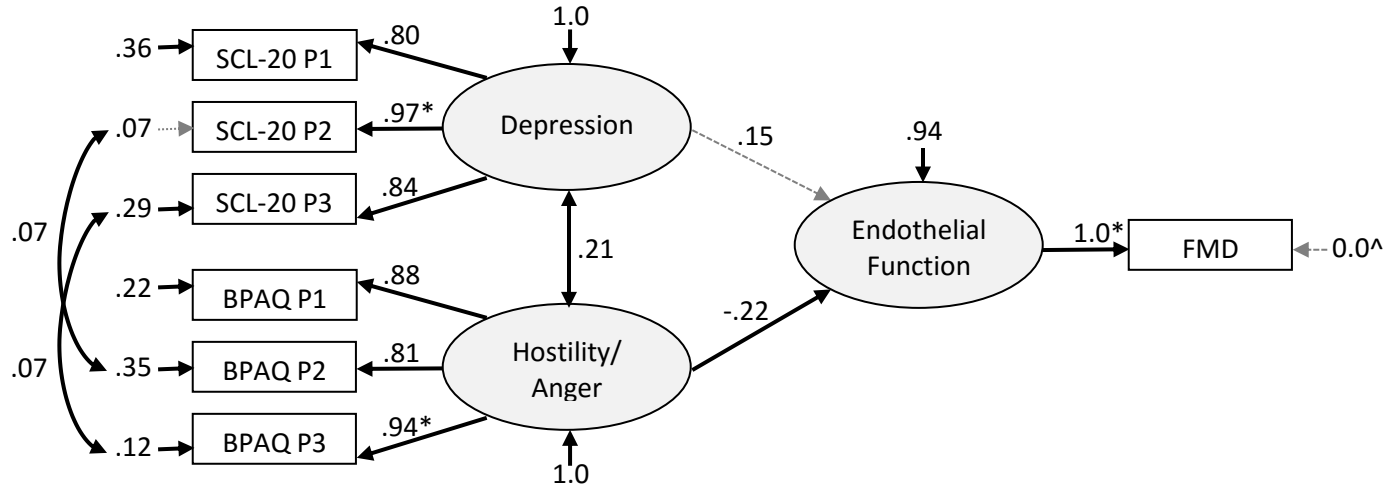


Figure 5. Model 9: Model of Depression and Hostility/Anger as simultaneous predictors of Endothelial Function. Unidirectional arrows between variables are standardized regression coefficients and unidirectional arrows pointing at a single variable represent error variances. Paths with significant values are solid. Paths with nonsignificant values are dashed. SCL-20 = Symptom Checklist-20. BPAQ = Buss-Perry Aggression Questionnaire. P1 = Parcel 1. P2 = Parcel 2. P3 = Parcel 3. FMD = flow-mediated dilation. $N = 138$. *Coefficient fixed to 1.0 prior to standardization. ^Error variance fixed to 0.

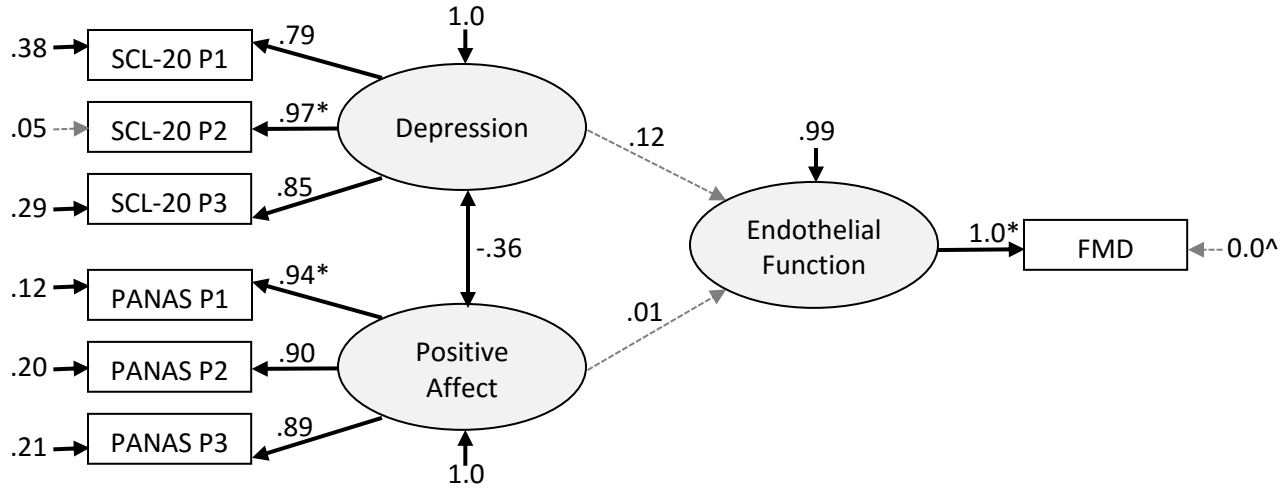


Figure 6. Model 10: Model of Depression and Positive Affect as simultaneous predictors of Endothelial Function. Unidirectional arrows between variables are standardized regression coefficients and unidirectional arrows pointing at a single variable represent error variances. Paths with significant values are solid. Paths with nonsignificant values are dashed. SCL-20 = Symptom Checklist-20. PANAS = Positive and Negative Affect Schedule-Positive Affect subscale. P1 = Parcel 1. P2 = Parcel 2. P3 = Parcel 3. FMD = flow-mediated dilation. $N = 138$. *Coefficient fixed to 1.0 prior to standardization. ^Error variance fixed to 0.

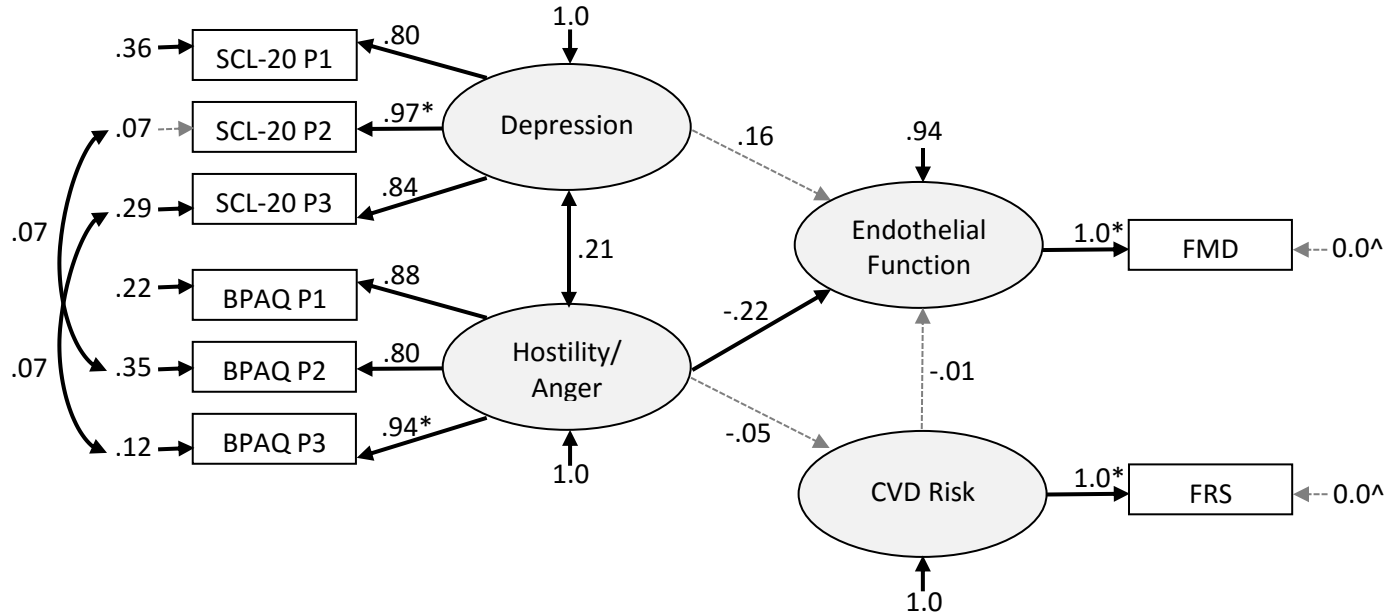


Figure 7. Model 11: Model of Depression and Hostility/Anger as simultaneous predictors of Endothelial Function with Traditional Cardiovascular Disease Risk Status as a mediator between Hostility/Anger and Endothelial Function. Unidirectional arrows between variables are standardized regression coefficients and unidirectional arrows pointing at a single variable represent error variances. Paths with significant values are solid. Paths with nonsignificant values are dashed. SCL-20 = Symptom Checklist-20. BPAQ = Buss-Perry Aggression Questionnaire. P1 = Parcel 1. P2 = Parcel 2. P3 = Parcel 3. FMD = flow-mediated dilation. FRS = Framingham Risk Score. CVD Risk = Traditional Cardiovascular Disease Risk Status. $N = 138$. *Coefficient fixed to 1.0 prior to standardization. ^Error variance fixed to 0.

APPENDIX A

Inclusion/Exclusion Criteria for the Three Randomized Controlled Trials

Inclusion/Exclusion Criteria	A	B	C
<i>Demographic Criteria</i>			
Primary care patient	X	X	X
Age \geq 40 years	X	X	
Age \geq 50 years			X
<i>Psychological Criteria</i>			
Clinically significant depressive symptoms, defined as PHQ-9 score \geq 10	X	X	X
Two or more PHQ-9 items have been present at least “more than half the days” over the past 2 weeks, and one of the symptoms is either depressed mood or anhedonia			X
No very severe depressive symptoms, defined as a PHQ-9 score \geq 24		X	
No acute risk of suicide	X	X	X
No history of bipolar disorder or psychosis	X	X	X
No current alcohol use problem (i.e., \geq 2 on CAGE questionnaire; Mayfield, McLeod, & Hall, 1974)	X	X	
No current evidence of abuse of prescription medications		X	
No current evidence of illicit drug use		X	
No severe cognitive impairment (i.e., \geq 3 errors on 6 item cognitive screener; Callahan, Unverzagt, Hui, Perkins, & Hendrie, 2002)	X	X	X
No ongoing treatment for depression with a psychiatrist or psychologist/counselor	X		
No ongoing depression treatment with a psychiatrist outside of Eskenazi Health			X
<i>Medical Criteria</i>			
Elevated CVD risk: \geq 1 (if 60+ years) or \geq 2 (if 50-59 years) of the following risk factors in medical record in past 5 years: hypertension, hypercholesterolemia, diabetes, or current smoking			X
No history of clinical cardiovascular disease prior to enrollment (i.e., no coronary artery disease, cerebrovascular disease, acute myocardial infarction, percutaneous coronary intervention, or coronary artery bypass graphing)	X	X	X
No history of cardiac arrhythmias or cardiomyopathy		X	
No history of carotid bruits		X	
No history of the following chronic disorders: HIV/AIDS, chronic kidney disease, systemic inflammatory disease, or past-year cancer	X	X	X
No history of bleeding disorder, gastrointestinal ulceration or bleeding, cerebrovascular aneurysm or bleeding, or retinal hemorrhage		X	
No history of migraine headaches		X	
No history of Raynaud’s phenomenon		X	
No current use of anticoagulants	X	X	X
No current use of acetazolamide, anticonvulsants, or thyroid replacements		X	

No current use of glucocorticoids – including topical, nasal, or oral steroids – or anabolic steroids		X	
No current use of anti-inflammatory agents		X	
No known allergy or intolerance to pentoxifylline or other methylxanthines, such as theophylline, caffeine, and theobromine		X	
No known allergy or intolerance to nitroglycerin		X	
No creatinine clearance < 50mL/min using a serum creatinine level at the pre-treatment visit		X	
No hemoglobin < 9.0 mg/dL at the pre-treatment visit		X	
No alanine aminotransferase level or aspartate aminotransferase level > 3 times the upper limit of normal at the pre-treatment visit		X	
No total bilirubin > 2.5 times the upper limit of normal at the pre-treatment visit		X	
No current pregnancy	X	X	X
Not currently breastfeeding		X	
Must be postmenopausal status for women (surgical menopause or the absence of menstruation in the past 12 months) or a history of tubal ligation		X	
Miscellaneous Criteria			
Must be able to lie flat for 30 minutes at a time	X	X	
No vision or hearing problems	X	X	
Must read and speak English	X	X	
Must use a computer at least once per year	X		

Note. A = Beating the Blues for Your Heart Trial, B = INFLAMED Trial, C = eIMPACT Trial.

APPENDIX B

Symptom Checklist 20 (SCL-20)

Below is a list of problems and complaints that people sometimes have. Please read each one carefully. After you have done so, please check one of the spaces to the right that best describes HOW MUCH THAT PROBLEM HAS BOTHERED OR DISTRESSED YOU DURING THE PAST WEEK, INCLUDING TODAY. Mark only one space for each problem and do not skip any.

How much were you bothered by:

	See Response Options
1. Loss of sexual interest or pleasure	
2. Feeling low in energy or slowed down	
3. Thoughts of ending your life	
4. Poor appetite	
5. Crying easily	
6. Feeling of being trapped or caught	
7. Blaming yourself for things	
8. Feeling lonely	
9. Feeling blue	
10. Worrying too much about things	
11. Feeling no interest in things	
12. Trouble falling asleep	
13. Feeling hopeless about the future	
14. Thoughts of death and dying	
15. Overeating	
16. Awakening in the early morning	
17. Sleep that is restless or disturbed	
18. Feeling everything is an effort	
19. Feelings of worthlessness	
20. Feelings of guilt	

Response options:

1. Not at all
2. A little bit
3. Moderately
4. Quite a bit
5. Extremely

Generalized Anxiety Disorder 7-item (GAD-7) Scale

Over the *last 2 weeks*, how often have you been bothered by the following problems?

	See Response Options
1. Feeling nervous, anxious or on edge	
2. Not being able to stop or control worrying	
3. Worrying too much about different things	
4. Trouble relaxing	
5. Being so restless that it is hard to sit still	
6. Becoming easily annoyed or irritable	
7. Feeling afraid as if something awful might happen	

Response options:

0. Not at all
1. Several days
2. More than half the days
3. Nearly every day

Buss Perry Aggression Questionnaire (BPAQ)

Please indicate how uncharacteristic (unlike you) or characteristic (like you) each of the following statements is in describing you. Place a check mark on the point on the scale that you feel is most appropriate in describing you.

	See Response Options
1. Some of my friends think I am a hothead.	
2. If I have to resort to violence to protect my rights, I will.	
3. When people are especially nice to me, I wonder what they want.	
4. I tell my friends openly when I disagree with them.	
5. I have become so mad that I have broken things.	
6. I can't help getting into arguments when people disagree with me.	
7. I wonder why sometimes I feel so bitter about things.	
8. Once in a while, I can't control the urge to strike another person.	
9. I am an eventempered person.	
10. I am suspicious of overly friendly strangers.	
11. I have threatened people I know.	
12. I flare up quickly but get over it quickly.	
13. Given enough provocation, I may hit another person.	
14. When people annoy me, I may tell them what I think of them.	
15. I am sometimes eaten up with jealousy.	
16. I can think of no good reason for ever hitting a person.	
17. At times I feel I have gotten a raw deal out of life.	
18. I have trouble controlling my temper.	
19. When frustrated, I let my irritation show.	
20. I sometimes feel that people are laughing at me behind my back.	
21. I often find myself disagreeing with people.	
22. If somebody hits me, I hit back.	
23. I sometimes feel like a powder keg ready to explode.	
24. Other people always seem to get the breaks.	
25. There are people who pushed me so far that we came to blows.	
26. I know that "friends" talk about me behind my back.	
27. My friends say that I'm somewhat argumentative.	
28. Sometimes I fly off the handle for no good reason.	
29. I get into fights a little more than the average person.	

Response options:

1. Extremely uncharacteristic of me
2. Somewhat uncharacteristic of me
3. Neither uncharacteristic nor characteristic of me
4. Somewhat characteristic of me
5. Extremely characteristic of me

The Positive and Negative Affect Schedule – Positive Affect (PANAS-PA) Scale

This scale consists of a number of words and phrases that describe different feelings and emotions. Read each item and mark the appropriate answer next to that word. Indicate to what extent you have felt this way in general, that is, on average.

	See Response Options
1. Interested	
2. Excited	
3. Strong	
4. Enthusiastic	
5. Proud	
6. Alert	
7. Inspired	
8. Determined	
9. Attentive	
10. Active	

Response options:

1. Very Slightly or Not at All
2. A Little
3. Moderately
4. Quite a Bit
5. Extremely