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Alzheimer caregiving stress and atherosclerotic disease: psychosocial and physiological pathways linking chronic stress to disease

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Alzheimer Caregiving Stress and Atherosclerotic Disease: Psychosocial and Physiological Pathways Linking Chronic Stress to Disease

A dissertation submitted in partial satisfaction of the requirements for the Degree of Doctor of Philosophy in Clinical Psychology by Susan Kyung Buehler

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2012
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stress, depressive symptoms, leisure satisfaction, and endothelial function in caregivers. *Health Psychology.*


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ABSTRACT OF THE DISSERTATION

Alzheimer Caregiving Stress and Atherosclerotic Disease: Psychosocial and Physiological Pathways Linking Chronic Stress to Disease

by

Susan Kyung Buehler

Doctor of Philosophy in Clinical Psychology

University of California, San Diego, 2012
San Diego State University, 2012

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One in eight Americans over the age of 65 is diagnosed with Alzheimer’s disease and the annual incidence is expected to double by the year 2050. Unpaid family caregivers provide 80% of the healthcare for these individuals. Extensive research suggests that caregiving takes a substantial toll on health and is associated with increased coronary heart disease risk. Recent evidence suggests that chronic stress associated with caregiving may accelerate the atherosclerotic disease process. Although the processes driving such consequences are complex, heightened sympatho-adrenal-medullary (SAM) axis arousal and inflammation represent potential mechanisms linking stress to atherosclerosis.

A conceptual framework modeling the translation of caregiving stress to
downstream evidence of atherosclerosis was formulated. The present study aimed to
determine if this model represented a parsimonious and valid characterization of
observed data from a sample of 126 Alzheimer caregivers. In brief, this model
specified a positive relationship between stress and markers of atherosclerosis with
SAM arousal and inflammation as mediators. Coping resources were expected to
buffer the relationship between caregiving stress and physiologic mediators.
Confirmatory factor analysis was used to test latent variable measurement models and
regression was used to assess structural relationships. Exploratory analyses assessed
the impact of stress and coping on atherosclerotic progression over time.

Results indicated that caregiving stress was unassociated with evidence of
atherosclerosis and neither SAM arousal nor inflammation mediated this relationship.
Coping did not moderate the relationship between stress and atherosclerosis or
physiologic mediators. However, coping was associated with reduced SAM arousal
and inflammation. Longitudinal analyses suggested that higher use of problem-
focused coping was significantly associated with slower atherosclerotic progression.

In sum, this comprehensive model did not fit the observed data in this sample,
possibly due to power limitations and strength of measurement models. However,
prior work in this cohort of caregivers does support specific components of this model.
Longitudinal analyses suggested that problem-focused coping was associated with
slower atherosclerotic progression, a finding that converges with past research
suggesting that active coping strategies have a beneficial impact on cardiovascular
health. Future work might examine the impact of coping skills training on
atherosclerotic progression.
I. INTRODUCTION

Alzheimer’s Disease Caregiving and Health

One in eight Americans over the age of 65 is diagnosed with Alzheimer’s disease and the annual incidence is expected to double by the year 2050 (Alzheimer's Association, 2012; Hebert, Beckett, Scherr, & Evans, 2001). Unpaid family caregivers to those suffering with such diseases constitute a valuable national health resource, providing approximately 70-80% of healthcare to Alzheimer’s patients in the U.S. (Alzheimer's Association, 2008, 2012). However, caring for a loved-one with dementia can be extremely burdensome for the caregiver, potentially increasing risk for psychiatric morbidity (Mahoney, Regan, Katona, & Livingston, 2005; Schulz, O'Brien, Bookwala, & Fleissner, 1995), physical health problems (P. P. Vitaliano, Zhang, & Scanlan, 2003), and all-cause mortality (Schulz & Beach, 1999).

Evidence suggests that caregivers are at twice the risk for developing depression compared to their non-caregiving peers (Baumgarten et al., 1992). Further, Mahoney and colleagues (2005) found that nearly a quarter of Alzheimer caregivers had clinically significant anxiety and about 10% had clinically significant depression. Some factors predicting caregiver anxiety and depression were (1) care-receiver impairment and behavior problems, (2) poor relationship quality with the care-receiver, and (3) poor self-rated health. Emerging research also suggests that caregivers exhibit impaired cognition compared to non-caregivers, demonstrating poorer performance on tasks of attention, memory, verbal fluency, and general cognitive function (Caswell et al., 2003; de Vugt et al., 2006; S. Lee, Kawachi, &
Depression has been shown to mediate the relationship between caregiving status and cognitive decline (P. P. Vitaliano et al., 2009).

In addition to increased psychiatric morbidity and cognitive impairment, providing care for a spouse diagnosed with Alzheimer’s disease is associated with increased risk for physical health problems. Past research suggests that caregivers exhibit impairment in immune system functioning compared to non-caregiving controls as evidenced by slowed wound healing (Kiecolt-Glaser, Marucha, Malarkey, Mercado, & Glaser, 1995), deficits in antibody response to pneumococcal bacterial vaccine (Glaser, Sheridan, Malarkey, MacCallum, & Kiecolt-Glaser, 2000), and reduced E-NK cell cytotoxicity to cytokine stimulation (Esterling, Kiecolt-Glaser, & Glaser, 1996). Caregivers also exhibit poorer metabolic function compared to non-caregivers as evidenced by increased fasting insulin levels (P. P. Vitaliano, Scanlan, Krenz, Schwartz, & Marcovina, 1996).

In recent years, a great deal of attention has been focused on the deleterious effects of chronic caregiving stress on cardiovascular health (Mausbach, Patterson, Rabinowitz, Grant, & Schulz, 2007; Mills et al., 2004; von Känel et al., 2006). Dementia caregivers have elevated Framingham coronary heart disease risk scores compared to non-caregivers (von Känel et al., 2008) and have increased risk for developing hypertension (Shaw et al., 1999) and coronary heart disease (P. P. Vitaliano et al., 2002). Several elements of the caregiving role have been associated with increased cardiovascular impairment including behavioral and cognitive impairment of the Alzheimer patient (Aschbacher et al., 2006), caregiver burden (Mausbach, Mills et al., 2007), depression (Mausbach, Patterson, Rabinowitz, Grant,
& Schulz, 2007), and poor sleep quality (von Känel et al., 2010).

Given that caregivers are at increased risk for coronary artery diseases in general, it is possible that the chronic stress associated with caring for a loved one may accelerate the atherosclerotic disease process. Throughout this disease process, changes in vascular walls occur which can result in vascular wall thickening and narrowing, as well as plaque formation. This process can begin in early childhood with the development of a fatty streak (Napoli et al., 1997) and evolve into an advanced, complicated arterial lesion. If a lesion advances to an unstable fibrous plaque, rupture of this plaque can cause thrombosis and possible occlusion of the artery (Ross, 1999). Injury of the endothelium and subsequent endothelial dysfunction is thought to be a key pathogenetic mechanism driving atherosclerosis (Celermajer, 1997; Ross, 1993, 1999). The inability of the endothelium to balance vasodilating and vasoconstricting factors can trigger compensatory responses that change the homeostatic properties of the endothelium. These changes can promote procoagulant and proinflammatory states (Blanco, Rodríguez-Yáñez, Sobrino, Leira, & Castillo, 2005; Ross, 1999). Indeed, accumulating evidence suggests that caregiving is associated with biomarkers of atherosclerotic disease including inflammation, coagulation, and endothelial dysfunction (Lutgendorf et al., 1999; Mausbach et al., 2010; Mills et al., 2009; von Känel et al., 2010; von Känel et al., 2006).

The Role of the Sympatho-Adrenal-Medullary Axis in Stress and Disease

Although the direct causes for impaired cardiovascular health in elderly caregivers remain unclear, neuroendocrine activity might play an important role.
Specifically, heightened sympatho-adrenal-medullary (SAM) axis arousal may represent one potential mechanistic link explaining how chronic stress translates to downstream disease (P. P. Vitaliano, Zhang, & Scanlan, 2003). Upon encountering a challenge or stressor, the hypothalamus secretes corticotropin releasing hormone (CRH), which stimulates pituitary secretion of adrenocorticotropic hormone (ACTH), thereby stimulating the sympathetic ganglia to release catecholamines, including norepinephrine and epinephrine from the adrenal medulla (Black & Garbutt, 2002; Straub, 2002). This surge of catecholamines catalyzes a number of physiological changes that prepare the body for a challenge (i.e., “fight or flight” response) including increased heart rate and blood pressure (McEwen, 2003).

Indeed, accumulating research has supported the postulation that acutely stressful situations activate the sympathetic nerves, triggering an upsurge of circulating plasma catecholamines (Kop et al., 2008; Mills et al., 2004). Although this response may have evolutionary advantages in preparing an organism for a challenge, research suggests that acute catecholamine surge may also catalyze changes that promote atherothrombotic events, such as hemostatic activation, vasoconstriction, and inflammatory responses (Bhattacharyya & Steptoe, 2007; Krantz & Manuck, 1984; von Känel &Dimsdale, 2000). For example, Wirtz and colleagues (2006) found that norepinephrine activity independently predicted d-dimer response to an acute stressor task in healthy adult men. Another study by Kop and colleagues (2008) found that norepinephrine hyperreactivity to an acute mental stressor task was associated with increased inflammatory responses of c-reactive protein (CRP) and interleukin-6 (IL-6) in patients with coronary artery disease.
Frequent and persistent SAM activation is also hypothesized to contribute to worsened cardiovascular health outcomes such as hypertension, hypercoagulable states, endothelial injury, metabolic syndrome, and atherosclerosis (Black & Garbutt, 2002). Individuals enduring chronic stress are expected to have increased SAM tone and might be particularly vulnerable to these effects. Indeed, a great deal of evidence suggests that distressed caregivers exhibit worsened SAM tone. For example, dementia caregivers reporting high life stress have higher plasma norepinephrine levels than caregivers reporting low life stress and non-caregivers reporting low life stress (Mills et al., 1997). Another study by Aschbacher and colleagues (2008) found that negative affect (depressive and anxious symptoms) was associated with prolonged sympathetic activation in caregivers, but not in non-caregiving controls. Furthermore, a study by Mausbach et al. (2005) found that caregivers reporting more severe depressive symptoms exhibited elevated norepinephrine responses to an acute stress task, potentially attributable to coping skills deficits and/or distorted cognitive appraisals. These findings provide evidence suggesting that elevated circulating catecholamine levels may be an important mediator between caregiving distress and indices of poor physical health in caregivers both in resting conditions and with acute stress. These findings are also consistent with the general notion that the SAM axis is a mediator of physiological adaptation to challenges of daily life (McEwen, 2003).

The validity of the link between chronic stress and the SAM axis is also supported by findings suggesting that providing respite for caregivers has a beneficial impact on SAM tone. Grant and colleagues (2003) found that vulnerable caregivers (those reporting a large mismatch between caregiving demands and help received)
who received an in-home respite intervention showed a significant decrease in plasma epinephrine, while those who were wait-listed experienced increases in epinephrine. Therefore, it seems that relieving caregivers of their responsibilities periodically may help improve SAM tone.

Excessive SAM activation may also promote a physiologic environment that increases the risk for atherosclerosis. Specifically, sustained increases in catecholamines with dementia caregiving stress might contribute to physiologic changes such as increased metabolism, heart rate, and blood pressure, all of which accelerate development of atherosclerosis (Grant, 1999; Grant et al., 2002). Further, research using human (Santos et al., 2005) and animal models (Pettersson, Bejne, Björk, Strawn, & Bondjiers, 1990) confirms that chronic sympathetic arousal is associated with endothelial injury and dysfunction. Although the specific physiologic mediators driving the relationship between chronic stress and atherosclerotic progression remain unclear, much evidence supports the theory that excessive and unabated inflammatory response (enhanced by SAM arousal) in the vascular walls plays a key role in the development of atherosclerosis (Clinton & Libby, 1992a; McCully, 1990; Ross, 1986, 1999). Activation of the SAM axis by stress catalyzes a number of physiological events promoting cardiovascular activity, endothelial injury, production of cytokines, induction of adhesion molecules on the endothelium, and adherence of monocytes and lymphocytes to those molecules. A stressor can also prompt an acute phase response promoting the inflammatory process via macrophage and mast cell activation as well as cytokine and acute phase protein production (Black
& Garbutt, 2002). If this process is frequently repeated and persistent, it can contribute to the progression of atherosclerotic disease.

**Coping**

Although challenges are virtually a certainty in dementia caregiving, not all caregivers will experience adverse health outcomes. Caregivers who are resilient to these adverse health outcomes can provide valuable information regarding the conditions under which the impact of chronic stress on health might be mitigated. Lazarus and Folkman (1984) developed their *Transactional Model* of stress in order to explain the role that cognitive appraisals and coping might play in the stress process. According to this model, individuals encountered with stressful environmental stimuli make both primary and secondary appraisals of these stimuli. Primary appraisals involve evaluation of the significance of the stressor to one’s well-being (i.e., whether a stressor is a threat or a challenge). Secondary appraisals involve the evaluation of the controllability of the stressor and one’s perceived ability to cope with it. Theoretically, stressors perceived as threatening and uncontrollable would likely elicit the greatest psychological and physiological response.

This model suggests that appraisal and coping may play an important role in moderating the relationship between caregiving stressors and upstream and downstream cardiovascular outcomes. Within this framework, individuals who frequently make positive secondary appraisals when faced with a challenge should exhibit an attenuated stress response. That is, individuals who appraise themselves as capable of managing stressors may either perceive an event as less threatening or...
experience a greater subjective sense of control, thereby resulting in less physiologic arousal.

Consistent with this theory, research has found that personal mastery, or the global belief that one has control over life’s obstacles (Pearlin, Mullan, Semple, & Skaff, 1990), is associated with both psychological and physical health outcomes. For example, previous work in Alzheimer caregivers has found that high personal mastery has a protective effect on global measures of psychological distress (Mausbach et al., 2006), medical and depressive symptoms (Mausbach, Patterson et al., 2007), and fatigue (Roepke et al., 2009). Furthermore, sense of control might buffer the putative relationship between caregiving stress and atherosclerosis given that mastery has been associated with reduced sympathetic activation to stress (Roepke et al., 2008), reduced coagulation (Mausbach, von Känel et al., 2008), and increased β2-adrenergic receptor sensitivity (Mausbach, Mills et al., 2007). Mastery has also been associated with decreased mortality risk in older adults (Penninx et al., 1997).

The tendency to actively approach problems in order to find a solution might also serve as a coping strategy protective against the negative impact of stress. Kneebone and Martin (2003) reviewed studies examining stress and coping in the context of the Transactional Model in dementia caregivers and concluded that the literature generally supports that problem-focused coping is beneficial for caregiver health. Furthermore, past work in caregivers has found that high use active problem solving coping strategies might protect against procoagulant activity to an acute laboratory stressor (Aschbacher et al., 2005). Likewise, evidence suggests that high self-efficacy for using problem-focused coping might protect against increased blood
pressure (Harmell et al., 2011) and inflammation (Mausbach et al., 2011) in dementia caregivers. Given that mastery and the proclivity for using problem solving or approach style coping have been shown to be associated with better sympathetic and inflammatory functioning in caregivers, it is plausible these factors may also be associated with improved arterial health.

**Measurement of Large Vessel Disease**

High resolution ultrasound imaging technology has allowed for non-invasive assessment of vascular wall thickening, plaque formation, and endothelial function. Carotid artery intima-media thickness (IMT) and brachial artery flow-mediated dilation (FMD) are two widely-used research tools to assess arterial structure and function, respectively.

**Carotid IMT**

Assessment of carotid artery IMT involves measurement of the span between the intimal-luminal and the medial-adventitial interfaces of the carotid artery derived from ultrasound images. Carotid IMT is considered a surrogate of subclinical coronary atherosclerosis (Chambless et al., 1997; Lorenz, Markus, Bots, Rosvall, & Sitzer, 2007a), given that the presence of atherosclerosis in the carotid arteries is a strong indicator of generalized atherosclerosis throughout the vasculature, including the coronary arteries (Craven et al., 1990; Salonen & Salonen, 1991). Ultrasound measurement of IMT has been established as a reliable (Chambless et al., 1996) and valid (Persson, Formgren, Israelsson, & Berglund, 1994) measure of subclinical
atherosclerosis. Carotid IMT has been associated with several cardiovascular disease risk factors including age, sex, body mass index (BMI), smoking, hypertension, diabetes, and cholesterol (Mackinnon et al., 2004). Notably, the predictive validity of IMT as a surrogate marker of atherosclerosis has been demonstrated in several studies. A prospective study by O’Leary and colleagues (1999) found that increases in IMT of the common carotid artery were associated with increased risk for myocardial infarction and stroke in older adults without a history of cardiovascular disease. Additionally, a review and meta-analysis of the literature testing the predictive value of IMT found eight studies examining the ability of IMT to predict future cardiovascular events (Lorenz, Markus, Bots, Rosvall, & Sitzer, 2007b). Results of this study indicated that IMT is a strong predictor of future CVD events and that IMT is a slightly better predictor of stroke than for myocardial infarction.

In further support for IMT as a marker of atherosclerotic disease, IMT has also been shown to be sensitive to cardiovascular disease risk factor interventions. For example, Mukherjee et al. (2002) conducted a review of studies examining IMT and found that people taking HMG-CoA reductase inhibitors (Statins) (Byington, 1999; Hodis et al., 1996; Mukherjee & Yadav, 2002), Amlodipine (calcium blocker) (Koshiyama, Tanaka, & Minamikawa, 1999), and Ramipril (Lonn et al., 2001) experience a reduction in IMT. Furthermore, those undergoing behavioral interventions (e.g., diet, exercise) may also experience reductions in IMT (Karason, Wikstrand, Sjostrom, & Wendelhag, 1999; Markus, Mack, Azen, & Hodis, 1997).
**Brachial FMD**

Brachial FMD is a non-invasive method used to assess endothelial functioning in peripheral circulation (Moens, Goovaerts, Claeys, & Vrints, 2005). This method involves placement of an occlusion cuff on the upper arm in order to induce distal hypoxia. The cuff is then deflated, resulting in reactive hyperemia and increased shear stress. This increased shear stress stimulates the endothelium to output nitric oxide (NO), a potent local vasodilator. Ultrasound images capture the arterial diameter at baseline (before cuff inflation) and at several time points post-cuff deflation. Healthy endothelial function is characterized by rapid output of NO by the endothelium, stimulating smooth muscle relaxation, and vasodilation.

Brachial FMD has demonstrated high reproducibility and reliability (Pala et al., 2009; Sorensen et al., 1995). Further, research has established that FMD has excellent validity. It has been correlated with invasive measures of coronary artery endothelial dysfunction (Anderson, Uehata, & Gerhard, 1995; Takase et al., 1998) and several cardiovascular risk factors (Benjamin et al., 2004; Celermajer et al., 1994; Hamburg et al., 2008; Schnell, Robertson, Houston, Malley, & Anderson, 1999). FMD has also been shown to be an independent predictor of short term (Gokce et al., 2002) and long term (Gokce et al., 2003) cardiovascular events in patients undergoing vascular surgery. Furthermore, brachial FMD was predictive of incident cardiovascular events in asymptomatic, lower risk individuals in a population-based study (Shimbo et al., 2007).
Association between Stress and Markers of Large Vessel Disease

An emerging body of research suggests that carotid IMT and its progression over time may be sensitive to chronic stress (Gallo, Troxel, Kuller et al., 2003; Gallo, Troxel, Matthews et al., 2003; Hintsanen et al., 2007; Hintsanen et al., 2005; Janicki, Kamarck, Shiffman, Sutton-Tyrrell, & Gwaltney, 2005; Kamarck, Muldoon, Shiffman, & Sutton-Tyrrell, 2007; Rosvall et al., 2002; Troxel, Matthews, Bromberger, & Sutton-Tyrrell, 2003). For example, individuals working in professions characterized by high demand and low control have higher levels of carotid IMT overall, as well as progression over time (Hintsanen et al., 2005; Kamarck, Muldoon, Shiffman, & Sutton-Tyrrell, 2007). Similar results have been found in women reporting poor marital satisfaction (Gallo, Troxel, Kuller et al., 2003). Another study by Troxel and colleagues (Troxel, Matthews, Bromberger, & Sutton-Tyrrell, 2003) found that African American women who reported experiencing racial discrimination had more carotid plaques compared to those not reporting racial discrimination. Finally, vital exhaustion, an indicator of chronic mental stress characterized by low physical and mental energy, irritability, and demoralization, has also been associated with increased IMT in young healthy adults with impaired endothelial function (Chumaeva et al., 2009).

Cardiovascular reactivity to acute emotional stress has been associated with increased carotid IMT (Alevizaki, Cimponeriu, Lekakis, Papamichael, & Chrousos, 2007; Heponiemi et al., 2007; Steptoe, Donald, O'Donnell, Marmot, & Deanfield, 2006). A study by Low and colleagues (2009) found that increased diastolic blood pressure reactivity to a laboratory stressor task over time (an average of 3.3 ± 0.8 year
follow-up) was associated with carotid IMT in a sample of healthy adolescents.

Additionally, a randomized clinical trial by Castillo-Richmond and colleagues (2000) tested the effect of a stress reduction intervention (Transcendental Meditation) on coronary heart disease in 60 African American men and women. Participants were randomly assigned to participate in either the Transcendental Meditation group or a health education (control) group for six to nine months. Results indicated that participants in the Transcendental Meditation intervention experienced a significant decrease in IMT compared to an increase in IMT in the control group.

Research also has found links between stress and endothelial dysfunction measured by brachial FMD. A recent study by Mausbach and colleagues (2010) examining FMD in dementia caregivers and non-caregiving controls found that caregivers of moderately to severely demented spouses exhibited poorer FMD compared to caregivers of mildly demented spouses and non-caregivers. Another study by Violanti and colleagues (2009) examined police work as a model of chronic stress and found that cortisol secretion after awakening, an index of hypothalamic-pituitary-adrenal (HPA) axis activation, was associated with poorer FMD in female police officers. This relationship was not apparent in male officers. Acute stress may also bring forth transient endothelial dysfunction, evidenced by findings that FMD was reduced after an acute mental stress task (Ghiadoni et al., 2000).

In sum, there is a great deal of evidence to suggest that chronic stress may predispose downstream arterial disease. However, the stress process in the context of Alzheimer caregiving is quite complex and elucidating the psychosocial and physiological pathways linking caregiving stress to downstream disease is worthy of
detailed investigation.

Specific Aims of the Current Study

Overview of Study Aims

A simplified conceptual model characterizing the translation of caregiving stress to atherosclerosis is presented in Figure 1. Measurement models for each factor in this model are presented in Figure 2. Aims 1-3 of the current study utilized a 2-step modeling approach (i.e., assessment of measurement models and analysis of the relations among latent factors) to test specific paths in this proposed model. Aim 4 was intended to use the same approach to test the complete model of the translation of caregiving stress to atherosclerosis. Finally, exploratory analyses were conducted to assess the relationships between caregiving stressors, coping, and carotid IMT longitudinally.

Figure 1. Simplified conceptual model of the translation of caregiving stress to atherosclerotic disease
Aim 1

The first aim of this study was to determine if the stress of caring for a spouse with Alzheimer’s disease is associated with increased evidence of atherosclerosis in the caregiver. Specifically, the relationship between the latent variable representing Caregiving Stress and the latent variable representing evidence of Large Vessel Disease (atherosclerotic disease) was examined.
Aim 1 Rationale

Previous work in several populations suggests that chronic stress is associated with increased carotid IMT (Gallo, Troxel, Kuller et al., 2003; Gallo, Troxel, Matthews et al., 2003; Hintsanen et al., 2005; Janicki, Kamarck, Shiffman, Sutton-Tyrrell, & Gwaltney, 2005; Kamarck, Muldoon, Shiffman, & Sutton-Tyrrell, 2007; Rosvall et al., 2002) and carotid plaque (Troxel, Matthews, Bromberger, & Sutton-Tyrrell, 2003). Furthermore, research in Alzheimer’s caregivers suggests that care-receiver dementia severity and length of time caregiving are associated with endothelial dysfunction (Mausbach et al., 2010). Given that caregivers reporting higher “objective” and “subjective” stress exhibit poorer cardiovascular outcomes and dysregulation in physiological processes associated with atherosclerosis (Aschbacher et al., 2006; Mausbach, Patterson, Rabinowitz, Grant, & Schulz, 2007; Mills et al., 2009), it is possible that similar relationships may exist between caregiving stress and markers of atherosclerotic disease.

Aim 1 Hypothesis

The latent factor representing “Caregiving Stress” (including measures of (a) Alzheimer care-recipient impairment (e.g., clinical dementia rating and problem behavior frequency), (b) caregiver subjective stress (e.g., role overload and reaction to care-recipient problem behaviors), and (c) duration of care) is expected to be positively associated with the latent factor characterizing Large Vessel Disease (including measures of mean common carotid IMT, carotid plaque, and brachial FMD). A conceptual model illustrating this relationship is presented in Figure 3.
**Aim 2**

The second aim of this study was to investigate the physiological mediators of the relationship between chronic caregiving stress and evidence of atherosclerotic disease.

**Aim 2 Rationale**

Substantial evidence suggests that SAM and inflammatory processes play important roles in the cascade of events contributing to atherogenesis (Black & Garbutt, 2002; Clinton & Libby, 1992b; Ross, 1999). Given the evidence that caregiving stress is associated with sympathetic arousal (Aschbacher et al., 2008; Mausbach et al., 2005) and inflammation (von Känel et al., 2006), these processes represent plausible mechanisms linking caregiving stress to downstream disease.

**Aim 2 Hypothesis**

The latent variable representing “Physiological Mediators” of atherosclerosis (including observed indicators of SAM tone (e.g., norepinephrine, epinephrine, and blood pressure) and inflammation (e.g., c-reactive protein (CRP) and proinflammatory...
cytokines IL-1β, IL-2, IL-6, IL-8, and IL-12) are expected to mediate the relationship between Caregiving Stress and evidence of Large Vessel Disease. Specifically, increased Caregiving Stress is hypothesized to bring forth increases in Physiological Mediators, thereby exacerbating Large Vessel Disease. A conceptual model illustrating this relationship is presented in Figure 4.

**Figure 4.** Structural model representing the putative mediating effect of Physiological Mediators of atherosclerosis (SAM tone and inflammation) on the association between Caregiving Stress and Large Vessel Disease.

**Aim 3**

The third aim of this study was to determine if Coping Resources moderated the relationship between Caregiving Stress and Large Vessel Disease.

**Aim 3 Rationale**

Previous work in caregivers suggests that personal mastery may exert a protective effect on sympathetic reactivity (Roepke et al., 2008), coagulation (Mausbach, von Känel et al., 2008), and β2-adrenergic receptor sensitivity (Mausbach,
Aschbacher et al., 2008). Further, self-efficacy for using problem-focused coping may have a protective effect on inflammation (Mausbach et al., 2011) and blood pressure (Harmell et al., 2011). Considering that use of positive coping strategies is associated with improved functioning of systems associated with atherosclerosis, it is possible that these strategies may buffer the relationship between caregiving stress and atherosclerotic disease.

**Aim 3 Hypothesis**

Coping Resources (e.g., personal mastery, problem-focused coping, and coping self-efficacy) are expected to moderate the association between Caregiving Stress and evidence of Large Vessel Disease (see Figure 5). Specifically, the relationship between Caregiving Stress and Large Vessel Disease is expected to be strongest for those reporting poor positive coping and less apparent for those endorsing high positive coping.

![Figure 5](image.png)

**Figure 5.** Model illustrating Coping Resources as a moderator of the relationship between Caregiving Stress and Large Vessel Disease
**Aim 4**

The fourth aim of this study was intended to test the conceptual model characterizing the translation of caregiving stress to atherosclerosis (Figure 6) as a whole.

**Aim 4 Hypothesis**

Statistical as well as descriptive indices of fit are expected to support the proposed model characterizing the translation of caregiving stress to atherosclerosis.

![Figure 6. Complete model of the translation of caregiving stress to atherosclerosis](image)

Note. CDR = Clinical Dementia Rating; CRP = C-reactive Protein; DBP = Diastolic Blood Pressure; EPI = Epinephrine; IMT = Intima-media Thickness; IL-1β = Interleukin-1beta; IL-2 = Interleukin-2; IL-6 = Interleukin-6; IL-8 = Interleukin-8; IL-12 = Interleukin-12; NE = Norepinephrine; SAM = Sympatho-adrenal-medullary Axis; SBP = Systolic Blood Pressure.
Exploratory Analyses

Relationships between caregiving stressors, coping resources, and carotid IMT were assessed longitudinally over 24 months.

Rationale

Accelerated carotid IMT progression has been demonstrated in men experiencing high job strain (Kamarck, Muldoon, Shiffman, & Sutton-Tyrrell, 2007) and in women in reporting low-satisfaction in their marriages (Gallo, Troxel, Kuller et al., 2003), therefore, it may be possible that the stress associated with dementia caregiving may also predispose accelerated IMT progression.

Hypothesis 1

Caregivers endorsing higher stress (i.e., role overload) at year 1 are expected to have increased IMT progression over time compared to caregivers reporting less stress.

Hypothesis 2

Caregivers endorsing higher use of positive coping strategies (e.g., mastery, problem-focused coping, and coping self efficacy) at year 1 are expected to have slower IMT progression over time compared to caregivers reporting lower use of positive coping.
II. METHODS

Participants

Participants were 126 community-dwelling, older adults caring for a spouse diagnosed with Alzheimer’s disease. The caregivers in this study were a subset of participants enrolled in the University of California, San Diego (UCSD) Alzheimer Caregiver Study, a 5-year study examining the psychobiologic effects of stress on physical and psychological health. To be eligible for this study, caregivers were required to be at least 55 years of age, married, and living with their spouse at home at the time of enrollment. Caregivers were excluded if they were diagnosed with or receiving treatment for a serious or terminal medical condition (e.g., Parkinson’s disease), receiving or had received treatment for cancer within the past 5 years, or reported severe hypertension (BP > 200/120) at time of enrollment. Caregivers were recruited from Alzheimer caregiver support groups, senior health fairs, flyers, referrals from the UCSD Alzheimer’s Disease Research Center (ADRC), and recommendation from other participants enrolled in the study. All caregivers provided written, informed consent to participate in the study, which was approved by the UCSD Institutional Review Board (IRB). The specific aims of the current dissertation study were approved by IRB committees from both UCSD and San Diego State University. Assessments were conducted at baseline and repeated annually. For the current study, data from baseline, 12-month follow-up, and 24-month follow-up were available for analysis. Seventy-eight caregivers went through a transition (i.e., spouse placed in institutionalized care or bereavement) after baseline, and therefore, his/her data from that point on was excluded from analysis.
Procedure

Assessments were administered in each participant’s home by a trained research assistant, nurse, and sonographer. After obtaining informed consent, the research assistant administered a semi-structured interview assessing medical history (e.g., current diagnoses, symptoms), health behaviors (e.g., smoking history, physical activity), psychosocial variables (e.g., coping and burden), and care-recipient impairment (e.g., dementia severity, problem behaviors). The interviewer also recorded the caregiver’s current medications and demographic information.

Within one week, the nurse and sonographer collected biological data including blood pressure, blood draw for catecholamines and inflammatory markers, and ultrasound assessment of brachial FMD, plaque and common carotid IMT. In order to minimize the effects of diurnal variations, biological assessments were exclusively conducted from 8AM-10AM for each participant. The nurse first inserted a 22-gauge indwelling venous catheter into the forearm while the participant rested in a supine position. After catheter insertion, participants rested for a period of 5 minutes while keeping the hand level with the heart to control for hydrostatic differences. The first blood pressure measurement was then taken. The participant then rested for an additional 10 minutes, after which the second blood pressure measurement was recorded. The blood draw was then obtained, while discarding the first 2 ml. Bloods for the inflammatory marker assays were dispensed into EDTA tubes and centrifuged at 3,000 g for 10 minutes at 4-8°C. Samples were placed on crushed ice and were then processed for storage in a -80°C freezer until assayed. The blood draw was followed by
the final blood pressure recording. Ultrasound assessment of brachial FMD, plaque, and carotid artery IMT were then conducted with the participant lying in the same position.

Self-Report Measures

Demographic Information

Participants provided demographic information including their age, gender, ethnicity, educational attainment, monthly income, and years of caregiving.

Care-receiver Dementia Severity

The dementia severity of participants’ spouses was assessed using the Clinical Dementia Rating (CDR) scale (Morris, 1993). Participants rated their spouse’s abilities in six cognitive and behavioral domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. Dementia severity ratings ranged from 0-3 (0 = no dementia; 3 = severely demented) on each domain, and the overall dementia severity score represented the average rating across these dimensions. Cronbach’s alpha in this sample was 0.87.

Patient Problem Behaviors

The Revised Memory and Behavior Problem Checklist (RMBPC) was utilized to assess the problem behaviors of participants’ spouses (Teri et al., 1992). The RMBPC has demonstrated strong psychometric properties among dementia caregivers (Roth et al., 2003). Participants rated the frequency in the past week that their spouse
exhibited 24 problematic behaviors, such as disrupting the participant’s sleep and asking the same question repeatedly. Frequency of behaviors was rated on a 4-point scale (0 = “never;” 1 = “1-2 times;” 2 = “3-6 times;” 3 = “daily or more often”) and the sum of these ratings was used as a total problem behaviors frequency score. For each problem behavior endorsed, participants rated the extent to which they were bothered or upset by the behavior on a 5-point Likert scale ranging from 0 = “not at all” to 4 = “extremely.” The sum of these item scores reflected the participant’s negative reaction to their spouse’s problem behaviors. Cronbach’s alpha in this sample was 0.81 for problem behavior frequency.

Role Overload

The Role Overload scale (Pearlin, Mullan, Semple, & Skaff, 1990) was used to assess perceived level of burden. Participants rated their agreement with four statements such as, “I have more things to do than I can handle” on a 4-point scale (0 = “not at all”; 3 = “completely”). Items were summed in order to derive a total overload score. Cronbach’s alpha in this sample was 0.76.

Depressive Symptoms

The 10-item form of the Center for Epidemiologic Studies Depression Scale (CESD-10) (Andresen, Malmgren, Carter, & Patrick, 1994) was used to assess depressive symptoms. Participants rated their agreement with statements such as, “I felt depressed” and “I felt lonely,” on a 4-point scale (0 = “rarely or none of the time (< 1 day);” 3 = “most or almost all the time (5-7 days)”). This instrument has
established reliability and validity in older adults (Andresen, Malmgren, Carter, & Patrick, 1994). Cronbach’s alpha in this sample was 0.53.

Sleep Quality

Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI) (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). This self-report measure assesses seven components of sleep quality: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleep medication, and daytime dysfunction. A global sleep quality score was derived by summing the scores on each of the seven components. Scores ranged from 0-21, with higher scores indicating poorer sleep. Past work has found high internal consistency of the PSQI with a Cronbach’s alpha of 0.83 (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). Cronbach’s alpha in this sample was 0.68.

Physical Activity

Participant physical activity was assessed using the Rapid Assessment of Physical Activity (RAPA) (Topolski et al., 2006). The RAPA was developed for older adults based on the Center for Disease Control and Prevention (CDC) recommendation for physical activity (≥30 minutes of moderate physical activity on most days of the week). Participants were provided with descriptions and examples of light, moderate, and vigorous activities and were asked to respond “yes” or “no” to nine items assessing the frequency, duration, and intensity of their physical activity. Based on these responses, a dichotomous variable was created indicating if the
participant met the CDC recommendation for physical activity, such that “0” specified that the recommendation was not met and “1” specified that the recommendation was met (i.e., regularly active).

**Duration of Care**

Caregivers provided the year that their spouse was diagnosed with Alzheimer’s disease (i.e., the year that one became a caregiver). The time elapsed between the diagnosis year and the time of the baseline assessment was considered the duration of care.

**Coping Strategies**

The Revised Ways of Coping Checklist (P. P. Vitaliano, Russo, & Carr, 1985) was used to assess participants’ utilization of several coping strategies. This 42-item measure instructed participants to recall a recent stressor (e.g., marital, caregiving). Participants rated the extent to which they used certain strategies (e.g., “made a plan of action and followed it,” “went on as if nothing had happened,” and “criticized or lectured yourself”) to cope with the conflict on a 4-point scale (0 = “never used;” 1 = “used somewhat;” 2 = “used quite a bit;” 3 = “used a great deal”). Responses were summed within five coping subscales: problem-focused coping, seeks social support, blamed self, wishful thinking, and avoidance coping. The Revised Ways of Coping Checklist has demonstrated satisfactory reliability and validity across several distressed samples, including spousal caregivers of Alzheimer’s disease patients (P. P. Vitaliano, Russo, & Carr, 1985). For the purpose of this study, problem-focused
coping was the subscale of interest for analyses. Cronbach’s alpha in this sample was 0.85.

**Personal Mastery**

The 7-item Personal Mastery scale (Pearlin et al., 1990) was administered to determine participants’ sense of control over their life circumstances. The Personal Mastery Scale has been shown to have strong structural validity, with principal component factor loadings ranging from -0.47 to 0.76 (Pearlin and Schooler, 1978). Participants were asked to rate the extent to which they agreed with statements such as, “I have little control over the things that happen to me” and, “I can do just about anything I really set my mind to do.” Responses were given on a 4-point scale (0 = “strongly disagree;” 1 = “disagree,” 2 = “agree;” 3 = “strongly agree”). Two items were reverse scored and items were summed to create an overall mastery score (range = 7-28), with higher scores indicating greater sense of mastery. Cronbach’s alpha in this sample was 0.53.

**Coping Self-efficacy**

The 13-item reduced form of the Coping Self-efficacy Scale (Chesney, Neilands, Chambers, Taylor, & Folkman, 2006) assessed participant self-efficacy in three domains: self-efficacy for using problem-focused coping, self-efficacy for stopping unpleasant thoughts, and self-efficacy for getting support from friends and family. This measure instructed participants to rate their confidence in their ability to perform certain actions associated with these domains on a scale of 0-10 (0 = “cannot
Items included “break an upsetting problem into separate parts” (problem-focused coping), “make unpleasant thoughts go away” (stopping unpleasant thoughts), and “get emotional support from friends and family” (getting support from friends and family). Scores were summed within each scale to obtain a total score within each domain. The subscales of the Coping Self-efficacy Scale have demonstrated strong reliability and validity (Chesney, Neilands, Chambers, Taylor, & Folkman, 2006). For the purposes of the current study, the 6-item subscale measuring self-efficacy for using problem-focused coping was used to assess coping self-efficacy given its association with physiological mediators of stress in previous literature (Harmell et al., 2011; Mausbach et al., 2011). Cronbach’s alpha in this sample was 0.87.

**Biological Measures**

**Blood Pressure**

Systolic and diastolic blood pressure measurements were collected using a Microlife blood pressure monitor, model #3AC1-1PC. Three resting blood pressure measurements were averaged to obtain a more stable assessment.

**Plasma Catecholamines**

Norepinephrine and epinephrine were extracted using a catechol-O-methyltransferase (COMT) radioenzymatic assay that removed the catecholamines from 1 ml of plasma and concentrated them into 0.1 ml of dilute acid. This process is ten times as sensitive as basic catecholamine assays routinely conducted, has an 81%
efficiency rate, and removes Ca 2+ and other components that inhibit the COMT assay (Kennedy & Ziegler, 1990).

**Inflammatory Markers**

Circulatory levels of proinflammatory cytokines IL-1β, IL-2, IL-6, IL-8, IL-12 were assessed by high-sensitive ELISA (Quantikine, R&D Systems, Minneapolis, MN). Circulating CRP was assessed in plasma using the high-sensitivity Denka-Seiken assay.

**Carotid Artery Imaging for Common Carotid IMT and Plaque**

Images of the carotid artery were obtained using an Acuson Cypress portable ultrasound unit which collected high quality B-mode ultrasound images of the near and far walls of the right and left common, internal, and bifurcation segments from 2 standardized interrogation angles (right: 180° and 120°; left: 180° and 240°). The carotid flow divider was used as a reference point from which segments were defined: (a) the common carotid was defined as the segment 1 to 2 cm proximal to the flow divider, (b) the bifurcation was defined as the segment 0 to 1 cm proximal to the flow divider, and (c) the internal carotid was defined as the segment 0 to 1 cm distal to the flow divider. A single sonographer collected images for all participants, thereby avoiding issues of inter-sonographer variability. Images were saved, archived, and read off-line using the computer program Vascular Research Tools (Medical Imaging Applications, Coralville, IA) by a reader blinded to participant characteristics.
Common carotid IMT was defined as the distance between the intimal-luminal and the medial-adventitial interfaces of the common carotid artery. Common carotid IMT was used as an outcome of interest given that past research has found common carotid IMT to be a strong predictor of stroke and myocardial infarction (O'Leary et al., 1999). Moreover, IMT data of the common carotid tends to be more complete compared to other arterial segments (Crouse, Craven, Hagaman, & Bond, 1995; Howard et al., 1993), and research suggests that measuring common carotid IMT at several interrogation angles yields the best reproducibility (Kanters, Algra, van Leeuwen, & Banga, 1997). For these reasons, the Mannheim Intima-Media Thickness Consensus concluded that measurement of IMT of the common carotid arteries is preferred (Touboul et al., 2004). In the current study, mean common IMT was calculated as the mean of all eight IMT measurements of the common carotid artery.

A focal plaque was defined as a discrete area of hyperechogenicity and/or a focal protrusion into the lumen of the vessel at any segment (i.e., common, internal, or bifurcation). A dichotomous variable characterized the presence or absence of plaque in any of the arterial segments, with individuals scoring a “1” if one or more of the segment images exhibited a visible plaque, and individuals scoring a “0” if all images were absent of visible plaques.

Brachial Artery FMD

Brachial artery FMD was measured according to a modified method described in Celemajer and colleagues (1992). An occlusion cuff was placed on the participant’s right upper arm and a longitudinal section of the brachial artery 4-10 cm proximal to
the antecubital fossa was scanned using the same Acuson Cypress portable ultrasound system with a high resolution 5.4-6.6 MHz linear array transducer (Siemens Medical Solutions USA, Mountain View, CA). Three baseline images of the anterior and posterior walls were saved. The occlusion cuff was then inflated to 50 mmHg above the participant’s systolic blood pressure for 5 minutes in order to induce distal hypoxia. The cuff was then deflated and images of the artery were saved every 15 seconds for the first minute and then once every 30 seconds during the next 8 minutes. FMD was calculated as the maximum percent change in the brachial diameter (FMD%\textsubscript{max}), from the average baseline diameter in cm (D\textsubscript{FMD(base)}) to the maximum diameter post-cuff deflation in cm (D\textsubscript{FMD(max)}): \[ FMD%\textsubscript{max} = [(D\textsubscript{FMD(max)}/D\textsubscript{FMD(base)}) - 1]*100. \]

Data Analyses

Data Preparation

In preparation for analysis, the following precautions were taken in order to screen and clean the data and to ensure that assumptions for the statistical tests were met. Missing values were analyzed in order to determine if there were any patterns of “missingness.” Specifically, dummy-coded variables indicating completeness of data (i.e., 0 = value is missing; 1 = value is present) were used to determine if these groups differed based upon other study variables. Depending on the amount and nature of missing data, multiple imputation was used to impute missing values. The data was also screened for outliers. Outliers were handled on a case-to-case basis depending on the nature of the outlier (i.e., deletion of unrealistic or impossible values).
Multivariate normality was assessed using the normalized estimate of Mardia’s coefficient.

_Aim 1 Analytic Plan_

A 2-step structural equation modeling (SEM) approach was used to assess the path diagram presented in Figure 3. Using the SEM software program, EQS 6.1 (Bentler & Wu, 1995a, 1995b), the measurement models of latent factors were first assessed to derive latent factor scores for use in analysis. Assessment of the structural model using those derived latent factors followed.

First, confirmatory factor analysis (CFA) was used to test each a priori measurement model for the latent constructs of “Caregiving Stress” and “Large Vessel Disease.” That is, direct relationships between the observed variables 1) role overload, 2) duration of care, 3) CDR, 4) problem behavior frequency, and 5) problem behavior reactivity, and the latent factor, Caregiving Stress, were modeled. Likewise, direct relationships between observed variables 1) IMT, 2) FMD, and 3) carotid plaque, and the latent factor, Large Vessel Disease, were modeled. Equations specifying the factor loadings of observed variables onto their latent factor were modeled in order to attempt to explain the variance-covariance matrix among observed variables.

Overall model fit for the measurement models was assessed using maximum likelihood estimation to derive a fit function. Both statistical (e.g., chi-squared) and descriptive (e.g., standardized root mean squared residual (SRMR), comparative fit index (CFI), root mean square error of approximation (RMSEA), etc.) indices of fit
were examined. A non-significant chi-squared test indicated good model fit (Hu & Bentler, 1999). Descriptive fit indices supplemented information from the statistical test of fit, given the impact that sample size can have on the significance of chi-squared tests. Descriptive fit index cutoffs used included SRMR < .08 (Hu & Bentler, 1999), CFI > .95 (Hu & Bentler, 1999), and RMSEA < .07 (Steiger, 2007). The determination of which fit indices to report has not been clearly established, however; Tabachnick and Fidell (2001) suggest reporting multiple indices of fit to support the acceptance or rejection of models, and Hu and Bentler (1999) propose optimal cutoffs for combinations of fit indices.

Tabachnick and Fidell (2001) recommend that SEM models have approximately 10 participants per estimated parameter when the effect size is large and when observed variables are normally distributed. Others have recommended that small- to medium-sized models have at least 200 participants (Boomsma, 1983). MacCallum and colleagues (1996) developed a framework for hypothesis testing and power analysis for testing model fit in covariance structure models. In this method of power estimation, effect size is defined based upon the null and alternative values of the RMSEA. They use guidelines derived by Browne and Cudeck (1993) stating that RMSEA values in the range of 0.05 to 0.08 are indicative of fair model fit. They also provide statistical program code for calculating power for SEM models in which the null and alternative values, model degrees of freedom, alpha level, and sample size are specified. For tests of close fit, the RMSEA null value was specified as 0.05 and the alternative value was specified as 0.08. In order to test the complete model proposed in Aim 1 simultaneously, power was estimated at 0.28. Therefore, it was decided that
utilizing a 2-step approach of (1) running CFA for measurement models separately and then (2) assessing the structural path in a separate step using regression with derived latent factor scores would be a more powerful and preferred approach.

**Aim 2 Analytic Plan**

The 2-step analytic approach described for Aim 1 (i.e., CFA of measurement models and regression of the relationships among derived latent variables) was also used to assess the model presented in Figure 4. CFA was used to derive the latent variable, Physiological Mediators. The same latent variables for Caregiving Stress and Large Vessel Disease derived in Aim 1 were used in this analysis. The mediation effect was tested using Sobel tests (Sobel, 1982).

**Aim 3 Analytic Plan**

In order to test the moderating effect of the latent “Coping Resources” variable on the relationship between latent Caregiving Stress and Large Vessel Disease variables (presented in Figure 5), the 2-step approach described in Aim 1 was employed. After deriving the Coping Resources variables via CFA, the structural path model of the relations among latent variables was assessed using regression. An interaction term was created by grand mean centering the Caregiving Stress and Coping Resources variables and multiplying them together.

**Aim 4 Analytic Plan**

The complete model of the translation of caregiving stress to atherosclerosis is
presented in Figure 6. Depending on the outcome of analyses for Aims 1-3, this complete model will be tested simultaneously using path analysis. The same latent variables derived in Aims 1-3 will be used to test this model. Statistical and descriptive indicators of fit described in Aim 1 will be used to assess overall model fit and individual parameters.

**Exploratory Analyses**

Exploratory analyses were conducted to assess the relationships between caregiving stress, coping resources, and carotid IMT over time. Mixed (random effects) regression modeling was used in order to determine the effect of stress and coping on IMT over time. This technique estimates an intercept and a slope for each participant based on his/her available data, therefore, a mixed assessment at a single time point does not exclude a participant from analysis. Linear predictors were centered at their means in order to reduce problems associated with multicollinearity and to produce interpretable coefficients (Kraemer & Blasey, 2004). Specifically, caregiving stress (i.e., role overload) and coping resources (i.e., personal mastery, problem-focused coping, and coping self-efficacy) were centered at their means for the entire sample. Age at baseline assessment (mean centered) and gender (males coded -0.5 and females coded 0.5) were entered as covariates.

Mixed regression models assessed the relationship between each indicator of stress/coping at baseline and IMT over time. For each model, the dependent variable was mean common carotid IMT. Time (in years) and the indicator of stress/coping were entered as fixed effects in the model. Random effects included random
intercepts and slopes. The main effects of each stress/coping indicator and time were assessed, as well as the interactions between each stress/coping indicator and time. Based on previous reports finding effects of chronic psychosocial stress on carotid IMT and IMT progression over a period of 1-3 years (Gallo, Troxel, Kuller et al., 2003; Gallo, Troxel, Matthews et al., 2003; Hintsanen et al., 2005), the effect size of this analysis was estimated to be small-medium.
III. RESULTS

Participant Characteristics

One hundred and twenty-six caregivers were included in the statistical analyses. Caregivers were a mean age of 74 ± 8 years-old and 71% were women. Caregivers had provided care to their spouse for an average of 4.3 years and caregiving duration ranged from 0.5 to 17 years. The average CDR score of the Alzheimer’s disease patient was 1.6 (mild to moderate dementia). A majority of caregivers were taking at least one antihypertensive medication. Table 1 presents demographic characteristics of this sample before and after imputing missing data for select variables.

Table 1. Caregiver Characteristics (N=126)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Before Multiple Imputation</th>
<th>After Multiple Imputation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, mean (SD)</td>
<td>73.7 (8.0)</td>
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</tr>
<tr>
<td>Female gender, n (%)</td>
<td>89 (70.6)</td>
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</tr>
<tr>
<td>Caucasian ethnicity, n (%)</td>
<td>120 (95.2)</td>
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<tr>
<td>Graduated college, n (%)</td>
<td>56 (44.4)</td>
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</tr>
<tr>
<td>Monthly household income in dollars, median *</td>
<td>4,000</td>
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</tr>
<tr>
<td>Taking antihypertensive medication, n (%)</td>
<td>76 (60.3)</td>
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<tr>
<td>Body mass index, mean (SD)</td>
<td>26.5 (4.7)</td>
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</tr>
<tr>
<td>Past or current smoker, n (%)</td>
<td>58 (46)</td>
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</tr>
<tr>
<td>Regular physical activity (CDC criteria), n (%)</td>
<td>42 (33.3)</td>
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</tr>
<tr>
<td>Global PSQI score, mean (SD)</td>
<td>6.7 (3.6)</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>Before Multiple Imputation</td>
<td>After Multiple Imputation</td>
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<td>---------------------------</td>
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<tr>
<td>CESD score, mean (SD)</td>
<td>8.8 (5.8)</td>
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<tr>
<td>Role overload, mean (SD)</td>
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<tr>
<td>Duration of caregiving in years, mean (SD)</td>
<td>4.3 (3.4)</td>
<td>4.4 (3.4)</td>
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<td>AD patient CDR score, mean (SD)</td>
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<td>Frequency of problem behaviors, mean (SD)</td>
<td>23.7 (9.5)</td>
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<td>Problem behaviors reactivity, mean (SD)</td>
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<td>Personal mastery, mean (SD)</td>
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<td>22.4 (6.9)</td>
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<tr>
<td>Coping self-efficacy, mean (SD)</td>
<td>43.9 (10.1)</td>
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<tr>
<td>Resting systolic blood pressure in mmHg, mean (SD)</td>
<td>134.3 (15.3)</td>
<td>134.4 (15.0)</td>
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<tr>
<td>Resting diastolic blood pressure in mmHg mean (SD)</td>
<td>75.8 (8.6)</td>
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<tr>
<td>Plasma norepinephrine in pg/mL, mean (SD)</td>
<td>510.2 (243.3)</td>
<td>507.4 (229.4)</td>
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<td>Plasma epinephrine in pg/mL, mean (SD)</td>
<td>42.7 (42.9)</td>
<td>41.5 (40.0)</td>
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<td>C-reactive protein in mg/l, mean (SD)</td>
<td>3.7 (6.4)</td>
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<td>IL-1β in pg/mL, mean (SD)</td>
<td>1.9 (6.3)</td>
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<td>IL-6 in pg/mL, mean (SD)</td>
<td>1.5 (2.0)</td>
<td>1.6 (2.0)</td>
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<td>IL-8 in pg/mL, mean (SD)</td>
<td>7.3 (4.7)</td>
<td>7.3 (4.5)</td>
</tr>
<tr>
<td>IL-12 in pg/mL, mean (SD)</td>
<td>10.2 (37.2)</td>
<td>12.1 (36.4)</td>
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<tr>
<td>Mean common carotid IMT in mm, mean (SD)</td>
<td>0.7 (0.1)</td>
<td>0.7 (0.1)</td>
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Table 1. Continued

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<tr>
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<th>Before Multiple Imputation</th>
<th>After Multiple Imputation</th>
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</thead>
<tbody>
<tr>
<td>FMD in %, mean (SD)</td>
<td>14.5 (5.7)</td>
<td>14.7 (5.7)</td>
</tr>
</tbody>
</table>

AD=Alzheimer’s disease; CDC=Centers for Disease Control; CDR=Clinical Dementia Rating; CESD= Center for Epidemiologic Studies Depression Scale; FMD=Flow-mediated dilation; IMT=Intima-media Thickness; PSQI=Pittsburg Sleep Quality Index.

*Data on income was based on 113 participants because 13 declined to respond.

**Data represented as mean (SD) given that multiple imputation yielded continuous scores.

Missing Data

With regards to common carotid IMT data, 69 caregivers had a complete set of 8 IMT measurements. That is, the remaining caregivers had 1-7 common carotid IMT measurements. The amount of missing values on any one IMT measurement ranged from 14-33 cases. Missingness of IMT data (i.e., caregivers having at least 1 of 8 IMT measurements missing) was significantly associated with CDR score ($\chi^2(3)= 15.59, p = 0.001$) and duration of care ($t(122)= 3.12, p = 0.002$), such that caregivers with more demented spouses and who had provided care for more years were more likely to have complete data. IMT data missingness was not significantly associated with any other study variable.

Missing data for the other observed indicators included in the complete model of the translation of caregiving stress to atherosclerotic disease were also examined. Sixty-five (52%) caregivers were missing IL-2 data, and therefore, it was decided to exclude this variable from analysis and from the measurement model of Inflammation. For the remaining observed indicators in the model, caregivers were missing at most 16% of data on any one indicator. Table 2 presents missingness data for observed
variables included in the complete model.

### Table 2. Missing data information

<table>
<thead>
<tr>
<th>Observed Indicator</th>
<th>Number of Missing Cases (out of 126 total)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Caregiving Stress</strong></td>
<td></td>
</tr>
<tr>
<td>Role Overload</td>
<td>0</td>
</tr>
<tr>
<td>Years of Caregiving</td>
<td>2</td>
</tr>
<tr>
<td>CDR Score</td>
<td>0</td>
</tr>
<tr>
<td>Problem Behavior Frequency</td>
<td>0</td>
</tr>
<tr>
<td>Problem Behavior Reactivity</td>
<td>0</td>
</tr>
<tr>
<td><strong>Coping</strong></td>
<td></td>
</tr>
<tr>
<td>Personal Mastery</td>
<td>0</td>
</tr>
<tr>
<td>Problem-focused Coping</td>
<td>0</td>
</tr>
<tr>
<td>Coping Self-efficacy</td>
<td>0</td>
</tr>
<tr>
<td><strong>SAM Arousal</strong></td>
<td></td>
</tr>
<tr>
<td>Resting Systolic Blood Pressure</td>
<td>6</td>
</tr>
<tr>
<td>Resting Diastolic Blood Pressure</td>
<td>6</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>15</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>15</td>
</tr>
<tr>
<td><strong>Inflammation</strong></td>
<td></td>
</tr>
<tr>
<td>C-reactive Protein</td>
<td>14</td>
</tr>
<tr>
<td>IL-1β</td>
<td>20</td>
</tr>
<tr>
<td>IL-2*</td>
<td>65</td>
</tr>
<tr>
<td>IL-6</td>
<td>10</td>
</tr>
<tr>
<td>IL-8</td>
<td>10</td>
</tr>
<tr>
<td>IL-12</td>
<td>10</td>
</tr>
<tr>
<td><strong>Large Vessel Disease</strong></td>
<td></td>
</tr>
<tr>
<td>IMT (range of missing cases from all 8 measurements)</td>
<td>14-33</td>
</tr>
<tr>
<td>Plaque</td>
<td>6</td>
</tr>
<tr>
<td>FMD</td>
<td>10</td>
</tr>
</tbody>
</table>

*IL-2 excluded from further analysis given the large about of missing data.

Multiple imputation was used to generate 5 imputed datasets for observed indicators in the overall model (Rubin, 1987). Pooled estimates were used in the final dataset. Imputed values for years of caregiving were estimated based upon existing CDR scores. Imputed data for SAM Arousal observed indicators were estimated.
based upon existing data for SAM Arousal variables, age, gender, BMI, smoking history (i.e., current or past smoker), and antihypertensive medication use. Imputed data for Inflammation observed indicators were estimated based upon existing data for Inflammation variables, age, gender, BMI, and smoking history. Imputed data for Large Vessel Disease indicators were estimated based upon existing data for Large Vessel Disease variables, age, gender, BMI, smoking history, and antihypertensive medication use.

The rationale for conducting multiple imputation separately for observed indicators within proposed latent variables was because it allowed for specifying a unique set of predictors for each group of imputed datasets based upon theoretical relationships. This is important because the aforementioned predictors would not be expected to be valuable predictors for all variables in which data were imputed. For example, one would expect that CDR might be a good predictor of years of care, however one would not expect variables such as smoking history and antihypertensive medication use to predict years of care. Therefore, predictor variables were specifically chosen in order to improve imputation of variables within each proposed measurement model.

**Confirmatory Factor Analysis (Measurement Model) Results**

Tables 3 through 7 present bivariate correlations between observed variables included in the complete Model of the Translation of Caregiving Stress to Atherosclerotic Disease. Table 8 presents bivariate correlations between latent factor scores included in the complete model.
Table 3. Pearson correlations between observed variables indicated in the Caregiving Stress factor score

<table>
<thead>
<tr>
<th></th>
<th>1.</th>
<th>2.</th>
<th>3.</th>
<th>4.</th>
<th>5.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Role Overload</td>
<td>1.000</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2.</td>
<td>Years</td>
<td>0.032</td>
<td>1.000</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2.</td>
<td>Caregiving</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>CDR Score</td>
<td>0.347**</td>
<td>0.274**</td>
<td>1.000</td>
<td>-</td>
</tr>
<tr>
<td>4.</td>
<td>Problem</td>
<td>0.424**</td>
<td>0.021</td>
<td>0.200*</td>
<td>1.000</td>
</tr>
<tr>
<td>5.</td>
<td>Problem</td>
<td>0.339**</td>
<td>-0.061</td>
<td>0.115</td>
<td>0.419**</td>
</tr>
<tr>
<td></td>
<td>Behavior Reaction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p< 0.05

**p< 0.01

Table 4. Pearson correlations between observed variables indicated in the Coping factor score

<table>
<thead>
<tr>
<th></th>
<th>1.</th>
<th>2.</th>
<th>3.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Personal Mastery</td>
<td>1.000</td>
<td>-</td>
</tr>
<tr>
<td>2.</td>
<td>Problem-focused Coping</td>
<td>0.145</td>
<td>1.000</td>
</tr>
<tr>
<td>3.</td>
<td>Coping Self-efficacy</td>
<td>0.348**</td>
<td>0.279**</td>
</tr>
</tbody>
</table>

*p< 0.05

**p< 0.01

Table 5. Pearson correlations between observed variables indicated in the SAM Arousal factor score

<table>
<thead>
<tr>
<th></th>
<th>1.</th>
<th>2.</th>
<th>3.</th>
<th>4.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Systolic Blood Pressure</td>
<td>1.000</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2.</td>
<td>Diastolic Blood Pressure</td>
<td>0.579**</td>
<td>1.000</td>
<td>-</td>
</tr>
<tr>
<td>3.</td>
<td>Norepinephrine</td>
<td>0.179*</td>
<td>0.021</td>
<td>1.000</td>
</tr>
<tr>
<td>4.</td>
<td>Epinephrine</td>
<td>0.194*</td>
<td>0.116</td>
<td>0.579**</td>
</tr>
</tbody>
</table>

*p< 0.05

**p< 0.01
Table 6. Pearson correlations between observed variables indicated in the Inflammation factor score

<table>
<thead>
<tr>
<th></th>
<th>1.</th>
<th>2.</th>
<th>3.</th>
<th>4.</th>
<th>5.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. C-Reactive Protein</td>
<td>1.000</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2. IL-1ß</td>
<td>0.024</td>
<td>1.000</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3. IL-6</td>
<td>0.544**</td>
<td>0.004</td>
<td>1.000</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4. IL-8</td>
<td>-0.050</td>
<td>-0.117</td>
<td>0.036</td>
<td>1.000</td>
<td>-</td>
</tr>
<tr>
<td>5. IL-12</td>
<td>0.005</td>
<td>0.034</td>
<td>0.165</td>
<td>-0.085</td>
<td>1.000</td>
</tr>
</tbody>
</table>

* p< 0.05  
**p< 0.01

Table 7. Pearson correlations between observed variables indicated in the Large Vessel Disease factor score

<table>
<thead>
<tr>
<th></th>
<th>1.</th>
<th>2.</th>
<th>3.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. IMT</td>
<td>1.000</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2. Plaque</td>
<td>0.265**</td>
<td>1.000</td>
<td>-</td>
</tr>
<tr>
<td>3. FMD</td>
<td>-0.019</td>
<td>&lt;0.001</td>
<td>1.000</td>
</tr>
</tbody>
</table>

* p< 0.05  
**p< 0.01

Table 8. Pearson correlations between latent variables (factor scores) in the complete model

<table>
<thead>
<tr>
<th></th>
<th>1.</th>
<th>2.</th>
<th>3.</th>
<th>4.</th>
<th>5.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Caregiving Stress</td>
<td>1.000</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2. Coping Resources</td>
<td>-0.419**</td>
<td>1.000</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3. SAM Arousal</td>
<td>-0.106</td>
<td>-0.151</td>
<td>1.000</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4. Inflammation</td>
<td>0.131</td>
<td>-0.190*</td>
<td>-0.040</td>
<td>1.000</td>
<td>-</td>
</tr>
<tr>
<td>5. Large Vessel Disease</td>
<td>-0.082</td>
<td>0.048</td>
<td>0.121</td>
<td>0.127</td>
<td>1.000</td>
</tr>
</tbody>
</table>

* p< 0.05  
**p< 0.01

Caregiving Stress

The measurement model of the Caregiving Stress factor was indicated by 5 observed variables. Mardia’s coefficient for this model was 3.77. Statistical measures
of model fit were significant ($\chi^2(5) = 16.61, p = 0.005$). The model fit fairly well descriptively ($SRMR = 0.080$). Standardized factor loadings were statistically significant for CDR score (0.38), role overload (0.67), problem behavior frequency (0.66), and problem behavior reactivity (0.54). The factor loading for years of caregiving was not statistically significant (0.06).

**Coping**

The measurement model for the Coping factor was indicated by 3 observed variables. Mardia’s coefficient was 1.16. This model was just identified based on zero degrees of freedom. All standardized factor loadings were statistically significant: personal mastery (0.43), problem-focused coping (0.34), and coping self-efficacy (0.82).

**SAM Arousal**

The measurement model for the SAM Arousal factor was indicated by 4 observed variables. Mardia’s coefficient was 34.88, indicating multivariate non-normality. Therefore, robust statistical and descriptive fit indices were examined to adjust for non-normality. Satorra-Bentler scaled chi-square indicated poor model fit ($\chi^2(2) = 15.92, p < 0.001$). Descriptive indices of fit also suggested poor model fit (CFI = 0.59; RMSEA = 0.24). Standardized factor loadings were significant for systolic blood pressure (0.93) and diastolic blood pressure (0.68).
**Inflammation**

The measurement model for Inflammation was indicated by 5 observed variables. Mardia’s coefficient was 203.23, indicating multivariate non-normality. Therefore, robust statistical and descriptive fit indices were examined to adjust for non-normality. Satorra-Bentler scaled chi-square indicated poor model fit ($\chi^2(5) = 14.61$, $p = 0.012$). Descriptive indices of fit also suggested poor model fit (CFI = 0.50; RMSEA = 0.12). Standardized factor loadings for C-reactive protein (0.54), IL-6 (1.00), and IL-12 (0.17) were significant.

**Large Vessel Disease**

The measurement model for the Large Vessel Disease factor was indicated by 3 observed variables. Mardia’s coefficient was -2.59. This model was just identified based on zero degrees of freedom. No standardized factor loadings were significant: IMT (0.27), plaque (1.00), and FMD (<0.001).

**Aim 1 Analysis**

The relationship between Caregiving Stress and Large Vessel Disease was assessed using factor scores derived from CFA measurement models described above. Multiple regression was conducted to determine the unique association of the Caregiving Stress factor and the Large Vessel Disease factor controlling for age, gender, BMI, antihypertensive medication use, physical activity, smoking history, depressive symptoms (CESD score), and global sleep quality (PSQI). The only covariate significantly associated with Large Vessel Disease was age ($\beta = 0.33$, $p =$
0.001). The addition of the Caregiving Stress factor was not significant ($\beta = 0.02, p = 0.846$). The full model accounted for 18.3% of the variance in Large Vessel Disease.

**Aim 2 Analysis**

SAM Arousal and Inflammation latent factor scores were uncorrelated, and were therefore examined separately (rather than aggregated as “Physiological mediators”). Although there was not a direct association between Caregiving Stress and Large Vessel Disease, potential mediating effects of SAM Arousal and Inflammation on this relationship were examined. Previous literature recommends testing for mediation effects in the absence of a direct association between an independent variable and dependent variable if small effect size is suspected (Shrout & Bolger, 2002). Latent factor scores derived from CFA models for SAM Arousal and Inflammation were used in analysis. Sobel tests were conducted to determine these potential mediating effects. Neither SAM Arousal (Sobel Test Statistic = $-0.23$, SE = 0.01, $p = 0.816$) nor Inflammation (Sobel Test Statistic = 0.87, SE = 0.02, $p = 0.384$) were significant mediators of the Caregiving Stress-Large Vessel Disease relationship.

**Aim 3 Analysis**

The potential moderating effect of the Coping Resources factor on the relationship between Caregiving Stress and Large Vessel Disease was assessed with multiple regression using factor scores derived from CFA measurement models described above. The following covariates were entered in the first block of the
regression model: age, gender, BMI, antihypertensive medication use, physical activity, smoking history, depressive symptoms, and global sleep quality. Standardized scores for Caregiving Stress and Coping Resources were entered in the second block of the model. Finally, the Caregiving Stress-by-Coping Resources interaction term was entered in the final block of the regression model. The only significant covariate in the model was age (β = 0.32, p = 0.001). Caregiving Stress (β = 0.02, p = 0.889) and Coping Resources factors (β = 0.02, p = 0.866) did not significantly predict Large Vessel Disease. The interaction of Caregiving Stress and Coping Resources also did not significantly predict Large Vessel Disease (β = -0.04, p = 0.703).

Aim 4 Analysis

Before testing the complete model as a whole using path analysis, the Caregiving Stress-by-Coping Resources interaction was examined for the outcomes of SAM Arousal and Inflammation (i.e., the proposed Physiological Mediators). Linear regression models were conducted to assess this interaction controlling for the first-order effects of Caregiving Stress and Coping Resources as well as the following covariates: age, gender, BMI, antihypertensive use, physical activity, smoking history, depressive symptoms, and sleep quality.

**SAM Arousal**

Data from the regression predicting SAM Arousal is presented in Table 9. In the first block of the regression model, no covariates significantly predicted SAM
Arousal. In the second block of the model, the first-order effects (standardized scores) for Caregiving Stress and Coping Resources were added. Coping Resources was significantly associated with SAM Arousal ($\beta = -0.32, p = .003$), such that higher levels of coping were associated with reduced SAM Arousal. In the final step of the model, the Caregiving Stress-by-Coping Resources interaction term was entered and was not significant ($\beta = -0.15, p = 0.114$). In the final block of the model, female gender ($\beta = -0.21, p = 0.032$) and Coping Resources ($\beta = -0.32, p = .004$) significantly predicted SAM Arousal. The full model accounted for 16.9% of the variance in SAM Arousal.

Although the Caregiving Stress-by-Coping Resources interaction was not statistically significant, post-hoc probing of this interaction effect was conducted for exploratory purposes given the effect size of the interaction term. Post-hoc probing of this moderation effect was conducted by plotting the relationships between Caregiving Stress and SAM Arousal for low (-1 SD) and high (+1 SD) levels of Coping Resources in order to determine the nature of the conditional first-order effects of Caregiving Stress on SAM Arousal at varying levels of Coping Resources. This method of post-hoc probing of moderation effects allows for interpretation of the simple slopes conditional upon levels of the moderator variable (Holmbeck, 2002). Results indicated that Caregiving Stress significantly predicted SAM arousal under the condition of high levels of Coping Resources ($t = -2.06, p = 0.042$), but not under the condition of low Coping Resources ($t = 0.29, p = 0.774$). That is, higher Caregiving Stress was associated with lower SAM arousal for those who report higher use of positive coping strategies. There was no association between level of stress and SAM
arousal for those who reported lower use of positive coping strategies. Figure 7 presents the plots of the conditional first-order effects.

![Figure 7](image_url)

**Figure 7. Simple effects of Caregiving Stress on SAM Arousal at high and low levels of Coping Resources.** Caregivers reporting high levels of positive coping strategies had lower SAM Arousal at high levels of Caregiving Stress. The Caregiving Stress-by-Coping Resources interaction was not significant ($\beta = -0.153$, $p = 0.114$).

Given that this model included a large number of predictors potentially limiting power, an alternate model without covariates was tested to determine if the first-order effects or interaction term might strengthen with more degrees of freedom. In this alternate analysis, Caregiving Stress and Coping Resources were entered into the first block and the Caregiving Stress-by-Coping interaction term was entered in the second block. In this model, both the Caregiving Stress ($\beta = -0.22$, $p = 0.027$) and Coping Resources ($\beta = -0.23$, $p = 0.019$) first-order effects were significantly associated with SAM Arousal. That is, lower levels of caregiving stressors and lower
levels of coping were associated with increased SAM axis tone. The strength of the Caregiving Stress-by-Coping Resources interaction weakened ($\beta = -0.12$, $p = 0.168$).

**Table 9. Linear regression model predicting the SAM Arousal factor variable score**

<table>
<thead>
<tr>
<th></th>
<th>Block 1</th>
<th></th>
<th>Block 2</th>
<th></th>
<th>Block 3</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B(SE)</td>
<td>$p$</td>
<td>B(SE)</td>
<td>$p$</td>
<td>B(SE)</td>
<td>$p$</td>
</tr>
<tr>
<td>Intercept</td>
<td>-1.05 (1.15)</td>
<td>.362</td>
<td>.37 (1.14)</td>
<td>.748</td>
<td>.13 (1.17)</td>
<td>.911</td>
</tr>
<tr>
<td>Age</td>
<td>.02 (.01)</td>
<td>.150</td>
<td>.01 (.01)</td>
<td>.386</td>
<td>.01 (.01)</td>
<td>.629</td>
</tr>
<tr>
<td>Female Gender</td>
<td>-.28 (.12)</td>
<td>.159</td>
<td>-.37 (.19)</td>
<td>.060</td>
<td>-.42 (.19)</td>
<td>.032</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>-.01 (.02)</td>
<td>.719</td>
<td>-.01 (.02)</td>
<td>.620</td>
<td>-.02 (.02)</td>
<td>.343</td>
</tr>
<tr>
<td>Antihypertensive Use</td>
<td>.18 (.19)</td>
<td>.337</td>
<td>.25 (.18)</td>
<td>.174</td>
<td>.23 (.18)</td>
<td>.223</td>
</tr>
<tr>
<td>Physical Activity</td>
<td>.04 (.18)</td>
<td>.813</td>
<td>.03 (.18)</td>
<td>.887</td>
<td>.02 (.18)</td>
<td>.913</td>
</tr>
<tr>
<td>Ever Smoked</td>
<td>.23 (.17)</td>
<td>.183</td>
<td>.28 (.17)</td>
<td>.104</td>
<td>.34 (.17)</td>
<td>.051</td>
</tr>
<tr>
<td>Depressive Symptoms</td>
<td>.01 (.02)</td>
<td>.565</td>
<td>-.01 (.02)</td>
<td>.728</td>
<td>-.01 (.02)</td>
<td>.753</td>
</tr>
<tr>
<td>Global Sleep Quality</td>
<td>-.01 (.03)</td>
<td>.603</td>
<td>-.01 (.03)</td>
<td>.693</td>
<td>-.00 (.03)</td>
<td>.923</td>
</tr>
<tr>
<td>Caregiving Stress</td>
<td></td>
<td></td>
<td>-.14 (.10)</td>
<td>.192</td>
<td>-.17 (.10)</td>
<td>.113</td>
</tr>
<tr>
<td>Coping Resources</td>
<td>.30 (.10)</td>
<td>.003</td>
<td>-.30 (.10)</td>
<td>.004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caregiving Stress-by-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-1.89 (.12)</td>
<td>.114</td>
</tr>
<tr>
<td>Coping Resources</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$R^2 = 0.17$

Adjusted $R^2 = 0.09$

$F(11,114) = 2.11, p = .025$

**Inflammation**

Data from the regression predicting Inflammation is presented in Table 10. In the first block of the regression model, no covariates significantly predicted Inflammation. In the second block of the model, the first-order effects (standardized scores) for Caregiving Stress and Coping Resources were entered. Neither
significantly predicted Inflammation. In the final block of the model, the Caregiving Stress-by-Coping Resources interaction term was entered and was not statistically significant ($\beta = -0.063$, $p = 0.528$). The full model accounted for 9.6% of the variance in Inflammation.

Table 10. Linear regression model predicting the Inflammation score

<table>
<thead>
<tr>
<th></th>
<th>Block 1</th>
<th>Block 2</th>
<th>Block 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B(SE)</td>
<td>$p$</td>
<td>B(SE)</td>
</tr>
<tr>
<td>Intercept</td>
<td>-2.08 (1.24)</td>
<td>.095</td>
<td>-0.93 (1.25)</td>
</tr>
<tr>
<td>Age</td>
<td>.01 (.01)</td>
<td>.284</td>
<td>.01 (.01)</td>
</tr>
<tr>
<td>Female Gender</td>
<td>.30 (.21)</td>
<td>.161</td>
<td>.26 (.21)</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>.03 (.02)</td>
<td>.230</td>
<td>.03 (.02)</td>
</tr>
<tr>
<td>Antihypertensive Use</td>
<td>.16 (.20)</td>
<td>.434</td>
<td>.20 (.20)</td>
</tr>
<tr>
<td>Physical Activity</td>
<td>-.05 (.20)</td>
<td>.821</td>
<td>-.01 (.20)</td>
</tr>
<tr>
<td>Ever Smoked</td>
<td>-.10 (.19)</td>
<td>.594</td>
<td>-.12 (.19)</td>
</tr>
<tr>
<td>Depressive Symptoms</td>
<td>.01 (.02)</td>
<td>.449</td>
<td>-.01 (.02)</td>
</tr>
<tr>
<td>Global Sleep Quality</td>
<td>.00 (.03)</td>
<td>.906</td>
<td>-.01 (.03)</td>
</tr>
<tr>
<td>Caregiving Stress Score</td>
<td>.11 (.11)</td>
<td>.333</td>
<td>.10 (.12)</td>
</tr>
<tr>
<td>Coping Resources Score</td>
<td>-.17 (.11)</td>
<td>.131</td>
<td>-.17 (.11)</td>
</tr>
<tr>
<td>Caregiving Stress-by-Coping Resources</td>
<td>-.08 (.13)</td>
<td>.528</td>
<td></td>
</tr>
</tbody>
</table>

$R^2 = 0.10$
Adjusted $R^2 = 0.01$
$F(11,114) = 1.10, p = .372$
Given that there was not a significant Caregiving Stress-by-Coping Resources interaction effect on either SAM Arousal or Inflammation, the complete model of the translation of caregiving stress to atherosclerosis was not analyzed using path analysis.

**Exploratory Analysis**

A total of 139 data points were available for longitudinal analysis. Sixty-nine caregivers had IMT data at baseline assessment, 44 caregivers had IMT data at 12-month follow-up, and 26 caregivers had IMT data at 24-month follow-up. Mean (SD) IMT values at baseline, 12-month follow-up, and 24-month follow-up were 0.70 mm (0.10), 0.77 mm (0.11), and 0.80 mm (0.12), respectively.

Results indicated that IMT significantly varied as a function of time (coefficient = 0.04, t = 5.03, p < 0.001), such that IMT significantly increased over time. Role overload (coefficient < -0.01, t = -0.26, p = 0.789), personal mastery (coefficient < 0.01, t = 0.21, p = 0.837), and their interactions with time (role overload-by-time coefficient < 0.01, t = 0.95, p = 0.347; personal mastery-by-time coefficient < -0.01, t = -0.14, p = 0.890) did not significantly predict IMT. There were no first order effects of problem-focused coping (coefficient < -0.01, t = -0.54, p = 0.591) or coping self-efficacy (coefficient < -0.01, t = -1.03, p = 0.307) on IMT.

There was a significant problem-focused coping-by-time interaction on IMT (coefficient < -0.01, t = -2.80, p = 0.008). Post-hoc probing of this interaction indicated that caregivers with lower use of problem-focused coping at baseline had a steeper rate of change in IMT over time (i.e., increased IMT progression). Caregivers reporting higher problem-focused coping had slower IMT progression. Figure 8
presents the plotted means of IMT by high (+1SD) and low (-1SD) problem-focused coping over time.

There was a marginally significant coping self-efficacy-by-time interaction on IMT (coefficient < -0.01, t = -1.81, p = 0.078). Post-hoc probing of this interaction suggested that caregivers with lower coping self-efficacy at baseline had increased IMT progression over time. Figure 9 presents the plotted means of IMT by high (+1SD) and low (-1SD) coping-self efficacy over time.

Figure 8. Simple effects of problem-focused coping (PFC) on IMT at baseline, 12-month follow-up, and 24-month follow-up. Error bars reflect the standard error of the mean.
Caregivers with lower coping self-efficacy at baseline have increased IMT progression.

Figure 9. Simple effects of coping self-efficacy on IMT at baseline, 12-month follow-up, and 24-month follow-up. The coping self-efficacy-by-time interaction was marginally significant. Error bars reflect the standard error of the mean.
IV. DISCUSSION

The current investigation aimed to examine the validity of a proposed model characterizing the translation of Alzheimer’s disease caregiving stress to atherosclerotic disease. Measurement models of latent variables in this proposed model were first examined using confirmatory factor analysis given the a priori hypothesized associations between observed indicators in the model. Latent factor scores derived from these measurement models were then used to assess structural relationships in specific components of the model. Exploratory analyses assessed the relationship between stress, coping, and IMT longitudinally.

The results from confirmatory factor analyses indicated that the measurement model for the Caregiving Stress latent variable adequately fit the observed data descriptively. Measurement models for the Coping Resources and Large Vessel Disease latent variables were just identified. Measurement models for SAM Arousal and Inflammation were poorly fit.

With regards to structural associations, the proposed relationship of Caregiving Stress and Large Vessel Disease in Aim 1 was not statistically significant. For the analyses in Aim 2, SAM Arousal and Inflammation latent factor scores were uncorrelated, and were therefore examined separately (rather then aggregated as “Physiological Mediators,” as was originally planned in Aim 2). Neither SAM Arousal nor Inflammation mediated the relationship between Caregiving Stress and Large Vessel Disease in caregivers. For Aim 3, the Coping Resources latent factor score did not significantly moderate the association between Caregiving Stress and
Large Vessel Disease. Similarly, there were not statistically significant Caregiving Stress-by-Coping Resources interactions on SAM Arousal or Inflammation. However, the interaction had a small effect size for SAM Arousal and therefore, post-hoc probing of this interaction was conducted for exploratory purposes. The simple effects of Caregiving Stress on SAM Arousal at varying levels of Coping Resources indicated that Caregiving stress was negatively associated with SAM Arousal for those reporting high levels of coping resources. Given this pattern of results, it was contraindicated to test the complete model as a whole.

Exploratory longitudinal analyses indicated that caregivers who reported higher problem-focused coping at baseline had decreased IMT progression over 24-months. Similarly, coping self-efficacy marginally predicted IMT progression, such that caregivers reporting high coping self-efficacy also had decreased IMT progression over time.

The primary hypotheses regarding the associations between caregiving stress and biological markers were not supported in these particular analyses. There are several potential explanations for these findings. First and foremost, issues with the measurement model for the primary outcome, Large Vessel Disease, likely contributed to the lack of an association between stress and evidence of atherosclerosis. It is important to note that none of the observed indicators included in the measurement model for Large Vessel Disease (IMT, plaque, and FMD) loaded significantly onto the latent factor, obscuring the interpretation of what this latent factor score actually captures. Therefore, drawing conclusions about the lack of an association between stress and atherosclerosis is premature. This also implies that these observed
indicators might represent three separate markers in the context of the atherosclerotic
disease process, and therefore, should be examined separately. Indeed, published
work in this cohort of caregivers (described later in this discussion) has reported
relationships between caregiving stress and each of these markers of atherosclerosis
independently.

Furthermore, it is possible that this statistical approach might not capture the
ture nature of the relationship between stress and biological markers. The analyses
conducted were designed to capture a linear association between caregiving stress and
disease; however it is plausible that the actual relationship might be nonlinear.
Although a key feature of Alzheimer’s disease is degenerative cognitive decline, it is
important to note that some of the problem behaviors associated with dementia
increase over time, while others decrease over time (Aneshensel, Pearlin, Mullan,
Zarit, & Whitlach, 1995). For example, a caregiver might struggle to manage their
demented spouse’s wandering behavior in moderate stages of the disease, however, as
the dementia progresses; this behavior diminishes with reductions in mobility (Hebert
et al., 2010). Therefore, it is possible that some caregivers might actually experience
attenuation of particular stressors as their spouse’s disease progresses to more
advanced stage.

Another possibility is that the measurement model for Caregiving Stress might
be overly-simplistic. Specifically, the inclusion of both objective and subjective
primary caregiving stressors into the “Caregiving Stress” factor might have clouded
the associations between specific stressors and disease markers. Past research
indicates great variability in characteristics of caregivers and care-recipients
(Aneshensel, Pearlin, Mullan, Zarit, & Whitlach, 1995; Bauer, Maddox, Kirk, Burns, & Kuskowski, 2001), which might explain differences in subjective stress associated with caregiving. Although care-recipient impairment (i.e., objective stressors) with regards to cognitive abilities and activities of daily living increases over time in the dementia patient, role overload (i.e., subjective stressors) that a caregivers experiences does not always follow this pattern. Indeed, cross-sectional and longitudinal studies indicate a flat and stable distribution of role overload over the course of caregiving (Aneshensel, Pearlin, Mullan, Zarit, & Whitlach, 1995). Variability within ratings of overload might be explained by a number of factors not examined in the present study, such as utilization of formal support services (e.g., home health aids, day care services, etc.), informal support from friends and family, and presence of role conflict. The current study’s Caregiving Stress factor was heavily influenced by role overload, problem behaviors, and reactivity to problem behaviors, with minimal influence of duration of care and CDR. It is possible that the stressors captured in this measurement model might be less associated with biological dysregulation. Importantly, past work examining specific stressors in this cohort does support an association between duration of care and carotid IMT (Roepke et al., 2012).

Consistent with prediction, the current study demonstrated that individuals using more positive coping strategies had lower levels of SAM axis arousal. Similarly, there was a significant bivariate association between the Coping and Inflammation factor scores, indicating that caregivers reporting higher use of positive coping strategies had reduced inflammation. These results are consistent with previous work finding negative associations between coping resources and indicators
of SAM arousal (Harmell et al., 2011; Roepke et al., 2008) and inflammation (Mausbach et al., 2011) in caregivers.

Contrary to prediction, there was not a significant Caregiving Stress-by-Coping Resources interaction on SAM Arousal or inflammation. Given that there was a small effect size of this interaction on SAM Arousal, post-hoc probing was conducted for exploratory purposes. The nature of this interaction was counterintuitive, such that caregivers who reported high use of positive coping and also reported high levels of Caregiving Stress had the least SAM axis arousal. One potential explanation for this finding could be that caregivers who sustain a high sense of control, self-efficacy, and use of problem-focused coping strategies in the face of high stress might be more likely to be efficacious in engaging in health-promoting behaviors such as antihypertensive medication compliance, thus resulting in lower blood pressure. However, these findings are not statistically significant and should be replicated before drawing such conclusions.

Although the comprehensive model of the translation of caregiving stress to large vessel disease did not fit observed data in this sample of caregivers, prior work in this cohort of caregivers does indeed support components of this model. For example, previous work in this cohort has demonstrated a link between chronic stress and carotid artery IMT, consistent with this study’s Aim 1 hypothesis. Specifically, this study found that years of caregiving was positively associated with IMT measured in the internal and bifurcation segments of the carotid artery (Roepke et al., 2012). That study did not find an association between duration of care and IMT measured in the common carotid.
Those findings suggest that there might be segment-specific associations between chronic stress and IMT. Differences in hemodynamics, shear stress, and histology of the internal and bifurcation segments make them more prone to atherosclerotic plaque and lesions compared to the common carotid artery (Heath, Smith, Harris, & Winson, 1973; Touboul et al., 2004). For this reason, IMT from these segments may more accurately estimate true atherosclerosis compared to the common carotid artery (Mackinnon et al., 2004). Some research suggests that measuring IMT at the internal carotid rather than the common carotid alone improves prediction of vascular events (O'Leary et al., 1999). Therefore, the differential association between chronic stress and IMT at the internal and bifurcation compared to the common carotid artery might reflect pathophysiologic processes that operate via risk factors that have a stronger association with internal/bifurcation IMT, rather than common IMT.

Indeed, previous studies have found segment-specific cardiovascular risk factor associations for common, bifurcation, and internal IMT. For example, a study by Polak and colleagues (2010) reported that hypertension, diabetes, and smoking have qualitatively stronger associations with IMT in the bifurcation, compared to the common and internal segments. Low-density lipoprotein cholesterol was more strongly associated with internal IMT compared to other segments. The research examining segment-specific associations between IMT and cardiovascular disease risk factors is relatively limited; therefore future research can help establish the specific mechanisms that might explain these differences. Moreover, further investigation of
the current study’s model might examine IMT from the internal and bifurcation segments of the carotid artery.

Moreover, past work has found that caregivers have a higher prevalence of carotid plaque compared to non-caregiving older adults (Roepke et al., 2011). These groups differ based upon their role of providing care, and theoretically differ in their level of chronic stress. Therefore, one might infer that the presence of the chronic stressor of caregiving might be related to the presence of atherosclerosis. This study also found that epinephrine recovery to an acute stressor task moderated the association between caregiver status and carotid plaque. Specifically, the combination of prolonged epinephrine recovery to stress and caregiving seemed to be important in the presence of plaque. There was no mediating effect of epinephrine on plaque, which is contradictory to the model examined in the present study. Therefore, future work clarifying the nature of the role of SAM Arousal in the context of the stress-to-disease relationship is warranted.

Another study in this cohort of caregivers has found that duration of care and dementia severity of the demented spouse were associated with poorer endothelial functioning, measured by brachial FMD (Mausbach et al., 2010). This study provides further evidence for the stress-to-large vessel disease relationship proposed in Aim 1 of this current study.

Previous work in this cohort has also found a protective effect of coping resources on both inflammation and SAM arousal, as proposed in Aim 3 of the current study. A 2011 study found that coping self-efficacy moderated the association between caregiving stress and inflammation, such that when self-efficacy was low,
stress was positively associated with IL-6. When self-efficacy was high, stress was unassociated with IL-6 (Mausbach et al., 2011). Other studies have found negative associations between coping resources and indicators of SAM arousal in similar caregiver cohorts, although they did not test specific moderating effects of coping on the stress-to-SAM arousal relationship. One such study found that higher levels of coping self-efficacy was associated with lower resting blood pressure (Harmell et al., 2011). Another study found that higher levels of mastery was associated with reduced norepinephrine reactivity to an acute stressor task (Roepke et al., 2008). This finding is consistent with other work demonstrating that a higher sense of personal mastery or control is associated with lower physiological response to acute stress (Ma, Faber, & Dubé, 2007).

Although the exact reasons for why the observed data did not fit the present study’s model are likely complex, there are some key factors to consider. First, it is important to recognize that measurement models for Large Vessel Disease, SAM Arousal, and Inflammation latent variables were poorly fit. Therefore, conclusions drawn regarding the structural relationships among these variables would be unsubstantiated. It is also important to note that sample size likely limited the power to detect Caregiving Stress-by-Coping Resources interactions on SAM Arousal and Inflammation.

Another potential explanation may be that responses to the psychosocial interview only reflected a caregiver’s experience at the present moment, rather than the cumulative experience of chronic stress. Previous studies have demonstrated that self-report measurement of psychological variables, do indeed fluctuate over time
(Mausbach, Coon, Patterson, & Grant, 2008). Therefore, it is possible that data collected at a single moment in time may not accurately reflect the accumulation of caregiving stress or burden over time. In support of this hypothesis, Low and colleagues (2009) found that neither self-report measures of chronic stress nor cardiovascular reactivity to an acute stressor were associated with carotid IMT. Rather, increasing diastolic blood pressure reactivity over time (an average of 3.3 years after baseline) was significantly associated with increased IMT measured at follow-up. Finally, the literature on the relationship between caregiver role overload and physical health outcomes has been equivocal, with some studies finding that role overload is associated with poorer physical health outcomes (Mausbach, Mills et al., 2007), and others finding non-significant relationships (von Känel et al., 2010).

The current study did find support for the hypothesis that coping resources might impact the progression of atherosclerosis over time. In this sample of caregivers, IMT significantly increased over a period of 24-months. Caregivers who reported higher use of problem-focused coping strategies had a slower rate of IMT progression over time. Self-efficacy for using problem-focused coping had a similar relationship with IMT progression that trended toward significance. These data suggest that these coping resources might act as a protective factor in atherosclerotic progression in caregivers. This is the first study to date that has found a link between problem-focused coping style and progression of subclinical atherosclerosis.

Relatively few studies have examined active coping strategies in the context of subclinical atherosclerosis. One such study by Bugajska and colleagues (2008) found a null association between coping and IMT. However, the coping measure used in this
study aggregated multiple coping strategies and did not specifically examine problem-focused coping. Another study found that optimism was associated with slower IMT progression in middle-aged women (Matthews, Raikkonen, Sutton-Tyrrell, & Kuller, 2004), and a substantial body of literature suggests that optimistic people tend to use more active coping strategies (Carver, 1989; Moffat & Clark, 1993). A 2009 study also found that use of active coping strategies was associated with reduced arterial stiffness (Y. J. Lee, Baek, Yun, Lim, & Lim, 2009). The results of this study corroborate research suggesting that active/approach-style coping strategies are associated with improved cardiovascular outcomes and suggest that problem-focused coping might slow the atherosclerotic disease process.

There are limitations of this study that are worthy of mention. First, these analyses were cross-sectional in nature. Therefore, causality cannot be inferred from these results. In addition, this sample was highly educated, with 44% being college graduates. They also reported a relatively high income level. Therefore, the generalizability of these results is uncertain. Future work would benefit from examining the role of socioeconomic status in atherosclerotic burden in a more diverse group of dementia caregivers. Indeed, there is a large body of literature to suggest that low socioeconomic status is associated with poorer health outcomes (Adler et al., 1994; Adler & Rehkopf, 2008; Marmot, Shipley, & Rose, 1984). There is also literature to suggest that low socioeconomic status is associated with greater levels of subclinical atherosclerosis (Kestilä et al., 2012; Nash et al., 2011). Indeed, financial burden is an important factor that can contribute to stress in Alzheimer caregivers (Alzheimer's Association, 2011). For example, medical bills and/or loss of one or
more sources of income associated with dementia or caregiving responsibilities can contribute to financial burden.

Finally, one limitation regarding the exploratory analyses was the availability of longitudinal IMT data. The data available for longitudinal analysis was relatively small; therefore future work might examine the relationships between stress, coping, and atherosclerotic progression in a larger sample. Moreover, these analyses only controlled for age and gender in order to avoid over-fitting the models given the sample size. Future work might consider controlling for other important covariates such as medication use, exercise, smoking history, sleep quality, depression, etc.

Lastly, IMT progression was measured over a period of 24 months. Longitudinal data examining IMT over a longer timeframe would likely increase the power to detect changes in IMT given that atherosclerosis is a slowly developing disease process. Yet, past work has found significant changes in IMT associated with psychosocial intervention over periods as brief as 6-9 months (Castillo-Richmond et al., 2000).

In summary, the current investigation did not find that the proposed model characterizing the translation of caregiving stress to large vessel disease fit the observed data in this cohort of 126 Alzheimer caregivers. However, previous work in this cohort has indeed found evidence to support components of this model. Specifically, past work has found associations between indicators of caregiving stress and markers of large vessel disease including FMD (Mausbach et al., 2010), plaque (Roepke et al., 2011), and IMT measured in the internal and bifurcation segments of the carotid (Roepke et al., 2012). Past work has also found a moderating effect of coping resources on biomarkers of stress including those indicative of SAM arousal.
and inflammation (Ma, Faber, & Dubé, 2007; Mausbach, von Känel et al., 2008; Mausbach et al., 2011). Future investigations might focus on examining the validity of this model in a larger sample, modifying measurement models of latent variables, and examining alternative outcomes of large vessel disease to capture specific pathways of the stress-to-disease relationship. In a longitudinal analysis, the current study found that higher use of problem-focused coping was associated with slower atherosclerotic progression. This finding converges with past research suggesting that active coping strategies have a beneficial impact on cardiovascular health and suggest that interventions aimed at coping skills training might also have a protective impact on the development of atherosclerosis.


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