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A Longitudinal Analysis of the Relations Among Stress, Depressive Symptoms, Leisure Satisfaction, and Endothelial Function in Caregivers

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Objective: Stress and depressive symptoms have been associated with impaired endothelial function as measured by brachial artery flow-mediated dilation (FMD), possibly through repeated and heightened activation of the sympathetic nervous system. Behavioral correlates of depression, such as satisfaction with leisure activities (i.e., leisure satisfaction), may also be associated with endothelial function via their association with depressive symptoms. This study examined the longitudinal associations between stress, depressive symptoms, leisure satisfaction, and endothelial function as measured by FMD. ***Method:*** Participants were 116 older Alzheimer's caregivers (M age = 74.3 ± 8.1; 68% women; 87% White) who underwent 3 yearly assessments of FMD, stress, depressive symptoms, and leisure satisfaction. Mixed-regression analyses were used to examine longitudinal relationships between constructs of interest. ***Results:*** A significant and positive association was found between leisure satisfaction and FMD (p = .050), whereas a negative relationship was found for stress (p = .017). Depressive symptoms were not associated with FMD (p = .432). Time (p < .001) and the number of years caregiving (p = .027) were also significant predictors of FMD, suggesting that FMD decreased over time and was worse the longer a participant had been a caregiver prior to study enrollment. ***Conclusions:*** These results suggest that behavioral correlates of depression (i.e., engagement in pleasurable activities) may be related to endothelial function in caregivers, and behavioral treatments for depression may be particularly useful in improving cardiovascular outcomes in caregivers.

Keywords: behavioral activation, depression, flow-mediated dilation, stress

Providing care to a loved one who is disabled has been implicated in the onset of cardiovascular disease (CVD; Lee, Colditz, Berkman, & Kawachi, 2003; Vitaliano et al., 2002), possibly via the psychological distress resulting from providing this care (Mausbach, Patterson, Rabinowitz, Grant, & Schulz, 2007). Although there are potentially multiple mechanisms linking caregiving strain to CVD, it has been hypothesized that repeated and sustained sympathetic nervous system activation resulting from exposure to environmental and psychological stressors may promote atherosclerotic processes (von Känel, Mills, Fainman, & Dimsdale, 2001; Widmaier, Raff, & Strang, 2006). Other data suggest that mood disturbances, particularly depressive symptoms, may increase caregivers' risk for cardiovascular morbidity (Mausbach et al., 2007). Indeed, caregivers are at significant risk for depressive symptoms relative to their noncaregiving counterparts (Ory, Hoffman, Yee, Tennstedt, & Schulz, 1999).

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Although the specific physiologic pathways from depressive symptoms to CVD outcomes are likely complex, one potential pathway is through injury of the endothelial lining, which plays a key role in the development and progression of atherosclerosis (Celermajer, 1997; Ross, 1993). In particular, injury to the endothelium may occur in caregivers via repeated and heightened activation of the sympathetic nervous system (Grant, 1999). Indeed, caregivers with increased stress (Mills et al., 2004) have significant elevations to resting catecholamine levels, and caregivers with greater depressive symptoms demonstrate heightened sympathetic nervous system (SNS) response to stressors (Mausbach et al., 2005). This heightened response promotes acute hemodynamic changes (e.g., increased heart rate and blood pressure) that result in shear stress-related damage to the endothelium. Moreover, depression has been associated with increased oxidative stress (Maes, Kubera, Obuchowiczwa, Goehler, & Brzeszcz, 2011) and decreased nitric oxide (NO) production by the vascular wall (Chrapko et al., 2004). The resulting reduction in bioavailability of NO hampers the anticoagulant and anti-inflammatory properties of the endothelium, thereby promoting atherothrombotic vascular disease (Poredos, 2001).

One method for evaluating endothelial dysfunction is by brachial artery flow-mediated dilation (FMD), which is a noninvasive method designed to assess endothelial function of the peripheral conduit artery in humans (Celermajer et al., 1992). In brief, this technique uses upper arm occlusion to induce distal hypoxia followed by the reactive hyperemia and local vasodilation after cuff deflation. The distal vasodilation, in turn, will induce large increase in the shear stress upstream, in the brachial artery. In response to the increased shear, the brachial artery endothelial cells increase the production of NO causing the vascular smooth muscle to relax and the artery to dilate (Moens, Goovaerts, Claeys, & Vrints, 2005). Reduced artery dilation via this method is suggestive of compromised endothelial function.

A number of studies have evaluated the cross-sectional and longitudinal associations between elevated symptoms of depression and impaired endothelial function, as measured by FMD. For example, Broadley, Korszun, Jones, and Frenneaux (2002) compared FMD of 22 patients with depressive symptoms with 10 matched controls and found significant impairment in the depressed group. Another study by Cooper et al. (2010) found a significant correlation between depressive symptoms and FMD among 70 healthy adults, such that increased depressive symptoms were associated with reduced FMD. In a sample of 143 individuals with coronary heart disease, Sherwood, Hinderliter, Watkins, Waugh, and Blumenthal (2005) reported that patients with elevated depressive symptoms (Beck Depression Inventory scores $\geq$10; Beck & Steer, 1987) had reduced FMD. Finally, a recent meta-analysis of 12 studies and nearly 1,500 subjects reported a significant correlation between increased depressive symptoms and impaired FMD (Cooper et al., 2011).

Although depressive symptoms may directly relate to FMD, other correlates of depression also may be directly, or indirectly, associated with FMD. In particular, stress in caregivers has repeatedly been linked with depressive symptoms (Schulz, O'Brien, Bookwala, & Fleissner, 1995) and has been linked with CVD diagnosis and endothelial functioning in caregivers (Mausbach et al., 2007; Mausbach et al., 2010). In addition, behavioral models of distress suggest that an imbalance between negative and reinforcing environmental stimuli is a key correlate of psychological distress. Specific to these models, individuals subjected to low levels of pleasurable experiences are more likely to experience affective disturbance, particularly depressive symptoms (Lewinsohn, 1975; Lewinsohn & Amenson, 1978). Among caregivers, low engagement in pleasurable activities is not believed to be a function of their inability to experience pleasure, but rather a result of believing they cannot participate in these activities due to the constraints brought about by caregiving (Williamson & Shaffer, 2000). This effect has been demonstrated in numerous studies of caregivers (Mausbach, Chattillion, et al., 2011; Mausbach, Patterson, & Grant, 2008). Indeed, previously studies have demonstrated that even daily fluctuations in pleasurable activities are associated with concomitant fluctuations in affective arousal in caregivers (Mausbach, Coon, Patterson, & Grant, 2008; Mausbach, Harmell, Moore, & Chattillion, 2011) and that restriction of social and recreational activities is strongly linked with depressive symptoms (Mausbach, Chattillion, et al., 2011).Thus, behavioral inactivity or restriction of pleasurable activities may be directly associated with FMD or indirectly associated through its relation to depressive symptoms.

The purpose of the current study was to investigate the association between (a) behavioral activation, as measured by engagement in leisure activities; (b) stress; (c) depressive symptoms; and (d) FMD. Given that low engagement in leisure activities and stress are both strongly linked to experience of depressive symptoms (Mausbach, Chattillion, et al., 2011), and that depressive symptoms are linked to impaired FMD (Cooper et al., 2011), we hypothesized the following:

Hypothesis 1: There would be a direct association between levels of leisure satisfaction and FMD, whereby lower levels of leisure satisfaction would be associated with impaired FMD.

Hypothesis 2: There would be a direct association between stress levels and FMD, whereby greater stress would be associated with impaired FMD.

Hypothesis 3: Depressive symptoms would be associated with FMD, whereby greater depressive symptoms would be associated with impaired FMD.

Hypothesis 4: The correlations between stress and FMD, as well as leisure satisfaction and FMD, would be mediated by depressive symptoms.

Method

Participants

There were 116 caregivers who participated in this study (*M* age = 74.3 $\pm$ 8.1 year; 68% women, 87% White). All participants were enrolled in the University of California, San Diego (UCSD) Alzheimer's Caregiver Study, which was designed to determine the extent to which chronic stress is associated with physiologic changes associated with CVD. To be eligible, caregivers were required to be providing in-home care for a spouse with a physician diagnosis of Alzheimer's disease (AD), be 55 years of age or

older, and be free from major illnesses (e.g., cancer). Participants were excluded if at baseline they self-reported a diagnosis of heart failure or had experienced a heart attack or stroke during the past 12 months. However, if participants reported these conditions after baseline they were allowed to continue. Participants were also excluded if they suffered from extreme hypertension (>200/120 mm Hg), were unwilling to undergo flow mediated dilation testing, or were taking medications known to affect biomarkers of specific interest to the study design. Participants were recruited from local caregiver support groups, referrals from local caregiver agencies (e.g., the UCSD AD Research Center), from community health fairs, and through referrals from enrolled participants.

Measures

The study employed a longitudinal design in which all caregivers underwent annual in-home assessment of the measures described below for a period of 3 years. Eleven participants were willing to undergo a fourth assessment during the 3 years and these 11 cases were also included in the analysis. During each assessment, participants provided relevant demographic and health characteristics, including (among others) age, smoking history (i.e., years smoked), all medications used over the past 30 days, and years of caregiving (i.e., years since spouse was diagnosed with AD). Trained research staff also administered questionnaires to assess psychological variables (e.g., depressive symptoms). The interview was followed by measurement of FMD.

Dependent Variable

Brachial artery FMD. A single, trained ultrasound technician conducted all testing of endothelium-dependent FMD using the modified method first described by Celermayer et al. (1992). In particular, after participants rested comfortably, an occlusion cuff was placed on the right upper arm, after which the brachial artery was scanned, in longitudinal section 4 to 10 cm proximal to the antecubital fossa, using an Acuson Cypress portable ultrasound system with 5.4 to 6.6 MHz linear array transducer (Model 7L3; Siemens Medical Solutions, Mountain View, CA).

After the brightest views of the anterior and posterior artery walls had been obtained, three baseline images were saved. Then, the occlusion cuff was inflated to 50 mm Hg above systolic blood pressure (SBP) thereby producing distal hypoxia for 5 min. After the cuff was deflated, arterial images were saved every 15 s during the first minute postocclusion and then once every 30 s for an additional 8 min. A technician measured artery diameters manually from the saved digital ultrasound images with the Acuson Cypress built-in vascular measurements software module (Siemens Medical Solutions, Mountain View, CA). All measurements were taken by placing electronic calipers on the anterior and posterior intima line (i-i line). FMD was calculated as the maximum percentage change in the brachial artery diameter, $FMD\%_{(\max)}$, from the average baseline diameter value, $D_{FMD(b)}$, to the maximum diameter value after the cuff deflation, $D_{FMD(\max)}$:

$$FMD\%_{(\max)} = \left[\frac{D_{FMD(\max)}(cm)}{D_{FMD(b)}(cm)} - 1 \right] * 100.$$

Primary Independent Variables

Leisure satisfaction. Caregivers' engagement in leisure activities was assessed using a modified version of the Pleasant Events Schedule–AD (PES–AD; Logsdon & Teri, 1997). Participants rated the frequency with which they engaged in 20 leisure activities over the past month based on a scale ranging from 0 (*not at all*), 1 (*a few times, 1–6 times*), to 2 (*often, 7 or more times*). In addition to frequency, participants rated the level of enjoyment they received when they engaged in each activity. Response choices for the enjoyment question were based on a scale ranging from 0 (*not at all*), 1 (*somewhat*), to 2 (*a great deal*). A cross product of the frequency and enjoyment scores was computed for each item (range = 0–4 for each item). The total leisure satisfaction score (range = 0–80) was computed as the sum of these cross products. For the purposes of this study, we defined leisure satisfaction as more frequent engagement in satisfying or enjoyable leisure activities. It should be noted that only one item on the PES–AD related to physical leisure activities (e.g., "exercising (walking, dancing, etc.)"), with the remaining items corresponding to social/recreational leisure activities (e.g., "watching TV," "reading or listening to stories," "shopping or buying things," "going for a ride in the car," "having coffee, tea, etc. with friends").

Depressive symptoms. Participants completed the short form of the Center for Epidemiologic Studies Depression scale (CESD–10; Andresen, Malmgren, Carter, & Patrick, 1994). This scale contains 10 items assessing participants' experience of depressive symptoms during the past week, with response options ranging from 0 (*none of the time*) to 3 (*most of the time*). Two of the items are reverse scored (i.e., "you felt hopeful about the future"; "you were happy"), and the 10 items are summed to create an overall score reflecting depressive symptoms.

Global stress. The Pearlin Role Overload scale was used to measure each participant's global stress level (Pearlin, Mullan, Semple, & Skaff, 1990). For this scale, participants were asked to rate the extent to which four items described them (e.g., "You have more things to do than you can handle") using a 4-point Likert scale ranging from 0 (*not at all*) to 3 (*completely*). The four items were summed to create an overall score.

Covariates

Health and health behaviors. As per self-report, we assessed caregiver body mass index (BMI) as their weight in kilograms divided by height in meters squared (kg/m^2). We also assessed whether caregivers had ever been smokers during their lifetime and the number of years they had smoked.

We administered the Rapid Assessment of Physical Activity (RAPA) scale (Topolski et al., 2006), a validated scale that assessed the participants' typical weekly level of physical activity. The RAPA was developed based on the Centers for Disease Control and Prevention (CDC) guidelines for physical activity, which recommend 30 min or more of moderate physical activity on most days of the week. As recommended by the authors of the scale, a dichotomous variable was created for this analysis indicating whether the participant met the CDC guidelines for recommended level of weekly physical activity (i.e., 0 = *participant did not meet CDC guidelines*; 1 = *participant met CDC guidelines*).

At each assessment, participants were asked whether they had ever been diagnosed by a physician as having each of three

cardiovascular conditions (yes vs. no): (a) heart attack, (b) heart failure, and (c) stroke or transient ischemic attack (TIA). If participants responded "yes" to any of these conditions it was recorded for use as a covariate in all analyses. Finally, all participants reported all medications taken at least once during the previous 30-day period. Because FMD may be affected by use of nitrates, estrogens, calcium channel blockers, and angiotensin-converting enzyme inhibitors, use of any of these medications (yes vs. no) was used as a covariate in all analyses. Participants did not report the number of times they took these medications, and we did not assess adherence to medications.

Care Recipient Characteristics

Dementia rating of spouses. Participants were interviewed using the Clinical Dementia Rating (CDR) scale (Morris, 1993), whereby participants indicated the extent to which their spouses exhibited symptoms of dementia in six domains: (a) memory, (b) orientation, (c) judgment and problem solving, (d) community affairs, (e) home and hobbies, and (f) personal care. Based on responses to these items, an overall dementia severity score is given, using the following scale ranging from 0 (*no dementia*), 1 (*mild dementia*), 2 (*moderate dementia*), to 3 (*severe dementia*). In addition, all caregivers were required to have spouses with at least mild dementia, so spouses of caregivers had CDR scores of at least 1.

Statistical Analyses

Our primary analytic approach involved fitting linear mixed models with FMD as our dependent variable. In predicting FMD over time, we fit all models with a random intercept and used restricted maximum likelihood (REML) estimation to handle missing data. Predictors of FMD over time were as follows: (a) primary independent variables—time varying values for leisure satisfaction, depressive symptoms, and global stress. Each of these variables was centered around each participant's personal mean. That is, each participant's personal mean score across time was subtracted from each of his or her yearly observations. Thus, significant effects for leisure satisfaction, stress, and CESD scores denoted that FMD changed in conjunction with the caregiver's within-person yearly fluctuation in these variables; (b) covariates—sex (*female* = 1, *male* = 0), use of FMD-altering medications (yes vs. no), history of CVD, time (in years), age at baseline assessment (in years), years of caregiving at the baseline assessment, time-varying values for BMI, and years smoked. BMI scores and years smoked were group-mean centered, such that the grand mean scores (i.e., the mean score for all participants across all time points) were subtracted from each participant's yearly value. Age at baseline and years caregiving at baseline were also centered around the mean of all participants at the baseline assessment. Finally, time was coded with 0 corresponding to the baseline assessment. Physical exercise was time varying such that values of 0 corresponded to not meeting CDC criteria for at least moderate exercise, and 1 corresponded to meeting CDC criteria; (c) interactive effects—Finally, we entered a time-by-age and a time-by-years caregiving interaction term to evaluate if older caregivers or those who had been caring for longer showed steeper change in FMD over time.

Results

Sample Characteristics

Baseline demographic and health characteristics of caregivers and their loved ones are presented in Table 1. There were a total of 295 FMD observations over the course of the study for a mean of 2.5 observations per participant. There was a great deal of variation across participants with regard to FMD. In particular, in terms of quartiles, the bottom 25% of our sample had FMD responses between 0% to 9%, the second quartile had dilation between 9% to 14%, the third quartile had responses from 14% to 18%, and the top quartile had responses greater than 18%. The relations between leisure satisfaction and depressive symptoms was significant across the study, with a mean correlation of −.36, as was the correlation between role overload and depressive symptoms ($r = .47$). Further, role overload was significantly correlated with leisure satisfaction ($r = -.29$). No other variables (e.g., clinical variables, smoking, exercise) were significantly related to depressive symptoms, overload, or leisure satisfaction.

Model 1—Leisure Satisfaction and FMD

Results of our first mixed-model analysis, evaluating the direct relationship of leisure satisfaction with FMD over time, indicated four significant predictors of FMD. The first was years caregiving at baseline, $B = -0.36$, $t(261.38) = -2.27$, $p = .024$, suggesting that the longer caregivers had provided care prior to enrollment the worse their arterial dilation. In particular, approximately three years of care was associated with a 1% reduction in arterial dilation. The second significant predictor was time, $B = -1.90$, $t(233.85) = -4.42$, $p < .001$, indicating that caregivers' FMD decreased significantly over time at a rate of 1.90% per year. The third significant predictor of FMD was BMI, $B = -0.18$, $t(112.23) = -2.02$, $p = .046$, where increased body mass was associated with reduced arterial dilation. Finally, leisure satisfaction was significantly associated with FMD, $B = 0.15$, $t(187.65) = 2.54$, $p = .012$, indicating that arterial dilation was greater in years when caregivers had increased leisure satisfaction and endothelial function was worsened in years when they had lower leisure satisfaction. Neither the time-by-years caregiving, $B = 0.16$, $t(226.15) = 1.25$, $p = .213$, nor the age-by-time, $B = 0.05$, $t(236.03) = 0.84$, $p = .403$, interactions were significant, indicating that change in FMD over time was not significantly altered by the length of time caregivers had been providing care or their age at baseline. The coefficients for age, $B = -0.10$, $t(254.16) = -1.45$, $p = .149$; years smoked, $B = -0.04$, $t(124.78) = -1.34$, $p = .182$; exercise, $B = -1.24$, $t(229.88) = -1.41$, $p = .160$; female sex, $B = -1.11$, $t(94.95) = -0.84$, $p = .189$; use of FMD-altering medications, $B = 1.35$, $t(270.63) = 1.63$, $p = .104$; and history of CVD, $B = 0.02$, $t(142.71) = 0.01$, $p = .990$ were all nonsignificant.

Model 2—Stress and FMD

Our second model examined the direct relationship between role overload scores and FMD over time, while controlling for the same covariates in Model 1. In this model, time, $B = -2.19$, $t(236.50) = -4.87$, $p < .001$; years caregiving, $B = -0.36$,

Table 1
Characteristics of the Sample

Variable	Baseline ($N = 116$)	Year 2 ($N = 95$)	Year 3 ($N = 73$)	Year 4 ($N = 11$)
Age: *M* (*SD*)	74.3 (8.1)	75.2 (7.9)	76.3 (7.7)	76.1 (7.7)
Female: *n* (%)	79 (68.1)	66 (69.5)	50 (68.5)	6 (54.5)
Race: *n* (%)				
White, non-Hispanic	101 (87.1)	86 (90.5)	69 (94.5)	11 (100.0)
Hispanic	9 (7.7)	6 (6.3)	4 (5.5)	0 (0.0)
Black	3 (2.6)	1 (1.1)	0 (0.0)	0 (0.0)
Asian	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
Native American	2 (1.7)	2 (2.1)	0 (0.0)	0 (0.0)
Education: *n* (%)				
<High school	3 (2.6)	2 (2.1)	1 (1.4)	0 (0.0)
High school graduate	22 (19.0)	20 (21.1)	15 (20.5)	2 (18.2)
Some college	40 (34.5)	33 (34.7)	22 (30.1)	2 (18.2)
College graduate	18 (15.5)	12 (12.6)	12 (16.4)	3 (27.3)
Professional degree	33 (28.4)	28 (29.5)	23 (31.5)	4 (36.4)
History of CVD: *n* (%)[a]	13 (11.2)	12 (12.6)	7 (9.6)	1 (9.1)
Taking FMD-altering medicine: *n* (%)	29 (25.0)	38 (40.0)	21 (28.8)	0 (0.0)
Systolic blood pressure (mm Hg): *M* (*SD*)	134.2 (15.5)	130.5 (15.7)	128.3 (13.8)	127.8 (10.9)
Diastolic blood pressure (mm Hg): *M* (*SD*)	76.0 (8.5)	72.4 (9.9)	69.9 (7.9)	71.4 (7.4)
Ever smoked: *n* (%)	54 (46.6)	44 (46.3)	29 (39.7)	3 (27.3)
BMI: *M* (*SD*)	26.6 (4.8)	26.3 (4.5)	26.1 (5.0)	25.1 (3.0)
FMD: *M* (*SD*)	14.5 (5.7)	17.1 (7.1)	9.8 (5.3)	12.0 (6.7)
CESD–10: *M* (*SD*)	8.5 (5.8)	8.0 (5.8)	8.0 (6.2)	6.4 (3.6)
Leisure satisfaction: *M* (*SD*)	55.7 (12.4)	59.3 (10.8)	56.6 (14.0)	57.8 (12.3)
Role overload: *M* (*SD*)	5.1 (3.2)	4.2 (2.9)	4.0 (3.0)	2.5 (2.0)
Care recipient CDR score: *n* (%)[a]				
1	50 (43.1)			
2	59 (50.9)			
3	7 (6.0)			

Note. CVD = cardiovascular disease; FMD = flow-mediated dilation; BMI = body mass index; CESD–10 = Center for Epidemiologic Studies Depression scale (Short Form); CDR = Clinical Dementia Rating score.
[a] Values for individuals' diseases do not equal 20 because some participants had more than one condition. [b] CDR was not systematically evaluated across years.

$t(260.52) = 2.27$, $p = .024$; BMI, $B = -0.18$, $t(112.01) = -2.03$, $p = .045$; and role overload, $B = -0.66$, $t(188.83) = 2.90$, $p = .004$; were significantly related to FMD. As with Model 1, the coefficients for age, $B = -0.12$, $t(253.82) = -1.63$, $p = .104$; age-by-time, $B = 0.06$, $t(235.65) = 1.08$, $p = .280$; years smoked, $B = -0.05$, $t(124.76) = -1.40$, $p = .165$; gender, $B = -1.17$, $t(94.73) = -1.39$, $p = .169$; history of CVD, $B = 0.09$, $t(143.00) = 0.07$, $p = .948$; use of FMD-altering medications, $B = 1.53$, $t(269.88) = 1.86$, $p = .064$; and exercise, $B = -0.95$, $t(234.28) = -1.09$, $p = .277$ were all nonsignificant.

Model 3—Depressive Symptoms and FMD

In our model that included depressive symptoms, only two variables emerged as significant correlates of FMD, namely time, $B = -1.79$, $t(235.11) = -4.09$, $p < .001$, and years caregiving at baseline, $B = -0.37$, $t(263.15) = -2.30$, $p = .022$. No other variables, including depressive symptoms, $B = -0.05$, $t(184.83) = -0.38$, $p = .703$ were significant correlates of FMD.

Model 4—Full Model Including Leisure Satisfaction, Stress, and Depressive Symptoms

We conducted a final analysis predicting FMD using leisure satisfaction, depressive symptoms, and global stress as predictors of FMD. In this model depressive symptoms were not significantly related to FMD, $B = 0.11$, $t(182.26) = 0.79$, $p = .432$, while both leisure satisfaction, $B = 0.12$, $t(185.73) = 1.97$, $p = .050$, and stress, $B = -0.57$, $t(186.24) = 2.41$, $p = .017$ remained significant. Results of this final model are presented in Table 2.

Discussion

This study of 116 older caregivers of spouses with AD examined the associations between stress, depressive symptoms, leisure satisfaction, and endothelial function as measured by FMD. We hypothesized that stress, depressive symptoms, and engagement in enjoyable leisure activities would be significantly associated with FMD. Results of our study partially confirmed our hypotheses. In particular, we found that caregiver stress and increased engagement in leisure activities were associated with fluctuations in FMD over time such that FMD was significantly higher in years when participants reported lower stress and increased leisure satisfaction. However, depressive symptoms were not significantly associated with FMD over time.

Relative to the general population, caregivers are well-known to suffer from elevated levels of depressive symptoms and to be at risk for depressive disorders (Cuijpers, 2005). Further, caregivers also engage in fewer leisure activities than noncaregivers (Mausbach, Patterson, & Grant, 2008). Our sample appeared representative of the caregiving population in terms of depressive

Table 2
Model Predicting FMD Over Time

Variable	*B*	*SE*	*t* value	*p* value	95% CI lower	95% CI upper
Time	−2.20	0.45	−4.93	<.001	−3.09	−1.32
Baseline age (in years)	−0.12	0.07	−1.63	.105	−0.26	0.02
Years caregiving at baseline	−0.35	0.16	−2.23	.027	−0.66	−0.04
Time × Age	0.06	0.06	1.06	.289	−0.05	0.17
Time × Years Caregiving	0.15	0.12	1.22	.224	−0.09	0.39
Female	−1.15	0.84	−1.36	.176	−2.82	0.52
Taking an FMD-altering medication	1.39	0.82	1.70	.090	−0.22	3.01
CVD history	0.07	1.31	0.06	.957	−2.52	2.66
BMI	−0.19	0.09	−2.09	.039	−0.36	−0.01
Years smoked	−0.04	0.03	−1.33	.186	−0.11	0.02
Physical exercise	−1.23	0.88	−1.40	.163	−2.97	0.50
Global stress	−0.57	0.24	−2.41	.017	−1.04	−0.10
Depressive symptoms	0.11	0.14	0.79	.432	−0.16	0.37
Leisure satisfaction	0.12	0.06	1.97	.050	0.00	0.25

Note. FMD = flow-mediated dilation; CVD = cardiovascular disease; BMI = body mass index.

symptoms (Cohen & Eisdorfer, 1988; Williamson & Schulz, 1993), with approximately 35% of our participants exceeding the cutoff of 10 or greater on the brief (10-item) version of the CESD. However, despite the elevated levels of depressive symptoms in our sample, we did not see a significant relationship between depressive symptoms and FMD, which is generally not consistent with existing literature showing that greater depressive symptoms are associated with decreased FMD (Cooper et al., 2011). However, depressive symptoms appear more strongly related to FMD in clinical populations (e.g., those with existing CVD) than among nonclinical populations (Cooper et al., 2011). Further, studies of clinically depressed populations appear to show greater effect of depressive symptoms on FMD than studies using nonclinical samples (e.g., range of depression scores). Thus, although our sample showed meaningful symptoms of depression (mean CESD–10 score > 8), a limitation of our study is we did not assess whether individuals met *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV; American Psychiatric Association, 2000) criteria for major depression. Further, our sample did not primarily consist of individuals suffering from existing CVD diagnoses (i.e., participants were excluded if they had recently been diagnosed with major cardiovascular conditions). In addition, limitations associated with measurement of endothelial function using the FMD technique may have contributed to the lack of association observed between FMD and depressive symptoms. Although FMD has been the accepted standard for measuring endothelial function in research and has been shown to be associated with coronary risk factors and to be predictive of cardiovascular events, small changes in methodology when using the FMD technique can affect the nature and magnitude of the FMD response (Thijssen et al., 2011). These changes can influence validity and reproducibility of results of studies using FMD, which may account for variable findings with regard to associations between FMD and cardiovascular (Thijssen et al., 2011) and depression (Cooper et al., 2011) outcomes.

Depression is noted to encompass a number of emotional (e.g., sadness; guilt), cognitive (e.g., hopelessness), and behavioral (e.g., low energy; low environmental reinforcement) factors (Beck & Alford, 2009; Lewinsohn, 1974; Lewinsohn, 1975). To our knowledge, our study is the first to examine one such specific component of depression, namely engagement in enjoyable activities, in relation to endothelial function. Results of our study suggest that leisure activities may be a significant factor driving the depression–FMD relationship, such that greater engagement in enjoyable activities was associated with improved FMD. We found that increases in caregiver stress (i.e., role overload) were associated with impaired FMD, which may be explained by caregivers' increased SNS arousal in response to stress and subsequent hemodynamic changes (e.g., increase in blood pressure and heart rate) that may damage the endothelium. However, increases in leisure satisfaction were associated with improved FMD, suggesting that leisure satisfaction may attenuate the negative physiological changes induced by stress. One potential mechanism for this relationship is through increases in positive affect. Engagement in satisfying leisure activities has been shown to increase positive affect in caregivers (Mausbach, Coon, et al., 2008), and positive emotions have been shown to reduce the detrimental impact of negative emotions on cardiovascular outcomes in older adults. For example, positive emotions have been associated with decreased systolic and diastolic blood pressure reactivity and more rapid systolic blood pressure recovery from daily negative affect (Ong & Allaire, 2005). Thus, increases in positive affect produced by engagement in satisfying leisure activities may mitigate stress-related physiological changes that lead to endothelial damage.

Although future research must confirm these results, there are some important implications that may be drawn from the finding that increased leisure satisfaction is associated with improved FMD over time. To the extent that depression is related to FMD, treatments for depression would be expected to improve endothelial function over time. However, our findings lend initial support to the notion that specific behavioral treatments may produce better outcomes. In particular, therapies that emphasize engagement in enjoyable activities may be associated with better FMD over time. One such treatment is behavioral activation (BA) therapy (Jacobson, Martell, & Dimidjian, 2001), which is an evidence-based treatment for depression (Sturmey, 2009) focusing on helping individuals more frequently engage in enjoyable activities while simultaneously countering patterns of avoidance, with-

drawal, and inactivity. Examination of such forms of therapy, which have already been used to treat depression in caregivers (Coon, Thompson, Steffen, Sorocco, & Gallagher-Thompson, 2003; Gallagher-Thompson & Coon, 2007), would help elucidate the nature of the relationship between leisure satisfaction and endothelial function, and may reveal additional cardiovascular health benefits of these treatments.

There are some limitations of the present study that are worthy of mention. First, these results may not generalize to a broad sample of dementia caregivers. The current sample was predominantly White, and the findings require replication in a larger sample of ethnic minority caregivers. It is also important to note that these analyses were conducted in a sample of relatively healthy caregivers. The study's inclusion criteria required that participants be free of serious medical illness such as cancer, and caregivers with extreme hypertension were also excluded. Therefore, it is possible that our results may represent a conservative bias. In addition, although we controlled for caregivers' BMI, smoking history, exercise, and history of CVD, these measures were obtained by self-report, which could impact the accuracy of the measurements obtained (e.g., BMI is often underestimated by self-report; Davis, 2007). We were also unable to control for all relevant variables that may impact endothelial function. For example, although caregivers were asked to report medications taken, we did not collect data on medication adherence and were therefore unable to control for potential effects of antihypertensive or cholesterol-lowering medications on FMD. Finally, our measure of leisure satisfaction may have been influenced by factors that were not assessed (e.g., noncaregiving-related stressors that may encourage or prevent leisure engagement; caregiver personality traits). Future research investigating the impact of leisure satisfaction on caregiver outcomes should control for the influence of such variables when possible.

In sum, the current investigation found that increased engagement in leisure activities was associated with fluctuations in FMD over time in caregivers of spouses with AD. That is, FMD was significantly higher in the years when caregivers endorsed higher leisure satisfaction. We did not find that depression was associated with FMD over time. Results from this study build on previous work finding that stressors associated with the caregiving role were associated with poorer FMD cross-sectionally (Mausbach et al., 2010) and begin to fill in the links between caregiving stressors and downstream evidence of large vessel disease.

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