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Longitudinal Relationship of Low Leisure Satisfaction but not Depressive Symptoms With Systemic Low-Grade Inflammation in Dementia Caregivers

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Objectives. This study aimed to further elucidate the biobehavioral mechanisms linking dementia caregiving with an increased cardiovascular disease risk. We hypothesized that both elevated depressive symptoms and a behavioral correlate of depression, low leisure satisfaction, are associated with systemic inflammation.

Method. We studied 121 elderly Alzheimer's disease caregivers who underwent 4 annual assessments for depressive symptoms, leisure satisfaction, and circulating levels of inflammatory markers. We used mixed-regression analyses controlling for sociodemographic and health-relevant covariates to examine longitudinal relationships between constructs of interest.

Results. There were inverse relationships between total leisure satisfaction and tumor necrosis factor-α (TNF-α; $p = .047$), interleukin-8 (IL-8; $p < .001$), and interferon-γ (IFG; $p = .020$) but not with IL-6 ($p = .21$) and C-reactive protein ($p = .65$). Lower enjoyment from leisure activities was related to higher levels of TNF-α ($p = .045$), IL-8 ($p < .001$), and IFG ($p = .002$), whereas lower frequency of leisure activities was related only to higher IL-8 levels ($p = .023$). Depressive symptoms were not associated with any inflammatory marker (all p values > .17). Depressive symptoms did not mediate the relationship between leisure satisfaction and inflammation.

Discussion. Lower satisfaction with leisure activities is related to higher low-grade systemic inflammation. This knowledge may provide a promising way of improving cardiovascular health in dementia caregivers through behavioral activation treatments targeting low leisure satisfaction.

Key Words: Biomarkers—Blood coagulation—Cardiovascular disease—Depression—Inflammation—Psychological stress.

PROVIDING sustained care to a spouse with Alzheimer's disease (AD) impairs both physical and mental health of caregivers. Dementia caregivers are particularly prone to develop cardiovascular disease (CVD), including coronary heart disease (CHD; Vitaliano, Zhang, & Scanlan, 2003; von Känel et al., 2008) and depression (Schulz, & Williamson, 1991). Several meta-analyses report that depression is associated with a 1.5- to 2.7-fold increased risk of incident CHD (Frasure-Smith, & Lespérance, 2010) with the risk spanning the continuum of severity of depressive mood (Rugulies, 2002). Concurrent with this literature, we previously showed that increased depressive symptoms shortened the time to a diagnosis of CVD in dementia caregivers (Mausbach, Patterson, Rabinowitz, Grant, & Schulz, 2007). Also, relative to no strain and some strain, high strain from providing ongoing care to a family member with a chronic illness or disability has been associated with higher all-cause mortality during a 5-year follow-up in men and women aged 45 years and older (Perkins et al., 2012).

One important reason for becoming depressed may be that the dementia caregivers endorse lower levels of pleasurable activities because caregiving duties restrict participation in these activities (Mausbach, Patterson, & Grant, 2008; Williamson, & Shaffer, 2000). In this regard, low leisure satisfaction is the amount of positive affective experience a person gains from performing leisure activities that are perceived as pleasurable. Individuals who endorse low levels of pleasurable experiences are more likely to experience affective disturbance, particularly depressive symptoms (Lewinsohn, 1975; Lewinsohn & Amenson, 1978).

Low-grade systemic inflammation is a key mechanism in atherosclerosis and may explain part of the increased risk of CHD in depressed individuals (Nemeroff & Goldschmidt-Clermont, 2012). Meta-analyses have shown that depression is positively associated with circulating

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levels of tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP; Dowlati et al., 2010; Howren, Lamkin, & Suls, 2009). Similarly, IL-8 and interferon-γ (IFG) have also been found to be higher in depressed compared with nondepressed individuals (Simon et al., 2008). Elevated circulating levels of these inflammatory markers variously predict the initiation, progression, and clinical manifestation of atherosclerosis (Apostolakis, Vogiatzi, Amanatidou, & Spandidos, 2009; Mahmoudi, Curzen, & Gallagher, 2007; McKellar, McCarey, Sattar, & McInnes, 2009; Sarwar, Thompson, & Di Angelantonio, 2009; Schroecksnadel, Frick, Winkler, & Fuchs, 2006). A range of sociodemographic, psychological, and care-recipient behaviors are associated with depressive symptoms in dementia caregivers from the community (Piercy et al., 2012). Moreover, the relation of depression with inflammatory markers appears to be partially explained by sociodemographic and traditional CVD risk factors, including poor health behaviors (Dowlati et al., 2010).

Inflammation-driven loss of physiologic properties of endothelial cells lining coronary vessels occurs early on in atherosclerosis (Blake & Ridker, 2001). A dysfunctional endothelium loses its anti-inflammatory properties, thereby predisposing to the initiation and progression of the inflammatory and immunological processes of atherosclerosis. This includes the production/elaboration of inflammatory cytokines like TNF-α, IL-6, and IFG for atherosclerotic narrowing of conduit vessels (Szmitko et al., 2003). In this respect, we showed among AD caregivers that low leisure satisfaction, but not depressive symptoms, reduced endothelial function for a period of 3 years (Mausbach et al., 2012). We also found greater severity of chronic AD caregiving stress to be associated with impaired endothelial function (Mausbach et al., 2010) and elevated levels of inflammatory markers, including TNF-α and CRP (von Känel et al., 2012).

This previous research suggests a conceptual framework according to which an important antecedent, but also perpetuating factor of depressive symptoms in AD caregivers, namely low satisfaction from leisure activities, may be related to increased inflammation (cf. Figure 1 for conceptual model). Depending on the amount of caregiving duties (e.g., total activities of daily living [ADL]/instrumental ADL [IADL] requiring help from the caregiver), the time to engage in leisure activities may vary between caregivers; nonetheless, they still may derive substantial enjoyment from leisure activities for which they find time. Therefore, helping AD caregivers to engage more frequently both in pleasurable activities and/or in activities from which they derive the most pleasure increases the level of total leisure satisfaction, thereby possibly reducing the risk of CVD, even before caregivers become clinically depressed. Depressive symptoms might relate to inflammation in caregivers directly or via mediating the effect of low leisure satisfaction, but this has not previously been investigated.

Upon this background, the aim of this study was to investigate the longitudinal association of leisure satisfaction and depressive symptoms with circulating levels of TNFα, IL-6, IL-8, IFG, and CRP to further elucidate the biobehavioral mechanisms linking AD caregiving with CVD risk. Health behaviors, including leisure time physical activity, and ADL/IADL requiring help from the caregiver were treated as covariates to partial out their possible contribution to these relationships. Given that, in AD caregivers, leisure satisfaction is associated with increased depressive symptoms and endothelial dysfunction (independent of depression) and that numerous studies find elevated depressive symptoms and endothelial dysfunction to be associated with inflammation, we tested the following hypotheses:

(a) Lower total leisure satisfaction, lower frequency of leisure activities, and lower enjoyment from leisure activities are associated with higher levels of inflammatory markers.
(b) Depressive symptoms are directly associated with levels of inflammatory markers.
(c) Depressive symptoms mediate the relation between leisure satisfaction and inflammation.

Method

Study Participants and Design

All participants were enrolled in the University of California, San Diego (UCSD) Alzheimer's Caregiver Study, which investigates mechanisms that may link chronic mental stress in AD caregivers with an increased risk of CVD. The UCSD Institutional Review Board approved the study protocol and all participants provided written consent. Participants were recruited from local caregiver support groups, through referrals from local caregiver agencies, community health airs, and other participants. To be eligible, participants were required to be at least 55 years old, married, and dwelling in the community with their spouse. Exclusion criteria were presence of any major illnesses (e.g., cancer), severe hypertension (blood pressure [BP] > 200/120 mm Hg), or treatment with medications that affect inflammation and hypercoagulability markers (i.e., oral anticoagulants, nonselective beta blockers, steroids). Caregivers had to provide primary care for a spouse with a physician-based diagnosis of Alzheimer's disease. Of the originally enrolled 126 caregivers, we considered for this study 121 participants who provided blood samples for the assessment of inflammation and hypercoagulability markers.

The study applied a longitudinal design in which all participants underwent annual in-home assessments by trained research staff for a period of up to 4 years (one participant also underwent an assessment after 5 years). During each assessment, participants provided relevant

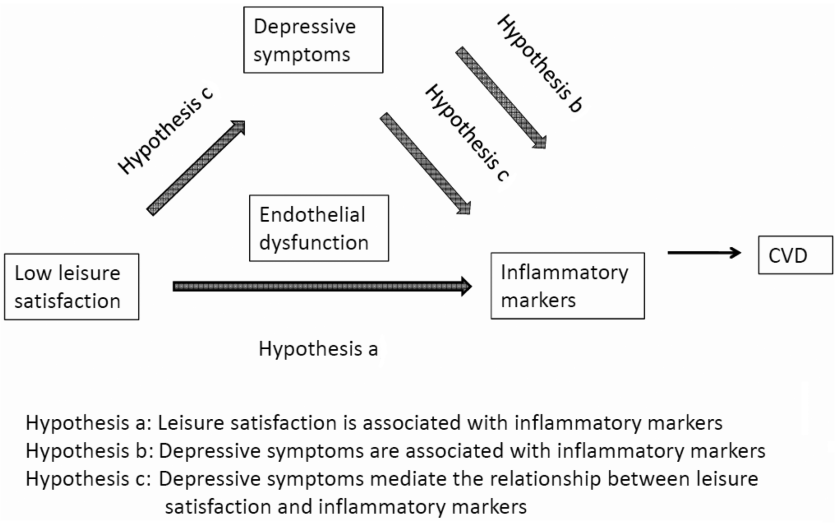

Figure 1. Conceptual framework of the study with the stated hypotheses.

sociodemographic and health characteristics. The interview was followed by collection of blood samples between 10:00 and 10:45 a.m. Participants were additionally encouraged to call research staff should there be a major transition in the relationship with their spouse (i.e., placement or bereavement). If so, staff set up an assessment appointment to occur approximately three months after the date of the transition. By design, posttransition assessments occurred at 3, 15, 27, and 39 months.

Leisure Satisfaction

We used the modified version of the Pleasant Events Schedule-AD (PES-AD) to assess participants' engagement in leisure activities (Logsdon & Teri, 1997). Only one item on the PES-AD relates to physical leisure activities (e.g., exercising [walking, dancing]), 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, and so on with friends).

Caregivers rated the frequency with which they engaged in 20 leisure activities in the past month based on a scale including the following response options: 0 (*not at all*), 1 (*a few times*, 1–6 times), and 2 (*often*, 7 or more times), yielding a "leisure activities frequency" score between 0 and 40. Caregivers also rated the level of enjoyment they experienced when they engaged in each activity. Response options included: 0 (*not at all*), 1 (*somewhat*), and 2 (*a great deal*), yielding a "leisure activities enjoyment" score between 0 and 40. We then calculated a cross-product of the frequency and enjoyment scores for each item (range = 0–4), of the total 20 items, yielding a "total leisure satisfaction" score between 0 and 80 indicating how much the caregiver engaged in enjoyable activities.

Depressive Symptoms

We used the short form of the Center for Epidemiologic Studies Depression (CES-D-10) scale (Andresen, Malmgren, Carter, & Patrick, 1994). This scale contains 10 items assessing participants' experience of depressive symptoms during the past week. Response options range from 0 (*none of the time*) to 3 (*most of the time*) yielding a total score of depressive mood (0–30). The cutoff score for clinically increased levels of depressive symptoms is greater than or equal to 10.

Markers of Inflammation

Fasting state was not a prerequisite in order to not interfere with caregivers' daily routine. Obtained plasma was stored at −80°C until analyzed. Concentrations of biomarkers were determined in duplicates using commercially available high-sensitive enzyme-linked immunosorbent assays per the manufacturers' instructions (Meso Scale Discovery, Gaithersburg, MD: TNF-α, IL-6, IL-8, IFG, CRP). Intra- and interassay coefficients of variation were less than 10% for all biomarkers.

Sociodemographic and Health Characteristics

Sociodemographic data.—We collected information on gender, age, years of education (to define socioeconomic status), and years caregiving.

Medical history.—Participants were asked to indicate whether a physician had informed them that they currently have or have ever had diabetes and/or any CVD that included myocardial infarction, congestive heart failure, angina, additional heart diseases, and stroke (but not systemic hypertension). Participants also indicated whether

they had used any medications during the past 30 days: the use of aspirin, cholesterol-lowering drugs, and antidepressants was noted.

Blood pressure.—Using a noninvasive Microlife BP monitor, three systolic and diastolic BP measurements were collected by the research nurse for a 15-minute resting period. The participant's mean arterial pressure (MAP) was computed as [diastolic BP + 1/3(systolic BP − diastolic BP)] and was used for the analysis.

Body mass index.—We asked participants for their weight and height to calculate body mass index (BMI).

Dyslipidemia.—We determined plasma low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) using standard methodology at the clinical chemistry laboratories at the UCSD medical center. We used the LDL-C:HDL-C ratio for the analyses whereby a higher ratio indicates greater dyslipidemia.

Smoking status.—We defined smoking status in terms of ever (i.e., former plus current) smoker versus never smoker.

Physical activity.—We used the Rapid Assessment of Physical Activity scale to assess the amount of light, moderate, and strenuous physical activities in a typical week, including strength and flexibility exercises (total score = 0–6; Topolski et al., 2006).

Alcohol consumption.—We scored the amount of consumed alcohol in the past month based on the number of days participants had at least one alcoholic drink and the number of alcoholic drinks they usually drank on these days.

Sleep quality.—We used the Pittsburgh Sleep Quality Index global score to assess subjective sleep quality. Higher scores indicate poorer sleep (total score = 0–21; Buysse et al., 1991).

Activities of daily living/instrumental ADL.—We used a 15-item measure of ADL/IADL to assess the number of activities for which the AD spouse is dependent upon the caregiver (Pearlin, Mullan, Semple, & Skaff, 1990).

Data Analysis

Data were analyzed using Predictive Analytics Software (PASW) 18.0 statistical software package (SPSS Inc., Chicago, IL), with two-tailed level of significance at $p < .05$. We did not adjust p values for multiple comparisons because there were prespecified hypotheses regarding the direction of the relations between variables. Moreover, the studied biomarkers are indicative of the same biological process (i.e., chronic low-grade systemic inflammation) and are actual observations in nature (Perneger, 1998; Rothman, 1990). To approximate a normal distribution, all biomarker values were $\log_{10}$ transformed, and values 3 *SDs* greater than or less than the mean $\log_{10}$-transformed value were deleted as outliers; there were two outliers for IFG and CRP, three outliers for TNF-α, four outliers for IL-8, and six outliers for IL-6.

We conducted a mixed (random-effects) regression analysis to examine the impact of leisure satisfaction (i.e., separate models with total leisure satisfaction, leisure activities frequency, and leisure activities enjoyment) and of depressive symptoms on circulating levels of inflammatory markers over time. Adjustments were made for sociodemographic factors, health behaviors, and medical and mental health variables. To diminish problems associated with multicollinearity and to increase interpretability of regression coefficients, we centered independent variables around their grand mean and dummy-coded categorical variables at +0.5 (e.g., women) and −0.5 (e.g., men). With this approach, the intercept corresponds to the whole sample and the coefficient is the difference between categorical groups (e.g., women and men). "Time" corresponds to the number of assessments and is linear in nature with the baseline assessment coded as "0."

The model included the following fixed effects: age, gender, education, years caregiving, placement status of the spouse with dementia (yes/no), deceased status of the spouse (yes/no), CVD (yes/no), diabetes (yes/no), aspirin (yes/no), cholesterol-lowering medication (yes/no), antidepressant medication (yes/no), MAP, BMI, LDL-C:HDL-C ratio, smoking status, physical activity, alcohol consumption, sleep quality, total ADL/IADL, depressive symptoms, and leisure satisfaction. Of these, age, years caregiving, placement and deceased status of the spouse, CVD, diabetes, medication categories, MAP, BMI, LDL-C:HDL-C ratio, smoking status, physical activity, alcohol consumption, sleep quality, total ADL/IADL, depressive symptoms, and leisure satisfaction were all entered as time varying. Random intercepts were modeled for participants.

Results

Characteristics of Study Participants

Table 1 shows the sociodemographic and health characteristics, leisure satisfaction scores, depressive symptom scores, and levels of inflammation markers of study participants for the baseline and subsequent yearly assessments. The 121 caregivers completed a total of 484 assessments over the course of the study for a mean of four assessments per participant. Data for all of the fixed effect and time-variant variables were complete in more than 98.5% of assessments, except for LDL-C:HDL-C ratio, which was available in 92.8%. After deleting outliers, values of inflammatory markers were available in 94.4% for IFG, in 95.7%

Table 1. Characteristics of the Sample

Variables	Baseline (n = 121)	Year 1 (n = 111)	Year 2 (n = 107)	Year 3 (n = 98)	Year 4 (n = 46)
Age (years)	74.3 ± 8.0	75.3 ± 7.8	76.4 ± 7.9	77.8 ± 7.6	78.1 ± 7.3
Women (%)	69.4	69.4	71.0	69.4	73.9
Education (years)	15.1 ± 3.1	15.2 ± 3.1	15.1 ± 3.1	15.2 ± 3.2	15.3 ± 3.3
Years caregiving	4.39 ± 3.43	5.29 ± 3.52	6.28 ± 3.48	7.33 ± 4.31	8.52 ± 3.55
Spouse placed (%)	0	12.6	27.1	38.8	50.0
Spouse deceased (%)	0	6.3	18.7	32.7	58.7
Cardiovascular disease (%)	18.2	19.8	20.6	23.5	17.4
Diabetes (%)	12.4	13.5	15.0	14.3	13.0
Aspirin (%)	28.1	23.4	28.0	25.5	34.8
Cholesterol-lowering drug (%)	47.1	50.5	52.3	52.0	50.5
Antidepressant drug (%)	26.4	27.0	27.1	22.4	17.4
MAP (mm Hg)	95.3 ± 9.6	92.4 ± 10.7	90.6 ± 10.8	91.4 ± 11.2	88.8 ± 8.7
BMI (kg/m^2)	26.6 ± 4.8	27.0 ± 5.2	26.4 ± 5.1	26.9 ± 4.9	25.9 ± 4.0
LDL-C:HDL-C	2.17 ± 0.82	1.90 ± 0.69	1.76 ± 0.69	1.70 ± 0.68	1.58 ± 0.53
Ever smoker (%)	46.3	46.8	43.0	48.0	45.7
Physical activity	3.43 ± 1.65	3.11 ± 1.37	2.99 ± 1.71	2.80 ± 1.62	3.46 ± 1.53
Alcohol consumption	5.52 ± 5.79	5.88 ± 6.65	5.80 ± 6.11	5.94 ± 6.74	7.13 ± 7.05
Pittsburgh sleep quality index	6.55 ± 3.51	6.25 ± 3.59	6.56 ± 3.34	6.06 ± 3.86	5.92 ± 3.44
ADL/IADL requiring help	9.11 ± 3.69	8.96 ± 4.34	8.31 ± 5.79	5.78 ± 6.40	1.59 ± 4.29
Depressive symptoms	8.62 ± 5.80	8.50 ± 5.99	7.54 ± 6.11	8.08 ± 6.25	7.26 ± 5.63
Total leisure satisfaction	55.6 ± 12.3	57.5 ± 11.4	55.6 ± 14.1	49.9 ± 14.2	51.0 ± 13.2
Leisure activities frequency	30.9 ± 4.5	31.1 ± 4.9	30.8 ± 5.6	29.4 ± 5.7	30.8 ± 4.7
Leisure activities enjoyment	32.5 ± 5.8	34.1 ± 5.0	32.8 ± 6.1	29.9 ± 6.5	30.6 ± 5.7
TNF-α (pg/mL)	5.74 (4.09–7.81)	5.13 (3.85–6.99)	4.69 (3.79–6.19)	6.24 (5.15–7.60)	5.40 (4.67–6.96)
IL-6 (pg/mL)	1.07 (0.76–1.53)	1.06 (0.63–1.82)	0.96 (0.60–1.91)	1.46 (1.01–2.32)	1.29 (0.93–2.04)
IL-8 (pg/mL)	6.72 (4.12–8.54)	3.82 (3.01–5.67)	4.07 (2.84–5.38)	5.28 (4.11–7.02)	3.97 (3.22–5.25)
IFG (pg/mL)	1.56 (0.97–2.41)	0.66 (0.32–1.29)	0.73 (0.40–1.27)	0.91 (0.58–1.26)	0.35 (0.18–0.74)
CRP (mg/mL)	1.49 (0.80–4.28)	1.87 (0.71–4.33)	1.93 (0.67–4.50)	1.81 (0.89–4.00)	2.60 (1.30–6.56)

Notes. ADL = activities of daily living; CRP = C-reactive protein; IADL = instrumental ADL; IFG = interferon-γ; IL-6 = interleukin-6; IL-8 = interleukin-8; LDL-C:HDL-C = low-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio; *SD* = standard deviation; TNF = tumor necrosis factor.

Values are given as percentages, mean ± *SD*, or median (interquartile range).

for IL-6, in 95.9% for CRP, in 96.1% for IL-8, and in 96.3% for TNF-α of all assessments.

Before enrollment into the study, caregivers had been providing care for their AD spouse for an average of 4.4 years (range = 0.5–17.1). Baseline total leisure satisfaction scores were normally distributed with 45 (37.2%), 35 (29.9%), and 41 (33.9%) participants, respectively, scoring in the top (range = 62–76), middle (range = 51–61), and bottom (range = 21–50) tertiles. Forty-seven (48.8%) caregivers scored greater than or equal to 10 on the baseline CES-D-10 scale indicative of clinically relevant depressive symptomatology. During the course of the study, 45 caregivers placed their spouse in a long-term care facility and 42 caregivers experienced the death of their spouse.

Correlations Among Key Variables Over Time

Table 2 shows the unadjusted bivariate relationships among key variables over the entire study period. Total leisure satisfaction, leisure activities frequency, and leisure activities enjoyment were all lower with more depressive symptoms (all p values < .001) and with less physical activity (all p values < .027). Greater enjoyment from leisure activities (p = .011) and more depressive symptoms (p = .043) were associated with more ADL/IADL requiring help from the caregiver. Total leisure satisfaction (p = .42), frequency of leisure activities (p = .16), and physical activity (p = .16) were not associated with ADL/IADL.

In terms of inflammatory markers, more depressive symptoms were related to higher levels of IFG (p = .027). Lower total leisure satisfaction was associated with higher levels of IL-6 (p = .004) and IL-8 (p = .012); lower enjoyment from leisure activities was related to higher levels of TNF-α (p = .006), IL-6 (p = .001), and IL-8 (p = .006), whereas lower frequency of leisure activities was associated only with higher IL-8 levels (p = .034). More ADL/IADL requiring help from the caregiver was associated with lower levels of TNF-α (p = .004) and IL-6 (p < .001), as well as with higher IFG levels (p = .034). Greater amount of physical activity was associated with lower levels of IL-6 (p = .041) and CRP (p = .022).

Separate Relationships of Leisure Satisfaction and Depressive Symptoms With Biomarkers

Table 3 shows the fully adjusted relations over time between total leisure satisfaction, leisure activities frequency, and leisure activities enjoyment (Models 1a-c), as well as depressive symptoms (Model 2), all as separate predictors, and the inflammatory markers.

Model 1a: Total leisure satisfaction and inflammation.—Lower total leisure satisfaction was associated with higher levels of TNF-α (p = .047), IL-8 (p = .001), and IFG (p = .020). Total leisure satisfaction was unrelated to IL-6 (p = .21) and CRP (p = .65) levels.

Model 1b: Leisure activities frequency and inflammation.—Lower frequency of leisure activities was associated with higher IL-8 levels (p = .023) but not with TNF-α (p = .12), IL-6 (p = .39), IFG (p = .43), and CRP (p = .67) levels.

Model 1c: Leisure activities enjoyment and inflammation.—Lower enjoyment from leisure activities showed an association with higher levels of TNF-α (p = .045), IL-8 (p < .001), and IFG (p = .002); no relationships were observed with IL-6 (p = .10) and CRP (p = .99) levels.

Model 2: Depressive symptoms and inflammation.—There were no relationships between depressive symptoms and levels of TNF-α (p = .90), IL-6 (p = .27), IL-8 (p = .18), IFG (p = .45), and CRP (p = .39). There also were no associations between the categorical definition of clinically elevated levels of depressive symptoms (i.e., CESD-10 score ≥ 10) and any biomarker level (all p values > .21).

Table 2. Bivariate Relationships Between Key Variables for the Entire Study Period

	ADL/IADL		Physical activity		Depressive symptoms		Total leisure satisfaction		Leisure activities frequency		Leisure activities enjoyment	
Variables	Estimate	*SE*	Estimate	*SE*	Estimate	*SE*	Estimate	*SE*	Estimate	*SE*	Estimate	*SE*
ADL/IADL			−0.016	0.011	**0.069***	0.034	0.070	0.086	−0.047	0.034	**0.104***	0.040
Physical activity					−0.011	0.144	**1.079****	0.355	**0.524*****	0.138	**0.372***	0.167
Depressive symptoms							**−0.729*****	0.104	**−0.292*****	0.041	**−0.281*****	0.049
Total leisure satisfaction									**0.347*****	0.008	**0.409*****	0.010
Leisure activities frequency											**0.835*****	0.038
TNF-α	**−0.004****	0.001	−0.004	0.005	<0.001	0.001	−0.003	0.002	−0.003	0.002	**−0.004****	0.001
IL-6	**−0.010*****	0.003	**−0.021***	0.010	0.004	0.003	**−0.004****	0.001	−0.006	0.003	**−0.009****	0.003
IL-8	0.001	0.002	−0.011	0.007	< −0.001	0.002	**−0.002***	0.001	**−0.005***	0.002	**−0.005****	0.002
IFG	**0.008***	0.004	−0.010	0.013	**0.008***	0.004	< −0.001	0.002	0.001	0.004	−0.001	0.003
CRP	−0.005	0.004	**−0.038***	0.016	0.006	0.005	−0.003	0.002	−0.007	0.005	−0.004	0.004

Notes. ADL = activities of daily living; CRP = C-reactive protein; IADL = instrumental ADL; IL-6 = interleukin-6; IL-8 = interleukin-8; IAG = interferon-γ; *SE* = standard error; TNF-α = tumor necrosis factor-α.

Data are given as slopes (log-transformed slopes for inflammatory biomarkers) with *SE* and significance level: *p < .05. **p < .01. ***p < .001.

Table 3. Mixed Models for the Separate Relationships Between Leisure Satisfaction, Depressive Symptoms, and Inflammatory Biomarkers

	TNF-α		IL-6		IL-8		IFG		CRP	
Predicting variables	Estimate	*SE*	Estimate	*SE*	Estimate	*SE*	Estimate	*SE*	Estimate	*SE*
Total leisure satisfaction (Model 1a)	**−0.001***	0.001	−0.002	0.001	**−0.003****	0.001	**−0.004***	0.002	**−0.001**	0.002
Leisure activities frequency (Model 1b)	−0.003	0.002	−0.003	0.004	**−0.005***	0.002	−0.004	0.005	−0.003	0.006
Leisure activities enjoyment (Model 1c)	**−0.003***	0.002	−0.005	0.003	**−0.008*****	0.002	**−0.012****	0.004	< −0.001	0.005
Depressive symptoms (Model 2)	<0.001	0.002	0.004	0.003	-0.003	0.002	0.003	0.004	0.005	0.006

Notes. BMI = body mass index; CRP = C-reactive protein; IL-6 = interleukin-6; IL-8 = interleukin-8; IAG = interferon-γ; MAP = mean arterial pressure; *SE* = standard error; TNF-α = tumor necrosis factor-α.

Data are given as log-transformed slopes (*SE*).

Estimates were adjusted for time of assessment, baseline age, gender, education, years caregiving, placement status of spouse, deceased status of spouse, cardiovascular disease, diabetes, aspirin, cholesterol-lowering drugs, antidepressant drugs, MAP, BMI, low-density cholesterol to high-density cholesterol ratio, smoking, physical activity, alcohol consumption, and subjective sleep quality.

*$p < 0.05$. **$p < 0.01$. ***$p < 0.001$.

Table 4. Mixed Model for the Mutual Relationship Between Total Leisure Satisfaction, Depressive Symptoms, and Inflammatory Biomarkers

	TNF-α		IL-6		IL-8		IFG		CRP	
Parameter	Estimate	*SE*	Estimate	*SE*	Estimate	*SE*	Estimate	*SE*	Estimate	*SE*
Intercept	**0.728*****	0.029	−0.007	0.058	**0.712*****	0.037	0.034	0.069	0.170	0.094
Time	0.011	0.008	**0.036***	0.016	**−0.027***	0.011	**−0.108*****	0.021	0.045	0.027
Age baseline	**0.005****	0.001	0.005	0.003	0.001	0.002	<0.001	0.003	0.003	0.005
Female gender	0.020	0.024	0.038	0.053	**0.064***	0.029	0.184**	0.055	0.072	0.082
Education	< −0.001	0.003	−0.006	0.008	−0.003	0.004	0.002	0.008	−0.011	0.012
Years caregiving	−0.003	0.003	0.002	0.007	0.002	0.003	0.006	0.007	0.016	0.010
Spouse placed	−0.001	0.026	−0.047	0.050	−0.059	0.033	−0.043	0.063	0.016	0.082
Spouse deceased	−0.008	0.032	0.011	0.061	−0.064	0.041	−0.063	0.078	−0.119	0.100
CVD	0.009	0.024	0.010	0.048	−0.013	0.031	−0.020	0.059	−0.029	0.079
Diabetes	0.016	0.030	−0.061	0.062	**0.097***	0.038	0.074	0.071	−0.054	0.099
Aspirin	−0.008	0.020	−0.045	0.038	0.006	0.027	−0.034	0.049	−0.015	0.062
Cholesterol drug	0.036	0.020	0.031	0.041	0.037	0.025	0.035	0.047	−0.089	0.066
Antidepressant drug	0.015	0.021	0.001	0.044	0.030	0.027	0.029	0.052	0.122	0.070
Mean arterial pressure	<0.001	0.001	<0.001	0.002	−0.001	0.001	< −0.001	0.002	−0.001	0.003
Body mass index	−0.001	0.002	0.009	0.005	−0.004	0.003	−0.009	0.005	**0.016***	0.007
LDL-C:HDL-C	0.021	0.014	0.020	0.028	0.027	0.017	−0.022	0.033	0.066	0.045
Ever smoker	0.019	0.020	0.078	0.044	0.036	0.025	−0.017	0.048	0.023	0.068
Physical activity	0.002	0.006	−0.007	0.012	−0.008	0.008	−0.013	0.015	−0.027	0.019
Alcohol consumption	0.001	0.002	0.001	0.003	0.003	0.002	0.004	0.004	−0.002	0.005
PSQI	0.003	0.003	0.007	0.006	0.006	0.004	0.005	0.007	−0.006	0.009
ADL/IADL	−0.004	0.002	−0.008	0.004	**−0.007***	0.003	−0.005	0.005	−0.006	0.007
Depressive symptoms	−0.001	0.002	0.003	0.004	**−0.007****	0.002	−0.001	0.005	0.004	0.006
Total leisure satisfaction	−0.002*	0.001	−0.001	0.002	**−0.004*****	0.001	−0.004*	0.002	< −0.001	0.002

Notes. ADL/IADL = total activities of daily living/instrumental ADL requiring help; CRP = C-reactive protein; CVD = cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; IL-6 = interleukin-6; IL-8 = interleukin-8; IFG = Interferon-γ; LDL-C = low-density lipoprotein cholesterol; PSQI = Pittsburgh Sleep Quality Index; TNF-α = tumor necrosis factor-α.

All independent variables were centered to the mean such that the intercepts show the mean biomarker concentrations in the entire sample. Categorical variables were contrast coded as female gender (+0.5) vs. male gender (−0.5), CVD (+0.5) vs. no CVD (−0.5), diabetes (+0.5) vs. no diabetes (−0.5), medications (+0.5) vs. no medications (−0.5), ever smoker (+0.5) vs. never smoker (−0.5), and caregiver (+0.5) vs. noncaregiver (−0.5). "Placed spouse" and "spouse deceased" indicate the immediate change in the biomarker concentration assessed 3 months after the respective transition. "Time" indicates the change in the biomarker concentration per each assessment the participant was in the study.

Data are given as log-transformed slopes (*SE*): *$p < .05$. **$p < .01$. ***$p < .001$.

Mutual Relationships of Leisure Satisfaction and Depressive Symptoms With Biomarkers

The following analyses predicted levels of inflammatory markers over time using total leisure satisfaction, frequency of leisure activities, and enjoyment from leisure activities, respectively, along with depressive symptoms as predicting variables in the same model. Each analysis was fully adjusted for covariates.

Model 3a: Including total leisure satisfaction and depressive symptoms.—Table 4 shows the fully adjusted results of this model, taking into account mutual effects of total

leisure satisfaction and depressive symptoms. Lower total leisure satisfaction was related to higher levels of TNF-α ($p = .034$), IL-8 ($p < .001$), and IFG ($p = .027$) but not to IL-6 ($p = .36$) and CRP ($p = .88$) levels. More depressive symptoms were associated with lower levels of IL-8 ($p = .003$) but not with TNF-α ($p = .47$), IL-6 ($p = .49$), IFG ($p = .81$), and CRP ($p = .46$) levels.

Model 3b: Including leisure activities frequency and depressive symptoms.—Lower frequency of leisure activities was associated with higher IL-8 levels over time ($B = -0.008 \pm 0.003$, $p = .003$); there were no relationships between frequency of leisure activities and levels of TNF-α ($B = -0.003 \pm 0.002$, $p = .11$), IL-6 ($B = -0.002 \pm 0.004$, $p = .62$), IFG ($B = -0.003 \pm 0.005$, $p = .58$), and CRP ($B = -0.001 \pm 0.006$, $p = .89$). Depressive symptoms were associated with IL-8 levels ($B = -0.006 \pm 0.002$, $p = .019$) but not with levels of the other inflammatory markers (all p values > .38).

Model 3c: Including leisure activities enjoyment and depressive symptoms.—Lower enjoyment from leisure activities was associated with higher levels of TNF-α ($B = -0.003 \pm 0.002$, $p = .036$), IL-8 ($B = 0.010 \pm 0.002$, $p < .001$), and IFG ($B = -0.012 \pm 0.004$, $p = .002$); no relationships emerged for IL-6 ($B = -0.004 \pm 0.003$, $p = .18$) and CRP ($B = 0.002 \pm 0.005$, $p = .77$) levels. Depressive symptoms were associated with IL-8 ($B = -0.007 \pm 0.002$, $p = .004$) but not with levels of the other biomarkers (all p values > .36).

Effect of categorical depression.—If depressive symptoms were replaced by the categorical definition of depression (i.e., CESD-10 score ≥ 10) in Models 3a-c, depression did not relate to levels of any biomarker (all p values > 0.26).

Depressive Symptoms as a Mediator of the Relation Between Leisure Satisfaction and Inflammatory Markers

When comparing the results from Models 1a-c with those from Models 3a-c, it becomes apparent that the significance of the associations of total leisure satisfaction (Model 1a vs. Model 3c), frequency of leisure activities (Model 1b vs. Model 3b), and enjoyment from leisure activities (Model 1c vs. Model 3c) with inflammatory markers were identical. In other words, the significance of the relations between leisure satisfaction and inflammatory markers did not change when depressive symptoms were added to the models. This suggests that depressive symptoms did not formally mediate the relationship between total leisure satisfaction and any inflammatory marker (Baron, & Kenny, 1986).

Discussion

The main goal of our study was to investigate in caregivers of a spouse with AD whether leisure satisfaction was associated with markers of low-grade systemic inflammation and whether this relationship was mediated by depressive symptoms. We found that low satisfaction with leisure activities is longitudinally associated with an elevation in circulating levels of several markers of systemic low-grade inflammation in spousal AD caregivers (cf. Hypothesis a in Figure 1). Specifically, we found that caregivers with lower total leisure satisfaction had higher levels of the pro-inflammatory cytokines such as TNF-α, IL-8, and IFG that are implicated in the atherosclerotic processes pertinent to CHD. We found these relationships to be independent of a range of important correlates of inflammation and leisure activities, including physical activity. We conceptualized total leisure satisfaction as a combination of the frequency of engagement in leisure activities with the amount of enjoyment gained from these. Lower enjoyment from leisure activities seemed more reliably associated with elevated levels of inflammatory markers than lower frequency of leisure activities, as the former was significantly related to increased levels of TNF-α, IL-8, and IFG, whereas the latter was significantly associated with increased IL-8 levels only. We also made efforts to control for the amount of time caregivers had available to spend on even the nonphysical leisure activities by taking into account ADL/IADL for which the AD spouse was dependent upon the caregiver. IL-6 levels were increased with lower total leisure satisfaction in the bivariate analysis only, suggesting covariates, including health behaviors like physical activity might help to explain this relationship.

Our findings imply that low leisure satisfaction for a period of 4 years is associated with an increased risk for higher levels of certain inflammatory markers that have been linked to the development of CHD in AD caregivers. For instance, and as was previously reviewed (Libby, 2002; Szmitko et al., 2003), IFG and IL-8 both play an important role as leukocyte chemoattractants, which facilitate adherence of leukocytes to endothelial cells with their subsequent migration into the intima. Atheroma-associated cells then secrete TNF-α and IL-6 both of which further enhance leukocyte recruitment into the vessel wall. IFG that is secreted by activated T-cells can limit the synthesis of new collagen required for the preservation of the fibrous cap of an atherosclerotic plaque, thereby contributing to plaque vulnerability. Within plaques, TNF-α contributes to overexpression of matrix metalloproteinases, which in turn are further thinning the fibrous cap, thereby facilitating plaque rupture further narrowing coronary vessels or leading to the onset of acute coronary syndromes.

Depressive symptoms were significantly related to increased levels of IFG in the unadjusted analysis only; this concurs with a previous study on patients with major depression (Simon et al., 2008). However, we found no significant association between depressive symptoms and levels of biomarkers over time after covariates were taken into account (cf. Hypothesis b in Figure 1). The same was

observed when testing for a relationship with a categorical measure of clinically elevated symptoms of depression. There even emerged an inverse association between depressive symptoms and IL-8 when controlling for leisure satisfaction. These observations were partially contrast with two meta-analyses showing greater levels of proinflammatory cytokines and CRP with greater severity of depressive mood (Dowlati et al., 2010; Howren et al., 2009). However, there also are studies in which depression was inversely associated with IL-6 and CRP cross-sectionally (Whooley et al., 2007) or showed no association with IL-6 and CRP longitudinally after adjustments for health behaviors, including physical activity, smoking, and BMI (Duivis et al., 2011). Moreover, previous studies on the relationship between depression and inflammatory markers did not control for leisure satisfaction.

Our data might contribute to the current discussion about the need of identifying the "cardiotoxic" components of depression (Frasure-Smith, & Lespérance, 2010). Low satisfaction from pleasurable activities is an important precursor and perpetuating factor of depression (Lewinsohn, 1975; Lewinsohn & Amenson, 1978). In agreement with this concept, we found a significant and inverse association between low leisure satisfaction and depressive symptoms. However, depressive symptoms were not a mediating variable of the relation between leisure satisfaction and inflammatory markers (cf. Hypothesis c in Figure 1). This concurs with our previous study showing that the relation between total leisure satisfaction and endothelial function was not mediated by depressive symptoms (Mausbach et al., 2012). Thus, in the context of AD caregiving, there is currently little evidence that depressive symptoms importantly affect the association of leisure satisfaction with two key mechanisms of atherosclerosis, namely endothelial dysfunction and inflammation. To the extent that enjoyment from leisure activities belongs to the positive affect spectrum, our results also add to the growing evidence that low positive affect is adversely associated with psychobiological processes relevant to poor cardiovascular health, including elevated levels of inflammatory markers (Steptoe, Dockray, & Wardle, 2009). It might be that the absence of positive affect (i.e., low leisure satisfaction) might be more detrimental for cardiovascular health of AD caregivers than the presence of negative affect (i.e., depressive symptoms).

Our data lend support to the assumption that cardiovascular health in dementia caregivers might be improved through behavioral activation treatments aimed at increasing positive interactions with caregivers' environment and to increase the number of pleasant activities in order to improve mood (Cuijpers, van Straten, &Warmerdam, 2007). When it comes to tailor these interventions for AD caregivers to possibly mitigate systemic inflammation, increasing the amount of leisure gained from activities might be a more promising target than increasing engagement in a preferably high number of leisure activities.

The interpretation of our study results needs to consider some important limitations. All caregivers were dwelling in the community, providing care for their AD spouse, and in good health overall given their average age was more than 70 years at study enrollment. Therefore, our findings may not generalize to younger individuals and those with more impaired physical and mental health. However, the recruitment of spousal dementia caregivers with a Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, diagnosis for cognitive behavioral therapy interventions poses unique challenge and results may not unequivocally be transferable to the larger community of dementia caregivers (Wiprzycka, Mackenzie, Khatri, & Cheng, 2011). Factors not assessed in our study, including personality characteristics of the care recipient might also have an impact on caregiver physical health and levels of inflammatory markers, respectively (Riffin et al., 2012). The relation between variables of interest might partially be bidirectional. For instance, proinflammatory cytokines may induce sickness behavior that resembles depressive behavior in many ways (e.g., both are characterized by behavioral inhibition; Maes et al., 2012).

Taken together, the findings from this study suggest that low satisfaction with leisure activities is related to increased circulating levels of systemic markers of inflammation in spousal AD caregivers from the community. All of these biomarkers have been implicated in the initiation, progression, and clinical manifestation of atherosclerosis, thereby suggesting that they might link low leisure satisfaction, a behavioral correlate of depression, with CHD. Future studies should investigate whether cardiovascular health in dementia caregivers might be improved through behavioral activation treatments targeting leisure satisfaction.

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