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Carotid plaque in Alzheimer caregivers and the role of sympatho-adrenal arousal

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Abstract

Objective—Providing care for a spouse diagnosed with Alzheimer's disease has been associated with an increased risk of coronary heart disease, potentially due to the impact of caregiving stress on the atherosclerotic disease process. We hypothesized that Alzheimer caregivers would have increased prevalence of carotid artery plaque compared to non-caregiving controls and that prolonged sympatho-adrenal arousal to acute stress would relate to this difference.

Methods—Participants were 111 spousal caregivers (74±8 years of age, 69% women) to patients with Alzheimer's disease and 51 non-caregiving controls (75±6 years of age, 69% women). In-home assessment of carotid artery plaque via B-mode ultrasonography was conducted. Plasma catecholamine response to an acute speech stressor task was also measured.

Results—Logistic regression indicated that caregiving status (i.e., caregiver vs. non-caregiver) was significantly associated with a 2.2 times greater odds for the presence of plaque independent of other risk factors of atherosclerosis (95% CI=1.01–4.73, $p=.048$). Decreased recovery to basal levels of epinephrine after a psychological stress task was significantly associated with the presence of plaque in caregivers, but not in non-caregivers. Norepinephrine recovery post-stressor was not associated with plaque in either group.

Conclusions—Caregivers had a higher prevalence of carotid plaque compared to non-caregivers. Poorer epinephrine recovery after acute stress was associated with the presence of plaque in caregivers but not in non-caregivers. A prolonged sympatho-adrenal response to acute stress might enhance the development of atherosclerosis in chronically stressed Alzheimer caregivers.

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Conflicts of Interest

The funding agency did not participate in the study design, the collection, analysis, or interpretation of the data, in writing the report, or in the decision to submit the manuscript for publication. All authors of this manuscript have no financial or personal conflicts of interest.

Keywords

caregiving; stress; Alzheimer's disease; carotid artery plaque; atherosclerosis; catecholamines

Introduction

Providing care to a spouse diagnosed with Alzheimer's disease can be mentally, emotionally, and physically taxing for the caregiver. Caregiving has been associated with increased mortality(1), most likely due to increased risk for coronary heart diseases (CHD) (2). Caregivers' increased CHD risk might be due to the influence that chronic stress can have on several pathophysiologic processes that can accelerate atherosclerosis(3). For instance, caregiving has been associated with elevated biomarkers of atherosclerosis including inflammatory and coagulation markers(4,5). Furthermore, a recent study by Mausbach and colleagues(6) found that caregivers of spouses with more severe dementia exhibited poorer endothelial functioning compared to caregivers of spouses with milder dementia and non-caregivers. Caregivers also experience disturbed sleep, which has been associated with increased risk for CHD events(7) as well as sympatho-adrenal arousal and other markers of atherosclerosis in both caregivers(8) and in healthy adults(9).

Previous work has also found that diverse types of chronic emotional stress are associated with morphological evidence of large vessel disease. For example, a study by Troxel and colleagues(10) found that African American women reporting racial discrimination had more carotid plaques compared to those not reporting racial discrimination. In addition, individuals working in professions characterized by high demand and low control exhibited increased carotid artery intima-media thickness(IMT), a marker of early atherosclerosis, as well as accelerated progression over time(11). Women reporting poor marital satisfaction have demonstrated similar patterns(12). The evidence supporting a link between chronic stress and morphological evidence of large vessel disease is accumulating, but has yet to be examined in Alzheimer caregivers.

In response to a stressor, sympathetic nerves stimulate the release of catecholamines, including epinephrine and norepinephrine, that trigger a cascade of physiologic changes such as increased heart rate and blood pressure(3). Sympatho-adrenal arousal also enhances inflammation, a key process involved in atherosclerosis(3), thereby inducing endothelial injury and dysfunction(13). Over time, this arousal can also result in hypertension, metabolic syndrome, and hypercholesterolemia(14).

Given that the physiological response to stress promotes pathological processes associated with atherosclerosis, it is expected that if stressor exposure is chronic, then the potential for arterial damage is enhanced. This persistent arousal might occur in chronically-stressed caregivers who encounter frequent daytime and nighttime challenges associated with providing care and also exhibit evidence of heightened and prolonged sympathetic arousal(15,16). Consistent with this idea, a recent meta-analysis(17) showed that poor cardiovascular recovery (i.e., prolonged activation) to laboratory mental stress tasks was significantly associated with future cardiovascular risk. Longitudinal increases in carotid IMT were more consistently associated with poorer stress recovery than with stressor reactivity itself (i.e., the magnitude of the stress response immediately following stress). Therefore, stress responses that are prolonged (i.e., poor recovery), rather than simply heightened, might be more strongly associated with atherosclerotic processes.

Considering that Alzheimer caregivers are at increased risk for CHD and show evidence of dysregulation on pathological process associated with atherosclerosis, it is expected that

caregivers might also exhibit stronger morphological evidence of large vessel disease compared to non-caregiving controls. The present study used ultrasound imaging techniques to test the primary hypothesis that caregivers would have a higher prevalence of carotid artery plaque compared to non-caregivers.

We also measured catecholamine levels before, immediately following, and 14-minutes after an acute stressor to determine if sympatho-adrenal response to acute stress was associated with the presence of plaque in caregivers. Given that past work suggests that prolonged stress responses, rather than heightened responses, are more strongly associated with atherosclerotic processes, we hypothesized that caregivers with prolonged catecholamine activity post-stressor would be more likely to have a carotid plaque. Specifically, we hypothesized that the relationship between prolonged catecholamine response to stress and plaque would be more apparent in caregivers compared to non-caregiving controls because caregivers are expected to be more frequently exposed to daily stressors related to their caregiving role and thus, more opportunity for physiological arousal.

Methods

Participants

Participants were 162 community-dwelling older adults who were enrolled in the University of California, San Diego (UCSD) Alzheimer Caregiver Study (approved by the UCSD Institutional Review Board). All data were collected between 2007–2010. All participants provided written, informed consent. The “caregiver” group included 111 participants who were providing in-home care to a spouse diagnosed with Alzheimer’s disease and the “non-caregiver” group included 51 older adults married to a spouse without a diagnosis of Alzheimer’s disease or other dementia.

All participants were at least 55 years of age, married, and living with their spouse at home. Caregivers and non-caregivers were excluded if they were currently diagnosed with or receiving treatment for a serious or terminal medical condition that requires ongoing medical care and was considered above and beyond the normal aging process. For example, Parkinson’s disease, advanced CHD, and/or any severe psychiatric disorder which was not under control or required rigorous ongoing medical attention were cause for exclusion. Previous heart attacks and strokes were not excluded. Participants were also excluded if they were currently receiving or had received treatment for cancer within the past 5 years, had organ transplantation requiring anti-rejection medication, or were taking anticoagulants and/or corticosteroids. Spouses of non-caregivers were required to function independently and be in generally good health. Control participants were excluded if their spouses were diagnosed with Alzheimer’s disease or any other form of dementia. Furthermore, control participants were excluded if their spouses were diagnosed with any major health problems that required ongoing and rigorous medical treatment or spouse assistance. Finally, control participants were never previously in a marital or long-term relationship with someone for whom they had cared and they were not responsible for any other person’s care.

Caregivers were recruited from Alzheimer caregiver support groups, senior health fairs, flyers, and referrals from the UCSD Alzheimer’s Disease Research Center or by recommendation of other participants enrolled in the project. Non-caregivers were recruited via senior health fairs and flyers or were recommended by enrolled caregivers or non-caregivers.

Procedures

Assessments were administered in participants’ homes by trained personnel including a research assistant, a research nurse, and a sonographer. First, the research assistant

administered a semi-structured interview including psychosocial questionnaires and assessment of caregiver health behaviors and medical history. Within one week, the nurse and sonographer returned to the participant's home to collect the biological assessments. Participants were informed that the blood draw was non-fasting. If participants were taking prescribed medications, they were instructed to continue use as instructed by their physician. A 22-gauge indwelling venous catheter was inserted into the participant's forearm. Resting blood pressure was measured after 5, 10, and 25 minutes of rest with the participant resting in a supine position. The first blood draw was collected after 10 minutes of the rest period to assess baseline catecholamine levels and the speech stressor protocol followed. In order to reduce the impact of diurnal fluctuations, all blood draws were collected exclusively between 8AM and 10AM for each participant. Carotid artery ultrasound was conducted in the same visit. Participants also wore an actigraphy watch which recorded objective assessment of sleep and wakefulness over a period of 72 consecutive hours.

Speech Stressor Task

After the rest period and baseline blood draw, participants were randomly presented with one of two vignettes. One vignette described a situation in which the participant was falsely accused of stealing a belt(18) and the other vignette described a situation in which the participant was unfairly charged by a disreputable auto repairmen. Previous work has demonstrated that the two vignettes elicit comparable reactivity(19). Participants were then given 3 minutes to mentally prepare to deliver a speech responding to the vignette. After preparation, participants delivered their speech for 3 minutes to the research personnel. Immediately following the speech, the "post-speech" blood draw was collected. Participants rested for 14 minutes, after which the final "14-minute recovery" blood draw was taken. The catheter was flushed with a physiological saline solution (NaCl 0.9%) between blood draws.

Measures

Blood Pressure—Blood pressure was assessed using a Microlife blood pressure monitor, model #3AC1-1PC. The mean of the 3 resting blood pressure measurements was used to obtain a more stable measurement of resting blood pressure. Mean arterial pressure (MAP) was calculated using the following formula: diastolic blood pressure + 1/3(systolic blood pressure – diastolic blood pressure).

Obesity—Body Mass Index (BMI) was calculated as the ratio between self-reported weight in kilograms and height in square meters. An "obesity" variable specified if a participant was obese. Participants with a BMI<30 were classified as "obese" and were coded 1. Participants with a BMI≤30 were classified as "non-obese" and were coded 0.

Plasma Catecholamines—Norepinephrine and epinephrine levels were extracted using a catechol-O-methyltransferase (COMT) radioenzymatic assay. This technique removes catecholamines from 0.5 ml of plasma and concentrated them into 0.1 ml of dilute acid, a process that has been shown to be 10 times as sensitive as basic catecholamine assays routinely conducted(20). This technique has an 81% efficiency rate and also removes Ca 2+ and other components that inhibit the COMT assay. Sensitivity for epinephrine (twice blank) was 4 pg/ml.

Objective Sleep Quality—Actigraphy was used to assess sleep and wakefulness. Participants wore the Actiwatch® L actigraphy watch (Mini Mitter Co., Inc., a Respironics, Inc. Co., Bend, OR) on their non-dominant wrist for 72 consecutive hours, beginning at 7:00 AM the first morning. The actigraphy watch detects and records participant movement continuously and stores data in 1-minute epochs. Digital integration mode (proportional integration mode) was used as it has been shown to be most highly correlated with

polysomnographic data(21) in older adults. Actigraphy data was processed using Respironics Actiware 5 software (Respironics, Inc.) algorithms that specified sleep versus wake periods as previously described by Blackwell and colleagues(22). Data processing was supplemented with sleep diaries completed by participants who logged their estimated bedtimes, wake times, and times the watch was removed. Sleep measurements were averaged over 3 nights. Sleep efficiency, or the percentage of time that the participant was actually asleep while in bed, was used as an indicator of sleep quality, given that past studies have found that was associated with catecholamine activity and biomarkers of atherosclerotic disease including coagulation and inflammation(23,24).

Physical Activity—The Rapid Assessment of Physical Activity (RAPA)(25) was used to assess participants' level of physical activity. The RAPA was developed for older adults and has been shown to be a valid assessment of physical activity in this population. Participants were presented with brief descriptions and illustrations of light, moderate, and vigorous activities. They then respond to 9 “yes or no” items assessing the frequency, duration, and intensity of their weekly physical activity that placed them in 1 of 5 physical activity categories. These items were designed based on the Centers for Disease Control and Prevention (CDC) recommendation for physical activity (i.e. ≥ 30 minutes of moderate physical exercise on most days of the week). For this study, we created the variable, “exercise,” indicating whether or not the participant met the CDC recommendation for physical activity (CDC recommendation was not met=0, CDC recommendation was met=1).

Carotid Artery Imaging—Ultrasound assessment of the carotid artery was conducted with the patient lying in a supine position. The carotid arteries were imaged using an Acuson Cypress Portable Ultrasound Unit with a 5.4–6.6 MHz Acuson 7L3 transducer. High resolution B-mode ultrasound images were collected from the near and far walls of the common, bifurcation, and internal carotid artery segments from 2 standardized interrogation angles for each vessel (right: 180° and 120°, left: 180° and 240°). The carotid flow divider was used as a reference point from which segments are 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. Imaging was conducted by a single sonographer for all participants in order to avoid problems associated with inter-sonographer variability.

Images were saved and read offline using the computer program, Vascular Research Tools (Medical Imaging Applications, Coralville, IA). The image reader confirmed that the carotid artery was imaged by viewing the color Doppler images and was blind to participant characteristics and group membership. A carotid plaque was defined as a focal and discrete area of hyperechogenicity and/or a focal protrusion into the lumen of the vessel. If any of the segment images had a visible plaque, the participant received a “1” on the “plaque status” variable, whereas if all images were absent of visible plaques the individual received a “0” on the variable. Plaque assessment was limited plaque presence or absence given that 2-dimensional imaging does not allow for determination of the size or composition of plaque.

Psychological Questionnaires

The semi-structured interview included the following questionnaires to assess perceived stress, psychological distress, and duration of care to one's spouse. The Role Overload Scale(26) is a 4-item scale to assess level of burden. Participants rated their agreement with statements such as, “I have more things to do than I can handle” on a 4-point scale (0=“not at all”; 3=“completely”). Ratings were summed in order to derive a total overload score. Depressive symptoms were assessed using the 10-item short form of the Center for

Epidemiologic Studies Depression Scale (CESD-10)(27). Participants rated the extent to which they agreed with statements such as, “I felt depressed” on a 4-point scale (0=rarely or none of the time (<1 day); 3=most of almost all the time (5–7 days)). Ratings were summed to derive a total depression score. Finally, caregivers were asked to estimate the year that their spouse was first diagnosed with Alzheimer’s disease. Duration of care was defined as the amount of time in years that has elapsed since the spouse received a diagnosis of Alzheimer’s disease.

Data Analysis

For the primary analysis, logistic regression was used to determine if caregiving status was associated with plaque status. Covariates were entered in the first step of the model with plaque status as the response variable. Covariates included age in years, gender (male=0, female=1), use of cholesterol-lowering medication (not using=0, using=1), use of antihypertensive medication (not using=0, using=1), diabetes status (non-diabetic=0, self-reported diabetic and/or non-fasting glucose level ≥ 140 mg/dl=1 (based on criteria from Rolka and colleagues(28)), years of smoking history (lifetime estimate of years of smoking regardless of current smoking status), resting MAP, exercise, sleep efficiency, and obesity. Covariates were selected based on their theoretical and empirical relation to plaque and CHD. Covariates included relevant CHD risk factors, antihypertensive and cholesterol lowering medication use, and health behaviors, all of which are expected to be associated with the development of atherosclerosis(7,29–31). Caregiving status (non-caregiver=–0.5, caregiver=0.5) was entered in the second step of the model.

Secondary analyses were conducted to determine if catecholamine recovery to the stress task and the interaction between caregiving status and catecholamine recovery significantly predicted plaque status. Recovery scores were derived by saving the unstandardized residuals from linear regression models with baseline catecholamine levels predicting 14-minute recovery catecholamine levels. This method creates a recovery score that controls for baseline catecholamine levels. Therefore, participants with positive recovery values had higher catecholamine levels relative to the sample average 14 minutes after the speech task and participants with negative recovery values had lower catecholamine levels relative to the sample average 14 minutes after the speech task. Two logistic regression models were tested: 1) assessing the effect of epinephrine recovery score and its interaction with caregiving status on plaque status, and 2) assessing the effect of norepinephrine recovery score and its interaction with caregiving status on plaque status. The same set of covariates specified in the primary analysis was entered in the first step of each model, caregiving status and catecholamine recovery scores (i.e., epinephrine recovery scores or norepinephrine recovery scores) were entered in the second step, and the caregiving status-by-catecholamine recovery score interaction term was entered in the third step. Significant interactions were further probed by running two conditional logistic regression analyses to determine the association between catecholamine recovery and plaque status in caregivers and in non-caregivers, a technique described by Holmbeck(32).

Due to occasional assay problems, 14 caregivers and 5 non-caregivers were missing one or more catecholamine measurement (i.e., baseline, post-speech, 14-minute recovery). Therefore, the secondary analysis was conducted with 143 of the original 162 participants. Participants with incomplete catecholamine data did not differ significantly from the rest of the sample on plaque status or caregiving status. Gender was the only study variable that was associated with “incompleteness” of catecholamine data such that women were more likely to have incomplete data compared to men ($\chi^2(1)=4.38, p=0.036$).

Kolmogorov-Smirnov tests indicated that distributions of several of the catecholamine measures significantly deviated from normality and were positively skewed. Therefore,

logistic regressions were also run with log-transformed catecholamine measures. Results indicated that the pattern of significant covariates, main effects, and interaction effects were consistent with analyses using non-transformed variables. Therefore, we have reported results from analyses utilizing non-transformed variables.

Results

Sample Characteristics

Demographic data and health information for the entire sample of caregivers and for non-caregivers is presented in Table 1. The mean age was 74 years for the caregiving group and 75 years for the non-caregiving group ($t(160) = -.87, p = .39$). Both groups were 69% female. Caregivers had a significantly higher prevalence of diabetes ($\chi^2(1) = 5.20, p = .02$) and higher MAP ($t(160) = 2.15, p = .03$) compared to non-caregiving controls. There were no significant differences between caregivers and non-caregivers in obesity, antihypertensive use, cholesterol-lowering medication use, years of smoking, sleep efficiency, and exercise. On average, participants in the caregiver group had been providing care to their spouse for an average of 4.2 ± 3.5 years. Years of caregiving was conceptualized as the time elapsed since a spouse was diagnosed with Alzheimer's disease. One caregiver was excluded from this average because there was no report of the spouse's diagnosis date.

Caregivers did not differ from non-caregivers significantly on epinephrine or norepinephrine levels at any time point throughout the laboratory stressor task. Further, caregivers and non-caregivers did not differ significantly on epinephrine or norepinephrine reactivity (reactivity scores similarly derived by saving the unstandardized residuals from linear regression models with baseline catecholamine levels predicting post-speech levels) or recovery from the stressor task. Out of these stress response indicators, epinephrine recovery was the only variable associated with plaque status ($r = 0.18, p = .03$).

Primary Analysis: Caregiving Status and Carotid Artery Plaque Status

Logistic regression analysis indicated that caregiving status was significantly associated with plaque status, such that caregivers had a 2.2 times greater odd of have a carotid plaque compared to non-caregivers ($B = 0.78, SE = 0.39, df = 1, p = .048$). This association was independent of age, gender, use of cholesterol-lowering medication, use of antihypertensive medication, diabetes, years of smoking, MAP, exercise, sleep efficiency, and obesity. Predictors that were significantly associated with having a carotid plaque included age ($B = 0.08, SE = 0.03, df = 1, p = .004$) and use of antihypertensive medication ($B = 0.95, SE = 0.37, df = 1, p = .01$). Years of smoking was marginally associated with presence of plaque ($B = 0.03, SE = 0.02, df = 1, p = .05$). Results for the full logistic regression model including all covariates are presented in Table 2. As a whole, the model had an accuracy rate of 67% in predicting whether or not participants actually had a plaque.

Secondary Analysis: Interaction of Caregiving Status and Catecholamine Recovery to Stress on Plaque Status

There were no significant main effects of epinephrine or norepinephrine recovery on plaque status. However, there was a significant interaction between epinephrine recovery and caregiving status on plaque status ($B = 0.08, SE = 0.04, df = 1, p = .04$). Results for the full logistic regression model examining epinephrine recovery and the caregiving status-by-epinephrine recovery interaction are presented in Table 3. The interaction between caregiving status and norepinephrine recovery was insignificant.

Follow-up tests to interpret the caregiving status-by-epinephrine recovery interaction indicated that poorer epinephrine recovery was significantly associated with the presence of

carotid plaque in caregivers ($B=0.07$, $SE=0.03$, $df=1$, $p=.02$), but not in non-caregivers ($B=-0.02$, $SE=0.03$, $df=1$, $p=.57$). That is, reduced ability to recover to basal levels of epinephrine quickly after a stressor task was associated with the presence of carotid plaque in caregivers, but not in non-caregivers. As a whole, the model had an accuracy rate of 71% in predicting whether or not participants actually had a plaque or not. Further inspection indicated that caregivers characterized as having poorer epinephrine recovery (determined by median split) had the highest prevalence of plaque at 63%. Caregivers with better epinephrine recovery, non-caregivers with poorer epinephrine recovery, and non-caregivers with better epinephrine recovery had plaque rates of 43%, 48%, and 36%, respectively.

Post-hoc Analyses: Potential Effects of Psychological Distress and Duration of Care

Post-hoc analyses were conducted with the complete sample of 162 participants to determine the potential role of psychological distress. Caregivers reported higher levels of role overload ($t(160)=7.9$, $p<.001$) and depression ($t(160)=6.6$, $p<.001$) compared to non-caregivers. Two logistic regressions were conducted to determine if a) depressive symptoms and/or b) role overload moderated the relationship between caregiver status and plaque. The same set of covariates was used in analyses. Neither depressive symptoms nor role overload predicted presence of plaque in either model. Furthermore, there was not a caregiving status-by-depressive symptoms interaction or a caregiving status-by-role overload interaction on plaque status.

We also conducted an analysis within caregivers only to determine if duration of care was associated with plaque ($N=110$; one caregiver did not report diagnosis date). There was not a simple association between duration of care and plaque. Duration of care was also unassociated with plaque in a logistic regression model controlling for covariates previously used in this study.

Discussion

This study found that caregivers had a significantly higher prevalence of carotid plaque compared to demographically similar non-caregiving controls. The presence of an asymptomatic plaque assessed via ultrasound has been shown to increase one's risk for stroke by 63% and myocardial infarction by 35%(33). The results from this study are consistent with past studies reporting associations between chronic stress and the presence of plaque(10) as well as arterial wall thickening(11,12). These results are also consistent with past research finding that caregivers are at increased risk for CHD(2) and suggest that stress-related atherosclerotic acceleration might be a potential avenue through which caregiving might predispose increased risk for mortality. Although the cross-sectional design precludes causal inference, the findings from our study do provide a platform from which prospective research might examine if caregivers do indeed exhibit accelerated atherosclerotic progression over time compared to non-caregivers.

The current study also found that caregivers who have impaired ability to quickly return to resting levels of epinephrine after an acute stressor were more likely to have a plaque. Caregivers who have difficulty recovering from a stressful challenge likely experience prolonged exposure to physiologic conditions conducive for atherosclerotic progression. Prolonged norepinephrine arousal was not associated with plaque status in either group, suggesting that prolonged adrenal response might play a more significant role in plaque formation than sympathetic arousal. Indeed, past research suggests that coagulation response to acute mental stress is largely driven by epinephrine(34) and β -adrenergic receptor stimulation(35). Circulating epinephrine also influences the modulation of the inflammatory response(36). Notably, speech stressor tasks evoke a more pronounced response in epinephrine than in norepinephrine(37,38). In a study by Dimsdale and Moss(37), a speech

stressor task primarily triggered an epinephrine response whereas exercise triggered a strong norepinephrine response, indicating that psychological or emotional stressors, such as those expected in caregiving, likely elicit a primarily adrenal response.

Prolonged epinephrine response to acute stress might be associated with plaque in caregivers but not in controls because caregivers are more frequently exposed to challenges. Chida and Steptoe's(17) meta-analysis of cardiovascular stress responses explained that not all individuals who exhibit poor recovery will experience increases in cardiovascular progression. They hypothesized that the *combination* of frequent and prolonged arousal may be crucial to stress-related cardiovascular consequences. Alzheimer caregivers are typically exposed to repeated challenges over the day and night for many years and the relationship between caregiving and burden has well been documented(39,40).

These findings reinforce the value of examining duration of sympathetic arousal, or delayed recovery, to stress. Schwartz and colleagues(41) argued that measurement of cardiovascular reactivity to stress lacks important information if it only captures the magnitude of the stress response. In particular, the frequency with which stressors occur and the duration that the response persists should be studied. The duration of time "responding" to stressors may be more important given that those who are under chronic stress and experience frequent challenges might spend a great deal of time anticipating future stressors and recovering from past ones. Schwartz and colleagues speculated that the cumulative load resulting from moderate yet prolonged stress responses may exceed the damage caused by high peaks in reactivity upon exposure. Similarly, Chida and Steptoe(17) posited that recovery and reactivity are processes that might reflect separate pathways to disease that differentially affect future cardiovascular impairment. Specifically, heightened cardiovascular reactivity to stress repeated over time likely increases tonic level of blood pressure(42), whereas poor recovery likely promotes prolonged hemostatic and inflammatory responses critical in atherogenesis(43).

It is possible that subsets of caregivers may be more susceptible to caregiving stress related cardiovascular morbidity. For example, caregivers who report a large mismatch between caregiving demands and time for respite ("vulnerable"), exhibited poorer lymphocyte beta2-adrenergic receptor density and sensitivity compared to "non-vulnerable" caregivers and non-caregivers(44). In addition, caregivers with high mastery, or a global sense of control, have reduced sympathetic reactivity to stress(45) and increased beta2-adrenergic receptor sensitivity(46). Therefore, there may be factors within caregivers that are associated with less efficient catecholamine recovery from acute stress, and caregivers with this proclivity might be particularly susceptible to downstream atherosclerosis.

In our post-hoc investigation, depressive symptoms, role overload, and duration of care did not emerge as predictors of plaque or moderators of the relationship between caregiving status and plaque. One potential explanation for why depressive symptoms and role overload were not associated with plaque is that responses to the perceived stress questionnaires may have only reflected a participant's experience at that given moment. Indeed, self-reports of psychological variables fluctuate over time(47) and single measurements may not accurately capture the accumulation of stress over time. That said, one might expect that duration of care would capture this component. Although one cannot be certain of the exact reasons for this finding, one limitation in the analysis of caregiving duration is that the sample (and thus power) was reduced significantly because it only included caregivers. Therefore, future work aimed at examining the psychosocial factors that might link caregiving to plaque formation could help elucidate this area of research.

There are limitations of this study that are worthy of mention. First, this was a cross-sectional analysis, thus, causal inferences cannot be made. The timeframe within which plaques developed was unknown, and therefore, it is unclear if providing care to a demented spouse prompted or exacerbated plaque formation. Longitudinal research investigating plaque development in caregivers and controls is currently underway to determine if caregiving stress does contribute to atherosclerotic progression. Also, we cannot rule out the possibility that the effect of the relationship between caregiver status and carotid plaques could be inflated due to sampling biases. For example, 20% of caregivers versus 6% of non-caregivers in our sample are classified as diabetic. Although diabetic status was included as a covariate in analyses, it is possible that residual confounding may be contributing to the association between caregiver status and carotid plaques.

Another point warranting discussion is that only age and antihypertensive use emerged as significant covariates in analyses. Due to the use of an elderly sample, it may be expected that gender would not be a significant predictor of plaque, given that gender differences in CHD prevalence diminish after age 70(48). Contrary to our predictions, sleep efficiency was also not a significant predictor of plaque. However, the participants in our sample were found to have greater sleep efficiency than was observed in previous research(24), suggesting that our sample may not have had poor enough sleep to observe the expected associations with plaque. It is also possible that participants' use of a variety of medications may be interfering with other study variables. Despite including antihypertensive and cholesterol-lowering medication use as covariates in analyses, we cannot completely control for the impact of medication. Although not all expected predictors entered into the analyses were uniquely predictive of plaque, overall, the model had an accuracy rate of 67% in predicting the presence of plaque.

Finally, it is possible that environmental differences were present between caregivers and non-caregivers during the speech stressor task. **One possible concern in interpreting our data is possibility that caregivers may have been more likely to have their spouse present during the speech stressor task.** While some evidence suggests that stressors involving evaluative threat (e.g., a speech task where others are observing) have been associated with increased hypothalamic-pituitary-adrenal axis activation(49), other research suggests that explicit negative social evaluation, rather than the mere presence of an observer, influences changes in physiological markers of stress(50). **However, in our study there were very few cases (i.e., fewer than 10% of visits) during which the care recipient was in attendance, and there were no instances of intrusive behavior; therefore we do not believe this was a substantial confound in our study.** It is also possible that caregivers perceived the in-home assessments as more burdensome than did non-caregivers. Although we do not have data to directly evaluate the extent of these potential environmental differences between groups during the stressor task, no significant group differences were observed in catecholamine levels at any point throughout the speech stressor task or in reactivity or recovery. Future research replicating the findings of the present study might explicitly examine the extent of any environmental differences between caregivers and non-caregivers during in-home assessments.

In sum, the current study found that Alzheimer caregivers had a higher risk of carotid artery plaque compared to non-caregiving controls. Furthermore, caregivers who exhibited prolonged epinephrine arousal to an acute laboratory stressor were more likely to have plaque compared to caregivers with less arousal and non-caregivers. These results are consistent with previous literature examining the link between chronic caregiving stress and cardiovascular outcomes and suggest that caregivers who experience prolonged epinephrine arousal in response to stress may particularly be at increased risk for atherosclerosis and CHD. These findings also build upon a progression of research from this team that has

examined the physiological mechanisms that might link caregiving to downstream disease. In particular, the current study supports that caregivers exhibited more “downstream” evidence of atherosclerosis, which is consistent with our past work observing that caregivers also had more “upstream” evidence of this disease process, including a procoagulant shift in hemostatic variables(51), increases in molecules linked to inflammation(4), and higher blood pressure(52). This study also converges with past work examining interactions between stress and sympatho-adrenal axis arousal(15,16).

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Abbreviations

BMI	body mass index
CDC	Centers for Disease Control
CESD	Center for Epidemiologic Studies Depression Scale
CHD	coronary heart disease
IMT	intima-media thickness
MAP	mean arterial pressure
RAPA	Rapid Assessment of Physical Activity
UCSD	University of California, San Diego

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Table 1

Participant Characteristics

	Caregivers (N=111)	Non-caregivers (N=51)	Test Statistic	p
Age in Years, M(SD)	73.6(8.2)	74.7(6.4)	t(160)= -.87	.39
Gender, n(%)			$\chi^2(1)<0.001$	.98
<i>Female</i>	76(68.5)	35(68.6)		
Ethnicity, n(%) [*]			$\chi^2(1)=3.23$	.07
<i>White</i>	102(91.9)	43(84.3)		
<i>Other</i>	6(5.4)	7(13.7)		
Education n(%) ^{**}			$\chi^2(1)=1.25$	.26
<i>College graduate or higher</i>	50(45.0)	28(54.9)		
Monthly Household Income in Dollars, median ^{***}	4000	4500	t(138)= -0.57	.57
Marital Duration in Years, M (SD)	43.2(16)	43.8(16)	t(159)= -0.23	.82
Obese, n(%)	24(21.6)	8(15.7)	$\chi^2(1)=0.78$	.38
Taking any Antihypertensives, n(%)	69(62.2)	28(54.9)	$\chi^2(1)=0.77$	.38
Taking Any Cholesterol-lowering medication, n(%)	52(46.8)	21(41.2)	$\chi^2(1)=0.45$	.50
Years of Smoking, M(SD)	7.9(11.6)	8.4(13.5)	t(160)= -0.25	.80
Diabetic, n(%)	22(19.8)	3(5.9)	$\chi^2(1)=5.20$	.02
Meets CDC Exercise Recommendation, n(%)	35(31.5)	23(45.1)	$\chi^2(1)=2.80$	.09
Nighttime Sleep Efficiency in %, M(SD)	87.7(4.8)	87.3(5.7)	t(160)=0.44	.66
Resting MAP in mmHg, M(SD)	95.6(9.9)	92.0(10.3)	t(160)=2.15	.03
Duration of Caregiving in Years, M(SD) [†]	4.2(3.5)	n/a	n/a	n/a
Role Overload, M(SD)	5.3(3.2)	1.5(2.0)	t(160)=7.94	<.001
Depressive Symptoms, M(SD)	8.7(5.8)	2.7(4.3)	t(160)=6.60	<.001
Baseline Epinephrine in pg/ml, M(SD) [§]	32.4(15.4)	28.9(11.2)	t(141)=1.37	.17
Post-speech Epinephrine in pg/ml, M(SD) [§]	35.4(16.7)	36.8(16.2)	t(141)= -0.49	.63
14-min Recovery Epinephrine in pg/ml, M(SD) [§]	31.4(17.6)	29.1(16.3)	t(141)=0.77	.45
Baseline Norepinephrine in pg/ml, M(SD) [§]	481.3(210.9)	484.0(190.6)	t(141)= -0.07	.94
Post-speech Norepinephrine in pg/ml, M(SD) [§]	490.1(203.9)	528.1(206.1)	t(141)= -1.04	.30
14-min Recovery Norepinephrine in pg/ml, M(SD) [§]	473.3(207.8)	501.3(201.0)	t(141)= -0.76	.45
Carotid Artery Plaques, n(%)	63(56.8)	21(41.2)	$\chi^2(1)=3.40$	.07

Note. BMI=Body Mass Index; CDC=Centers for Disease Control; MAP=Mean Arterial Pressure

^{*} Some participants did not disclose ethnicity information; data is based on 108 caregivers and 50 non-caregivers.

^{**} Some participants did not disclose education information; data is based on 110 caregivers and 51 non-caregivers.

^{***} Some participants did not disclose this information; data is based on 101 caregivers and 39 non-caregivers.

[†] One caregiver did not report Alzheimer's disease diagnosis date, data is based on 110 caregivers.

[§] Data based on available sample size for the secondary analysis including 97 caregivers and 46 non-caregivers.

Table 2

Odds ratio and 95% CI predicting presence of plaques

Variable	OR	95% CI	Wald	p-value
Age	1.08	1.02–1.14	8.27	.004
Gender (female)	0.99	0.47–2.11	<0.01	.98
Cholesterol lowering drug use	1.06	0.53–2.15	0.03	.87
Antihypertensive use	2.59	1.25–5.34	6.51	.01
Diabetic	1.45	0.48–4.40	0.43	.51
Years of Smoking	1.03	1.00–1.06	3.78	.05
MAP	0.99	0.95–1.03	0.25	.62
Meets CDC Exercise Recommendation	1.32	0.63–2.75	0.53	.47
Sleep Efficiency	1.01	0.94–1.08	0.07	.79
Obese	0.81	0.31–2.16	0.17	.68
Caregiver Status	2.18	1.01–4.73	3.92	.048
Constant	<0.01		2.65	.10

Note. CDC=Centers for Disease Control; MAP=Mean arterial pressure. This analysis was conducted with the entire sample of participants, N=162.

Table 3

Model testing the interaction between caregiving status and epinephrine recovery

Variable	OR	95% CI	Wald	p-value
Age	1.09	1.03–1.12	7.87	.005
Gender (female)	1.12	0.48–2.59	0.07	.80
Cholesterol lowering drug use	0.81	0.36–1.82	0.26	.61
Antihypertensive use	3.11	1.34–7.23	6.98	.008
Diabetic	2.00	0.53–7.53	1.05	.31
Years of Smoking	1.03	1.00–1.07	2.84	.09
MAP	0.98	0.94–1.02	1.25	.26
Meets CDC Exercise Recommendation	1.67	0.72–3.84	1.43	.23
Sleep Efficiency	1.03	0.95–1.11	0.40	.53
Obese	0.83	0.27–2.57	0.11	.74
Caregiver Status	2.11	0.89–5.00	2.88	.09
EPI Recovery	1.03	0.99–1.07	1.79	.18
Caregiver Status X EPI Recovery	1.09	1.01–1.17	4.41	.04
Constant	<0.001		2.80	.09

Note. CDC=Centers for Disease Control; MAP=Mean arterial pressure; EPI=Epinephrine. This analysis was conducted with the subset of participants with complete catecholamine data, N=143.