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Psychophysiological Mediators of Caregiver Stress and Differential Cognitive Decline

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The authors examined relationships between chronic stress and cognitive decline and whether such relationships were mediated by psychophysiological factors. Ninety-six caregivers of spouses with Alzheimer's disease (AD) were compared with 95 similar noncaregiver spouses. All were free of diabetes. Although the groups started similarly, over 2 years caregivers declined by a small but significant amount (1 raw score point and 4 percentile points, each $p < .05$) on Shipley Vocabulary. In contrast, noncaregivers did not change. Higher hostile attribution ($\beta = -.09$; $p < .05$) and metabolic risk ($\beta = -.10$; $p < .05$) in caregivers mediated the cognitive decline. This is the first study of cognitive decline and mediators in caregivers. This work has implications for caregiver and care-recipient health and for research on cognition, psychophysiology, diabetes, and AD.

Keywords: caregivers, cognition, metabolic, hostility, stress

In this article, we examine relationships between chronic stress and cognitive decline in older adults and assess whether such relationships are mediated by psychophysiological factors. Previous studies have suggested that chronic stress is associated with decrements in short-term memory and attention (Brand, Hanson, & Godaert, 2000; Bremner, 1999; Levy, Dachir, Arvel, & Kadar, 1994; Mahoney, Dalby, & King, 1998) and that such relationships may be mediated by psychophysiological processes (de Kloet, Oitzl, & Joels, 1999; Lupien et al., 1994; McEwen & Magarinos, 1997; Newcomer, Craft, Hershey, Askins, & Bardgett, 1994). Potential psychosocial mediators are anxiety, depression, and hostility. Anxiety and depression are positively associated with chronic stress (Korte, 2001; Leonard & Song, 1997; Norris & Uhl, 1993) and negatively associated with cognitive functioning (Kizilbash, Vanderploeg, & Curtiss, 2002; Sinoff & Werner, 2003). Hostility is positively related to both chronic stress (Steptoe & Marmot, 2003) and lower metabolism in the prefrontal cortex (Shapiro et al., 2000). It is important to note that the lack of cerebral energy can negatively influence cognitive processes, including the encoding and retrieval of verbal memory (Saykin et al., 1999; Shallice et al., 1994), associated with this brain region.

Potential physiological mediators of chronic stress and cognitive functioning include elevated blood pressure and metabolic dysregulation such as greater risks for insulin resistance (e.g., obesity, elevated insulin). These physiological indices are positively associated with chronic stress (Schneiderman & Skyler, 1996) and negatively associated with cognitive functioning (Elias, Wolf, D'Agostino, Cobb, & White, 1993; Waldstein & Katzel, 2001; Walker, Berrish, James, & Alberti, 1994). Insulin resistance and its indicators are also associated with neurodegeneration and neurotoxicity (Coutinho, Gerstein, Wang, & Yusuf, 1999; Walker et al., 1994).

One chronic stressor that has received much attention is caring for a spouse with Alzheimer's disease (AD), a progressive degenerative disorder. Spouse caregivers of persons with AD are exposed to numerous long-term stressors as their care recipients' health declines. These stressors include helping care recipients with maintenance (e.g., eating, hygiene) and higher functioning (e.g., talking, writing) activities as well as contending with the mood (e.g., depression, anger) and behavioral (e.g., agitation, paranoia) problems of their care recipients (Haley, Levine, Brown,

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& Bartolucci, 1987; Teri et al., 1991). Indeed, meta-analyses conducted with caregivers have shown them to be at higher risks for physiological and health problems (Vitaliano, Zhang, & Scanlan, 2003) and psychosocial problems (Pinquart & Sorensen, 2003) than noncaregivers. Apart from our study, however, only two other articles have examined cognitive functioning in caregivers relative to noncaregivers (Caswell et al., 2003; Lee, Kawachi, & Grodstein, 2004). This is surprising because cognitive functioning is an important concomitant of chronic stress.

In the first article, spouse caregivers of persons with AD (n = 44) were shown to have lower digit symbol scores (a measure of psychomotor speed and problem-solving requiring code substitution) than demographically similar spouse noncaregivers (n = 77). In the second article, Lee et al. (2004) used the Nurse's Health Study of women (N = 11,000–13,000) and assessed immediate and delayed recall, verbal fluency, and digit span backward test results. Higher risks of a low score on three cognitive tests were observed among spouse caregivers than among spouse noncaregivers. Unfortunately, these studies were cross-sectional and did not assess cognitive decline or the physiological mediators of such decline, factors that are relevant to health maintenance in caregivers, care recipients, and older adults in general.

It is important to note that the same psychophysiological factors that may mediate relationships of chronic stress and cognitive functioning in the general population may also be relevant to caregivers. Caregivers have been found to exhibit higher levels of depression, anxiety, and anger and hostility than noncaregivers (Baumgarten et al., 1992; Gallagher, Wrabetz, Lovett, Del Maestro, & Rose, 1989; Harwood et al., 1998; Russo, Vitaliano, Brewer, Katon, & Becker, 1995; Vitaliano et al., 2002). Caregivers also have been found to have higher levels of insulin and obesity than demographically similar noncaregivers (Vitaliano, Scanlan, Krenz, Schwartz, & Marcovina, 1996), and, caregivers who are high in trait anger and/or hostility have been found to have higher glucose levels than noncaregivers who are high in trait anger and/or hostility (Vitaliano, Scanlan, Krenz, & Fujimoto, 1996). Studies of metabolic measures have been less prevalent than those of blood pressure, but the latter have yielded mixed results depending on the assessment procedure used and study environment. For example, laboratory and in-home (interviewer assessed) blood pressures have not resulted in main effect differences for caregivers and noncaregivers (Picot, Zauszniewski, & Delgado, 1997; Shaw et al., 1999; Vitaliano, Russo, Bailey, Young, & McCann, 1993). In contrast, caregivers and noncaregivers have been shown to differ in their ambulatory blood pressure depending on whether they are at home or at work. Caregivers' ambulatory blood pressure is higher in their homes than at work, whereas the noncaregivers' ambulatory blood pressure is higher at work than at home (A. C. King, Oka, & Young, 1994).

Given previously observed relationships among chronic stress, psychophysiological functioning, and cognitive factors, we hypothesized that spouse caregivers would show greater cognitive decline than demographically similar noncaregiver spouses. We also hypothesized that if a relationship between cognitive status and cognitive decline should exist, psychosocial (anxiety, depression, hostility) and physiological (insulin, obesity) variables would mediate this relationship, even after the consideration of other potentially important covariates (e.g., demographics, medications). By comparing cognitive decline in older adult caregivers with cognitive decline in older adult noncaregivers, we attempted to distinguish cognitive changes associated with caregiving from those associated with age and its correlates. This is important because older adults are at greater risk for cognitive impairment (Jorm, Korten, & Henderson, 1987; Park, 1996) and for chronic illnesses that may compromise cognitive function (Desmond, Tatemichi, Paik, & Stern, 1993; Elias et al., 1993; Haan, Shemanski, Jaqust, Manolio, & Kuller, 1999; Strachan, Deary, Ewing, & Frier, 1997) than younger adults.

Method

Design and Participants

We used the course of AD in care recipients as a chronic stressor for their spouse caregivers. We assessed spouse caregivers' temporal cognitive and psychophysiological reactions to stressors relative to noncaregivers twice, at study entry and at study follow-up 2 years later.

Caregiver couples were recruited from (a) mailings to physicians, (b) the University of Washington AD registry, (c) the AD Association, and (d) printed and electronic media. Criteria for care recipient inclusion were (a) living with 'a spouse who is the primary caregiver, (b) being at least 55 years old, and (c) having a diagnosis meeting the criteria for dementia of the Alzheimer's type (*Diagnostic and Statistical Manual of Mental Disorders*; 4th ed.; American Psychiatric Association, 1994) or possible or probable primary degenerative dementia (National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association criteria; McKhann et al., 1984). Exclusion criteria are provided in greater detail elsewhere (Vitaliano et al., 1993). Caregivers had to function independently. Demographically similar noncaregivers were recruited from senior centers, retirement organizations, and the media. Noncaregivers and their spouses had to be a minimum of 55 years old, functioning independently, and not providing care for another person on a regular basis. The University of Washington Human Subjects Review Board approved the study procedures, and informed consent was obtained from all participants.

At study entry, participants were 110 spouse caregivers and their spouses (care recipients with AD) and 105 noncaregiver spouses (and their spouses) who were free of frank diabetes as judged by medical records, self-reports, medication histories, and glucose levels. Over 2 years, 12 caregivers and 10 noncaregivers were lost to follow-up. Three caregivers and 1 noncaregiver died, 4 caregivers and 4 noncaregivers moved out of state, 3 caregivers and 1 noncaregiver reported being too ill and weak to continue in the study, and 2 caregivers and 4 noncaregivers refused to continue. Complete data were available on 98 nondiabetic caregivers and 96 nondiabetic noncaregivers. Two caregivers and 1 noncaregiver were missing cognitive data, leaving 96 caregivers and 95 noncaregivers for analyses.

Measures

Cognitive measures. We assessed participants with cognitive measures at study entry and 2-year follow-up using the Shipley Institute of Living Scale (SILS; Zachary, 1986). The SILS is a self-administered test, so prior to assessment, a trained interviewer reviewed the directions with each participant. This was done to ensure that the print was legible and the directions were clear. The SILS consists of two subtests. The Vocabulary subscale measures recognition of verbal knowledge and includes 40 multiple-choice items. For each item the respondent must choose which one of four words is closest in meaning to a target word (i.e., a synonym). Administration time is 10 min; coefficient alpha was .87 and the intraclass correlation was .73 ($p < .01$). The Abstraction subscale measures general reasoning and contains 20 items. Each item includes a sequence of numbers, letters, or words that have their final element omitted. For each item, the respondent is required to complete the sequence. The Abstraction subscale relies more on prefrontal function than the vocabulary test. Ad-

ministration time is 10 min; coefficient alpha was .84 and the intraclass correlation was .70 ($p < .01$).

The participants completed the Vocabulary subscale first and then the Abstraction subscale. The Vocabulary raw score is computed from the total number of correct responses out of 40, and the Abstraction raw score is computed from the total number of correct responses out of 20. To interpret these scores, we first converted each to a *T* score (with a mean of 50 and a standard deviation of 10), then to norms that adjust for the respondent's age, and finally to a percentile score.

Psychosocial factors. Psychosocial factors were assessed using six measures previously used in caregiver and/or behavioral medicine research.

The Abbreviated Cook–Medley Hostility Scale is a 39-item measure (Barefoot, Larsen, von der Leith, & Schroll, 1995) derived from a longer measure (Cook & Medley, 1954). We used three of its four scales: Cynicism assesses negative beliefs about the trustworthiness or other qualities of people (e.g., "I think most people would lie to get ahead"), Hostile Attribution assesses suspicion that others intend harm to the respondent (e.g., "I tend to be on my guard with people who are somewhat friendlier than I had expected"), and Hostile Affect assesses the experience of negative emotions associated with interpersonal relationships (e.g., "Some of my family has habits that bother and annoy me very much"). (The Social Avoidance scale was not used because caregivers tend to be isolated and responses to this scale may be confounded with caregiving.) Participants are asked whether they agree with each statement. Our coefficient alphas were Cynicism (.80), Hostile Attribution (.74), and Hostile Affect (.70), and the intraclass correlations were .77, .77, and .72, respectively (ps $< .01$). We also summed the three scales to obtain a total score, for which alpha was .88 and intraclass correlation was .81.

The Beck Depression Inventory (BDI, short form; Beck & Beck, 1972) has 13 items and is a 4-point Likert-format self-report measure used to assess the severity of affective–cognitive depressive symptoms. The BDI short form correlates highly with the 21-item BDI ($r = .96$) and with clinicians' ratings of depression ($r = .61$; Beck & Beck, 1972; Beck, Steer, & Garbin, 1988). In this study, the coefficient alpha was .76 and the 2-year intraclass correlation was .72 ($p < .01$). Scores of 0–4 suggest no or minimal depression, scores of 5–7 suggest mild depression, scores of 8–15 suggest moderate depression, and scores greater than 15 suggest severe depression (Beck & Beck, 1972).

The Hamilton Depression Rating Scale (Hamilton, 1960; 24-item version) was used to assess depressive symptoms present for at least 2 days, on a scale ranging from 0 (*absent*) to 4 (*severe*). Content assesses mood, feelings of guilt, and agitation. In this study, the alpha was .82 and intraclass correlation was .48 ($p < .01$). The same interviewer performed all 191 ratings in face-to-face interviews. She had extensive experience administering the Hamilton Depression Rating Scale prior to this study. Scores of 20 or greater suggest a depressive state in older adults (Husain et al., 2004).

The State–Trait Anxiety Inventory (Spielberger, Gorusch, & Lushene, 1970) was used to assess state anxiety. It is a 20-item measure that asks participants to describe their current anxiety levels (e.g., worries), and it is scored on a 4-point Likert scale ranging from 1 (*not at all*) to 4 (*very much*). The alpha was .82 and intraclass correlation was .49 ($p < .01$). Scores above 44 are suggestive of clinical anxiety in older adults (Ashendorf, Constantinou, & McCaffrey, 2004).

The Maastricht Questionnaire (Appels, Hoppener, & Mulder, 1987) was used to measure vital exhaustion. It contains 21 true/false items consisting of symptoms of fatigue, irritability, stress (e.g., "inability to cope"), and demoralization. In this study the alpha was .88 and the intraclass correlation was .67 ($p < .01$).

Sleep quality (Vitaliano et al., 1999) was assessed using 19 items from the Pittsburgh Sleep Disorders Questionnaire (SDQI; Douglass et al., 1994). Because the SDQI contains items that we measured elsewhere (i.e., depression), we included only the sleep items. Each item contains four response options: 0 = *almost never*, 1 = *sometimes*, 2 = *often*, and 3 = *almost always*. In this study, the alpha was .79, and the intraclass correlation was .71 ($p < .01$).

Physiological measures. Our physiological measures included assessments of glucose and insulin level and blood pressure. Participants were asked to fast for 12 hr and to abstain from smoking cigarettes and consuming alcohol and caffeine for 12 hr before arriving at the University of Washington Medical Center at 9 a.m. A nurse used heparinized syringes to collect blood from the hand and forearm of each seated participant. After plasma was separated by centrifugation, it was frozen at −70 °C, transported in dry ice, and later analyzed at the Northwest Lipids Laboratory.

Glucose was measured by the combined Abbott Analyzer's (Abbott Technologies, Seattle WA) catalytic activities of hexokinase and glucose-6-phosphate dehydrogenase. The between-assays coefficient of variation was <3% and 2-year intraclass correlation was .77 ($p < .01$).

Insulin was assessed using a radioimmunoassay PEG-accelerated method with 48-hr incubation. The primary antibody is a guinea pig antibody, the precipitating antibody is a goat antiguinea pig antibody, and the tracer is mono-iodo-tyr-A14-insulin. The between-assays coefficient of variation was <3%, and the 2-year intraclass correlation was .72 ($p < .01$).

Blood pressure was assessed each time a participant was seen. In our laboratory, participants were asked to sit quietly for 10 min and listen to soft music over headphones. After this 10-min rest period, three systolic blood pressures (SBP) and diastolic blood pressures (DBP) were obtained 2 minutes apart with the right arm resting at heart level. A Dina map Adult/Pediatric Vital Signs Monitor Model 845XT (Tampa, FL) was used. The means of each of these three readings were then calculated to obtain measures of resting blood pressures. The intraclass correlations were .53 ($p < .01$) for SBP and .49 ($p < .01$) for DBP.

We assessed body mass index by weighing individuals in street clothes and measuring height without shoes using a standard ruler. Obesity was defined as ≥90th percentile of BMI (weight in kilograms/height in meters^2) on the age and gender norms of the Northwest Lipids Laboratory. These BMI cutoffs varied from 28 to 30. The intraclass correlation was .92 ($p < .01$).

Given well-known intercorrelations of insulin with obesity, we simplified the analyses by first performing a principal-components analysis that resulted in a linear composite of these measures. This metabolic risk composite explained 73% of the variance in insulin and obesity and provided an estimate of hyperinsulinemia (Schneiderman & Skyler, 1996). This composite was expected to correlate negatively with cognitive functioning (Walker et al., 1994).

Physical illnesses and medications taken were assessed by using medical records and self-reports. Medical records were obtained at follow-up and coded for the previous 5 years. Hence, the period assessed overlapped with when the participants first entered the study. Overall, 94% of medical records were obtained. Self-reports were used for the 6% of participants that did not have medical records. In the few cases in which self-reports suggested an illness or medication but the medical records did not, we used the self-report data. Puckett's (1993) criteria were used on the participants' medical records to obtain the date and nature of diagnosis, treatment, prognosis, and medications. The coder was blind to the participant's status as a caregiver or noncaregiver. Quality controls were used (Hanken, 1989), and it was shown that in 60% of the records, blood pressure was recorded for 4+ years and in 35% of the records it was recorded for 1 year. In 90% of the records, treatment/ICD-9 codes and/or diagnostic tests and dates for coronary heart disease (CHD) and cardiovascular disease (CVD) were listed: (arteriosclerosis, ICD-9-CM code = 414.0; ischemia, ICD-9-CM code = 414.9; angina, ICD-9-CM code = 413.9; other CHD, ICD-9-CM code = 414.8; atherosclerotic, ICD-9-CM code = 440; peripheral vascular disease, ICD-9-CM code = 440.2; aortic sclerosis, ICD-9-CM code = 440.0; stroke, ICD-9-CM code = 436; and diabetes, ICD-9-CM code = 250.0–250.5. We were especially interested in these illnesses because of their relationships with cognition (Verhaeghen, Borchelt, & Smith, 2003). Medications included antihypertensives (beta blockers, calcium channel blockers, ACE inhibitors), hormone replacement therapy, and so forth.

Statistical Analyses

Marginal distributions were obtained for all continuous variables, and they were acceptable. In cases in which skew was detected (e.g., insulin), natural log transformations were obtained. Independent *t* tests were also performed to assess whether relationships existed between caregiver status and variables of interest.

To test the first hypothesis, that greater cognitive decline in raw SILS scores would occur in caregivers relative to noncaregivers, we first performed a 2 × 2 split-plot analysis of variance (ANOVA) with caregiver status as the between-subjects variable and time (1, 2) as the within-subject variable. The Caregiver Status × Time interaction examined whether the groups declined differently. If the interaction was significant, it was followed by a hierarchical regression that used the follow-up SILS subscale as the criterion variable. The SILS raw score at study entry was entered at Step 1. At Step 2, caregiver status (coded 1 = caregiver, 2 = noncaregiver) was entered. After Step 2, the significance of the beta for caregiver status was examined as an adjunct test of the first hypothesis tested by the ANOVA. If the beta for caregiver status was significant, we then tested the second research hypothesis that psychophysiological measures mediated the relationship of caregiver status with cognitive decline. In the process, we evaluated confounders of this relationship. To do this in stages, we examined the two parts of mediation and/or confounding. The first part included the partial correlation of caregiver status with a putative mediator and/or confounder while controlling for the other variable in the model (here, SILS score at study entry). The second part included the partial correlation of the SILS score at follow-up with a putative mediator and/or confounder while controlling for the other variables in the model (here, SILS scores at study entry and caregiver status). As examples, potential confounders included demographic variables (e.g., gender, age, education, income, ethnicity) and medications (e.g., antihypertensive medications, hormone replacement therapy), and potential mediators included psychosocial (depression, anxiety, hostility) and physiological (metabolic, cardiovascular) variables. Variables that qualified as potential mediators and/or confounders were entered in the regression equations separately at Step 3. Those that were independently significant at Step 3 were examined together in the equation to assess their unique contributions to the explained variability in cognitive decline. Each regression analysis was accompanied by outlier tests to ensure that the results were not spurious.

Results

Univariate Comparisons of Caregivers Versus Noncaregivers

Demographic, health, psychosocial, and cognitive data for caregivers and noncaregivers are provided in Table 1. The groups did not differ in sex, race, age, education, income, hormone replacement therapy, antihypertensive medications, or several events reflective of cardiovascular/coronary disease (e.g., stroke, myocardial infarction). Caregivers scored higher on the Hamilton Depression Rating Scale, $t(189) = 4.6$, $p < .001$, Beck Depression Inventory, $t(189) = 5.4$, $p < .001$, Spielberger State Anxiety Inventory, $t(189) = 5.9$, $p < .001$, and Abbreviated Total Cook–Medley Hostility Scale, $t(189) = 1.9$, $p = .056$. Using the cutoffs referred to above, we observed that no caregivers or noncaregivers exhibited clinical states of anxiety at either time point. Using the Beck cutoffs, we observed that at study entry, 72% of caregivers and 89% of noncaregivers exhibited minimal depression, 14% of caregivers and 11% of noncaregivers exhibited mild depression, 14% of caregivers and 0% of noncaregivers exhibited moderate depression, and no caregivers or noncaregivers exhibited severe depression. At follow-up, 71% of caregivers and 91% of noncaregivers exhibited minimal depression, 20% of caregivers and 6% of noncaregivers exhibited mild depression, 7% of caregivers and 3% of noncaregivers exhibited moderate depression, and 1% of caregivers and 0% of noncaregivers exhibited severe depression. On the Hamilton cutoffs, no caregivers or noncaregivers had scores

Table 1
Caregivers Versus Noncaregivers: Demographic, Health, Psychosocial, Physiological, and Cognitive Measures

Variable	Caregivers (n = 96)	Noncaregivers (n = 95)
Demographic and health factors		
Women, %	60	62
Men, %	40	38
Caucasian, %	93	94
Non-Caucasian, %	7	6
Age, in years ($M \pm SD$)	72.2 ± 9.3	71.0 ± 6.9
Education (years)	15.2 ± 2.3	15.4 ± 2.5
Income (in $1,000s)	48.4 ± 27.9	50.3 ± 25.8
Hormone replacements in women, %	45	45
Antihypertensive medication, %	35	32
Myocardial infarction, %	6	6
Angina pectoris, %	12	5†
Coronary procedures, %	12	10
Other heart disease, %	18	13
Hypertension, %	40	40
Stroke, %	4	3
Psychosocial measures		
History of major depression, %	4	8
Spielberger State Anxiety Index, $M \pm SD$	15.7 ± 4.5	12.4 ± 3.2***
Beck Depression Inventory, $M \pm SD$	3.6 ± 2.9	1.7 ± 1.9***
Hamilton Depression Rating Scale, $M \pm SD$	2.3 ± 3.1	0.6 ± 1.6***
Total Cook–Medley Hostility, $M \pm SD$	6.9 ± 4.8	5.6 ± 4.9†
Sleep problems, $M \pm SD$	27.0 ± 6.4	24.1 ± 4.0***
Vital exhaustion, $M \pm SD$	7.7 ± 4.2	3.6 ± 3.7***
Physiological measure		
Insulin (mU/ml)	14.3 ± 8.5	10.6 ± 7.2**
Glucose (mg/dl)	99.9 ± 11.4	94.4 ± 8.4*
Obese, %	28	13*
Metabolic risk composite	0.28 ± 1.00	−0.29 ± 0.08**
Systolic blood pressure	141.6 ± 24.1	141.6 ± 24.1
Diastolic blood pressure	79.3 ± 13.0	77.3 ± 10.5
Cognitive measure		
Shipley V Raw Time 1, $M \pm SD$	35.5 ± 3.8	35.3 ± 4.9
Shipley V Raw Time 2, $M \pm SD$	34.5 ± 4.7	35.2 ± 4.3
Change in Shipley V Raw, $M \pm SD$	−1.0 ± 3.4	0.01 ± 2.6*
Shipley AR Raw Time 1, $M \pm SD$	27.7 ± 9.1	26.4 ± 9.4
Shipley AR Raw Time 2, $M \pm SD$	26.6 ± 9.0	25.5 ± 9.1
Change in Shipley AR Raw, $M \pm SD$	−1.10 ± 6.7	−0.90 ± 7.4

Note. V = vocabulary; AR = abstract reasoning.
† $p < .10$. * $p < .05$. ** $p < .01$. *** $p < .001$.

approaching the recommended cutoff of 20 (the highest score at either measurement was 12). Finally, caregivers reported more sleep problems, $t(189) = 4.7$, $p < .001$, and more vital exhaustion, $t(189) = 4.9$, $p < .001$, than did noncaregivers. On physiological measures, caregivers had higher insulin, $t(189) = -3.3$, $p < .01$, and glucose levels, $t(189) = -3.6$, $p < .01$], were more obese, $t(189) = -3.9$, $p < .01$, and had a higher metabolic risk composite, $t(189) = -4.1$, $p < .01$. Caregivers and noncaregivers neither differed in Vocabulary or Abstract Reasoning raw scores at Times 1 and 2 nor differed in change in Abstract Reasoning raw scores; however, caregivers Vocabulary raw scores declined relative to noncaregivers, $F(1, 188) = 3.89$, $p < .05$.

Tests of Cognitive Decline and Differential Decline in Caregivers Versus Noncaregivers

The split-plot analysis performed on the Abstraction raw scores was significant for time, $F(1, 189) = 4.17$, $p < .04$, but not for the interaction. Hence, a reliable decline occurred for the average of the groups (27.1 + 9.2 to 26.0 + 9.4), but the decline did not differ for caregivers and noncaregivers. For the Vocabulary raw scores, the Caregiver Status × Time interaction, $F(1, 189) = 3.84$, $p < .05$, and time, $F(1, 189) = 5.51$, $p < .02$, were each significant. However, the main effect for caregiver status was not significant. The results were very similar for the Vocabulary Percentile *scores*. Caregivers declined (from 35.5 to 34.5), but noncaregivers did not (from 35.2 to 35.2). This corresponds to an effect size of .33 for the difference in difference score means divided by the pooled standard deviation of the difference scores.

To better understand the degree to which individual differences in change occurred across caregivers and noncaregivers, we computed the number of persons who changed relative to two criteria—the standard deviation and standard error of measurement at study entry. Twenty-seven caregivers and 19 noncaregivers changed by a standard deviation of 0.5, 16 caregivers and 10 noncaregivers declined by 3.0 or more points; 11 caregivers and 6 noncaregivers declined by 4.0 or more points, and 9 caregivers and 3 noncaregivers declined by 5.0 or more points. The SEM was calculated by standard deviation (1 – coefficient alpha)$^{1/2}$ or 4.3 $(1 - 0.87)^{1/2}$ or 4.3 (0.36) = 1.55. Using this schema, we found with 95% confidence that scores that changed by 1.55 × 1.96 = 3.04, or approximately 3 raw score points, were likely to be different.

A final analysis found that in noncaregivers the amount of change was dependent on the participants' score in the first assessment—those with the lowest verbal IQ (VIQ)s at study entry ($n = 28$) had a mean change of 1.54 (3.3), those in the middle ($n = 31$) had a mean change of −0.08 (1.5), and those who began with VIQ scores in the highest tertile ($n = 37$) had a mean change of −1.29 (2.0). Hence, noncaregivers followed a trend toward regression to the mean. In contrast, caregivers showed declines regardless of where they started: Those in the lowest VIQ stratum ($n = 32$) had a mean change of −0.90 (4.9), those in the middle stratum ($n = 30$) had a mean change of −0.66 (8.1), and those in the highest stratum at study entry ($n = 30$) had a mean change of −1.39 (7.3). Regression to the mean usually increases with decreases in the test–retest correlation, but in these samples, the test–retest correlation for noncaregivers ($r = .80$) was not lower than that for caregivers ($r = .71$).

Correlational Assessment of Potential Mediators and Confounders

Prior to formally testing for mediators and confounders of the relationship of caregiving with vocabulary decline, we examined partial correlations of candidate variables (demographic, medications, psychophysiological, etc.) with caregiver status and VIQ decline. As shown in Table 2, no demographic variable, medication, or cardiovascular illnesses qualified as mediators or confounders. Only hostility, metabolic risk, and obesity were associated with both VIQ at follow-up (controlling for VIQ at study entry and caregiver status) and caregiver status (controlling for VIQ at entry).

Residualized Regression Analyses

Because the analyses of variance suggested that there was differential decline on VIQ, we performed regression analyses to examine mediation of these changes, our second research hypoth-

Table 2
Partial Correlations of Follow-Up Shipley V Raw Scores and Caregiver Status (CG) With Related Variables Controlling for Shipley V IQ at Entry, Age, and/or Caregiver Status

Variable	Shipley V follow-up (controlling for Shipley V IQ at entry, age, and CG status)	CG status (controlling for Shipley V IQ at entry)
Demographic and health variables		
Gender	−.05	.04
Ethnicity	−.20**	−.05
Education	.20**	.07
Income	−.06	.04
Hormone replacement therapy	.15*	.03
Beta blockers	.11	−.19*
Myocardial infarction	−.02	.00
Angina pectoris	−.07	−.12†
Coronary procedures	.05	.00
Other heart disease	.08	−.10
Hypertension	−.04	.00
Stroke	.03	−.02
Psychosocial measures		
Spielberger State Anxiety Index	−.02	−.40***
Beck Depression Inventory	0.01	−.36***
Hamilton Depression Rating Scale	−.02	−.32***
Total Cook–Medley Hostility	−.16*	−.14*
Vital exhaustion	.06	−.47***
Sleep problems	.05	−.26***
History of major depression	.06	.09
Physiological measures		
Metabolic risk composite	−.16*	−.25***
ln insulin	−.08	−.25***
ln glucose	−.04	−.25***
Obesity	−.16*	−.20**
Systolic hypertension	.02	.04
Diastolic hypertension	−.05	−.04

Note. V = vocabulary; ln = natural log.
† $p < .10$. * $p < .05$. ** $p < .01$. *** $p < .001$.

esis. Table 3 presents these results. Column 1 contains the variables that were included at each step of the analysis. Columns 2–5 contain four separate models respectively, each with the betas for the corresponding terms in Column 1. Column 2 contains the betas for the analysis with VIQ at study entry (Step 1) and caregiver status (Step 2). The betas were significant for VIQ, .77 ($p < .001$) and for caregiver status, .09 ($p < .05$). Hence, as with the Time × Caregiver Status interaction ANOVA, there was support for the first research hypothesis.

The potential mediators identified in Table 2 were used in the regressions (see Table 3). Column 3 of Table 3 contains the betas for when the total score for hostility (Step 3) was added to the model. Note that the beta for hostility (−.10) was significant ($p < .05$), suggesting that the higher the hostility at baseline, the more the drop in VIQ over 2 years. Also, the beta for caregiver status was no longer significant in the presence of hostility. Although this suggests that hostility may be a mediator of relationships between caregiver status and cognitive decline, the beta for caregiver status dropped only a small amount. Therefore, other factors may also qualify as mediators. One such factor was the metabolic risk composite. Column 4 contains the betas for VIQ at study entry, caregiver status, and metabolic risk composite. Note that the metabolic risk composite has a significant beta (−.10, $p < .05$), suggesting that the higher it was at study entry, the greater the VIQ decline over 2 years. Also note that the beta for caregiver status is no longer significant ($\beta = .07$) when metabolic risk is controlled. Thus, as with hostility, metabolic risk mediated the relationship between caregiving and VIQ decline, and the change in the beta was not substantial.

Column 5 of Table 3 contains the betas for Time 1 VIQ (.74, $p < .001$), caregiver status (.05, *ns*), hostility (−.10, $p < .05$), and metabolic risk (−.09, $p < .05$). Hostility and metabolic risk are both significant in the model, and when these terms are in the model together, the beta for caregiver status is almost half its original value (.09 vs. .05). From Table 3, one can see that at each of the four steps in the final equation, significantly greater variance in follow-up VIQ was explained. The full model was significant, $F(4, 186) = 76.2$, $p < .001$, adjusted $R^2 = .62$. Because the analyses were based on the total score for hostility, we reran them using the separate scales and observed that Hostile Attribution was driving the results. It was the only subscale to reproduce the result of the total hostility score.

Discussion

This study examined relationships of SILS VIQ and the Abstract Reasoning Scale (AR) with caregiver status and time. For AR, we observed an effect for time; over 2 years both groups declined by a small amount. In contrast, the Time × Caregiver Status interaction was significant for VIQ. On average, caregivers declined by 1 raw score point, which was greater than zero, the mean decline for noncaregivers.

We believe the VIQ decline did not result from age, differences in education, or decreases in intelligence, but rather the decline was influenced by chronic stress and its psychophysiological sequelae. In particular, both groups declined in AR over 2 years, but only caregivers experienced a "stress-related decline" in VIQ, and this decline was independent of age. The groups were also similar in VIQ at study entry, and the decline occurred over a brief period in persons whose mean ages were 71 to 72 years old. Vocabulary reflects premorbid intelligence, and up to age 70, it is relatively stable in adults who are free of disease and/or environmental insult (Nyberg et al., 2003). The SILS VIQ is a word recognition test that assesses a person's knowledge of his or her world, which generally does not decay until age 70 to 75 (Park et al., 2002). The difference in VIQ decline across groups was also not attributable to a differential ceiling effect because education levels were equivalent across groups. In contrast to these factors, the VIQ decline may have been influenced by chronic stress, as environmental stressors can disrupt one's ability to attend to tasks such as vocabulary tests (Buchanan, Kern, Allen, Tranel, & Kirschbaum, 2004; Echeverria, Aposhian, & Woods, 1998; Habib, McIntosh, Wheeler, & Tulving, 2003; Park et al., 2003). Moreover, the decline in caregivers was mediated by metabolic risk and hostility, factors that are theoretically and empirically relevant to cognition.

Metabolic risk was defined as a composite of obesity and insulin. As with previous samples, we found that caregivers were higher than noncaregivers on these measures (Vitaliano, Scanlan, Krenz, & Fujimoto, 1996). Elevated metabolic risk may have been related to VIQ decline because persons with high metabolic composite scores had higher risks for insulin resistance (Schneiderman & Skyler, 1996). Insulin resistance is related to neurodegeneration (Coutinho et al., 1999), neuritic tangles as in AD lesions (Carro & Torres-Aleman, 2004), cortisol neurotoxicity in the hippocampus (Walker et al., 1994), and depletion of neurotransmitters in the hippocampus (Durkin, Messier, Deboer, & Westerink, 1992), the brain region that largely controls episodic/explicit memory (Parkin, 1997). Insulin resistance and its cognitive correlates are also influenced by chronic stress via the hypersecretion of cortisol (Bremner, 1999; Conrad, Galea, Kuroda, & McEwen, 1996) that damages the hippocampus by possibly blocking its uptake of glucose, which can influence loss of hippocampal neurons (McEwen & Sapolsky, 1995). This is expressed by decreased glucose

Table 3
Hierarchical Regressions: Predictors and Mediators of Caregiving and Vocabulary Decline

	Without Steps 3–4		With Step 3		With Step 4		With Steps 3–4	
Variable	β	$\Delta \mathrm{Ad}R^2$	β	$\Delta \mathrm{Ad}R^2$	β	$\Delta \mathrm{Ad}R^2$	β	$\Delta \mathrm{Ad}R^2$
Step 1. Raw Vocabulary IQ at Time 1	.77***	.59	.75***	.59	.75***	.59	.74***	.59
Step 2. Caregiver status	.09*	.01	.08	.00	.07	.00	.05	.00
Step 3. Hostility			−.10*	.02			−.10*	.02
Step 4. Metabolic composite					−.10*	.02	−.09*	.01
Total $\mathrm{Ad}R^2$		.60		.61		.61		.62

Note. Dependent variable = raw vocabulary at Time 2; Change is in adjusted R^2 ($\mathrm{Ad}R^2$).
* $p < .05$. *** $p < .001$.

transport or metabolism (Simmons & Miles, 1987) and increased serum glucose levels (Horner, Munck, & Lienhard, 1987).

For these reasons, the VIQ decline in caregivers may be associated with deteriorating hippocampal function rather than frontal function. The hippocampus plays an important role in storage of information, such as vocabulary, so disruption of hippocampal function might well reflect decreased recognition of vocabulary. Moreover, there is evidence that chronic stress, such as that experienced by caregivers, may result in hypersecretion of cortisol, a substance damaging to the hippocampus. In support of the argument that stress may damage verbal ability, Park, Glass, Minear, and Crofford (2001) reported that patients with fibromyalgia (a stress-mediated disorder), showed decreased vocabulary relative to controls but performed like older adults on tests such as those of working memory that load more on prefrontal function.

Hostility also mediated the relationship of caregiver status with VIQ decline, in part because caregivers had higher hostility scores than did noncaregivers. Hostile attribution was the strongest correlate of caregiving. It focuses on the belief that others intend to do one harm. Higher scores at study entry were also associated with greater drops in vocabulary. Hostile attribution is associated with activation of the medial prefrontal cortex, orbitofrontal cortex, and amygdala (Wicker, Perrett, Baron-Cohen, & Decety, 2003), areas involved in language processing and in interactions with the hippocampus (Barbas & Blatt, 1995; Cavada, Company, Tejedor, Cruz-Rizzolo, & Reinoso-Suarez, 2000; Phelps, 2004). Hostile attribution was also related to blood glucose levels ($r = .21$, $p < .01$) and metabolic risk ($r = .15$, $p < .01$), which supports previous work (Vitaliano, Scanlan, Krenz, & Fujimoto, 1996). When hostile attribution (or total hostility) and metabolic risk were entered together in the regression equation, the beta for caregiver status was cut in half. In contrast, anxiety, depression, sleep problems, vital exhaustion, cardiovascular illness variables, and medications were unrelated to both caregiver status and vocabulary decline. The lack of relationships of anxiety and depression with poorer cognitive function contrasts with previous research (D. A. King, Caine, Conwell, & Cox, 1991; Kizilbash et al., 2002; Sinoff & Werner, 2003). This may have occurred because "clinical" depression and anxiety were largely absent in the samples. Airaksinen, Larsson, Lundberg, and Forsell (2004) observed that unlike major depression, mixed anxiety, and depression disorder, mild depression does not influence verbal memory.

Our results are subject to limitations. First, the decline in caregivers relative to noncaregivers is relatively modest ($d = .33$). Small effect sizes are useful, however, when the outcome is important, the number of persons at risk is large, and the result has public health significance. We believe these are all true for the current study. Second, in this study the samples are well-educated (57% of the caregivers and 61% of the noncaregivers had bachelor's degrees or higher degrees). Such homogeneous groups aid internal validity, but they may compromise external validity. The large number of educated caregivers does, however, strengthen our argument that cognitive decline was influenced by chronic stress and its sequelae, as these were the only ways that caregivers differed from noncaregivers. Third, we know of only one other study of chronic stress that has used the SILS (McNally & Shin, 1995). Future caregiver research would benefit from measures of attention, memory, concentration, and executive function. Fourth, we did not formally examine follow-up (or changes in) psychophysiological measures as mediators. Instead we focused on intervening variables that preceded follow-up VIQ. Exploratory analyses did, however, find that follow-up or changes in psychophysiological scores were not associated with decline in vocabulary. Fifth, as with most research on caregiver health, we used an observational design. One cannot evaluate whether caregiving causes health problems by creating it in a laboratory, but researchers can design doubly prospective studies in which persons are examined before exposure to caregiving and before health problems. Because caregivers have shared the same risk factors (stress, diet, etc.) with persons who have developed AD, they may already be at higher risk for health and cognitive problems independent of caregiving (Vitaliano et al., 2003). However, even if cognitive decline is influenced in part or in full by precaregiving, such a result would still be important. A final issue concerns the fact that blood pressure was not a mediator in this study. Previous studies have found relationships between blood pressure and deficits by using other cognitive measures (see Verhaeghen et al., 2003; Waldstein & Elias, 2003). Moreover, laboratory blood pressure may not be as sensitive to caregiver responses as ambulatory blood pressure measured in caregivers' homes (A. C. King et al., 1994).

Despite these limitations, we believe this study has advantages. First, most studies of metabolic disregulation and vocabulary decline have been done in persons with diabetes (Kovacs, Goldston, & Iyengar, 1992; Rovet, Ehrlich, & Czuchta, 1990). These studies have shown that Type 2 diabetes increases the risk for memory and/or attention deficits (Strachan et al., 1997) and AD (Arvanitakis, Wilson, Bienias, Evans, & Bennett, 2004; Ott et al., 1999; Peila, Rodriguez, & Launer, 2002). In contrast, in this study relationships between the metabolic composite and vocabulary decline occurred in preclinical (nondiabetic) states. This may have major consequences for older adults under chronic stress. Second, a recent review of studies of memory impairments following chronic stress was critical of the cross-sectional nature and level of stress present in the studies. It recommended longitudinal studies of persons with stressful occupations (Jelicic & Bonke, 2001). Given that caregiving for a spouse with AD is a full-time job, it is unfortunate that this is the only study to examine cognitive decline in caregivers relative to noncaregivers. Third, this study included physiological mediators, factors that are relevant to health maintenance in caregivers, care recipients, and older adults in general (Vitaliano et al., 2003). Even minor cognitive impairment in caregivers may have consequences when caregivers have to function as decision makers for themselves and their spouse. Many caregivers are over 65, and they may experience age-related declines in function and age-associated comorbidities (Spillman & Pezzin, 2000). Caregiving may include the interplay between the strengths and weaknesses of caregivers and care recipients (Cartwright, Archbold, Stewart, & Limandri, 1994). Family caregivers make substantial contributions to long-term care (Arno, Levine, & Memmott, 1999). Any decrease in the ability of families to provide support has implications for the burden on the formal system at a time when demand is increasing. Psychotherapeutic interactions that reduce hostility and insulin resistance should have the additional benefit of helping to maintain caregiver cognitive functioning.

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