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Stress-related reduction in personal mastery is associated with reduced immune cell β_2-adrenergic receptor sensitivity

Brent T. Mausbach,[1] Paul J. Mills,[1] Thomas L. Patterson,[1,2] Kirstin Aschbacher,[1] Joel E. Dimsdale,[1] Sonia Ancoli-Israel,[1,2] Roland von Känel[1,3] and Igor Grant[1,2]

[1] *Department of Psychiatry, University of California at San Diego, U.S.A.*
[2] *Veterans Affairs San Diego Health Care System, U.S.A.*
[3] *Department of General Internal Medicine, University Hospital, Bern, Switzerland*

ABSTRACT

Background: A growing body of literature suggests that caregiving burden is associated with impaired immune system functioning, which may contribute to elevated morbidity and mortality risk among dementia caregivers. However, potential mechanisms linking these relationships are not well understood. The purpose of this study was to investigate whether stress-related experience of depressive symptoms and reductions in personal mastery were related to alterations in ß$_2$-adrenergic receptor sensitivity.

Methods: Spousal Alzheimer's caregivers (N = 106) completed measures assessing the extent to which they felt overloaded by their caregiving responsibilities, experienced depressive symptoms, and believed their life circumstances were under their control. We hypothesized that caregivers reporting elevated stress would report increased depressive symptoms and reduced mastery, which in turn would be associated with reduced ß$_2$- adrenergic receptor sensitivity on peripheral blood mononuclear cells (PBMC), as assessed by in vitro isoproterenol stimulation.

Results: Regression analyses indicated that overload was negatively associated with mastery ($\beta = -0.36$, $p = 0.001$) and receptor sensitivity ($\beta = -0.24$, $p = 0.030$), whereas mastery was positively associated with receptor sensitivity ($\beta = 0.29$, $p = 0.005$). Finally, the relationship between overload and receptor sensitivity diminshed upon simultaneous entry of mastery. Sobel's test confirmed that mastery significantly mediated some of the relationship between overload and receptor sensitivity ($z = -2.02$, $p = 0.044$).

Correspondence should be addressed to: Brent T. Mausbach, Department of Psychiatry (0680), University of California, San Diego, 9500 Gilman Drive, La Jolla, CA 92093-0680, U.S.A. Phone: +1 858 822 5925; Fax: +1 858 534 7723. Email: bmausbach@ucsd.edu. Received 8 Jun 2006; revision requested 12 Jul 2006; revised version received 19 Jul 2006; accepted 20 Jul 2006. First published online 4 October 2006.

Conclusions: These results suggest that a reduced sense of mastery may help explain the association between caregiving burden and reduced immune cell $ß_2$-receptor sensitivity.

Key words: stress, coping, immune function, caregiver, Alzheimer's disease

Introduction

Caregivers of dementia patients have been described as an ideal model for studying the effects of chronic stress on both mental and physical health (Grant, 1999). For example, caregivers under strain are not only more likely to self-report worse physical health than their non-caregiving counterparts (Schulz *et al.*, 1995), but may also be at risk of elevated mortality relative to non-caregivers (Schulz and Beach, 1999).

Although the physiological mechanisms accounting for exaggerated mortality risk among strained caregivers are not clearly understood, a growing literature suggests that caregiving burden may impair immune system functioning and increase susceptibility to disease (Kiecolt-Glaser *et al.*, 1991). For example, dementia caregivers have been found to exhibit slowed wound healing associated with a reduced production of interleukin-1ß and poorer cytokine response to lipopolysaccharide (Kiecolt-Glaser *et al.*, 1995). $ß_2$-adrenergic receptors are important for T-cell and natural killer cell functions, including cytokine production (Sanders and Straub, 2002). Chronic stress provokes excessive activation of the autonomic nervous system, which may affect immune functioning via a desensitization of $ß_2$-adrenergic receptors (Kohm and Sanders, 2001; Kühlwein *et al.*, 2001) on immune cells. For instance, we recently demonstrated that highly stressed caregivers have a deficit in peripheral blood mononuclear cell (PBMC) $ß_2$-adrenergic receptors (Mills *et al.*, 2004). In that study, caregiving stress was characterized using a vulnerable/non-vulnerable classification, in which vulnerable caregivers were defined as those who provided more than 12 hours of care each day while receiving in-home respite less than once per month over the past 6 months. However, recent research suggests that subjective reports of stress (e.g. "My life circumstances are overwhelming"), rather than the more "objective" experience of stress (i.e. vulnerability) may better relate to health outcomes. For example, in a review of factors associated with psychiatric and physical morbidity in caregivers, Schulz and colleagues (1995) report that subjective stress (e.g. burden, perceived stress) was more strongly related to outcomes than objective stress measures (e.g. assistance provided, patient functional impairment). Further studies have demonstrated that subjective reports of strain are associated with increased mortality risk in caregivers (Schulz and Beach, 1999).

While stress has been associated with negative health outcomes, including immune functioning, little research has attempted to clarify factors associated with both stress and negative health outcomes which might provide a more detailed understanding of how stress might affect one's health. One potential

construct that is related to both stress and health outcomes is personal mastery, which is one's belief that he/she can control his/her future and life circumstances (Pearlin and Schooler, 1978). Indeed, the extant literature suggests that stress is directly related to a reduced sense of mastery (Bauer *et al.*, 2001; Skaff *et al.*, 1996), which in turn appears to impact emotional outcomes such as depressive mood and anger (Boss *et al.*, 1990; Hobfoll *et al.*, 2003; Parks and Pilisuk, 1991; Semple, 1992). Interestingly, previous research reports that depression is associated with blunted ß-adrenergic receptor sensitivity (Mazzola-Pomietto *et al.*, 1994), suggesting a series of interrelationship between stress, mastery and emotional disturbances which may all contribute to reduced ß-adrenergic receptor sensitivity. A separate line of inquiry has demonstrated that a reduced sense of personal mastery is directly linked with worsened health, lower life satisfaction and increased depressive symptoms (Lachman and Weaver, 1998). Perhaps most importantly, a reduced sense of mastery has been directly associated with mortality risk in the elderly (Penninx *et al.*, 1997). These data suggest that stress-related alterations to one's sense of personal mastery and/or emotional well-being may be related to alterations in one's health, including immune functioning.

Given the separate effects that: (a) stress is related to reduced feelings of personal mastery, (b) reduced mastery is related to negative health outcomes, and (c) caregiving stress is associated with alterations in immune system functioning (Kiecolt-Glaser *et al.*, 1995), we hypothesized that personal mastery serves as a partial mediator of the relationship between caregiving burden (i.e. role overload) and lymphocyte $ß_2$-adrenergic receptor functioning in elderly spousal caregivers of dementia patients. Also, given studies showing that depression may affect ß-adrenergic receptors (Mazzola-Pomietto *et al.*, 1994), we explored whether depressive symptoms better accounted for the reductions in ß-adrenergic receptor sensitivity.

Method

Participants

The participants for this study consisted of 106 spousal caregivers of patients with Alzheimer's disease who were enrolled in a study examining the psychobiological effects of stress. Data for 69 of these participants have been reported in our previous paper (Mills *et al.*, 2004), with 37 (35%) unique cases being presented in the current sample. The current participants were primarily elderly (mean age = 73.0 ± 8.7 years), female (67.9%), and Caucasian (92.5%). To participate, caregivers were required to be providing in-home care to a spouse with a physician's diagnosis of Alzheimer's disease and be at least 55 years of age. Participants were excluded if they were: (a) taking $ß_2$-adrenergic blocking medication, (b) using steroids, or (c) hypertensive as indicated by a blood pressure greater than 200/120 mm Hg. A complete description of the sample can be found in Table 1.

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Procedures

A research nurse met with study participants in their homes to obtain informed consent and complete a structured interview of caregivers' demographic characteristics and both physical and psychological health. Between 8 a.m. and 10 a.m. the following morning the nurse met caregivers in their homes to collect blood samples. A catheter was placed in the caregiver's non-dominant forearm and, after a 14-minute resting period, blood was drawn for assay.

Measures

β-ADRENERGIC RECEPTORS

ß$_2$-adrenergic receptor sensitivity was determined on PBMC's as previously described (Mills *et al.*, 1995; 2002). PBMC's were suspended in cold Dulbecco's Modified Eagle's Medium (DMEH). Incubations in triplicate were begun by adding 0.1 ml of approximately 2×10^5 cold cells to 0.9 ml of 37 °C DMEH containing 100 mmol/L isobutylmethylxanthine (IBMX) to inhibit cyclic nucleotide phosphodiesterase activity. Half of the tubes also contained 10 μM isoproterenol. Once the reactions were terminated, the tubes were frozen and later assayed for cyclic-AMP (Perkin Elmer, Boston, MA). Basal, non-stimulated cyclic-AMP was also determined. Isoproterenol, acting via the ß-adrenergic receptor, typically causes an approximate three- to five-fold increase (over basal) in intracellular cyclic-AMP levels. The ratio of isoproterenol-stimulated cyclic AMP to basal non-stimulated cyclic AMP was taken as the index of ß$_2$-adrenergic receptor sensitivity. We use the term "sensitivity" to denote how responsive the beta receptor is to stimulation with isoproterenol. Isoproterenol stimulation leads to activation of the beta-adrenergic receptor–Gs protein–adenylate cyclase complex. A sensitized or "coupled" receptor denotes that the beta receptor is coupled to the Gs protein which upon stimulation enables adenylate cyclase activation and cyclic AMP generation. A desensitized or uncoupled receptor cannot generate a cyclic AMP response. This sensitivity measure is independent of the specific number of cells, but rather an index of how well the entire beta receptor population is working among the cells responding to stimulation.

SUBJECTIVE CAREGIVER STRESS

Pearlin's Role Overload scale (Pearlin *et al.*, 1990) was used to assess the extent to which caregivers felt overwhelmed or overloaded by their caregiving responsibilities. This scale consists of four items ("You are exhausted when you go to bed at night", "You have more things to do than you can handle", "You don't have time just for yourself", You work hard as a caregiver but never seem to make any progress") and utilizes the following four-point Likert scale: 1 (not at all), 2 (somewhat), 3 (quite a bit), and 4 (completely). The scale has demonstrated good internal reliability (Cronbach's $\alpha = 0.80$; Pearlin *et al.*, 1990). For the present study, the four items were summed to create an overall overload score (range = 4–16).

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CAREGIVER MASTERY

Participants were administered the seven-item personal mastery scale developed by Pearlin and Schooler (1978), on which caregivers rated the extent to which they believed their life circumstances were under their own control (e.g. "I have little control over the things that happen to me", "What happens to me in the future mostly depends on me", "I often feel helpless in dealing with the problems of life"). With two items reverse scored, caregivers responded using a Likert scale ranging from 1 (strongly agree) to 4 (strongly disagree) so that higher scores indicated greater feelings of mastery.

CAREGIVER DEPRESSIVE SYMPTOMS

Depressive symptoms were assessed using the 17-item Hamilton Depression Rating Scale (Hamilton, 1969). This scale is administered by a trained observer and ratings are made on a 0–4 or 0–2-point scale on 17 items. The HAM-D is a brief yet comprehensive measure of depressive symptomatology, with well documented reliability (i.e. inter-rater reliability range = 0.8–0.9) (Hamilton, 1969) and validity (Endicott, 1984).

CAREGIVER HEALTH

Overall caregiver health was assessed using the Interim Medical History questionnaire (IMED), which is a guided interview in the form of a "review of systems." Participants were asked whether or not they experienced health-related symptoms associated with 14 major systems (e.g. eyes, ears, nose, throat, chest) during the past six months. For the present study, the total number of symptoms endorsed was summed to create an overall health score with higher scores indicating worse health (range = 0–32).

Beyond our review of systems, two additional assessments of caregiver health were evaluated. We assessed caregivers' systolic and diastolic blood pressure (BP) using a Critikon Dinamap 8100 adult/pediatric non-invasive blood pressure monitor. These data were used to calculate mean arterial pressure (MAP) according to the following formula: diastolic BP + 1/3* (systolic BP-diastolic BP). Body mass index (BMI) was calculated as the ratio of body weight in kilograms divided by the square of height in meters (kg/m^2).

CARE RECIPIENT COGNITIVE FUNCTIONING

The Clinical Dementia Rating scale (CDR; Hughes *et al.*, 1982) was administered by a research nurse to assess the cognitive status of the care recipient. Nurses assigned a score ranging from 0 (healthy) to 4 (severe dementia) on six domains, including memory, judgment/problem-solving and orientation, with the average score on these domains indicating overall severity of dementia symptoms.

Data analysis

Prior to conducting any analyses, the distribution of all variables was examined. Caregiver health (i.e. IMED scores), ß-adrenergic receptor sensitivity, and depressive symptoms (HAM-D scores) were all positively skewed. As a result,

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health and ß-adrenergic receptor sensitivity were log-transformed, whereas a square-root transformation was used to normalize depressive symptoms. No other variables were transformed.

The analytic strategy proposed by Baron and Kenny (1986) and Holmbeck (1997; 2002) was used to determine whether caregiver mastery significantly mediated the relationship between caregiver role overload and $ß_2$-adrenergic receptor sensitivity. As recommended by these authors, a series of regressions was conducted to determine the relationship between: (1) the independent variable (role overload) and the proposed mediator (mastery), (2) the independent variable and the dependent variable ($ß_2$-adrenergic receptor sensitivity), and (3) the mediator and the dependent variable. A final regression was also run which included both role overload and mastery as predictors of $ß_2$-adrenergic receptor sensitivity. Because age and physical health symptoms may be related to worsened immune functioning, we included these variables as covariates in our models. Further, blood pressure (Profant *et al.*, 2002) and obesity (Marti *et al.*, 2001) have been associated with $ß_2$-adrenergic receptor sensitivity, and immune system functioning, respectively. Therefore, we included mean arterial pressure and body mass index as covariates. Patient CDR score was included as a covariate to capture objective stress experienced by the caregiver. For a full mediating effect to exist, the impact of role overload on ß-adrenergic receptor sensitivity would be zero after mastery is included in the model. A partial mediating effect exists when the impact of overload on ß-adrenergic receptor sensitivity is significantly reduced when mastery is included in the model. In the latter circumstance, we conducted a Sobel test (Sobel, 1982) to determine whether the relationship between overload and $ß_2$-adrenergic receptor sensitivity was significantly reduced by the addition of mastery. Using a similar approach described above, we also conducted a final analysis using HAM-D scores as a covariate in predicting $ß_2$-adrenergic receptor sensitivity to evaluate the possibility that depressive symptoms better accounted for reduced receptor sensitivity than personal mastery.

Results

Demographic and health characteristics of the sample are presented in Table 1. Caregivers averaged 73 years of age and were predominately Caucasian. All participants had at least a high school education. The average impairment level of spouse care recipients, as measured by the Clinical Dementia Rating scale, was between mild and moderate.

Primary analyses

Results of the first regression, in which mastery was regressed onto role overload, indicated that role overload was negatively associated with personal mastery ($\beta = -0.36 \pm 0.10$, $t = -3.57$, $df = 99$; $p = 0.001$). That is, caregivers with greater role overload reported reduced feelings of personal mastery. Next, the relationship between role overload and $ß_2$-adrenergic receptor sensitivity was significant ($\beta = -0.23 \pm 0.11$, $t = -2.20$, $df = 99$; $p = 0.037$),

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Table 1. Characteristics of the sample[a]

VARIABLE	
Caregiver age in years, M (SD)	73.00 (8.73)
Gender, n (%)	
Male	34 (32.1)
Female	72 (67.9)
Caregiver race, n (%)	
Caucasian	98 (92.5)
Other	8 (7.5)
Years of education, n (%)	
high school	27 (25.5)
some college	26 (24.5)
college or above	53 (50.0)
Yearly household income, n (%)[b]	
less than $41,000	44 (48.4)
$41,000 and above	47 (51.6)
Lymphocyte ß$_2$-adrenergic receptor sensitivity (M ± SD)	4.6 (3.9)
Caregiver IMED score, M (SD)	5.70 (6.05)
Mean arterial pressure, M (SD)	88.68 (11.93)
Body mass index [kg/m2], M (SD)	25.53 (4.41)
Care recipient CDR score, M (SD)[c]	2.51 (0.89)
Caregiver overload, M (SD)	9.37 (3.28)
Caregiver mastery, M (SD)	19.14 (2.81)
HAM-D score, M (SD)	4.42 (3.97)

Notes: [a]Total sample size = 106; [b]15 participants refused to provide income data; [c]CDR = Clinical Dementia Rating score.

indicating reduced receptor sensitivity was associated with greater role overload. Third, mastery was positively associated with ß$_2$-adrenergic receptor sensitivity ($\beta = 0.29 \pm 0.11$, $t = 2.89$; $df = 99$; $p = 0.005$), whereby reduced feelings of mastery were associated with reduced ß$_2$-adrenergic receptor sensitivity. In our final regression, the relationship between role overload and ß$_2$-adrenergic receptor sensitivity was reduced when mastery was also included in the model. The Sobel test, conducted to determine whether personal mastery constituted a significant mediator, was significant ($z = -2.02$, $p = 0.044$), thereby confirming that reduced mastery accounted for a significant portion of the relationship between role overload and ß$_2$-adrenergic receptor sensitivity. Using the formula provided by MacKinnon and Dwyer (1993), we determined that approximately 39% of the role overload to ß$_2$-adrenergic receptor sensitivity path was accounted for by reduced levels of personal mastery. The mediational model is shown in Figure 1.

Secondary analysis

In our secondary analysis, we examined the relations between mastery, depressive symptoms and ß$_2$-adrenergic receptor sensitivity. In this analysis, no significant relation was found between depressive symptoms and

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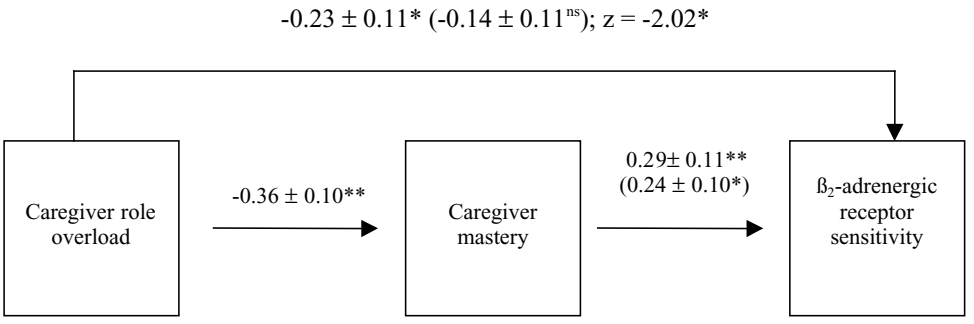

Figure 1. Mediational model for associations between caregiver role overload and β_2-adrenergic receptor sensitivity on lymphocytes in Alzheimer caregivers. Values on paths are standardized (β) coefficients ± Standard Error. Values outside parentheses are direct effects, whereas values inside parentheses represent coefficients when both caregiver role overload and mastery were simultaneously included in the model. z = Sobel test; * $p < 0.05$. ** $p < 0.01$.

ß$_2$-adrenergic receptor sensitivity ($p = 0.491$). When both depressive symptoms and mastery were included in the model, mastery remained a significant predictor of ß$_2$-adrenergic receptor sensitivity ($\beta = 0.26$, $t = 2.39$, $df = 97$; $p = 0.019$). Therefore, depressive symptoms did not explain away the relationship between mastery and ß$_2$-adrenergic receptor sensitivity.

Discussion

Caregivers of Alzheimer's patients undergo significant stress, which often results in both psychiatric and physical health consequences. While previous studies have demonstrated that Alzheimer's caregivers appear to suffer immune system deficits (Kiecolt-Glaser *et al.*, 1995; 1996) and that caregiving stress is associated with altered immune cell ß$_2$-adrenergic receptor functioning (Mills *et al.*, 2004), our findings extend this research by demonstrating that specific psychological factors (i.e. mastery) associated with chronic stress better account for alterations in immune cell functioning. Specifically, ours is the first study to suggest that stress-related reductions in personal mastery are associated with immune cell ß$_2$-adrenergic receptor sensitivity. ß$_2$-adrenergic receptors are important for PBMC trafficking and for cytokine production (Mills *et al.*, 1999; Sanders and Straub, 2002).

Although these results are preliminary and require replication using a prospective design, our data suggest directions for further development of a model linking psychological burden and mastery to health decline among caregivers. Specifically, our model suggests that as the stresses of caregiving increase, caregivers feel overwhelmed, exhausted, and unable to accomplish even short-term goals (i.e. overload). In dealing with caregiving burden over time, caregivers develop a sense of the degree to which they are capable of mastering the challenges they confront. Thus, the sense of overload may lead to a reduction in one's sense of control over his/her life and circumstances,

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which in turn is related to changes in immune system functioning and ultimately health-related declines. However, these claims are speculative, awaiting further evaluation using a longitudinal design.

One limitation of this study is its cross-sectional design. Therefore, we urge caution in interpreting the causality of our results. To determine the causality of the relationships presented here, a longitudinal design is needed. One means of determining whether mastery is causally related to ß$_2$-adrenergic receptor sensitivity is to evaluate systematically the effect of psychosocial interventions in increasing both the caregivers' sense of personal mastery and their ß$_2$-receptors' sensitivity. Within the context of this design, one can determine whether change in mastery significantly mediates change in ß$_2$-receptor sensitivity. Previous research indicates that psychoeducational interventions, designed to teach caregivers specific skills in managing the stresses associated with caregiving, can increase caregivers' beliefs that they can manage caregiving stressors (Coon *et al.*, 2003). Indeed, these authors demonstrated that increases in feelings of mastery were associated with reductions in both anger and depressive symptoms. Thus, we speculate that comparable interventions might similarly impact physiological outcomes.

Another limitation of our study is that we do not know if the loss of ß$_2$-adrenergic receptor sensitivity in those subjects with low mastery reflects an actual receptor desensitization or a change in the trafficking of lymphocyte subsets (Kohm and Sanders, 2001; Kühlwein *et al.*, 2001). ß$_2$-adrenergic receptors are expressed almost exclusively on Th-1 cells (Sanders *et al.*, 1997) and prior studies of highly stressed caregivers suggests that caregiving stress leads to a loss of cellular and hormonal responses attributed to the Th-1 subset (Kiecolt-Glaser *et al.*, 1996). Thus, the question remains whether our observation reflects an acute sympathetic-induced desensitization of the ß$_2$-adrenergic receptor, a partial loss of the ß$_2$-adrenergic receptor expressing Th-1 subset, or both.

While previous literature suggests that depressive symptoms are associated with reduced ß-adrenergic receptor sensitivity (Mazzola-Pomietto *et al.*, 1994), we did not find this effect. Rather, our data suggests that specific components of depression, such as reduced feelings of mastery, may better explain changes in receptor sensitivity. Indeed, depression is a multi-faceted condition, consisting of affective (e.g. sadness), cognitive (e.g. helplessness/reduced mastery), behavioral (e.g. behavioral deactivation), and somatic (e.g. biological, physical) components. Mastery, which represents a cognitive aspect of depression (e.g. "there is little I can do to change the important things in life"; "I have little control over the things that happen to me"), may contribute to a deactivation of self-care and self-reinforcing behaviors through a "what's the use" attitude (e.g. "if I'm going to get sick, I'll get sick. There's nothing I can do to stay well"), which in turn act to "upset" the immune system. These speculations, however, are beyond the scope of this study and require further examination.

Our failure to find a relationship between depression and ß-adrenergic receptor sensitivity might also reflect the fact that most participants in our study reported mild-to-moderate rather than clinical levels of depressive symptoms. However, previous research has demonstrated relationships between subclinical

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mood symptoms and other biological outcomes (von Känel *et al.*, 2004). Nonetheless, future studies may wish to examine the relations between overload, mastery, and ß$_2$-adrenergic receptor sensitivity in a more severely depressed sample of caregivers.

In sum, our study demonstrates that a reduced sense of personal mastery, likely resulting from increased caregiving burden, is significantly related to a loss of immune cell ß$_2$-adrenergic receptor function. Given that ß$_2$-adrenergic receptors on immune cells play a vital role in immune cell trafficking and functioning, these findings may argue for the importance of acquiring a sense of personal mastery over the burdens of caregiving. Future studies should utilize longitudinal designs to examine whether changes in mastery over time also relate to changes in immune cell function. Also, investigations of the efficacy of psychosocial interventions for improving both mastery and physiological outcomes related to immune cell functioning are strongly encouraged.

Conflict of interest

None.

Description of authors' roles

Brent T. Mausbach formulated the research question, contributed to writing the paper, and conducted the statistical analysis. Paul J. Mills contributed to writing the paper, contributed to the formulation of the research question, and conducted assays. Thomas L. Patterson co-designed the study, supervised the data collection, and contributed to writing the paper. Kirstin Aschbacher contributed to writing the paper. Joel E. Dimsdale contributed to the design of the study. Sonia Ancoli-Israel contributed to the design of the study. Roland von Kanel contributed to the writing of the paper. Igor Grant contributed to the design of the study and conceptualization of the research question.

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