Published in final edited form as:

J Neurooncol. 2016 May ; 128(1): 109–118. doi:10.1007/s11060-016-2083-3.

Neuro-oncology family caregivers are at risk for systemic inflammation

Paula R. Sherwood¹, Thomas J. Price¹, Jason Weimer¹, Dianxu Ren¹, Heidi S. Donovan¹, Charles W. Given², Barbara A. Given³, Richard Schulz⁴, Jennifer Prince¹, Catherine Bender⁵, Florian W. Boele¹, and Anna L. Marsland⁶

¹University of Pittsburgh, School of Nursing, 336 Victoria Bldg, Pittsburgh, PA 15261

²Michigan State University, Department of Family Medicine, Clinical Ctr, Tower B, 788 Service Road, Room B120, East Lansing, MI, 48824

³Michigan State University, College of Nursing, C383 Life Sciences Bldg, 1355 Bogue St., East Lansing, MI 48824

⁴University of Pittsburgh, Office of the Provost, 212 Forbes Ave, Pittsburgh, PA 15261

⁵University of Pittsburgh, School of Nursing, 415 Victoria Bldg, Pittsburgh, PA 15261

⁶University of Pittsburgh, School of Psychology, 3490 O'Hara St., Pittsburgh, PA 15261

Abstract

Background—Prolonged periods of family caregiving can induce stress levels that may negatively influence caregiver health. However, the physiologic effect of psychological distress in oncology family caregivers has received little attention. Therefore we aimed to determine longitudinal profiles of inflammatory cytokines (IL-6 and IL-1ra) in neuro-oncology caregivers and identify associations between psychological distress and cytokine levels.

Methods—Depressive symptoms, anxiety, caregiver burden and blood were collected from 108 adult caregivers at adult patients' diagnosis, 4-, 8-, and 12-months. Trajectory analyses of log transformed cytokine levels were performed. Multiple logistic regression analyses evaluated the impact of psychological distress on cytokine levels.

Results—For both cytokines, two distinct populations were identified, neither of which changed over time. High IL-1ra was associated with male caregivers with anxiety (OR=1.7; 95%CI 1.06-2.83) and obese caregivers (BMI=40) who felt burdened due to disrupted schedules (OR=1.3; 95%CI 1.02-1.77). Conversely, caregivers with a healthy weight (BMI=25) who felt burdened due to disrupted schedules were less likely to have high IL-1ra (OR=0.71; 95%CI 0.54-0.92). Caregivers 30 years old with lower self-esteem from caregiving were 1.16 times (95%CI 1.04-1.30) more likely to have high IL-6.

Corresponding author: Paula R. Sherwood, 336 Victoria Bldg, 3500 Victoria St., Pittsburgh, PA 15261, Phone: 412-624-4802, Fax: 412-383-7227, prs11@pitt.edu.

Conflict of interest: No conflict of interest exists for any author.

Conclusions—Analysis demonstrated groups of family caregivers with high and low levels of systemic inflammation and these levels did not change longitudinally over the care trajectory. Poor physical health in family caregivers may have a negative impact on the burden placed on the healthcare system in general and on the well-being of neuro-oncology patients in particular.

Keywords

caregiver; immune; brain tumor; IL-6; IL-1ra; psychological health

Introduction

Approximately 52 million Americans provide care to someone who is ill or disabled, making family caregivers the largest source of health care providers in the United States [1]. Schulz and Beach [2] were among the first to suggest that distress from providing care increases mortality risk for caregivers. These results have been both supported [2;3] and contradicted [4]; research studies on physiologic consequences from providing care in non-cancer populations show caregivers with psychological distress are at risk for increased levels of pro-inflammatory cytokines such as IL-6 [5], increased C-reactive protein [6], carotid artery plaque [7], and higher blood pressure [7;8]. Systemic inflammation is a precursor to multiple disease states, many of which have been associated with caregiver distress. For example, non-cancer studies have shown an increased risk for cardiovascular disease, diabetes, and poor overall health among distressed caregivers [8;9].

Evidence suggesting caregiver distress is associated with systemic inflammation has primarily been investigated in the context of Alzheimer's disease (AD) [10;11]. AD is characteristically a slow, steadily progressive disease where accompanying caregiver distress often has a similar trajectory. On the other hand, cancer, and brain tumors in particular, typically have an abrupt onset with a variable disease course. In oncology family caregivers, systemic inflammation known to accompany distress and lead to disease states may be a better marker of caregivers at risk for developing health conditions in the future. Specifically, both IL-1ra and IL-6 have been shown to vary as a result of depressive symptoms [48;49], although these findings were not in the field of caregiving. However, caregivers have demonstrated lower immunoreactivity in response to challenges than non-caregivers [50;51;52]. In particular, in caregivers of persons with dementia, altered levels of IL-1 [53], elevations of IL-6, and differences in rates of IL-6 increase over time have been found [54;55]. Caregivers of persons with cancer, however, likely have heightened stress responses (or activation of physiologic stress pathways), condensed into a shorter time span. Little is known regarding biologic responses in caregivers of persons with cancer and brain cancer in particular.

To date, few articles have evaluated systemic inflammation in oncology caregivers [12]. Physiologic studies in neuro-oncology have primarily focused on genetic predisposition to fatigue, depression, anxiety, and sleep disturbance in a mixed sample of patients and caregivers [13]. A small sample of family caregivers of persons with a brain tumor compared to controls were found to have elevations in C-reactive protein and IL-1ra [14]. However, studies that have evaluated the immunologic consequences of distress in neuro-oncology

caregivers over the care trajectory as the patient is diagnosed, undergoes treatment, faces possible recurrence and a high potential for death, are lacking. It is vital to focus on the presence of systemic inflammation in neuro-oncology caregivers as this has implications for thousands of Americans regarding both the caregivers' health and the potential impact on the quality of care delivered in the home to patients with a brain tumor.

Therefore, the aims of this prospective longitudinal study (R01 CA117811) were to: 1) describe profiles of two circulating markers of inflammation, IL-6 and IL-1ra, over the care trajectory in adult caregivers of adults with a primary brain tumor (PBT), and 2) evaluate the association between adult caregivers' psychological health (depressive symptoms, anxiety, and caregiver burden) and levels of IL-6 and IL-1ra after controlling for variables known to influence cytokine levels (caregivers' age, sex, body mass index (BMI), comorbid conditions, recent history of a cold/fever, medications, and alcohol, tobacco and caffeine use).

Materials and Methods

Participants

A convenience sample of newly diagnosed (within three months of diagnosis) caregiver/patient dyads was recruited from neuro-oncology and neurosurgery clinics at a university-based teaching hospital after obtaining Institutional Review Board approval. Caregiver eligibility criteria were: 21 years old, identified by the patient as the person who provided the majority of support, not a primary caregiver for anyone else except children under the age of 18, and able to speak and read English. Patient eligibility criteria were: 21 years old and diagnosed (verified via pathology) with a PBT within three months. All participants provided written informed consent.

Procedure and outcome measures

Data collection occurred at baseline (within three months of diagnosis) and 4-, 8-, and 12-months either at the participants' home or at the outpatient clinic. Data on socio-demographic characteristics and psychological distress were collected via telephone interview using measures with established reliability and validity. Depressive symptoms were measured by the shortened Center for Epidemiologic Studies-Depression ($\alpha=0.86$) [15;16]. Anxiety was measured using the shortened Profile of Mood States-Anxiety questionnaire ($\alpha=0.91$) [17]. Three constructs of caregiver burden were measured by the Caregiver Reaction Assessment [18;19]: the impact of providing care on caregivers' self-esteem ($\alpha=0.86$), the impact of providing care on caregivers' feelings of abandonment ($\alpha=0.89$), and the impact of providing care on disruptions in caregivers' schedule ($\alpha=0.79$).

Patients' tumor type was obtained from pathology report. Data regarding caregivers' comorbid conditions, recent history of a cold/fever, current medications, and alcohol, tobacco and caffeine use were obtained via in-person interview at the time of the blood draw. Body Mass Index (BMI) was calculated based on self-report measures of weight and height. Blood for caregiver cytokine levels was obtained by venipuncture in the home within 72 hours of measures of psychological distress and transported to a processing facility within

0.5-3 hours of the draw (statistical analysis revealed no difference in cytokine levels based on time from draw to processing). Circulating IL-1ra and IL-6 were selected because they are reliable markers of immune system activation [20]. These cytokines have both been associated with the susceptibility to and severity of many diseases [20;21]. Cytokine levels were batch analyzed in duplicate by high sensitivity quantitative sandwich enzyme immunoassay kits (R & D Systems, Minneapolis, MN). Average intra-assay coefficient of variance was 4.33 for IL-6 and 6.88 IL-1ra.

Statistical analyses

Data were used from caregivers who completed at least two data collection time-points. Participant demographics were reported using descriptive statistics. Cytokine levels were highly skewed and thus log transformed to normalize distribution and reduce variation. To determine caregivers' cytokine profiles over time, trajectory analysis was conducted. These models account for subject heterogeneity in temporal patterns of change by latent classes (trajectories) and allow a variety of straight and curved trajectories to capture different patterns of cytokines over time. The best fitting and most parsimonious models were selected based on Bayesian Information Criterion (BIC) [22], class sizes and interpretability.

Two-group (high and low) trajectory models were identified for both IL-1ra and IL-6, therefore logistic regression models were conducted to determine the impact of caregivers' psychological distress on whether they were in the high versus low cytokine group. Due to the number of potential predictor variables and the sample size, the decision was made a priori to perform exploratory univariate logistic regression analyses to discern potential relationships between trajectory group membership and hypothesized confounding variables (patient's tumor type [23], caregiver age, sex, relationship to patient [24], BMI, comorbid conditions [23], recent history of a cold/fever [25], medications, and alcohol tobacco and caffeine use) [26]. Variables with an association of $p \leq 0.10$ were included in final model testing. Separate multivariate logistic regression analyses were conducted using each measure of psychological distress along with the aforementioned confounding variables to predict membership in high or low IL-6 and IL-1ra group. Separate analyses were chosen versus adjusting for multiple comparisons as an a priori decision was made that the constructs were distinct. All potential two-way interaction effects between psychological variables and potential confounding variables were examined. All statistical analyses were conducted using SAS version 9.3 (SAS Institute, Inc., Cary, NC) and $p < 0.05$ was considered significant.

Results

In total, 134 participants were recruited (79% of those approached) over four years; data collection occurred at baseline (within three months of diagnosis) and 4-, 8-, and 12-months. Sample size was 108 at baseline, 91 (4 months), 77 (8 months), and 69 (12 months). The most common reason for dropout was patient death (12%). Trajectory analyses were compared between bereaved caregivers versus caregivers whose patients did not die during the study and no significant differences were found.

Table 1 provides sample characteristics and whether or not each characteristic was significantly ($p < .10$) related to cytokine trajectory group membership and thus used as a covariate. Most caregivers were Caucasian, middle-aged females spouses of a patient diagnosed with a glioblastoma multiforme. Approximately one-third of the caregivers had a history of hypertension and one-tenth a history of diabetes, cancer, coronary artery disease or arthritis. The most common medications used by caregivers were anti-hypertensive and non-steroidal anti-inflammatory agents.

Trajectory analysis (Figure 1, $N=108$) of IL-1ra levels revealed two significantly different groups ($BIC = -235.28$); neither changed significantly over time (from baseline to 12 months following the patient's diagnosis). In Figure 1, log transformed values of IL-1ra are plotted against data collection timepoints (baseline, 4, 8, and 12 months). The top line indicates the group of participants that had higher IL-1ra levels, the bottom line indicates those with lower IL-1ra levels over time. The dotted lines above and below each solid line represent confidence intervals. As these lines do not overlap, two distinct groups can be confirmed. One-third (34%) of the caregivers had high IL-1ra levels (raw Mean = 575.91 pg/ml; SD = 252.65) and the majority (66%) had low levels (raw Mean = 252.80 pg/ml; SD = 94.91). Trajectory analysis with IL-6 levels also revealed two significantly different groups ($BIC = -299.44$); neither changed significantly over time. Over half the sample (59%) had high IL-6 levels (raw Mean = 2.30 pg/ml; SD = 1.96) and 41% had low levels (raw Mean = 0.90 pg/ml; SD = 0.35). No significant relationship between being in the high IL-1ra group and being in the high IL-6 group (and vice versa) was found. Table 2 presents sociodemographic and clinical characteristics of the low and high groups of IL-1ra and IL-6.

Significant models for IL-1ra are detailed in Table 3. Figure 3 represents interactions that were found among predictor variables (Y axis) and IL-1ra (X axis); no significant interactions were found among predictor variables and IL-6. The dots represent the odds ratios with the corresponding lines representing their confidence intervals. There was a significant interaction between anxiety and sex. Specifically, there was no association between anxiety and IL-1ra in females (OR 0.99; 95%CI 0.78-1.26), but among males, each unit increase in anxiety was associated with being 1.7 times (95%CI 1.06-2.83) more likely to be in the high IL-1ra group (see Figure 3). As expected, two covariates (BMI and age) were associated with a significant increase ($p < .01$ and $p = 0.02$ respectively) in risk for being in the high IL-1ra group.

There was a significant interaction effect of caregiver burden due to schedule disruptions and BMI on IL-1ra group membership (see Figure 3). In the odds ratios, BMI was categorized according to national guidelines for interpretation [27]. For example, if a caregiver had a BMI of 40 (Class III obesity), each unit increase in burden due to schedule disruptions would be associated with being 1.3 times (95%CI 1.02-1.77) more likely to be in the high IL-1ra group. If a caregiver had a BMI of 25 (classified as "healthy"), caregivers with burden due to schedule disruptions would be less likely to be in the higher IL-1ra group (OR=0.71; 95%CI 0.54-0.92).

Significant models for IL-6 are included in the last section of Table 3. There was a significant interaction ($p = .03$) effect between feelings of burden related to caregivers' self-

esteem and age. In the odds ratios, age was categorized by decades. Burden was not related to IL-6 group membership among caregivers 40 and older, but among caregivers in their 30's, each unit increase in burden was associated with being 1.16 times (95%CI 1.04-1.30) more likely to be in the high IL-6 group.

No other significant effects were observed for other variables indicating psychological distress on IL-6 or IL-1ra group membership after controlling for covariates through regression analyses.

Discussion

Given the link between the distress of providing care and physical health [28], this study first sought to examine patterns of IL-1ra and IL-6 in neuro-oncology caregivers over time, from the onset of the stressor (diagnosis) through 12-months after diagnosis. For both cytokines, two distinct groups of caregivers were identified, those with persistently low and those with persistently high cytokine levels. Our previous work has shown that some aspects of psychological distress (depressive symptoms in particular) are also relatively unchanged over the year following diagnosis [29]. The stable nature of both caregivers' psychological and physical responses (e.g., no change in cytokine level over time) may suggest that the distress of providing care neither increases nor decreases over the disease trajectory (which may indicate poor physiologic adaptation). Other possible explanations for the lack of change in cytokine levels over time is that pre-study levels simply continued after diagnosis or that cytokine levels are primarily driven by factors not associated with caregiving (e.g. age, comorbid conditions).

Mean IL-1ra level of 576pg/ml for those in the high group exceeded the normal range of 100-400pg/ml, yet were lower than those reported in patients who have already been diagnosed with inflammatory diseases, e.g. rheumatoid arthritis (~2,500pg/ml) or sepsis (~5,000 to 10,000pg/ml) [30]. Because it can take years for chronic systemic inflammation to manifest as clinical disease, extremely high levels were not anticipated in this study. In a prospective cohort study, Cartensen et al. [31] reported significantly increased IL-1ra levels among persons who developed Type 2 diabetes at least six years prior to being diagnosed. The mean IL-1ra level detected six years prior to diagnosis in their sample was 100-200pg/ml lower than the mean in this sample. These results suggest that increased levels of IL-1ra may occur long before the diagnosis of a disease; levels seen in this sample may be similarly setting the stage for future development of disease processes.

Caregivers in the high IL-6 group (over one-half of the sample) reported a significantly higher mean level of IL-6 compared to those in the low group (2.30pg/ml versus 0.90pg/ml); both means are considered within the normal range of 0-7pg/ml [32]. Similar to IL-1ra, several studies of persons with active immune related diseases report IL-6 levels that are higher than the levels found in our 'high' group. Stone et al. reported levels of 20pg/ml in persons with immune restoration disease [33] and levels of 84pg/ml have been reported in persons with severe rheumatoid arthritis [34]. Although the sample mean of IL-6 was not above the 'normal' level, the statistical significance and amount of difference between the high and low groups warrants consideration. Data underscore that increases in IL-6 can be

detected years prior to the diagnosis of a chronic condition [35]. A prospective cohort study of men who suffered a myocardial infarction found IL-6 levels approximately 0.50pg/ml higher than men who did not have an infarction. Longer epidemiologic studies are necessary to predict the course from high, sustained IL-6 and IL-1ra and the diagnosis of a disease.

The second aim of the study was to determine whether commonly reported indices of caregiver distress (depressive symptoms, anxiety, and three constructs of caregiver burden) predicted cytokine levels. An interaction revealed that for men, anxiety was associated with an increased risk of being in the high IL-1ra group. Anxiety did not influence IL-1ra group membership in women. Meta-analyses have suggested that women have higher levels of IL-1ra [36], in part due to a gene polymorphism [37] and in part due to a higher stress response [38]. This is supported by the findings of this study in that women were significantly more likely to be in the high IL-1ra group.

There was also a significant interaction between BMI and burden related to disruptions in caregivers' schedules from providing care. Caregivers with a BMI less than 25 were less likely to be in the high IL-1ra group when they had schedule disruptions. Conversely, those with a high BMI and schedule disruptions were more likely to be in the high IL-1ra group. Especially with regard to BMI this is not unexpected, as high levels of IL-1 have consistently been related to being overweight [39]. Our data suggest that caregivers with a healthy BMI may be more likely to reach physical adaptation to stress in response to a changing and more demanding schedule.

Consistent with previous reports [40;41], caregivers with a high BMI and older caregivers were more likely to be in the high IL-6 group. Interestingly, caregivers' level of depressive symptoms did not affect IL-6 group membership. The mean IL-6 level of the high trajectory group in this sample (2.30 pg/ml) was well below levels reported in other studies with persons who have high levels of depressive symptoms (14.8pg/ml) [42] and those with posttraumatic stress disorders (65-75pg/ml) [32]. The relationship between depressive symptoms and IL-6 levels appears to be controversial; others have failed to find significant relationships between the two variables [40;43]. Clark and colleagues reported a significant relationship between burden and IL-6 and between burden and depressive symptoms in caregivers of older adults, but not between IL-6 and depressive symptoms [44]. One of the reasons for a lack of association between depressive symptoms and IL-6 in this sample may be the process by which depression develops. Our data from both neuro-oncology caregivers [29] and other cancer caregivers [45] suggests that depression is a long-term outcome of the unrelieved distress of providing care. This indicates that constructs of caregiver burden may be immediate psychological reactions to the distress of providing care, while depression occurs as a result of not being able to adapt to these stressors over time. A high BMI may intensify this relationship, as measures of adiposity have been associated with sensitization of IL-6 responses to repeated acute stress, and less efficient habituation to stress [46].

Finally, there was a relationship between lower self-esteem from providing care and IL-6 group in younger caregivers. Older caregivers may perceive assuming the responsibilities of providing care less negatively than younger caregivers. Another potential explanation for these findings is in the role of self-efficacy in providing care. Mausbach et al. found that in

caregivers with low self-efficacy, those who reported higher levels of caregiver burden were likely to have higher IL-6 levels [47]. In caregivers who reported higher levels of self-efficacy, there was no significant relationship between caregiver burden and IL-6 levels. Caregiver self-efficacy may be higher in older persons making age a proxy for self-efficacy in our analysis.

The limitations to this study include the following. Caregiver blood was not always possible to be drawn within three hours of original blood draw due to caregivers' desired time for data collection, and potential differences in cytokine levels due to circadian rhythm were not explored. Due to the increased likelihood of PBTs in Caucasians, the role of ethnicity in cytokine levels could not be explored. Only levels of circulating cytokines were examined, which does not account for whether cytokines are able to mount an effective response to disease. Furthermore, all grades of astrocytoma tumor patients were included in our study sample, which might influence the level of distress experienced by the caregivers. Finally, we could only use data of those participants who completed two time points, as missing data was determined to be at random, and subgroups identified were relatively small despite our decent sample size. This could limit the generalizability of our findings.

In summary, the data from this analysis are among the first to examine potential systemic inflammation in family caregivers of persons with cancer, particularly PBTs, and the role that psychological distress may play in resulting systemic inflammation. Although depressive symptoms were not associated with IL-1ra and IL-6 levels as has been shown in caregivers of persons with AD, higher levels of several constructs of caregiver burden were associated with risk for having higher levels of pro-inflammatory cytokines. This study also provides evidence that the negative effect of caregiver burden is higher among younger caregivers and obese caregivers. In addition, anxiety is a risk factor for higher levels of inflammation among male caregivers.

Overall, the data demonstrate the complexity in the relationships between measures of psychological distress and cytokine levels. This level of complexity, although time and resource intensive, is requisite to designing personalized interventions. E.g., when evaluating men's risk for high circulating cytokines, only men with higher levels of anxiety may need intervention, rather than a one-size-fits-all intervention approach. Therefore, understanding mechanisms through which the distress of providing care puts caregivers at risk for chronic inflammatory conditions is vital. More research into inflammatory cytokines in neuro-oncology caregivers is needed to further specify vulnerable subgroups of caregivers, identify additional biomarkers of emotional distress, explore the impact of increased cytokines on overall health in this population, and investigate the impact of caregiver interventions on cytokine levels. Maintaining good physical health in family caregivers is essential, as their wellbeing has the potential to influence institutionalization rates for patients, affect the quality of care delivered in the home, and affect the burden placed on an already strained healthcare system.

Acknowledgments

Funding: National Institutes of Health, National Cancer Institute (R01CA117811).

References

1. Coughlin J. Estimating the impact of caregiving and employment on well-being. *Outcomes & Insights in Health Management*. 2011; 2:1–7.
2. Schulz R, Beach S. Caregiving as a risk factor for mortality: the Caregiver Health Effects Study. *Journal of the American Medical Association*. 1999; 282:2215–9. [PubMed: 10605972]
3. Fredman L, Cauley J, Hochberg M, Ensrud K, Doros G. Mortality associated with caregiving, general stress, and caregiving-related stress in elderly women: results of caregiver-study of osteoporotic fractures. *Journal of the American Geriatrics Society*. 2010; 58:937–43. [PubMed: 20374395]
4. Brown S, Smith D, Schulz R, Kabeto M, Ubel P, Poulin M, Yin J, Kim C, Lange K. Caregiving behavior is associated with decreased mortality risk. *Psychological Science*. 2009; 20:488–94. [PubMed: 19320860]
5. Gouin J, Hantsoo L, Kiecolt-Glaser J. Immune dysregulation and chronic stress among older adults: a review. *Neuroimmunomodulation*. 2008; 15:251–9. [PubMed: 19047802]
6. Gouin J, Glaser R, Malarkey W, Beversdorf D, Kiecolt-Glaser J. Chronic stress, daily stressors, and circulating inflammatory markers. *Health Psychology*. 2012; 31:264–8. [PubMed: 21928900]
7. Roepke S, Chattillion E, von Kanel R, Allison M, Ziegler M, Dimsdale J, Mills P, Patterson T, Ancoli-Israel S, Calleran S, Harmell A, Grant I. Carotid plaque in Alzheimer caregivers and the role of sympathoadrenal arousal. *Psychosomatic Medicine*. 2011; 73:206–13. [PubMed: 21217096]
8. von Kanel R, Mausbach B, Patterson T, Dimsdale J, Aschbacher K, Mills P, Ziegler M, Ancoli-Israel S, Grant I. Increased Framingham Coronary Heart Disease Score in dementia caregivers relative to non-caregiving controls. *Gerontology*. 2008; 54:131–7. [PubMed: 18204247]
9. Pinquart M, Sorensen S. Correlates of physical health of informal caregivers: a meta-analysis. *J Gerontol B Psychol Sci Soc Sci*. 2007; 62:126–37.
10. Kiecolt-Glaser J, Glaser R, Shuttlesworth E, Dyer C, Ogrocki P, Speicher C. Chronic stress and immunity in family caregivers of Alzheimer's disease victims. *Psychosomatic Medicine*. 1987; 49:523–35. [PubMed: 3671639]
11. von Kanel R, Dimsdale J, Ancoli-Israel S, Mills P, Patterson T, McKibbin C, Archuleta C, Grant I. Poor sleep is associated with higher plasma proinflammatory cytokine interleukin-6 and procoagulant marker fibrin D-dimer in older caregivers of people with Alzheimer's disease. *Journal of the American Geriatrics Society*. 2006; 54:431–7. [PubMed: 16551309]
12. Lengacher C, Kip K, Barta M, Post-White J, Jacobsen P, Groer M, Lehman B, Moscoso M, Kadel R, Le N, Loftus L, Stevens C, Malafa M, Shelton M. A pilot study evaluating the effect of mindfulness-based stress reduction on psychological status, physical status, salivary cortisol, and interleukin-6 among advanced-stage cancer patients and their caregivers. *Journal of Holistic Nursing*. 2012; 30:170–85. [PubMed: 22442202]
13. Dunn L, Aouizerat B, Langford D, Cooper B, Dhruva A, Cataldo J, Baggott C, Merriman J, Dodd M, West C, Paul S, Miaskowski C. Cytokine gene variation is associated with depressive symptom trajectories in oncology patients and family caregivers. *European Journal of Oncology Nursing*. 2013; 17:346–53. [PubMed: 23187335]
14. Miller G, Murphy M, Cashman R, Ma R, Ma J, Arevalo J, Kobor M, Cole S. Greater inflammatory activity and blunted glucocorticoid signaling in monocytes of chronically stressed caregivers. *Brain, Behavior, and Immunity*. 2014; 41:191–9.
15. Radloff L. The CES-D Scale: A self-report depression scale for research in the general population. *Applied Psychological Measurement*. 1977; 1:385–401.
16. Andresen E, Malmgren J, Carter W, Patrick D. Screening for depression in well older adults: evaluation of a short form of the CES-D (Center for Epidemiologic Studies Depression Scale). *American Journal of Preventive Medicine*. 1994; 10:77–84. [PubMed: 8037935]
17. Usala P, Hertzog C. Measurement of affective states in adult: Evaluation of an adjective rating scale instrument. *Research on Aging*. 1989; 11:403–26. [PubMed: 2623354]
18. Given C, Given B, Stommel M, Collins C, King S, Franklin S. The caregiver reaction assessment (CRA) for caregivers to persons with chronic physical and mental impairments. *Research in Nursing & Health*. 1992; 15:271–83. [PubMed: 1386680]

19. Stommel M, Wang S, Given C, Given B. Confirmatory factor analysis (CFA) as a method to assess measurement equivalence. *Research in Nursing & Health*. 1992; 15:399–405. [PubMed: 1529124]
20. Milaneschi Y, Corsi A, Penninx B, Guralnik J, Ferrucci L. Interleukin-1 receptor antagonist and incident depressive symptoms over 6 years in older persons: the InCHIANTI study. *Biological psychiatry*. 2009; 65:973–8. [PubMed: 19111279]
21. Arend W. The balance between IL-1 and IL-1Ra in disease. *Cytokine & Growth Factor Reviews*. 2002; 13:323–40. [PubMed: 12220547]
22. Schwarz G. Estimating the dimension of a model. *the Annals of Statistics*. 1978; 6:461–4.
23. Miller A, Ancoli-Israel S, Bower J, Capuron L, Irwin M. Neuroendocrine-immune mechanisms of behavioral comorbidities in patients with cancer. *Journal of Clinical Oncology*. 2008; 26:971–82. [PubMed: 18281672]
24. Kiecolt-Glaser J, Gouin J, Hantsoo L. Close relationships, inflammation, and health. *Neuroscience & Biobehavioral Reviews*. 2010; 35:33–8. [PubMed: 19751761]
25. Eccles R. Understanding the symptoms of the common cold and influenza. *the Lancet Infectious Diseases*. 2005; 5:718–25. [PubMed: 16253889]
26. O'Connor M, Bower J, Cho H, Creswell J, Dimitrov S, Hamby M, Hoyt M, Martin J, Robles T, Sloan E, Thomas K, Irwin M. To assess, to control, to exclude: Effects of biobehavioral factors on circulating inflammatory markers. *Brain, Behavior, and Immunity*. 2009; 23:887–97.
27. Initiative, NHLBI Obesity Education. [Accessed 21 Oktober 2015] Obesity education initiative: clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults. 2010. http://web.archive.library.unt.edu/eot2008/20080916210618/http://hp2010nhlbihin.net/oei_ss/download/pdf/CORESET1.pdf
28. Moore R, Chattillion E, Ceglowski J, Ho J, von Kanel R, Mills P, Ziegler M, Patterson T, Grant I, Mausbach B. A randomized clinical trial of Behavioral Activation (BA) therapy for improving psychological and physical health in dementia caregivers: results of the Pleasant Events Program (PEP). *Behavior Research and Therapy*. 2013; 51:623–32.
29. Choi C, Stone R, Kim K, Ren D, Schulz R, Given C, Given B, Sherwood P. Group-based trajectory modeling of caregiver psychological distress over time. *Annals of Behavioral Medicine*. 2012; 44:73–84. [PubMed: 22585179]
30. Meier C, Bobbioni E, Gabay C, Assimacopoulos-Jeanet J, Golay A, Dayer J. IL-1 receptor antagonist serum levels are increased in human obesity: a possible link to the resistance to leptin? *the Journal of Clinical Endocrinology & Metabolism*. 2002; 87:1184–8. [PubMed: 11889184]
31. Carstensen M, Herder C, Kivimaki M, Jokela M, Roden M, Shipley M, Witte D, Brunner E, Tabak A. Accelerated increase in serum interleukin-1 receptor antagonist starts 6 years before diagnosis of type 2 diabetes: Whitehall II prospective cohort study. *Diabetes*. 2010; 59:1222–7. [PubMed: 20185814]
32. Maes M, Lin A, Delmeire L, van Gastel A, Kenis G, de Jongh R, Bosmans E. Elevated serum interleukin-6 (IL6) and IL-6 receptor concentrations in posttraumatic stress disorder following accidental man-made traumatic events. *Biological Psychiatry*. 1999; 45:833–9. [PubMed: 10202570]
33. Stone S, Price P, Keane N, Murray R, French M. Levels of IL-6 and soluble IL-6 receptor are increased in HIV patients with a history of immune restoration disease after HAART. *HIV Medicine*. 2002; 3:21–7. [PubMed: 12059947]
34. Robak T, Gladalska A, Stepień H, Robak R. Serum levels of interleukin-6 type cytokines and soluble interleukin-6 receptor in patients with rheumatoid arthritis. *Mediators of Inflammation*. 1998; 7:347–53. [PubMed: 9883970]
35. Ridker P, Rifai N, Stampfer M, Hennekens C. Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men. *Circulation*. 2000; 101:1767–72. [PubMed: 10769275]
36. Steptoe A, Hamer M, Chida Y. The effects of acute psychological stress on circulating inflammatory factors in humans: a review and meta-analysis. *Brain, Behavior, and Immunity*. 2007; 21:901–12.

37. Bessler H, Osovsky M, Beilin B, Alcalay Y, Sirota L. The existence of gender difference in IL-1 Ra gene polymorphism. *Journal of Interferon & Cytokine Research*. 2007; 27:931–5. [PubMed: 18052726]
38. Waschul B, Herforth A, Stiller-Winkler R, Idel H, Granrath N, Deinzer R. Effects of plaque, psychological stress and gender on crevicular IL-1 beta and IL-1ra secretion. *Journal of Clinical Periodontology*. 2003; 30:238–48. [PubMed: 12631182]
39. Elangovan S, Brogden K, Dawson D, Blanchette D, Pagan-Rivera K, Stanford C, Johnson G, Recker E, Bowers R, Haynes W, Avila-Ortiz G. Body fat indices and biomarkers of inflammation: a cross-sectional study with implications for obesity and peri-implant oral health. *the International Journal of Oral & Maxillofacial Implants*. 2014; 29:1429–34. [PubMed: 25397806]
40. Milaneschi Y, Corsi A, Penninx B, Bandinelli S, Guralnik J, Ferrucci L. Interleukin-1 receptor antagonist and incident depressive symptoms over 6 years in older persons: the InCHIANTI study. *Biological Psychiatry*. 2009; 65:973–8. [PubMed: 19111279]
41. von Kanel R, Dimsdale J, Mills P, Ancoli-Israel S, Patterson T, Mausbach B, Grant I. Effect of Alzheimer caregiving stress and age on frailty markers interleukin-6, C-reactive protein, and D-dimer. *J Gerontol B Psychol Sci Soc Sci*. 2006; 61:963–9.
42. Jehn C, Kuehnhardt D, Bartholomae A, Pfeiffer S, Krebs M, Regierer A, Schmid P, Possinger K, Flath B. Biomarkers of depression in cancer patients. *Cancer*. 2006; 107:2723–9. [PubMed: 17036362]
43. von Kanel R, Mausbach B, Mills P, Dimsdale J, Patterson T, Ancoli-Israel S, Ziegler M, Allison M, Chattillion E, Grant I. Longitudinal relationship of low leisure satisfaction but not depressive symptoms with systemic low-grade inflammation in dementia caregivers. *J Gerontol B Psychol Sci Soc Sci*. 2013 gbt020.
44. Clark M, Nicholas J, Wassira L, Gutierrez A. Psychosocial and biological indicators of depression in the caregiving population. *Biological Research for Nursing*. 2013; 15:112–21. [PubMed: 21765116]
45. Sherwood P, Given C, Given B, von Eye A. Caregiver burden and depressive symptoms: analysis of common outcomes in caregivers of elderly patients. *Journal of Aging and Health*. 2005; 17:125–47. [PubMed: 15750048]
46. McInnis C, Thoma M, Gianferante D, Hanlin L, Chen X, Breines J, Hong S, Rohleder N. Measures of adiposity predict interleukin-6 responses to repeated psychosocial stress. *Brain, Behavior, and Immunity*. 2014; 42:33–40.
47. Mausbach B, von Kanel R, Roepke S, Moore R, Patterson T, Mills P, Dimsdale J, Ziegler M, Ancoli-Israel S, Allison M, Grant I. Self-efficacy buffers the relationship between dementia caregiving stress and circulating concentrations of the proinflammatory cytokine interleukin-6. *the American Journal of Geriatric Psychiatry*. 2011; 19:64–71. [PubMed: 20808097]
48. Maes M, et al. Increased serum interleukin-1 receptor antagonist concentrations in major depression. *Journal of Affective Disorders*. 1995; 36(1-2):29–36. [PubMed: 8988262]
49. Alesci S, et al. Major depression is associated with significant diurnal elevations in plasma interleukin-6 levels, a shift of its circadian rhythm, and loss of physiological complexity in its secretion. *Journal of Clinical Endocrinological Metabolism*. 2005; 90(5):2522–2530.
50. Kiecolt-Glaser JK, et al. Chronic stress alters the immune response to influenza virus vaccine in older adults. *Proceedings of the National Academy of Sciences of the United States of America*. 1996; 93(7):3043–7. [PubMed: 8610165]
51. Mills PJ, et al. Plasma catecholamine and lymphocyte beta 2-adrenergic receptor alterations in elderly Alzheimer caregivers under stress. *Psychosomatic Medicine*. 1997; 59(3):251–6. [PubMed: 9178336]
52. Kiecolt-Glaser JK, Glaser R. Psychological stress and wound healing. *Advances in Mind-Body Medicine*. 1995; 17(1):15–6.
53. Kiecolt-Glaser J, et al. Chronic stress alters the immune response to influenza virus vaccine in older adults. *Proceedings of the National Academy of Sciences of the United States of America*. 1996; 93(7):3043–3047. [PubMed: 8610165]

54. Kiecolt-Glaser JK, et al. Chronic stress and age-related increases in the proinflammatory cytokine IL-6. *Proceedings of the National Academy of Sciences of the United States of America*. 2003; 100(15):9090–5. [PubMed: 12840146]
55. Lutgendorf SK, et al. Life stress, mood disturbance, and elevated interleukin-6 in healthy older women. *Journals of Gerontology Series A-Biological Sciences and Medical Sciences*. 1999; 54(9):M434–9.

Fig 1. Trajectories of log transformed IL-1ra levels in 108 neuro-oncology caregivers

Fig 2. Trajectories of log transformed IL-6 levels in 108 neuro-oncology caregivers

Fig 3. Odds ratios with 95% Wald confidence limits for significant two-way interactions; Panel a - effect of anxiety by gender on IL-1ra group membership, Panel b - effect of burden due to disruptions in schedule by body mass index on IL-1ra, Panel c - effect of burden due to self-esteem by age on IL-6

Table 1

Socio-demographic and clinical characteristics at baseline, N=108.

Variable	Frequency	Association with IL-1ra *	Association with IL-6 *
Caregiver gender: Female	68%	p=0.08	p=0.24
Caregiver relationship to patient:			
Spouse	75%	p=0.52	p=0.39
Adult child	8%		
Other	17%		
Caregiver currently diagnosed with:			
Hypertension	34%	p=0.02	p=0.09
Diabetes	11%	p=0.08	p=0.11
Cancer	10%	p=0.74	p=0.05
Coronary artery disease	14%	p=0.68	p=0.29
Arthritis	16%	p=0.28	
Recent cold or fever	20%	p=0.10	p=0.10
Caregiver medications:			
Hormone therapy	13%	p=0.34	p=0.58
Diabetic medication	11%		
Anti-hypertension	25%		
Non-steroidal Anti-Inflammatory	22%	p=0.43	p=0.20
Patient tumor type:			
Glioblastoma Multiforme	56%	p=0.67	p=0.48
Astrocytoma Grade I-III	19%		
Other	25%		
Variable	Mean (SD)	Association with IL-1ra *	Association with IL-6 *
Caregiver age	51.73 (11.27)	p=0.05	p<0.01
Caregiver body mass index	27.56 (6.09)	p<0.01	p<0.01
Caregiver baseline CES-D score	9.47 (6.63)	p=0.55	p=0.40
Caregiver baseline POMS score	9.02 (2.84)	p=0.36	p=0.53
Caregiver baseline Burden-SE score	30.31 (3.97)	p=0.22	p=0.92
Caregiver baseline Burden-Aban score	8.28 (3.90)	p=0.41	p=0.78
Caregiver baseline Burden-Sched score	15.16 (4.73)	p=0.46	p=0.86
Raw IL-1ra values, Group 1 (Range 74.22 to 1675.68; Median=227.83)	252.80 (SD=94.91)	N/A	N/A

Variable	Frequency	Association with IL-1ra *	Association with IL-6 *
Raw IL-1ra values, Group 2 (Range 126.71 to 2778.96; Median=461.56)	575.91 (252.65)	N/A	N/A
Raw IL-6 values, Group 1 (Range 0.22 to 4.03; Median=0.81)	0.90 (0.35)	N/A	N/A
Raw IL-6 values, Group 2 (Range 0.29 to 17.65; Median=1.85)	2.30 (1.96)	N/A	N/A

* Results from exploratory univariate logistic regression analysis used to determine the variable's inclusion as a covariate in multiple logistic regression models

Table 2

Sociodemographic and clinical characteristics of high and low IL-1ra and IL-6 groups.

Variable	Low IL-1ra	High IL-1ra	Low IL-6	High IL-6
Gender				
Female	76%	24%	47%	53%
Male	59%	41%	35%	65%
Age	M=50.01 (SD=11.23)	M=54.89 (SD=10.79)	M=46.90 (SD=11.88)	M=54.83 (SD=9.75)
BMI	M=25.71 (SD=5.03)	M=31.20 (SD=6.41)	M=25.31 (SD=4.18)	M=29.02 (SD=6.69)
CES-D	M=9.06 (SD=6.32)	M=10.22 (SD=7.21)	M=9.85 (SD=5.99)	M=9.22 (SD=7.05)
POMS	M=8.96 (SD=2.95)	M=9.15 (SD=3.32)	M=9.36 (SD=3.26)	M=8.78 (SD=2.94)
Burden-SE	M=30.84 (SD=3.57)	M=29.18 (SD=4.64)	M=30.32 (SD=4.08)	M=30.31 (SD=3.95)
Burden-Aban score	M=7.95 (SD=3.60)	M=9.00 (SD=4.51)	M=8.28 (SD=4.25)	M=8.28 (SD=3.64)
Burden-Schedule	M=14.99 (SD=4.61)	M=15.50 (SD=5.03)	M=15.03 (SD=5.06)	M=15.24 (SD=4.56)

Table 3

Logistic regression models of the effects of markers of psychological distress on belonging to a high or low cytokine group.

The impact of anxiety and confounding variables on IL-1ra high or low group			
Variable	Estimate	SE	p-value
Body mass index	0.16	0.05	<0.01
Recent cold or fever (yes/no)	1.19	0.71	0.09
Age	0.07	0.03	0.02
Gender	-6.46	2.79	0.02
Anxiety	-0.01	0.12	0.94
Anxiety by gender interaction	0.55	0.28	0.05
The impact of burden related to schedule and confounding variables on IL-1ra high or low group			
Variable	Estimate	SE	p-value
Recent cold or fever (yes/no)	1.36	0.80	0.09
Age	0.04	0.27	0.11
Gender	-1.23	0.73	0.09
Body mass index	-0.28	0.16	0.07
Burden related to schedule	-0.99	0.37	<0.01
Burden related to schedule by body mass index interaction	0.03	0.01	<0.01
The impact of burden related to self-esteem and confounding variables on IL-6 high or low group			
Variable	Estimate	SE	p-value
Body mass index	0.15	0.06	<.01
Diagnosis of arthritis (yes/no)	2.02	1.12	0.09
Recent cold or fever (yes/no)	-0.84	0.81	0.30
Gender	-0.44	0.67	0.51
Age	0.74	0.32	0.02
Burden related to self-esteem	1.17	0.52	0.03
Burden related to self-esteem by age	-0.02	0.01	0.03

Note. All potential covariates were explored in each logistic model, only significant and final models are shown.