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The Relationship Between Circulating Interleukin-6 Levels and Future Health Service Use in Dementia Caregivers

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Abstract

Objective: Older adults are among the most frequent users of emergency departments (EDs). Non-specific symptoms such as fatigue and widespread pain are among the most common symptoms in patients admitted at the ED. Interleukin-6 (IL-6) is an inflammatory biomarker associated with chronic stress (i.e., dementia caregiving) and non-specific symptoms. This study aimed to determine if IL-6 was prospectively associated with ED risk in dementia caregivers.

Methods: Participants were 85 dementia caregivers (CGs), who reported during 3 assessments (3, 9, and 15 months post-enrollment) if they had visited an ED for any reason. Cox proportional hazards models were used to examine the relations between resting circulating levels of IL-6 obtained at enrollment and subsequent risk for an ED visit, adjusting for age, sex, use of ED one month prior to enrollment, physical and mental health well-being, body mass index (BMI) and CG demands.

Results: (log) IL-6 significantly predicted ED visits during the 15-month follow-up (B = 1.96, SE = 0.82, p = .017). For every (log) pg/ml increase in IL-6, the risk of visiting an ED was 7.10 times greater. Exploratory analyses suggested that caregivers with levels of IL-6 above the 80th percentile and experiencing high CG demands, were at highest risk of an ED visit.

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Conclusions: IL-6 levels and CG demands may be useful for predicting vulnerability for future ED visits. Although further studies should be conducted to replicate and extend these findings, interventions that successfully modify inflammatory markers, including the underlying pathophysiology related to stress and/or comorbid illnesses, may be useful in preventing costly and detrimental outcomes in this population.

Keywords

Emergency Department; stress; healthcare use; inflammation; biomarkers; older adults

Introduction

Caring for a loved one with dementia has been shown to increase risk for hypertension (1), cardiovascular diseases (2), and immune system dysfunction (3–5). Further, the intensity of demands within caregiver populations has been shown to increase health risks, such that caregivers with higher demands and mental health vulnerabilities are at greater health risk (2, 6). Caregivers have been shown to have greater levels of stress and depression; and lower levels of subjective well-being, physical health, and self-efficacy compared to non-caregivers (7). Caring for a family member with dementia is particularly stressful and burdensome. Dementia caregivers spend more hours per week providing care and assisting with more activities of daily living (ADL) and instrumental activities of daily living (IADL) relative to nondementia caregivers (8). Dementia caregivers have also reported higher emotional and physical strain, as well as financial hardship compared to nondementia caregivers, with dementia status of the care recipient being a significant predictor of all three (8)(Ory et al., 1999). Chronic stress experienced by dementia caregiving has been associated with impaired immune function (9). For instance, dementia caregivers had worse immune response to influenza virus vaccination than matched non-caregiver control participants (4). Additionally, women caring for a family member with dementia showed slower wound healing compared to controls (5). In another study, spousal dementia caregivers experiencing chronic stress had reduced lymphocyte sensitivity to glucocorticoids and increased salivary cortisol compared to non-caregivers (10). And spousal dementia caregivers have demonstrated higher levels of plasma IL-6 and D-Dimer relative to non-caregiver controls (11). These stresses of caregiving, and in particular the health consequences that result, have the potential to place caregivers at elevated risk for increased healthcare utilization such as emergency department visits.

In 2014, Americans made 137.8 million visits to emergency departments, an increase of 14.8% since 2006 (12). The rate of emergency department visits was highest among individuals aged 65 years of age and older, at 538.3 visits per 1,000 population (12). In 2016, the average cost of an emergency department visit was $1,917, and emergency department visits accounted for 23% of all outpatient medical expenditures; second only to outpatient surgeries (13). Non-specific symptoms (14) rank among the top reasons for emergency department visits in all age groups. These symptoms include chest pain, abdominal and back pain, shortness of breath, and weakness (12, 15). As the origin of these symptoms is difficult to determine, prediction of who will make emergency department visits becomes challenging, as does treatment.

Recent evidence suggests that acute somatic experiences such as pain (16), fatigue (17), aches and pains, and muscular tension (18) are associated with increases in inflammatory biomarkers, including Interleukin-6 (IL-6). IL-6 is a glycoprotein produced by a variety of lymphoid and nonlymphoid cells (19) and is easily determined by standardized assays. IL-6 is involved as a pro-inflammatory cytokine in the acute phase response to activating stimuli such as infection or tissue injury (20). During the acute phase response, IL-6 can induce other acute phase proteins such as fibrinogen, serum amyloid A, and C-reactive protein (21). It also plays a role in the activation of the HPA-axis and regulation of hematopoiesis (19). Indeed, acute psychological stress is known to produce a transient rise in peripheral cytokines (22–24), including IL-6 (25). Further, chronic stress such as experienced by dementia caregivers, is associated with elevated IL-6 concentrations (26–28).

Several studies demonstrate that IL-6 contributes to nociceptor and central sensitization (29–31), and IL-6 levels increase following nerve injury (32, 33). In individuals with lumbar radicular pain, higher serum IL-6 levels were associated with higher visual analogue scale scores for low back pain and leg pain (34). Other research demonstrates that elevations in IL-6 are associated with "sickness behaviors," including complaints of headache, tired muscles, excessive fatigue, and self-reported fever (35). Therefore, we postulated that elevations in IL-6 might be a biomarker associated with symptoms driving visits to the emergency department.

In addition to explaining non-specific symptoms, elevations in IL-6 levels have been implicated in risk for various health conditions and diseases (19) that may prompt emergency department visits. For example, elevated levels of IL-6 have been associated with future risk for stroke occurrence (36, 37) as well as risk for other cardiovascular events such as acute myocardial infarction (AMI), coronary heart disease (CHD) and congestive heart failure (CHF) events (37). IL-6 is a significant predictor of all-cause and cardiovascular mortality (38). Higher circulating IL-6 levels have also been shown to predict disability onset among older adults (39), and among patients with community acquired pneumonia (CAP), elevated IL-6 levels are associated with mortality risk (40).

Given the association of IL-6 levels with illness symptoms and diseases potentially associated with emergency department visits, we sought to examine if IL-6 is a useful prognostic indicator of emergency department visits in a chronically stressed population of dementia caregivers. We hypothesized that among dementia caregivers, IL-6 would be prospectively associated with 15-month emergency department visit risk.

Methods

Participants

Participants were 85 dementia caregivers enrolled in the University of California San Diego (UC San Diego) Alzheimer's Caregiver Study; a clinical trial evaluating the effects of psychosocial treatments on psychosocial and cardiovascular disease (CVD) risk outcomes in caregivers. Our lab has previously investigated psychological and biological mechanisms of CVD in caregivers, including a clinical trial examining CVD risk (41). However, all

participants in this study were new to our research and had not participated in any of our previous studies of caregivers.

To be eligible, participants were required to be at least 55 years of age, providing at least 20 hours/week of in-home care to a spouse with a physician diagnosis of dementia, and endorse at least mild depressive symptoms (i.e., mild level of distress) as per a score of 5 on the Patient Health Questionnaire-9 (PHQ-9)(42) at the time of enrollment. Caregivers were excluded if: a) either they or their care receivers were diagnosed with a terminal illness with a life expectancy of less than one year, b) they lacked capacity to consent to the research project, c) they were enrolled in another formal intervention study or were receiving psychotherapy to improve well-being or reduce distress, d) they had blood pressure greater than 200/120 mm Hg (i.e., severe hypertension), or e) they received a diagnosis of cancer, heart failure, myocardial infarction, or stroke in the 12-months prior to enrollment in the study.

All participants were recruited through outreach to local community agencies serving older adults and/or caregivers, community health fairs, and through referrals from enrolled participants or dementia-specific agencies such as the UC San Diego Alzheimer's Disease Research Center (ADRC). Participants were enrolled between February 2015 and April 2017, and follow-up data collection was completed for all participants by July, 2018. All caregivers provided informed consent to participating in the study, which was approved by the UC San Diego Institutional Review Board.

Measures

Health Service Use.—The use of emergency medical services and overnight hospitalizations were the key healthcare services assessed in the current study. Participants were asked at intake (baseline), 3-months, 9-months, and 15-months assessments if they had visited an emergency department or urgent care clinic (for themselves, not for their care receivers) or been hospitalized overnight during the previous assessment period (or up to one month prior to the baseline assessment).Because dates of emergency department or hospital visits were not requested, the date of the interview was used as the visit date. Visits to a walk-in clinic were not included as an emergency visit. Participants answering in the affirmative were given a score of '1', and participants who had not used these services were given a score of '0'. The dependent variables in our analyses were either days from baseline to first Emergency Department visit or days to hospitalization.

Interleukin-6 (IL-6).—Blood was collected at the baseline assessment by a research nurse in the caregivers' homes through a 22-gauge forearm catheter after a 20 min rest. We collected blood in EDTA tubes and later centrifuged for 15 minutes at 1732 Relative Centrifugal Force at 4o C. Plasma was stored at −80 C until analyzed. The level of cytokine IL-6 was measured using an electrochemi-luminescence-based multi-array method through the Quickplex SQ 120 system (Meso Scale Diagnostics LLC, Rockville, MD). We utilized the human proinflammatory panel-1 10-plex kits to detect 2 cytokines, IL-6 and Tumor Necrosis Factor alpha (TNF-α). The system utilizes 96-well-based high throughput readout. 50 μl of prepared plasma samples or calibrator were added into the corresponding wells. The

array was then incubated at room temperature with shaking for 2 hours and then washed three times with PBS containing 0.05% Tween 20. Thereafter, 25 μl of detection antibody solution were added with 2 hours of incubation at room temperature. After rinsing, 2× read buffer was added and the signals were detected by a Quickplex SQ 120 system. IL-6 concentrations in the samples were determined with MSD Discovery Workbench (version 4) software, using curve fit mode. Intra- and inter-assay coefficients of variation were <10%.

Caregiver Physical and Mental Well-Being.—Caregiver physical and mental well-being were assessed using the physical composite score (PCS) and mental composite score (MCS) of SF-12 health questionnaire (43). The SF-12 is a global health measure that assesses multiple areas of physical and mental health functioning regardless of age or disease. The PCS was created by summing factor-weighted scores across 4 functioning domains (i.e., physical functioning, role physical, which indicates the impact of physical health symptoms on everyday functioning, bodily pain, and general health), with higher scores representing better physical health. The MCS was created by summing weighted scores across the four domains of vitality, social functioning, role emotional, which indicates the impact of emotional symptoms on everyday functioning, and mental health scales.

Caregiver Demands.—Functional impairment of care receivers was used as an indicator of caregiver demands. Caregivers were administered the Activities of Daily Living Questionnaire (ADLQ) (44), which contains 28 items assessing their care receivers' impairment in six areas encompassing self-care, household, employment, shopping, travel, and communication. All items are scored from 0-3, with higher scores reflecting greater impairment in that area of functioning. The total scale score expresses an individual's percent impairment in performing activities of daily living.

Caregiver demographics and health characteristics.—We collected caregivers' age, sex, and ethnicity/race. All participants were weighed and had height measured by the research nurse for body mass index (BMI) computation.

Statistical Analysis—Cox proportional hazards regression was used to determine the relationship between baseline continuous IL-6 values and prospective Emergency Department visit or hospitalization. Initial (unadjusted) models were used and included only (log) IL-6 as a predictor of outcomes. Subsequent models adjusted for the following demographic and health characteristics: age, sex, use of emergency department (or hospitalization) in the one month prior to enrollment, SF-12 PCS and SF-12 MCS, BMI, and caregiver demands. "Survival" time was the number of days between the baseline interview and the last interview or to the date of first Emergency Department visit/hospitalization. For variables in the model, Hazard Ratios (HRs) were computed as the primary measure of effect, along with their corresponding 95% confidence intervals. All statistical tests were two-sided with significance established at 0.05.

Results

Table 1 reports descriptive statistics for the sample, including all variables used in the cox regression analyses. At baseline, the sample of caregivers ranged in age from 56 to

90 years (M ± SD = 74.20 ± 7.99 years) and was 80% female. The mean length of time for participation was 326.5 days, and only 3.5% participants had made an emergency department visit in the thirty days prior to enrollment. IL-6 demonstrated significant positive skewness and a log transformation was conducted to reduce skew and log-transformed IL-6 was used in all subsequent analyses.

Association of IL-6 with Emergency Department Use.

Because one participant was censored at 72 days, prior to the earliest emergency department visit for the sample, this case was excluded from the cox regression analysis of emergency department use, leaving a total sample size of 85 participants. Of these participants, twelve (14.0%) experienced an emergency department visit during the 15-month follow-up period. Results of our initial (unadjusted) Cox model showed that log IL-6 was significantly associated with emergency department visits (B = 2.53, SE = 0.67, HR = 12.52, HR = 3.36-46.64; $p < .001$). Results of the adjusted model are presented in Table 2. In this analysis, previous emergency department visit (B = 3.06, SE = 1.17, $p = .009$), caregiver demands (B = 0.042, SE = 0.021, $p = .042$), and IL-6 levels (B = 1.96, SE = 0.82, $p = .017$) significantly predicted emergency department visit. The hazard ratio (HR) data suggest that those caregivers who had an emergency department visit one month prior to enrollment (N = 3) were at 21 times the risk of another visit during the follow-up period. For every point increase in caregiver demands caregivers experienced a 4.3% increased risk of an emergency department visit. Finally, each log pg/ml increase in IL-6 was associated with a 7-fold increased risk of an Emergency Department visit.

In the primary analyses, TNF-α was not associated with emergency department visits, and therefore not further examined in the exploratory analyses.

Exploratory Analyses.—We conducted several follow-up analyses. First, we examined the interaction between caregiver demands and IL-6 levels to determine if caregivers at higher levels of IL-6 combined with higher levels of caregiver demands were more likely to utilize emergency departments. Because caregivers with lower relative levels of IL-6 (e.g., 50-60th percentile) were deemed less likely to make use of emergency departments, we sought to determine the value at which IL-6 crossed from "non-significance" to significance. We conducted two analyses in this regard. The first examined the interaction between linear ADLQ scores and log IL-6. Results of this analysis indicated that there was not a significant interaction (B = −0.048, SE = 0.067, Wald = 0.52, df = 1, $p = .471$).

We then also conducted a median split of IL-6, whereby two groups were created at the 50th percentile to denote "high" vs "low" IL-6 values. We then replicated our original Cox Proportional Hazards analysis using this $IL-6_{50}$ variable in the model. If not significant, we continued these analyses by increasing our "high vs low" IL-6 split in 10-percentile increments until IL-6 significantly predicted emergencydepartment visits. Results of these analyses indicated that IL-6 became a significant predictor of emergency department visit at the 80th percentile (B = 1.72, SE = 0.69, Wald = 6.32, df = 1, $p = .012$), corresponding to an IL-6 value of 1.30 pg/ml (see Survival Plot in Figure 1).

Given the independent associations of both caregiver demands and IL-6 with emergency department risk, we conducted follow-up, exploratory analyses examining the combination of these factors for predicting Emergency Department visit. In this analysis, we examined the interaction between linear ADLQ scores and log IL-6. Results of this analysis incdicated no significant interaction between caregiver demansds (ADLQ scores) and IL-6 (B = Then, as mentioned above, we conducted exploratory analyses using the IL-6_{80} variable from the previous analysis to create "high" vs "low" IL-6 groups. We also created "High" vs "Low" demand groups whereby care receiver with mild or moderate ADLQ scores were "Low" demand group, and those with "severe" functional disability were the "High" demand group. Then, we combined these factors to make four groups as follows: a) low demand, low IL-6 (reference group; N = 30)), b) low demand, high IL-6 (N = 7), c) high demand, low IL-6 (N = 39), and d) high demand, high IL-6 (N = 9). We then repeated our original Cox Proportional Hazards model with this variable to predict emergency department visit. Unfortunately, coefficients did not converge for this model. Further exploration of the failure revealed this failure to converge was due to the fact that zero caregivers in our reference group (low demand, low IL-6) experienced an emergency department visit during the 15-month follow-up. Raw data on the number of events per group were as follows: a) low demand, low IL-6 (reference group; N = 0)), b) low demand, high IL-6 (N = 3), c) high demand, low IL-6 (N = 5), and d) high demand, high IL-6 (N = 4). Visual inspection of results showed a pattern of risk as follows: a) lowest risk among individuals with low demand, low IL-6 (100% free of emergency department visit), b) high IL-6, low demand (~88% free of emergency department visit, c) high demand, low IL-6 (approximately 81% free of emergency department visit, and d) high demand, high IL-6 (~43% free of emergency department visit). For graphical depiction of these results, see Figure 2).

Association of IL-6 with Caregiver Hospitalization.

Three participants were censored prior to the earliest hospitalization event for the sample, and were subsequently excluded from the cox regression analyses, leaving a total sample size of 83 participants. Of these, five (5 .8%) experienced a hospitalization during the 15-month follow-up period. Results of our initial (unadjusted) Cox model (B = 1.375; HR = 3.955, 95% CI = 0.268-58.277; p = .316) as well as the adjusted model (B = 0.773, HR = 2.167, 95% CI = 0.115-40.735; p = .605) showed that log IL-6 was not significantly associated with hospitalization. In this model, only female sex was significantly associated with hospitalization, whereby females were less likely to experience hospitalization than males (B = −3.068, HR = 0.047, 95% CI = 0.004-0.589; p = .018).

Discussion

Results of this study support our hypothesis that circulating IL-6 levels significantly predict the risk for emergency department visit in caregivers of those with dementia, independent of potential confounding factors including age, sex, recent emergency department visit, physical and mental well-being, and BMI. These results suggest that IL-6, whether associated with non-specific symptoms or with some disease state, may predict emergency department utilization. Also, caregivers experiencing high demands (i.e., providing care for a care receiver with more severe functional disability) were at significant risk of experiencing

an emergency department visit. In addition, because of our inclusion/exclusion criteria, our sample was relatively healthy and free of chronic illness. Therefore, our results are not restricted only to people experiencing specific diseases, but more broadly relate to healthy individuals as well. Unlike for IL-6, TNF-α did not emerge as a predictor of emergency department visit. Although TNF-α is also a marker of systemic inflammation, one explanation for this discrepancy could be that TNF-α has much less consistently been associated with pre-frailty and frailty in older adults than IL-6 (45). Frailty denotes a state of vulnerability to poor resolution of homeostasis after everyday stressors resulting in a cumulative decline in many physiological systems (46), thereby increasing the risk of emergency department visits (47).

These results are clinically interesting because IL-6 may serve as a predictor of emergency department use in an older adult population, who have the highest utilization rate of these costly outpatient services. Exploratory analyses from this study indicated that IL-6 levels of 1.3 pg/ml were prospectively associated with increased risk of emergency department visit. While we urge caution, this may serve as a preliminary benchmark for clinical use of IL-6 in determining health risk in this population, or as a benchmark for future research studies in determining risk in this and other older adult (non-caregiver) populations. While IL-6 elevations could be due to several causes, valid prediction of who needs greater services could lead to better preventative care and reduce healthcare costs. Furthermore, caregivers facing higher caregiving demands, such as taking care of care receivers with greater functional impairment, may be at even higher risk of emergency department visit. An exploratory analysis examining the interaction between caregiver demands (i.e., ADLQ scores) and IL-y6 was non-significant, suggesting that IL-6 may not exert stronger effects at different levels of caregiver demand. However, this interaction had low statistical power, and future studies with increased power should further examine this potential effect.

Multiple interventions have been shown to help decrease stress-related biomarkers and improve outcomes that often accompany high caregiver demand. For example, a behavioral activation intervention termed the Pleasant Events Program (PEP) significantly reduced IL-6 levels and depressive symptoms among spousal caregivers compared to an Informational-Support control condition (41). Another study found that caregivers receiving a group cognitive-behavioral intervention experienced a significant reduction in daily salivary cortisol secretion compared to those in an educational intervention (48). Likewise, mindfulness-based stress reduction (MBSR) interventions may benefit caregivers by reducing depression, caregiver burden, and increasing quality of life (49), and MBSR has been shown to significantly reduce IL-6 secretion in response to acute stressors (50). In addition to cognitive-behavioral interventions, respite services such as home help and adult day care may help to reduce stress and alleviate caregiver burden (51). Future research should continue to examine the role of stress reduction interventions on inflammatory biomarkers such as IL-6, as well as determine the impact of these interventions on healthcare service use.

This study has several limitations. First, the caregiver population was racially homogenous (80.2% White) and consisted of adults 55 years of age, limiting the generalizability of our study. Second, our study examined the relationship between IL-6 levels at baseline

assessment to 15-month risk of emergency department visit. Greater understanding of emergency department risk may be gained from more frequent collections of IL-6 data. Next, our was limited by a modest sample size and few emergency department and hospital visits. Next, IL-6 levels increase with age and measures are not standardized across laboratories and assessment methods, so cut-offs to identify individuals at risk may be different in younger populations and depend upon the IL-6 assay used (52). These limitations make it necessary to interpret these results as preliminary, and replication of these results in larger and more diverse samples is necessary for adequate decision-making in a clinical context.

Finally, our study focused on spousal dementia caregivers. On the one hand, while the mechanisms by which chronic stresses affect IL-6 may not be unique to dementia caregiving populations, there are unique elements involved in caring for a loved one with dementia. For example, the unique nature of caregiving requires ongoing care that is makes avoidance or escape from the stresses of caregiving a difficult undertaking. The increased reliance of care recipients on their caregivers over time makes respite increasingly difficult to achieve among caregiving populations. Indeed, the term "vulnerable caregiver" has been used to describe caregivers who experience a high degree of demand and low degree of respite (53). Thus, additional research, possibly with other chronic stress populations including military personnel or those experiencing work stress (e.g., firefighters or police), should be conducted to fully understand the nature of these effects. Therefore, our results, particularly regarding the interaction between IL-6 and caregiver demand may not generalize to other populations such as caregivers of patients with other chronic diseases.

To summarize, higher IL-6 levels significantly predicted risk for emergency department visit in dementia caregivers in a 15-month period controlling for confounding factors including age, sex, recent emergency department visit, physical and mental well-being, and BMI. Additionally, care receiver functional disability was also significantly associated with increased risk for emergency department visit. Exploratory analyses showed a possible interaction between these effects whereby individuals with higher levels of IL-6 caring for care receivers with high functional disability appeared to be at the greatest risk for emergency department visit during the follow-up period. Future research should explore whether this relationship holds in samples of other age groups, non-caregiver populations, and determine if early interventions can reduce both IL-6 and emergency department visit risk.

Conflicts of Interest and Source of Funding:

Abbreviations:

IL-6	Interleukin-6
BMI	Body Mass Index

PCS	Physical composite score
MCS	Mental composite score

References

1. Shaw WS, Patterson TL, Ziegler MG, Dimsdale JE, Semple SJ, Grant I. Accelerated risk of hypertensive blood pressure recordings among Alzheimer caregivers. J Psychosom Res. 1999;46:215–27. [PubMed: 10193912]

2. Lee S, Colditz GA, Berkman LF, Kawachi I. Caregiving and risk of coronary heart disease in U.S. women: A prospective study. Am J Prev Med. 2003;24:113–9. [PubMed: 12568816]

3. Kiecolt-Glaser J, Glaser R, Shuttleworth EE, Dyer CS, Ogrocki P, Speicher CE. Chronic stress and immunity in family caregivers of Alzheimer's disease patients. Psychosom Med. 1987;49:523–35. [PubMed: 3671639]

4. Kiecolt-Glaser JK, Glaser R, Gravenstein S, Malarkey WB, Sheridan J. Chronic stress alters the immune response to influenza virus vaccine in older adults. Proc Natl Acad Sci USA. 1996;93:3043–47. [PubMed: 8610165]

5. Kiecolt-Glaser JK, Marucha PT, Malarkey WB, Mercado AM, Glaser R. Slowing of wound healing by psychological stress. Lancet. 1995;346:1194–6. [PubMed: 7475659]

6. Mausbach BT, Patterson TL, Rabinowitz YG, Grant I, Schulz R. Depression and distress predict time to cardiovascular disease in dementia caregivers. Health Psychol. 2007;26:539–44. [PubMed: 17845105]

7. Pinquart M, Sorensen S. Differences between caregivers and noncaregivers in psychological health and physical health: A meta-analysis. Psychol Aging. 2003;18:250–67. [PubMed: 12825775]

8. Ory MG, Hoffman RR 3rd, Yee JL, Tennstedt S, Schulz R. Prevalence and impact of caregiving: A detailed comparison between dementia and nondementia caregivers. Gerontologist. 1999;39:177–85. [PubMed: 10224714]

9. Gouin S, Chevalier I, Gauthier M, Lamarre V. Prospective evaluation of the management of moderate to severe cellulitis with parenteral antibiotics at a paediatric day treatment centre. J Paediatr Child Health. 2008;44:214–8. [PubMed: 17944880]

10. Bauer ME, Vedhara K, Perks P, Wilcock GK, Lightman SL, Shanks N. Chronic stress in caregivers of dementia patients is associated with reduced lymphocyte sensitivity to glucocorticoids. J Neuroimmunol 2000;103:84–92. [PubMed: 10674993]

11. von Känel R, Dimsdale JE, Mills PJ, Ancoli-Israel S, Patterson TL, Mausbach BT, Grant I. Effect of Alzheimer caregiving stress and age on frailty markers interleukin-6, C-reactive protein, and D-dimer. J Gerontol A Biol Sci Med Sci. 2006;61:963–9. [PubMed: 16960028]

12. Moore BJ, Stocks C, Owens PL. Trends in emergency department visits, 2006–2014. Rockville, MD: Agency for Healthcare Research and Quality, 2017 September. HCUP Statistical Brief #227.

13. Frost A, Hargraves J, Rodriqguez S. 2016 Health Care Cost and Utilization Report. Washington, DC: Health Care Cost Institute, 2018.

14. Kroenke K. Patients presenting with somatic complaints: epidemiology, psychiatric comorbidity and management. Int J Methods Psychiatr Res. 2003;12:34–43. [PubMed: 12830308]

15. Pines JM, Mullins PM, Cooper JK, Feng LB, Roth KE. National trends in emergency department use, care patterns, and quality of care of older adults in the United States. J Am Geriatr Soc. 2013;61:12–7. [PubMed: 23311549]

16. Zhou YQ, Liu Z, Liu ZH, Chen SP, Li M, Shahveranov A, Ye DW, Tian YK. Interleukin-6: an emerging regulator of pathological pain. J Neuroinflammation. 2016;13:141. [PubMed: 27267059]

17. Rohleder N, Aringer M, Boentert M. Role of interleukin-6 in stress, sleep, and fatigue. Annals of the New York Academy of Sciences. 2012;1261:88–96. [PubMed: 22823398]

18. Maes M. Inflammatory and oxidative and nitrosative stress pathways underpinning chronic fatigue, somatization and psychosomatic symptoms. Curr Opin Psychiatry. 2009;22:75–83. [PubMed: 19127706]

19. Turnbull AV, Rivier CL. Regulation of the hypothalamic-pituitary-adrenal axis by cytokines: actions and mechanisms of action. Physiol Rev. 1999;79:1–71. [PubMed: 9922367]

20. Van Snick J. Interleukin-6: an overview. Annu Rev Immunol. 1990;8:253–78. [PubMed: 2188664]

21. Kishimoto T. The biology of interleukin-6. Blood. 1989;74:1–10. [PubMed: 2473791]

22. Miller GE, Rohleder N, Stetler C, Kirschbaum C. Clinical depression and regulation of the inflammatory response during acute stress. Psychosom Med. 2005;67:679–87. [PubMed: 16204423]

23. Steptoe A, Hamer M, Chida Y. The effects of acute psychological stress on circulating inflammatory factors in humans: a review and meta-analysis. Brain Behav Immun. 2007;21:901–12. [PubMed: 17475444]

24. Marsland AL, Walsh C, Lockwood K, John-Henderson NA. The effects of acute psychological stress on circulating and stimulated inflammatory markers: A systematic review and meta-analysis. Brain Behav Immun. 2017;64:208–19. [PubMed: 28089638]

25. von Kanel R, Kudielka BM, Preckel D, Hanebuth D, Fischer JE. Delayed response and lack of habituation in plasma interleukin-6 to acute mental stress in men. Brain Behav Immun. 2006;20:40–8. [PubMed: 15890495]

26. Kiecolt-Glaser JK, Preacher KJ, MacCallum RC, Atkinson C, Malarkey WB, Glaser R. Chronic stress and age-related increases in the proinflammatory cytokine IL-6. Proc Natl Acad Sci USA. 2003;100:9090–95. [PubMed: 12840146]

27. von Känel R, Dimsdale JE, Mills PJ, Ancoli-Israel S, Patterson TL, Mausbach BT, Grant I. Effect of Alzheimer caregiving stress and age on frailty markers interleukin-6, C-reactive protein, and D-dimer. J Gerontol A Biol Sci Med Sci. 2006;61:963–69. [PubMed: 16960028]

28. Gouin JP, Glaser R, Malarkey WB, Beversdorf D, Kiecolt-Glaser J. Chronic stress, daily stressors, and circulating inflammatory markers. Health Psychol. 2012;31:264–68. [PubMed: 21928900]

29. Brenn D, Richter F, Schaible HG. Sensitization of unmyelinated sensory fibers of the joint nerve to mechanical stimuli by interleukin-6 in the rat: an inflammatory mechanism of joint pain. Arthritis Rheum. 2007;56:351–9. [PubMed: 17195239]

30. Vazquez E, Kahlenbach J, Segond von Banchet G, Konig C, Schaible HG, Ebersberger A. Spinal interleukin-6 is an amplifier of arthritic pain in the rat. Arthritis Rheum. 2012;64:2233–42. [PubMed: 22246633]

31. Obreja O, Schmelz M, Poole S, Kress M. Interleukin-6 in combination with its soluble IL-6 receptor sensitises rat skin nociceptors to heat, in vivo. Pain. 2002;96:57–62. [PubMed: 11932061]

32. Kurek JB, Austin L, Cheema SS, Bartlett PF, Murphy M. Up-regulation of leukaemia inhibitory factor and interleukin-6 in transected sciatic nerve and muscle following denervation. Neuromuscul Disord. 1996;6:105–14. [PubMed: 8664561]

33. Bolin LM, Verity AN, Silver JE, Shooter EM, Abrams JS. Interleukin-6 production by Schwann cells and induction in sciatic nerve injury. J Neurochem. 1995;64:850–8. [PubMed: 7830079]

34. Schistad EI, Espeland A, Pedersen LM, Sandvik L, Gjerstad J, Roe C. Association between baseline IL-6 and 1-year recovery in lumbar radicular pain. Eur J Pain. 2014;18:1394–401. [PubMed: 24692238]

35. Vollmer-Conna U, Fazou C, Cameron B, Li H, Brennan C, Luck L, Davenport T, Wakefield D, Hickie I, Lloyd A. Production of pro-inflammatory cytokines correlates with the symptoms of acute sickness behaviour in humans. Psychol Med. 2004;34:1289–97. [PubMed: 15697055]

36. Aulin J, Siegbahn A, Hijazi Z, Ezekowitz MD, Andersson U, Connolly SJ, Huber K, Reilly PA, Wallentin L, Oldgren J. Interleukin-6 and C-reactive protein and risk for death and cardiovascular events in patients with atrial fibrillation. Am Heart J. 2015;170:1151–60. [PubMed: 26678637]

37. Cesari M, Penninx BW, Newman AB, Kritchevsky SB, Nicklas BJ, Sutton-Tyrrell K, Rubin SM, Ding J, Simonsick EM, Harris TB, Pahor M. Inflammatory markers and onset of cardiovascular events: results from the Health ABC study. Circulation. 2003;108:2317–22. [PubMed: 14568895]

38. Stork S, Feelders RA, van den Beld AW, Steyerberg EW, Savelkoul HF, Lamberts SW, Grobbee DE, Bots ML. Prediction of mortality risk in the elderly. Am J Med. 2006;119:519–25. [PubMed: 16750966]

39. Ferrucci L, Harris TB, Guralnik JM, Tracy RP, Corti MC, Cohen HJ, Penninx B, Pahor M, Wallace R, Havlik RJ. Serum IL-6 level and the development of disability in older persons. J Am Geriatr Soc. 1999;47:639–46. [PubMed: 10366160]

40. Ortqvist A, Hedlund J, Wretlind B, Carlstrom A, Kalin M. Diagnostic and prognostic value of interleukin-6 and C-reactive protein in community-acquired pneumonia. Scand J Infect Dis. 1995;27:457–62. [PubMed: 8588135]

41. Moore RC, Chattillion EA, Ceglowski J, Ho J, von Kanel R, Mills PJ, Ziegler MG, Patterson TL, Grant I, Mausbach BT. 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). Behav Res Ther. 2013;51:623–32. [PubMed: 23916631]

42. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001;16:606–13. [PubMed: 11556941]

43. Ware J Jr., Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care. 1996;34:220–33. [PubMed: 8628042]

44. Johnson N, Barion A, Rademaker A, Rehkemper G, Weintraub S. The Activities of Daily Living Questionnaire: a validation study in patients with dementia. Alzheimer Dis Assoc Disord. 2004;18:223–30. [PubMed: 15592135]

45. Soysal P, Stubbs B, Lucato P, Luchini C, Solmi M, Peluso R, Sergi G, Isik AT, Manzato E, Maggi S, Maggio M, Prina AM, Cosco TD, Wu YT, Veronese N. Inflammation and frailty in the elderly: A systematic review and meta-analysis. Ageing Res Rev. 2016;31:1–8. [PubMed: 27592340]

46. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet. 2013;381:752–62. [PubMed: 23395245]

47. Kojima G. Frailty as a Predictor of Emergency Department Utilization among Community-Dwelling Older People: A Systematic Review and Meta-Analysis. J Am Med Dir Assoc. 2019;20:103–5. [PubMed: 30470576]

48. Aboulafia-Brakha T, Suchecki D, Gouveia-Paulino F, Nitrini R, Ptak R. Cognitive-behavioural group therapy improves a psychophysiological marker of stress in caregivers of patients with Alzheimer's disease. Aging Ment Health. 2014;18:801–8. [PubMed: 24499394]

49. Jaffray L, Bridgman H, Stephens M, Skinner T. Evaluating the effects of mindfulness-based interventions for informal palliative caregivers: A systematic literature review. Palliat Med. 2016;30:117–31. [PubMed: 26281853]

50. Hoge EA, Bui E, Palitz SA, Schwarz NR, Owens ME, Johnston JM, Pollack MH, Simon NM. The effect of mindfulness meditation training on biological acute stress responses in generalized anxiety disorder. Psychiatry Res. 2018;262:328–32. [PubMed: 28131433]

51. Garces J, Carretero S, Rodenas F, Aleman C. A review of programs to alleviate the burden of informal caregivers of dependent persons. Arch Gerontol Geriatr. 2010;50:254–9. [PubMed: 19481274]

52. Leng SX, McElhaney JE, Walston JD, Xie D, Fedarko NS, Kuchel GA. ELISA and multiplex technologies for cytokine measurement in inflammation and aging research. J Gerontol A Biol Sci Med Sci. 2008;63:879–84. [PubMed: 18772478]

53. Mills PJ, Adler KA, Dimsdale JE, Perez CJ, Ziegler MG, Ancoli-Israel S, Patterson TL, Grant I. Vulnerable caregivers of Alzheimer disease patients have a deficit in beta 2-adrenergic receptor sensitivity and density. Am J Geriatr Psychiatry. 2004;12:281–6. [PubMed: 15126229]
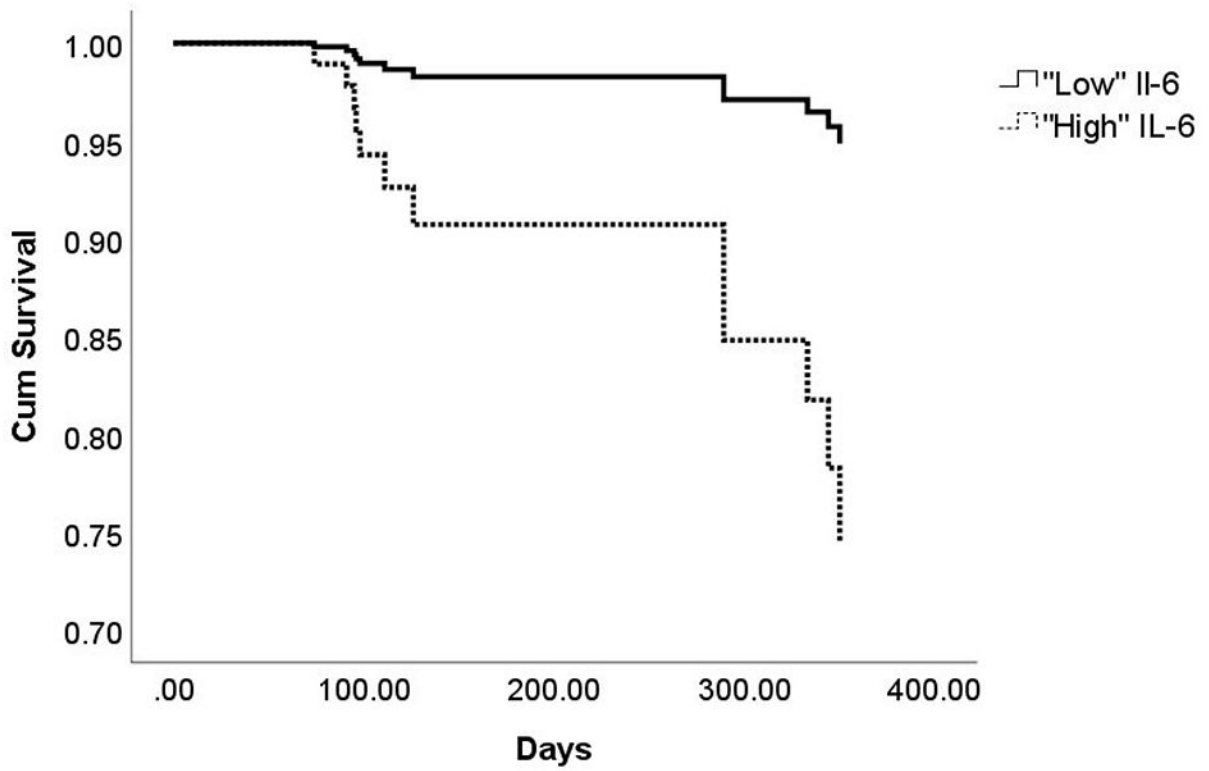
Figure 1.
ED survival for caregivers with "high" vs "low" IL-6. A total of 86 participants were available at the 3-month follow-up, 66 at the 9-month follow-up, and 45 at the 15-month follow-up.
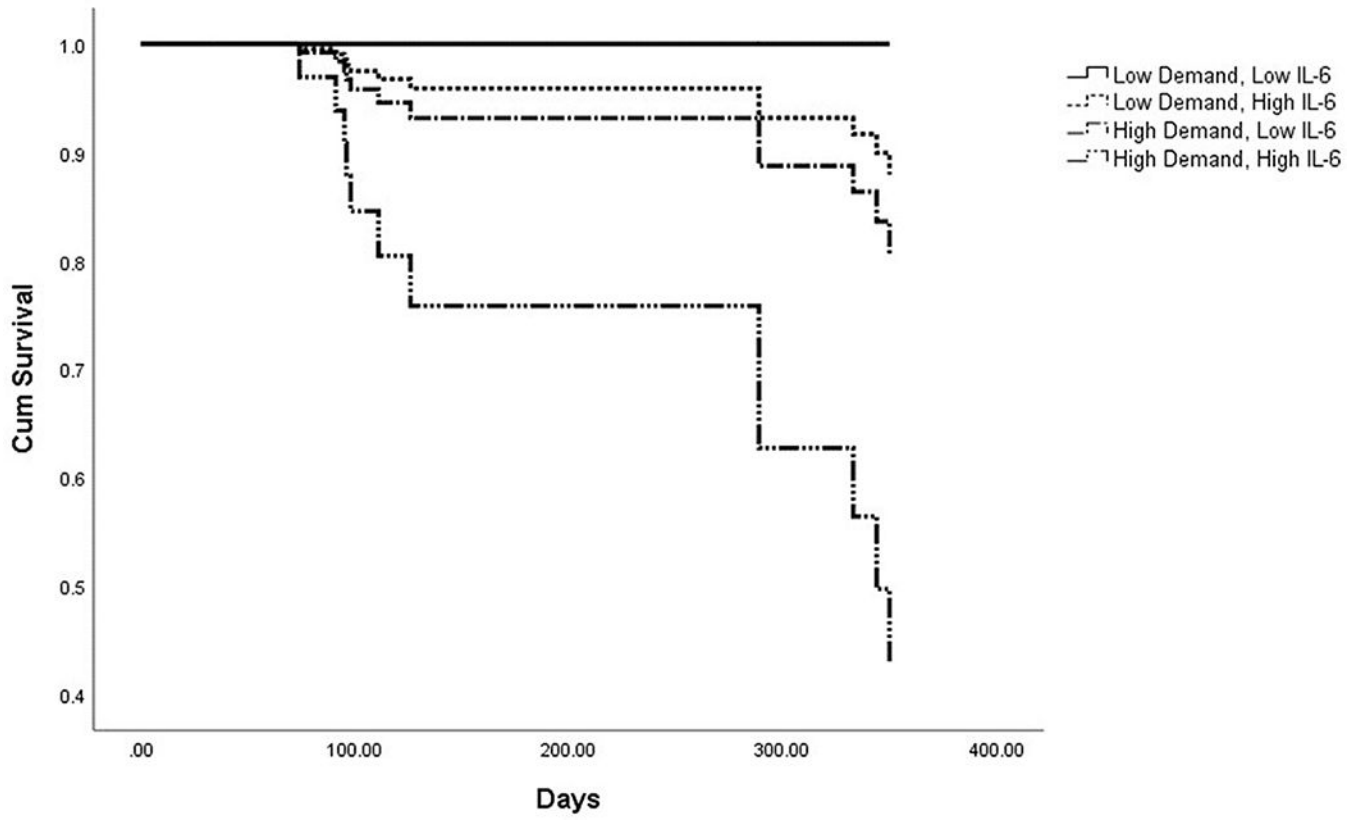
Figure 2.
ED survival for interaction between CG demand and IL-6. A total of 86 participants were available at the 3-month follow-up, 66 at the 9-month follow-up, and 45 at the 15-month follow-up.

Table 1.

Sample characteristics by 15-month follow-up emergency department use

Variables	With ED Visit (N = 12)		Without ED Visit (N = 74)		t-score; X^2	p-value
	M ± SD or N (%)	Range	M ± SD or N (%)	Range		
Age (years)	74.5 ± 9.6	56-88	74.1 ± 7.8	56-90	0.13	.90
Female	10 (83.3)		59 (79.7)		0.09	.77
Race/Ethnicity						
White, non-Hispanic	9 (75.0)		60 (81.1)			.60*
Hispanic	2 (16.7)		7 (9.4)			
Black	1 (8.3)		3 (4.1)			
Asian/Pacific Islander	0 (0.0)		4 (5.4)			
BMI (kg/m^2)	28.9 ± 4.2	21.6-35.3	27.1 ± 5.1	18.3-45.0	1.17	.25
Previous ED Visit	2 (16.7)		1 (1.4)			.05*
Hypertension	5 (41.7)		31 (41.9)		0.00	>.99
Heart Disease	1 (8.3)		3 (4.1)			.46*
Diabetes	3 (25.0)		7 (9.5)			.14*
Liver Disease	0 (0.0)		2 (2.7)			>.99*
Kidney Disease	3 (25.0)		5 (6.8)			.079*
ADLQ Score	72.8 ± 16.4	42.3-98.7	66.1 ± 18.6	16.7-96.0	1.18	.24
SF-12 Physical Composite Score	42.7 ± 12.5	23.2-63.5	50.2 ± 11.0	21.1-67.0	-2.14	.035
SF-12 Mental Composite Score	46.2 ± 12.6	23.7-64.1	46.2 ± 8.9	22.7-63.4	-0.02	.99
IL-6 (pg/ml)	2.7 ± 4.3	0.6-16.1	0.9 ± 0.7	0.2-4.4	3.40	.001

Note. M = Mean; SD = Standard Deviation. kg = kilograms; m = meters; pg = picograms; ml = milliliters; BMI = Body Mass Index; ED = Emergency Department; ADLQ = Activities of Daily Living Questionnaire; IL–6 = Interleukin – 6.

Table 2.

Survival Analyses Model Results

	B	SE	Wald	df	p	HR (95% CI)
Age	0.03	0.05	0.29	1	.592	1.03 (0.93-1.13)
Female	0.65	0.95	0.47	1	.495	1.91 (0.30-12.28)
BMI (kg/m^2)	0.02	0.07	0.11	1	.738	1.02 (0.89-1.18)
Prior ED use	3.06	1.17	6.86	1	.009	21.41 (2.16-212.00)
SF-12 PCS	−0.06	0.03	3.09	1	.079	0.94 (0.89-1.01)
SF-12 MCS	0.01	0.04	0.02	1	.888	1.01 (0.93-1.08)
ADLQ	0.04	0.02	4.12	1	.042	1.04 (1.00-1.09)
(log) IL-6	1.96	0.82	5.75	1	.017	7.10 (1.43-35.28)

Note. Statistical results are for Cox Proportional Hazards model; kg = kilograms; m = meters; BMI = Body Mass Index; ED = Emergency Department; ADLQ = Independent Activities of Daily Living Questionnaire; IL-6 = Interleukin – 6.