

COMMENTARY

The complexity of inflammatory activity in caregivers: Commentary on “Associations of perceived stress, depressive symptoms, and caregiving with inflammation: A longitudinal study” by Elayoubi *et al.*

There has been noteworthy progress in the ever-evolving understanding of inflammatory pathways and the pathophysiological role they play – in the aging process as well as in chronic, noncommunicable diseases ranging from diabetes mellitus to depressive disorders (Hunter, 2012). With a focus on caregivers and in contribution to this body of literature, Elayoubi *et al.* in their longitudinal study, have examined the association of perceived stress and depressive symptoms upon inflammatory biomarkers in persons who transitioned to caregiving (in comparison to healthy controls), over a period of approximately 9.3 years (Elayoubi *et al.*, 2022).

The aging process has been recognized as a complex, universal phenomenon, influenced by the interaction of genetic, epigenetic, stochastic, and environmental factors (Franceschi and Campisi, 2014). Associated with aging is a chronic, low-grade, nonspecific, multisystemic inflammatory process – inflammaging. The possible origins of the inflammatory process include (i) damaged cells and macromolecular compounds that accumulate with aging, (ii) microbial flora, including the gut microbiome, (iii) cellular senescence and the release of pro-inflammatory cytokines, (iv) increased activation of coagulatory pathways, and (v) age-related changes to the immune system (immunosenescence). In line with the inflammaging hypothesis, studies have shown that older adults have elevated levels of pro-inflammatory cytokines, including C-reactive protein (CRP), interleukin-6 (IL-6) and IL-8, and tumor necrosis factor alpha, receptor 1 (TNFR1) (Franceschi and Campisi, 2014). Further, several chronic noncommunicable diseases associated with the aging process and metabolic syndrome appear associated with inflammaging and the persistent, low-grade elevation of inflammatory biomarkers (Furman *et al.*, 2019; Hunter, 2012).

While inflammation appears to coexist with aging, at the other end of the aging process, the experience of early life adversity (ELA) appears to be associated with dysregulation of the HPA axis, alteration in cortico-striatal-thalamic-cortical connectivity, autonomic dysfunction, and greater increase in

pro-inflammatory cytokines in response to stress. ELA also predisposes those affected to increased inflammation in later life (Beurel *et al.*, 2020; Furman *et al.*, 2019). The experience of acute and chronic stress has been shown to be associated with an increase in the levels of pro-inflammatory cytokines. The experience of stress and affective disorders, particularly depressive disorders, have also been shown to have a fairly consistent association with a similar, chronic, low-grade, multisystemic inflammatory process (Maydych, 2019). Persons with depressive disorders also demonstrate a similar pro-inflammatory process, with higher levels of IL-1, IL-6, TNF- α , and CRP, when compared with controls without depressive disorders (Maydych, 2019).

A synthesis of literature on inflammatory theories of disease may suggest an intuitive, deceptively simple, telescopic relationship between adversity, stress, depression, inflammation, metabolic syndrome, chronic disease, and aging (Furman *et al.*, 2019). It has been postulated that chronic inflammation plays a role in the etiology of all diseases across the lifespan, suggesting a unified inflammatory theory of disease (Furman *et al.*, 2019). The influence of chronic stress upon the metabolism and immune system of the individual is clear, leading to the question of whether it may be possible to extend the inflammatory hypothesis from the intrapersonal to the interpersonal domain. Thus, it may be possible to identify individuals who, by virtue of their interpersonal relationships and life experiences, are vulnerable to chronic stress, depressive disorders, chronic inflammation, metabolic disorders, and poorer health outcomes – inflammaging. Caregiving – the activity or profession of regularly looking after a child or a sick, elderly, or disabled person – is an interpersonal relationship usually associated with chronic stress and one that can predispose the older adult to poorer physical and mental health outcomes (Jeste *et al.*, 2021). Elayoubi *et al.* have examined whether it would be possible to demonstrate an association between caregiver stress and inflammaging. This would render it possible to identify older adult caregivers vulnerable to inflammaging and develop

targeted interventions to address and mitigate this vulnerability.

An examination of the components of the research question is useful to contextualize the results of the study. Research indicates the existence of a bidirectional relationship between chronic stress and inflammation (Maydych, 2019). It similarly indicates the existence of a bidirectional relationship between depressive disorders and inflammation (Beurel *et al.*, 2020). Further, there is evidence to support the intuitive reasoning that caregiving is associated with higher levels of chronic stress and that caregivers are more likely to develop depressive disorders than noncaregivers, when controlled for other sociodemographic variables (Jeste *et al.*, 2021, Kim *et al.*, 2022). There is a paucity of evidence to support the reasoning that, since caregivers are more likely to express chronic stress and develop depressive disorders, they would also have greater systemic inflammation, and therefore experience acceleration of cellular senescence (and the resultant increase in morbidity and mortality). The longitudinal study by Elayoubi *et al.* is of considerable importance in that it serves to address this gap in scientific literature.

The study builds upon a previous meta-analysis by the same group of authors that examined the relationship between caregiving and baseline levels of biomarkers indicative of either immune system functioning or inflammatory processes (Roth *et al.*, 2019). The authors examined PubMed, Cochrane, and Embase databases to identify 2852 papers, of which 1804 abstracts were screened, and 132 full-texts reviewed, to identify 30 papers that addressed the research question. The papers reported on 86 relevant biomarkers (42 markers of immune functioning, 44 markers of inflammatory processes) from 1,848 caregivers and 3,640 controls. 29 studies provided information on the sociodemographic profile of the caregivers, of whom 70% were female, with a mean age of 64.8 years. The meta-analysis revealed a small, statistically significant effect size ($d = 0.164$) across all biomarkers. The effect size was larger for caregivers of persons with dementia ($d = 0.188$), though still small. The effect size was also larger for immune biomarkers ($d = 0.217$) than for inflammatory biomarkers ($d = 0.142$).

The authors went on to note the limitations of the analysis – studies generally had small sample sizes (15 studies had 50 or less caregivers) and the biomarkers examined were heterogeneous (with only two biomarkers being examined in more than five studies). More importantly, however, an analysis restricted to minimal or low bias studies did not reach statistical significance ($d = 0.059$) while a corresponding analysis from moderate bias studies had a much larger, significant effect size ($d = 0.302$). The

authors noted in their discussion that there was thus little replicable research evidence to support the hypothesis that stress associated with caregiving led to clinically significant alternation of immune or inflammatory biomarkers.

The longitudinal study under discussion in this commentary builds upon the meta-analysis and further examines this relationship between caregiving stress and inflammatory biomarkers. Elayoubi *et al.* examined transition to caregiving in persons recruited as part of the Reasons for Ethnic and Geographical Differences in Stroke (REGARDS) national longitudinal cohort study. The Caregiving Transitions Study (CTS) was an ancillary nested case-control study within REGARDS examining persons who transitioned to caregiving over a mean follow-up period of 9.3 years. The mean age of the caregivers was 72 years, 65% were women and 35.2% were Black. Caregivers were assessed for perceived stress and depressive symptoms using the Cohen Perceived Stress Scale and the Center for Epidemiological Studies-Depression Scale, respectively. The biomarkers examined were CRP, D-dimer, TNFR1, IL-2, IL-6, and IL-10.

A previous publication from this longitudinal study examined inflammation in caregivers to demonstrate an elevation of TNFR1 levels in 239 caregivers, when compared to 241 controls, over the duration of follow-up (Roth *et al.*, 2020). As with the prior meta-analysis, the effect size was small, but statistically significant ($d = 0.14$), after matching for age, sex, race, education, and marital status. The current publication also examined the same subset of data (239 caregivers, 241 controls, 9.3 years) to demonstrate a significant increase in perceived stress and depressive symptoms in persons who transitioned to caregiving over the course of the CTS case-control study, as was expected. Caregivers were also more likely to be obese, take medicines for diabetes mellitus, and be on antidepressants.

What was intriguing and contrary to expectations, however, was that the increase in perceived stress and/or depressive symptoms was not associated with an increase in the circulatory levels of any inflammatory biomarkers. Greater change in perceived stress over time was associated with an increase in IL-10 levels in caregivers and a decrease in IL-10 levels in controls. Baseline depressive symptoms were associated with higher D-dimer levels, but an increase in depressive symptoms over time or the magnitude of increase was not associated with elevation of levels of any of the inflammatory biomarkers assessed. Thus, transitioning to caregiving was associated with (i) elevation of TNFR1 and (ii) elevation of perceived stress and depressive symptoms but there was inadequate

evidence to suggest an association between both effects.

The authors have put forward two theories to contextualize and explain the findings from the studies. The first is that caregiving may be a positive or even rewarding experience for some caregivers, with adaptation occurring over time and social supports systems acting as a buffer for the caregiver. The resilience and attributes of the caregiver may also contribute to the perception of caregiving. Indeed, the increase in stress appeared to be linked to an increase in an anti-inflammatory cytokine (IL-10), rather than other pro-inflammatory biomarkers. The second is that age, race, obesity, being on medication for diabetes mellitus, hypertension, statins, and antidepressants had a significant association with elevation of some inflammatory biomarkers. Thus, while inflammaging occurs in older adults – socio-demographic and metabolic variables showed a statistically and clinically significant relationship with inflammation and cellular senescence. Perceived stress and depressive symptoms during the transition to caregiving did not show a relationship with inflammatory biomarkers. Controlling for variables such as age, sex, race, education, and marital status may have accounted for the within-group and between-group variance in inflammation.

In addition to the caveats noted by the authors, it is worth noting that nesting the CTS study within the REASONS cohort and the oversampling of older adults who had greater vulnerability to strokes may have been a potential confound when examining the relationship between perceived stress, depressive symptoms, and inflammation (Elayoubi *et al.*, 2022, Roth *et al.*, 2020). Notably, the elevation of TNFR1 in caregivers did not retain significance when the analysis was restricted to caregivers of persons with dementia (Roth *et al.*, 2020). The results of the CTS study may thus be more representative of caregivers of persons with stroke rather than dementia.

On a related note, a previous study published in *International Psychogeriatrics* showed that lower morning activity levels in caregivers of persons with dementia are associated with higher depressive symptoms at baseline and at follow-up 6 months later (Smagula *et al.*, 2019). While the authors suggested low levels of morning activity may be a risk factor for the development of depressive symptoms (and a potential area for intervention), it may also be possible that the low activity levels may be part of the somatic syndrome of depression and/or indicate a phenotypic vulnerability. A subsequent study published in the same journal demonstrated that a home-based exercise program reduced subjective burden and depressive symptoms in female caregivers of persons with dementia over 9 months (Madruga *et al.*, 2021).

Active behavioral interventions (including physical activity and aerobic exercise) improve the physical well-being of caregivers while also reducing the risk of development or exacerbation of physical comorbidities (Hill and Lee, 2021). Active behavioral interventions also improve mental well-being, including perceived stress and depressive symptoms (Jeste *et al.*, 2021). It may therefore be worth examining if (i) changes in the physical and mental well-being of caregivers is associated with changes in levels of immune or inflammatory biomarkers and (ii) active behavioral interventions may serve to modulate levels of immune or inflammatory biomarkers, over time. The association of inflammation with sociodemographic and metabolic variables in the CTS (and other longitudinal studies among older adults) may be an important pointer in this direction.

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References

- Beurel, E., Toups, M. and Nemeroff, C. B.** (2020). The bidirectional relationship of depression and inflammation: double trouble. *Neuron*, 107, 234–256. <https://doi.org/10.1016/j.neuron.2020.06.002>.
- Elayoubi, J. et al.** (2022). Associations of perceived stress, depressive symptoms, and caregiving with inflammation: a longitudinal study. *International Psychogeriatrics*, 34, 95–105. <https://doi.org/10.1017/S1041610222000370>.
- Franceschi, C. and Campisi, J.** (2014). Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. *The Journals of Gerontology: Series A*, 69, S4–S9. <https://doi.org/10.1093/geron/glu057>.
- Furman, D. et al.** (2019). Chronic inflammation in the etiology of disease across the life span. *Nature Medicine*, 25, 1822–1832. <https://doi.org/10.1038/s41591-019-0675-0>.
- Hill, K. D. and Lee, D.-C. A.** (2021). Exercise can provide multiple health benefits for carers. *International Psychogeriatrics*, 33, 319–321. <https://doi.org/10.1017/S1041610220003294>.
- Hunter, P.** (2012). The inflammation theory of disease. *EMBO Reports*, 13, 968–970. <https://doi.org/10.1038/embor.2012.142>.
- Jeste, D. V., Mausbach, B. and Lee, E. E.** (2021). Caring for caregivers/care partners of persons with dementia. *International Psychogeriatrics*, 33, 307–310. <https://doi.org/10.1017/S1041610221000557>.
- Kim, Y., Kim, H., Suh, S.-Y., Park, H. and Lee, H.** (2022). Association between inflammatory cytokines and caregiving distress in family caregivers of cancer patients. *Supportive Care in Cancer*, 30, 1715–1722. <https://doi.org/10.1007/s00520-021-06578-y>.

Madruza, M., Gozalo, M., Prieto, J., Rohlf

Domínguez, P. and Gusi, N. (2021). Effects of a home-based exercise program on mental health for caregivers of relatives with dementia: a randomized controlled trial. *International Psychogeriatrics*, 33, 359–372. <https://doi.org/10.1017/S104161022000157X>.

Maydych, V. (2019). The interplay between stress, inflammation, and emotional attention: relevance for depression. *Frontiers in Neuroscience*, 13, 384. <https://doi.org/10.3389/fnins.2019.00384>.

Roth, D. L. et al. (2020). The transition to family caregiving and its effect on biomarkers of inflammation.

Proceedings of the National Academy of Sciences, 117, 16258–16263. <https://doi.org/10.1073/pnas.2000792117>.

Roth, D. L., Sheehan, O. C., Haley, W. E., Jenny, N. S., Cushman, M. and Walston, J. D. (2019). Is family caregiving associated with inflammation or compromised immunity? A meta-analysis. *The Gerontologist*, 59, e521–e534. <https://doi.org/10.1093/geront/gnz015>.

Smagula, S. F., Hall, M. H. and Stahl, S. T. (2019). Rest-activity rhythms and depression symptoms in older bereaved adults. *International Psychogeriatrics*, 31, 1675–1676. <https://doi.org/10.1017/S1041610218002181>.