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Review Article

Is Family Caregiving Associated With Inflammation or Compromised Immunity? A Meta-Analysis

David L. Roth, PhD,[1],* Orla C. Sheehan, MD, PhD,[1] William E. Haley, PhD,[2] Nancy S. Jenny, PhD,[3],† Mary Cushman, MD,[3] and Jeremy D. Walston, MD[1]

[1]Center on Aging and Health, Division of Geriatric Medicine and Gerontology, Johns Hopkins University, Baltimore, Maryland.
[2]School of Aging Studies, University of South Florida, Tampa. [3]Department of Pathology and Laboratory Medicine, Larner College of Medicine, University of Vermont, Burlington.

*Address correspondence to: David L. Roth, PhD, Center on Aging and Health, Division of Geriatric Medicine and Gerontology, School of Medicine, Johns Hopkins University, 2024 E. Monument Street, Suite 2-700, Baltimore, MD 21205. E-mail: droth@jhu.edu
†Posthumous coauthor.

Abstract

Background and Objectives: Family caregiving stress has been widely reported to have negative effects on circulating biomarkers of immune system function and inflammation. Our goals were to systematically review this literature and conduct a meta-analysis on the extracted effects.
Research Design and Methods: A systematic search of published studies comparing caregivers and noncaregivers on biomarkers measured from blood samples was conducted in the PubMed, Embase, and Cochrane databases. This search identified 2,582 articles and abstracts. After removing duplicative papers and studies not meeting inclusion criteria, 30 articles were identified that reported analyses on 86 relevant biomarkers from 1,848 caregivers and 3,640 noncaregivers.
Results: Random-effects models revealed an overall effect size across all biomarkers of 0.164 *SD* units (*d*). A slightly larger overall effect (*d* = 0.188) was found for dementia caregivers only. Immune system comparisons yielded somewhat larger differences than inflammation comparisons. Most studies used small convenience samples, and effect sizes were larger for studies with moderate or high bias ratings than for studies with low bias ratings. No significant associations were found in studies that used population-based samples.
Discussion and Implications: Caregivers had small but significantly reduced immune system functioning and greater inflammation than noncaregivers, but associations were generally weak and of questionable clinical significance. The absence of clear associations from low bias studies and population-based studies underscores concerns with possible selection biases in many of the convenience samples. Population-based studies that assess biomarkers before and after the onset of caregiving might add much clarity to this literature.

Keywords: Biomarkers, Immune system, Systematic review, Stress

Beginning with the ground-breaking publication by Kiecolt-Glaser and colleagues (1987) reporting that caregivers of persons with Alzheimer's disease had decreased levels of several immune system biomarkers compared with noncaregiving controls, many subsequent studies have examined whether family caregivers experience altered biomarker indicators of compromised immune system functioning, increased inflammation, or other negative impacts on biological and physiological functioning. Most of these studies are inspired by a conceptual narrative of caregiving as

being a long-term, stressful situation that can have negative impacts on the caregivers' health. Many investigators interested in the biological consequences of stress have viewed caregiving as a "naturalistic stressor" that allows scientific inquiry into how the human body responds to chronic stress over many years in ways that would not be possible using controlled experimentation (Allen et al., 2017). Caregiving is often conceptualized as being particularly stressful and burdensome for persons caring for a family member with dementia or serious cognitive impairment, which is consistent with evidence that dementia caregivers report higher strain and more depressive symptoms than other groups of caregivers (Ory et al., 1999; Pinquart & Sörensen, 2003).

The chronic stress narrative of caregiving is further supported by many studies suggesting that caregiving is linked to adverse mental and physical health consequences. Family caregiving has been repeatedly linked to elevations in depressive symptoms and other indicators of psychological distress (Pinquart & Sörensen, 2003; Roth, Brown, Rhodes, & Haley, 2018; Roth, Perkins, Wadley, Temple, & Haley, 2009). The reported health effects of the chronic stress of caregiving have been extended to a variety of other potentially significant clinical outcomes including slower wound healing (Kiecolt-Glaser, Marucha, Malarkey, Mercado, & Glaser, 1995), decreased telomere length and possibly shortened life expectancy (Epel et al., 2004), and an increased risk for mortality among strained caregivers (Schulz & Beach, 1999). The idea that caregivers, particularly dementia caregivers, have clinically significant physiological changes that could increase risk for disease and even mortality has been widely cited and accepted both in scholarly reviews (Fonareva & Oken, 2014; Lovell & Wetherell, 2011) and in other influential sources including the annual report of the Alzheimer's Association (2018) and the web pages for organizations such as the Caregiver Action Network (2018) and the U.S. Office of Women's Health (2018). Ongoing research is often focused on filling in gaps of this narrative, such as which biomarker/physiological pathways are most impacted by caregiving stress, and what interventions or treatments might be designed or prescribed to prevent these adverse health consequences. This work is critical due to the large and increasing number of older adults with chronic disabilities who are likely to survive for many years and will depend on family members and other informal caregivers for assistance to meet their daily functional needs.

Although the caregiving-is-a-health-risk-factor narrative is important and compelling, it does not constitute the complete view of caregiving or all of the mechanisms by which the caregiving experience might influence health. Alternative, counteracting perspectives have emerged that increasingly recognize resilience in the face of psychological stress (Bonanno, 2004) and the potential health benefits of prosocial helping relationships (Brown & Brown, 2015; Poulin, Brown, Dillard, & Smith, 2013). Caregiving, like other family relationships, may involve stress in many ways, but these kinds of social engagements also undoubtedly have other effects on health and well-being, including possible positive effects. For example, a growing series of population-based studies has indicated rather conclusively that family caregiving is not linked to an increased risk for mortality. Conversely, several population-based studies in both the United States and Europe have found that family caregivers tend to live longer than comparable samples of persons who do not report family caregiving responsibilities (Brown et al., 2009; Fredman, Lyons, Cauley, Hochberg, & Applebaum, 2015; O'Reilly, Connolly, Rosato, & Patterson, 2008; O'Reilly, Rosato, Ferry, Moriarty, & Leavy, 2017; O'Reilly, Rosato, & Maguire, 2015; Ramsay, Grundy, & O'Reilly, 2013; Roth, Fredman, & Haley, 2015; Roth et al., 2013). Recent work inspired by models of the health benefits of volunteering and other prosocial helping behaviors (Brown & Brown, 2015; Poulin et al., 2013) has shown that caregiving is associated with a stress-buffering effect such that psychological distress is not associated with mortality in caregivers in the same way that it is for non-caregiving comparison participants (Roth et al., 2018). If one fundamental purpose of the research on caregiving, chronic stress, and biomarkers is to identify possible mechanisms that could explain the link between caregiving and increased mortality, then that literature requires reexamination in light of these replicated findings that caregivers live longer (and do not die faster) than more carefully matched noncaregiving comparison participants.

The literature on the association between family caregiving and circulating biomarkers of inflammation or immunity has been reviewed and summarized in at least four previous articles. An early meta-analysis by Vitaliano, Zhang, and Scanlan (2003) examined 12 studies that compared dementia caregivers and controls on "physiological indicators" including some measures of immunity. They found small but statistically significant associations, further clarified these effects as "weak," and cautioned that "questions remain regarding their magnitude and their clinical significance" (p. 961). Since the review by Vitaliano and colleagues (2003), many subsequent studies have been conducted, including numerous studies that have examined circulating biomarkers of inflammation (e.g., C-reactive protein [CRP], interleukin-6 [IL-6], D-dimer) as a function of caregiving. Although we are not aware of any more recent meta-analyses on the effect sizes emerging from this expanding literature, at least three more recent narrative reviews have been published.

Lovell and Wetherell (2011) reviewed 42 papers of "endocrine and immune" measures in relation to caregiving and concluded that "findings … consistently revealed dysregulation of cellular and humoral immune markers in elderly, spousal caregivers" (p. 1350). They interpreted these findings as supporting a "cumulative wear and tear" process that fosters "increased risk for deleterious health outcomes" including a "significantly greater risk for mortality" (p. 1350). Interestingly, only one of the 42 papers reviewed by Lovell and Wetherell (2011) used a population-based sample (as opposed to a convenience sample) of

participants. Furthermore, only five of the 42 studies had a sample size of over 100 caregiving participants, and 10 of those 42 studies had sample sizes of 20 or fewer caregivers. Also of note, many findings summarized in the Lovell and Wetherell (2011) review are of complex effects, for example, the relationship between caregiving stressors and biomarkers, or the effects of interventions on biomarkers, but do not focus on the simpler question of whether there are biomarker differences as a main effect of caregiving itself.

As part of larger reviews on the physiological effects of dementia caregiving, both Fonareva and Oken (2014) and Allen and colleagues (2017) reviewed effects on measures of immune system function and inflammation. Both reviews included many of the same articles reviewed by Lovell and Wetherell (2011), but their conclusions were somewhat different. Fonareva and Oken (2014) concluded that there is "agreement about CRP levels being increased in dementia caregivers with moderate effect sizes" (p. 741) and that "there is accumulating evidence that chronic dementia caregiver stress increases their vulnerability to disease" (p. 741). Allen and colleagues reviewed 54 studies of immune system activation and inflammation but offered conclusions that were considerably more tentative. They stated that "baseline measures of cytokines… such as IL-6, TNF-alpha, and CRP… have infrequently been assessed in caregivers and the results have been mixed" (p. 130) and that "although baseline low grade immune system activation is apparent in some caregiver studies, the evidence for this is mixed" (p. 130). Only 10 of the 54 papers reviewed by Allen and colleagues (2017) had sample sizes of 100 or more caregivers, but some of these were from the same research group and appear to represent duplicative data.

Recently, Potier, Degryse, and de Saint-Hubert (2018) reviewed 24 studies of inflammatory biomarkers associated with caregiving. They concluded that increases in inflammatory biomarkers were associated with some of the problems associated with caregiving (e.g., disturbed sleep, caregiving burden), but overall, they "found little evidence concerning the association between caregiving status and biomarkers of stress and inflammation" (p. 119).

None of the reviews since the Vitaliano and colleagues' (2003) article provided a meta-analytic summary of observed effect sizes, and some reviews included studies that did not include noncaregiving comparison participants. Although study quality ratings were made in some previous reviews, little attention was given to a potentially important factor—the use of convenience versus population-based sampling methods to assemble caregiving and noncaregiver comparison groups. In caregiving research that uses convenience samples, participants are enrolled from local clinics, support groups, and notices for research volunteers, with different recruitment sources and enrollment methods usually being used for caregivers and noncaregivers. In population-based studies, samples are assembled with the goal of being representative of a larger population, and both caregivers and noncaregiving

controls are recruited and enrolled using the same methods. In addition, none of the four more recent review papers explicitly addressed another important issue—the potential for duplicative reporting of the same data from the same samples across multiple papers published by some research groups.

In the present study, we focused on the association between family caregiving status and baseline measures of circulating biomarkers in two widely studied domains in this literature—immune system functioning and inflammation. In light of the fundamental importance of this primary research question—is the chronic stress of family caregiving associated with compromised immune system functioning and/or inflammation as assessed by circulating biomarkers—we conducted an updated systematic review of this literature and used meta-analysis methods to estimate overall effect sizes from the distinct effects that could be extracted from the relevant studies in this area of investigation. Consistent with the guidelines of the PROSPERO registry, we systematically searched the published literature in multiple databases, reviewed article titles and abstracts for relevance, identified overlap or duplicative findings from multiple papers from the same investigative group, rated retained studies for quality or potential bias in six methodological areas, and extracted caregiver versus noncaregiver comparison effect sizes on biomarkers of either inflammation or immunity. In addition to examining overall effects across all caregivers, we also evaluated effects specifically for dementia caregivers and from studies that differed on potential bias ratings.

Methods

Literature Search

This systematic review was preregistered with PROSPERO in 2017 (registration number CRD42017071123; http://www.crd.york.ac.uk/PROSPERO). Systematic searches of the literature were performed in April of 2017. The final PubMed search terms are provided in Figure 1. PubMed search terms were further refined to facilitate searches of EMBASE and the Cochrane library. Inclusion criteria for studies to be included were as follows: (i) full research articles published in English, such that abstracts without accompanying full articles and papers in non-English languages were excluded; (ii) biomarkers of immunity or inflammation were measured in blood samples from family or informal caregivers; and (iii) the same biomarkers of immunity or inflammation were measured from noncaregiving comparison participants. In addition, only original data-based research reports were included. Review papers and editorial commentaries were excluded. Caregivers were defined as persons caring for an adult with a chronic disease or disability, and studies that reported data from parents caring for children who were predominantly under 18 years of age, including children with developmental

("biomarkers"[mesh] OR "c-reactive protein"[mesh] OR "fibrin fragment d" [supplementary concept] OR "fibrinogen"[mesh] OR "immune tolerance"[mesh:noexp] OR "interleukin-10"[mesh] OR "interleukin-2"[mesh] OR "interleukin-6"[mesh] OR "receptors, tumor necrosis factor, type i"[mesh] OR "biochemical marker"[tw] OR "biochemical markers"[tw] OR "bioindicator"[tw] OR "bioindicators"[tw] OR "biologic indicator"[tw] OR "biologic indicators"[tw] OR "biologic marker"[tw] OR "biologic markers"[tw] OR "biological marker"[tw] OR "biological markers"[tw] OR "biological risk"[tw] OR "biological risks"[tw] OR "biomarker"[tw] OR "biomarkers" [tw] OR "blood coagulation factor"[tw] OR "c reactive protein"[tw] OR "c reactive proteins"[tw] OR "CD120a Antigens"[tw] OR "clinical marker"[tw] OR "clinical markers"[tw] OR "coagulation factor I"[tw] OR "CRP"[tw] OR "cytokine synthesis inhibitory factor"[tw] OR "d dimer"[tw] OR "DD"[tw] OR "fibrin fragment D"[tw] OR "fibrinogen"[tw] OR "IL 10"[tw] OR "IL 2"[tw] OR "IL 6"[tw] OR "IL10"[tw] OR "IL2"[tw] OR "IL6"[tw] OR "immune marker"[tw] OR "immune markers"[tw] OR "immune tolerance"[tw] OR "immunologic marker"[tw] OR "immunologic markers"[tw] OR "immunologic mediator"[tw] OR "immunologic mediators"[tw] OR "immunological tolerance"[tw] OR "interleukin 10"[tw] OR "interleukin 2"[tw] OR "interleukin 6"[tw] OR "laboratory marker"[tw] OR "laboratory markers"[tw] OR "serum level"[tw] OR "serum levels"[tw] OR "serum marker"[tw] OR "serum markers"[tw] OR "stress hormone"[tw] OR "stress hormones"[tw] OR "surrogate end point"[tw] OR "surrogate end points"[tw] OR "surrogate endpoint"[tw] OR "surrogate endpoints"[tw] OR "surrogate marker"[tw] OR "surrogate markers"[tw] OR "TNF R1"[tw] OR "TNFR 1"[tw] OR "TNFR I"[tw] OR "TNFR1"[tw] OR "CD120a antigen"[tw] OR "tumor necrosis factor receptor type 1"[tw] OR "tumor necrosis factor receptor type I"[tw] OR "tumour necrosis factor receptor 1"[tw] OR "tumour necrosis factor receptor type 1"[tw] OR "tumour necrosis factor receptor type I"[tw] OR "tumor necrosis factor receptor 1"[tw] OR "viral marker"[tw] OR "viral markers"[tw] OR immunosuppression*[tw] OR (("stress, psychological"[mesh] OR "stress, physiological"[mesh] OR "psychological stress"[tw] OR "psychological stresses"[tw] OR "psychological stressor"[tw] OR "psychological stressors"[tw] OR "physiological stress"[tw] OR "physiological stresses"[tw] OR "physiological stressor"[tw] OR "physiological stressors"[tw] OR "mental stress"[tw]) AND ("inflammation/blood"[mesh] OR "inflammation/physiopathology"[mesh] OR "inflammation/psychology"[mesh] OR "blood"[tw] OR "saliva"[tw] OR "metabolism"[tw] OR "immunology"[tw] OR "inflammation"[mesh] OR "inflammation"[tw] OR "inflammatory"[tw] OR "metabolism"[sh] OR "immunology"[sh] OR "physical health"[tw]))) AND ("Caregivers"[Mesh] OR "care giver"[tw] OR "care givers"[tw] OR "care giving"[tw] OR "care partner"[tw] OR "care partners"[tw] OR "care taker"[tw] OR "care takers"[tw] OR "caregiving"[tw] OR "carepartner"[tw] OR "carepartners"[tw] OR "carer"[tw] OR "carers"[tw] OR "caretaker"[tw] OR "caretakers"[tw] OR caregiver*[tw])

Figure 1. Final PubMed search terms. Search limited to articles in the English language. No time limits were applied.

disorders such as autism or other disabilities, were also excluded from this review.

Article Selection Process

Figure 2 illustrates our article review and selection process. The systematic searches of these databases identified 2,582 papers and abstracts. All articles were entered into a reference manager, Endnote v7, and 778 duplicates were removed. Each title and abstract of the 1,804 remaining articles was then reviewed independently by at least two coauthors, and 1,672 titles or abstracts were identified as not being eligible for inclusion in the present systematic review. This left 132 published papers that were then selected for full-text review by at least two coauthors. Specific biomarker measures used were listed for these papers, and two of the coauthors who are experts in biomarker research (N.S.J. and J.D.W.) determined whether each measure from this list qualified as a biomarker of immune system functioning, inflammation, or neither. In addition, biomarkers that were reported but did not represent baseline indicators of inflammation or immune system function (e.g., responses to vaccination over time) were not included in our meta-analysis.

In some cases, we discovered multiple articles from the same research group where data on the same biomarkers from the same participants were reported in more than one paper. Many papers quite reasonably added participants to
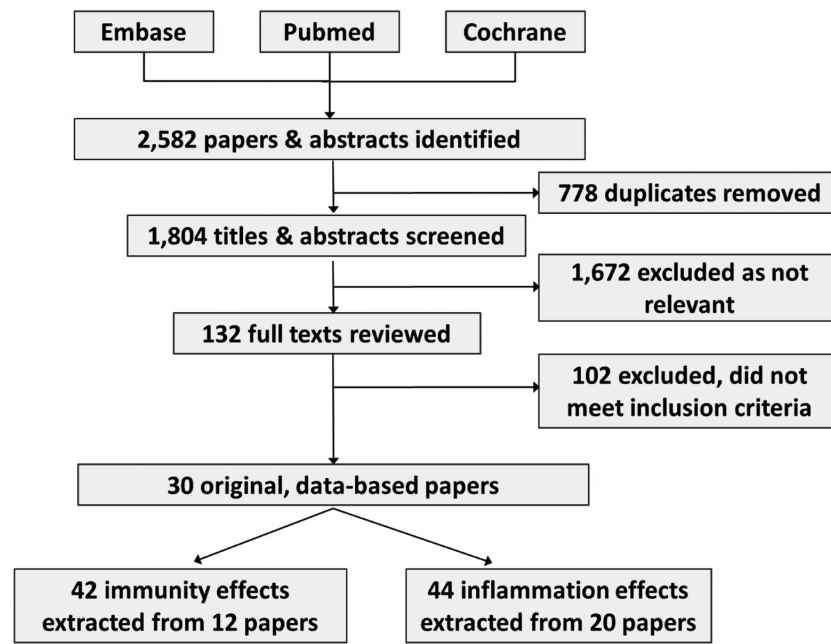
Figure 2. Flow diagram of study selection process.

their samples of caregivers and noncaregivers over time, and later papers sometimes focused on more complex research questions such as subgroup analyses, interaction effects, longitudinal changes, or added additional biomarkers. In cases where there were multiple publications from the same research group, we extracted an effect for each biomarker from the article with the largest sample size that contained data for both caregivers and controls on that biomarker or from the first article reporting that biomarker. When necessary, the authors were contacted to clarify whether they had reported on distinct versus overlapping samples across different papers.

In total, of the 132 papers that underwent full-text review, 102 were excluded as not meeting our inclusion criteria or containing any independent data from other papers. This yielded 30 original, data-based papers that met all of our inclusion criteria. These papers are listed in Table 1, including the biomarkers extracted from each paper for the meta-analysis and the immune system or inflammation category assigned to that biomarker.

Quality Reviews

Using a procedure adapted from Allen and colleagues (2017), at least two coauthors independently rated the quality of the methods reported in each of these 30 articles on six separate dimensions: (i) caregiving definition and selection methods, (ii) control definition and selection methods, (iii) descriptors or adequate definitions of caregiving exposure (e.g., hours per week or care, number of years of caregiving), (iv) adequacy of the descriptions of the biomarker assessment methods, (v) potential for confounding and the adequacy of methods to control for confounding

such as matching or statistical covariate adjustment, and (vi) sufficient explanation of the statistical methods for testing group differences, either before or after adjustment for potential confounders. Each rating was made on a 4-point scale of potential bias (1 = minimal, 2 = low, 3 = moderate, and 4 = high potential bias). Discrepancies between two raters that exceeded just one category difference (i.e., minimal-moderate, minimal-high, or low-high) were reviewed jointly by a panel of four coauthors and resolved by consensus. An overall quality rating was achieved by averaging the scores across the six dimensions. All quality ratings were obtained and consensus meetings occurred before any effects were extracted for meta-analysis purposes. This minimized any possibilities that the bias ratings themselves might be affected by any emerging trends from the analyses.

Meta-Analysis Procedures

Version 3.3 of the Comprehensive Meta-Analysis (2014) system was used to conduct the meta-analyses. Biomarker data were extracted by the first author for each biomarker from the 30 articles using published means and *SD* (or *SE*) when available, and *p* values and sample sizes from analytic models in cases where descriptive means and *SD* were not available. These methods allow for the calculation of a standardized effect size expressed as a difference in *SD* units (*d*) between the caregiver and noncaregiving control groups. Ninety-five percent confidence intervals (95% CI) were calculated for each standardized effect size, and the multiple standardized effect sizes were then pooled across the multiple measures within and across the 30 studies. We assumed that the effects from the different

Table 1. Serum Biomarkers of Immune System and Inflammation Extracted From Blood Samples in 30 Studies

Study	Caregivers	Controls	Biomarkers	Category	Potential bias
1. Kiecolt-Glaser et al. (1987)	34 dementia	34 demographically matched	% helper T lymphocytes	Immune	Moderate
			% NK cells	Immune	
			% suppressor T	Immune	
			% total T lymphocytes	Immune	
			EBV VAC	Immune	
			Helper/suppressor ratio	Immune	
2. Reese et al. (1994)	50; 25 dementia, 25 stroke	25 noncaregivers	% CD3	Immune	Moderate
			% CD4	Immune	
			% CD8	Immune	
			% leukocytes	Immune	
			% NK cells	Immune	
3. Irwin et al. (1997)	100 dementia, spouses only	33 volunteers	NK activity	Immune	Low
4. Mills et al. (1997)	27 dementia, spouses only	10 matched volunteers	CD16 count	Immune	Moderate
			CD4 count	Immune	
			CD8 count	Immune	
5. Cacioppo et al. (1998)	27 dementia, spouses only, women only	37 controls	Cell Prolif to Con A	Immune	Moderate
			Cell Prolif to PHA	Immune	
			NK cell cytotoxicity	Immune	
6. Scanlan, Vitaliano, Ochs, Savage, and Borson (1998)	81 dementia, spouses only	82 age- and gender-matched spouses of persons without dementia	%CD4	Immune	Low
			%CD8	Immune	
7. Vitaliano et al. (1998)	80 dementia, spouses only	85 age- and gender-matched spouses of persons without dementia	NK activity	Immune	Low
8. Lutgendorf et al. (1999)	18 dementia, women only	15 noncaregiving (and nonmoving) women	IL-6	Inflammation	Moderate
9. Bauer et al. (2000)	49 dementia, spouses only	67 "closely matched" controls	Cell Prolif to PHA	Immune	Low
			IL-2	Inflammation	
10. Stowell, Kiecolt-Glaser, and Glaser (2001)	61 dementia	78 "comparison" participants	% CD3	Immune	Moderate
			% helper T cells	Immune	
			% T (suppressor/cytotoxic)	Immune	
			Log Con A	Immune	
			Log PHA	Immune	
			Helper/suppressor ratio	Immune	
11. Vedhara et al. (2002)	41 multiple sclerosis, spouses only	62 noncaregiving controls	IFN-γ	Inflammation	Low
			IL-4	Inflammation	
12. Provinciali et al. (2004)	38 caregivers of home health care patients, nonspouses only	37 age- and sex-matched controls	% CD16	Immune	Minimal
			% CD56	Immune	
			NK activity	Immune	
13. Vitaliano, Persson, Kiyak, Saini, and Echeverria (2005)	123 dementia, spouses only	117 noncaregiving spouses	CRP	Inflammation	Low
			WBC	Inflammation	
14. Graham et al. (2006)	113 dementia, spouses only	101 controls	CRP	Inflammation	Moderate
			IL-6	Inflammation	
15. von Kanel et al. (2006)	116 dementia, spouses only	54 noncaregivers	CRP	Inflammation	Low
			D-dimer	Inflammation	
			IL-6	Inflammation	
16. Aschbacher et al. (2007)	51 dementia, spouses only, women only	27 noncaregiving women	% Aggregates	Inflammation	Low

Table 1. *Continued*

Study	Caregivers	Controls	Biomarkers	Category	Potential bias
17. Damjanovic et al. (2007)	38 dementia	38 age- and gender-matched controls	B cell (CD19) count	Immune	Low
			CD4 count	Immune	
			CD8 count	Immune	
			GM-CSF	Inflammation	
			IFN-γ	Inflammation	
			IL-2	Inflammation	
			IL-4	Inflammation	
			IL-6	Inflammation	
			IL-8	Inflammation	
			Monocyte (CD14)	Immune	
			NK cell	Immune	
18. Miller et al. (2008)	11 glioblastoma (brain tumor) caregivers	10 matched controls	IL-1	Inflammation	Moderate
19. Segerstrom, Schipper, and Greenberg (2008)	14 dementia	30 controls	IL-6	Inflammation	Low
20. Rohleder, Marin, Ma, and Miller (2009)	18 glioblastoma (brain tumor) caregivers	19 matched controls	CRP	Inflammation	Moderate
			IL-6	Inflammation	
21. Fonareva, Amen, Zajdel, Ellingson, and Oken (2011)	20 dementia	20 noncaregivers free of "any major stress"	CRP	Inflammation	Low
			IL-6	Inflammation	
			TNF-α	Inflammation	
22. Kiecolt-Glaser et al. (2011)	58 dementia	74 noncaregivers	IL-6	Inflammation	Moderate
			TNF-α	Inflammation	
23. Gouin, Glaser, Malarkey, Beversdorf, and Kiecolt-Glaser (2012)	53 dementia	77 noncaregivers	CRP	Inflammation	Minimal
24. von Kanel, Mausbach, et al. (2012)	93 dementia, spouses only	43 married controls	Endothelin-1	Inflammation	Low
			IC adhesion	Inflammation	
			IL-8	Inflammation	
			IFN-γ	Inflammation	
			Plasminogen activator inhibitor	Inflammation	
			Serum amyloid A	Inflammation	
			TNF-α	Inflammation	
			VC adhesion	Inflammation	
25. von Kanel, Mills, et al. (2012)	118 dementia, spouses only	51 controls	IL-10	Inflammation	Low
			IL-12	Inflammation	
26. Wong et al. (2013)	55 caregivers of multiple conditions, spouses only	61 age- and sex-matched noncaregivers	% B lymphocyte	Immune	Minimal
			% cyto T	Immune	
			% NK	Immune	
			% T helper	Immune	
			% T suppressor	Immune	
			% total T cell	Immune	
27. Kang and Marks (2014)	49 adult child caregivers	914 noncaregivers	Inflammatory composite	Inflammation	Minimal
28. Kim and Ferraro (2014)	313 caregivers of "day-to-day activities"	1477 noncaregivers	CRP	Inflammation	Minimal
29. Miller et al. (2014)	33 glioblastoma (brain tumor) caregivers	47 controls "without major stressors … during the previous year"	CRP	Inflammation	Moderate
			NF-κB	Inflammation	
30. Bevans et al. (2016)	20 stem cell transplant caregivers	20 noncaregivers	IL-6	Inflammation	Low
			TNF-α	Inflammation	

Notes: CRP = C-reactive protein; IFN = interferon; IL = interleukin; NF-κB = nuclear factor kappa B; NK = natural killer; TNF = tumor necrosis factor; WBC = white blood cell; EBV VAC = Epstein-Barr virus capsid antigen; GM-CSF = Granulocyte-macrophage colony-stimulating factor; PHA = phytohemagglutinin; VC = Vascular Cellular.

studies represented randomly sampled estimates of an underlying caregiver versus noncaregiving control effect size distribution and used random-effects methods to estimate the overall average effect size and 95% confidence interval. The Q-statistic was examined as a test of the heterogeneity of individual study effect sizes.

We conducted one overall analysis for all 86 effects that were extracted from the 30 studies. We also conducted separate meta-analyses for the 42 effects that were characterized as tests of immune system functioning and the 44 effects that were characterized as tests of chronic inflammation. In all analyses, the standardized effects from each study and measure were coded such that higher scores on the biomarker indicated the direction expected from greater stress (e.g., more inflammation, lower measures of immune system functioning). Higher overall average effects, therefore, represented potential stress-induced effects on that biomarker in the caregivers compared with the noncaregiving controls. Additional analyses also examined the effect sizes found in studies that focused only on dementia caregivers and on subgroups of studies defined by different levels of potential bias.

Results

Descriptive Information of the Included Studies

Table 1 lists the 30 studies that were included in the meta-analysis in chronological order. These studies reported biomarker data collected from 1,848 caregivers and 3,640 noncaregiving controls. Biomarker indices of immune system function dominated the literature in the late 1980s and throughout the 1990s, whereas studies assessing inflammation became more prevalent in the decade of 2000–2010. Only 6 of the 30 studies (20%) enrolled 100 or more caregivers, and only 3 of the 30 studies (10%) were characterized by us as using population-based samples (Kang & Marks, 2014; Kim & Ferraro, 2014; Provinciali et al., 2004),

The studies varied substantially in their recruitment and inclusion methods and in the level of detail provided for the quality ratings (e.g., caregiving exposure). The overall average quality rating for each study in terms of potential bias is summarized in Table 1 (1.00–1.99 = minimal bias; 2.00–2.50 = low bias; 2.51–3.25 = moderate bias). The average quality ratings tended to improve over time, with more recent studies generally receiving lower potential bias ratings than earlier studies. Quality ratings within individual categories indicated higher possibilities for bias, on average, for caregiver and noncaregiver sample selection issues (e.g., poorly described inclusion criteria, insufficient matching, or possible confounding) and for caregiving exposure descriptions (e.g., hours of care per week, whether activities of daily living [ADL] or instrumental ADL care was provided) than for other aspects that were rated such as quality of the biomarker assays or statistical analysis

methods. It should be noted that several studies with overall "low" bias ratings nonetheless had "moderate" or even "high" bias ratings on sample selection or caregiving exposure features.

All 30 studies referred to the persons providing care as "caregivers" even if robust definitions of a caregiving were not always provided. Kim and Ferraro (2014) reported demographic information across four potentially stressed groups combined, so demographics specific to caregivers alone could not be determined in that study. Of the remaining 29 studies, 25 reported on the relationship between the caregiver and the care recipient, with 15 studies including only spouse caregivers, 2 (Kang & Marks, 2014; Provinciali et al., 2004) including only nonspouse caregivers, and 8 studies including a mix of spouses, adult children, and others. Across the 29 studies, 70% of the caregivers were female and the mean age was 64.8 years. Only one study specified a requirement that the caregiver had to provide assistance with ADL (Wong et al., 2013). The number of caregiving hours per day was reported by eight studies with a mean number of 8.7 hr/day. Twenty studies referred to the living arrangements of the care recipient and caregiver. The spouse-only studies all described living with the care recipient, whereas 30%–72% of the caregivers in the five other studies reporting living arrangements indicated that the caregivers lived with the care recipients.

Meta-analytic Findings

The results of the random-effects models for the meta-analyses are summarized in Table 2. The analysis of all 86 effects extracted from the 30 studies in Table 1 yielded a point estimate of $d = 0.164$ ($SE = 0.042$, 95% CI = 0.081, 0.247). This overall effect is somewhat below the typical "small" effect size of $d = 0.20$ as defined by Cohen (1988). An effect of $d = 0.20$ corresponds to a group difference that explains 1% of the variance in the outcome measure, so the caregiving versus control difference of $d = 0.164$ accounted for less than 1% of the total variance of the biomarker measures. An examination of the 95% CIs from the individual studies indicated a high degree of study-to-study variability, but the Q-statistic of heterogeneity only approached conventional levels of statistical significance ($Q = 41.3$, $df = 29$, $p = .064$).

The separate meta-analyses for grouped immunity and inflammation biomarkers across all studies indicated that the random-effects model estimate from the 42 immunity effects ($d = 0.217$) was somewhat larger than the corresponding estimate from the 44 inflammation effects ($d = 0.142$). An examination of the individual biomarkers listed in Table 1 indicates that only two biomarkers were assessed in more than five studies. For IL-6, an effect of $d = 0.134$ ($p = .129$) was observed across nine studies, and for CRP, an effect of $d = 0.152$ ($p = .117$) was observed across eight studies.

Table 2. Meta-analysis Random-Effects Estimates

Type of analysis	Number of studies	Number of effects	*d*	*SE*	*p*	95% CI	*Q*-statistic of heterogeneity	*p*
Total								
Overall	30	86	0.164	0.042	<.001*	0.081–0.247	41.3	.064
Immune	12	42	0.217	0.066	.001*	0.088–0.347	13.4	.267
Inflammation	20	44	0.142	0.053	.008*	0.057–0.246	30.0	.052
Dementia caregivers								
Overall	21	66	0.188	0.042	<.001*	0.105–0.271	19.0	.519
Immune	10	33	0.241	0.065	<.001*	0.004–0.113	12.6	.184
Inflammation	13	33	0.155	0.052	.003*	0.052–0.257	11.1	.521
Minimal or low bias studies								
Overall	19	53	0.086	0.038	.028*	0.009–0.162	19.1	.386
Immune	7	19	0.197	0.081	.015*	0.038–0.355	7.7	.262
Inflammation	14	34	0.059	0.045	.194	-0.030–0.147	14.1	.370
Moderate bias studies								
Overall	11	33	0.302	0.095	.002*	0.116–0.489	16.9	.076
Immune	5	23	0.272	0.129	.035*	0.019–0.525	5.5	.236
Inflammation	6	10	0.356	0.153	.020*	0.056–0.655	11.4	.045

Notes: CI = confidence interval.

*p < .05.

Twenty of the studies included in this meta-analysis included samples of dementia caregivers only, and one study (Reese, Gross, Smalley, & Messer, 1994) reported data separately for dementia and stroke caregivers. Table 2 summarizes the effect sizes from the meta-analyses for these 21 studies with samples of dementia caregivers. Those effect sizes are only slightly larger than those obtained across all caregiving samples and are still in the "small" effect size range.

Separate meta-analyses were conducted on the effects from the 19 studies that had overall quality ratings of 2.50 or less (i.e., the minimal and low potential bias designations in Table 1) and for the 11 studies with moderate overall potential bias. These analyses are also summarized in Table 2. Interestingly, the overall analysis for minimal or low bias studies revealed a very small effect for caregiving (*d* = 0.086), and the analysis focusing on the 34 effects of inflammation from these minimal or low bias studies yielded an effect (*d* = 0.059) that was not significantly different statistically from a null effect of no difference between caregivers and noncaregivers. Conversely, the moderate bias studies showed much stronger effects, with the overall effect (*d* = 0.302, *p* = .002) being more than 3.5 times larger than the corresponding effect from the low bias studies.

Of the five effects extracted from the three population-based studies (Kang & Marks, 2014; Kim & Ferraro, 2014; Provinciali et al., 2004), none showed a statistically significant difference between caregivers and noncaregiving controls. Only one population-based study (Kim & Ferraro, 2014) involved a comparison of more than 100 caregivers and 100 noncaregivers. That study was limited to CRP and found no difference between caregivers and controls on this measure of inflammation.

Discussion

The results of this systematic review and meta-analysis suggest that family caregiving is associated with statistically significant effects on measures of immunity and inflammation collected from baseline blood samples. The overall effect size of 0.164 was highly significant statistically (*p* < .001), and analyses grouped by biomarker type tended to indicate somewhat stronger effects for immune system biomarker than for measures of inflammation. In general, though, the magnitude of the meta-analytic effects was close to or less than the 0.20 "small" effect size (Cohen, 1988). Contrary to widely accepted beliefs that dementia caregiving can have particularly strong effects on health-related biomarkers, associations remained in the small range (*d* = 0.188) when analyses were restricted to dementia caregivers only.

There are recurring features in the studies reviewed that warrant caution and indicate that more research is needed. The sample sizes used in this area of investigation are often quite small, with 15 of the 30 studies included in the meta-analysis having 50 or fewer caregivers. This led to wide study-specific confidence intervals and may have contributed to a pattern of findings being inconsistent from one study to the next (Allen et al., 2017). Although the findings were highly variable across studies, formal tests of heterogeneity were generally not statistically significant. Power for the heterogeneity tests may have been limited by the relatively small sample sizes used in many studies.

The generally small effect sizes suggest questionable clinical significance for individual family caregivers. Most effect sizes from the meta-analyses were less than 0.20, indicating that the caregiver versus control difference generally accounted for less than 1% of the variance in the outcome measures. By way of comparison, a recent meta-analysis indicated that obesity accounts for 13% of the variance in CRP (Choi, Joseph, & Pilote, 2013), whereas our analysis across eight studies found that caregiving status accounted for less than 1% of the variance in CRP. In a meta-analysis of possible race differences on caregiving variables, Pinquart and Sörensen (2006) characterized effects that explained "less than 1% of the variance" as being "too small to be meaningful" (p. 96). Vitaliano and colleagues (2003) also characterized similar effect sizes as "weak" and that "questions remain regarding their magnitudes and their clinical relevance" (p. 961). Vitaliano and colleagues proceeded to explain how even very small relationships that have little or no relevance at the individual person level might, nonetheless, still account for a nontrivial number of health events, such as myocardial infarctions, at the population level, due to the fact that millions of persons are serving in family caregiving roles.

The findings that the overall effect size was much smaller from studies with lower potential bias ratings and that none of the population-based studies found any significant effects for caregiving on these biomarkers are noteworthy and underscore possible concerns with sample selection biases from many of the convenience samples. There is considerable evidence that caregivers recruited in convenience samples have more psychological distress than those identified in population-based studies (Pinquart & Sörensen, 2003; Pruchno et al. 2008). In addition, many of the studies reviewed here that used convenience samples provided very little information on the recruitment or characteristics of the noncaregiving control participants. In almost all cases, recruitment and enrollment methods appeared to differ for caregivers and noncaregiving controls. When recruitment information was provided for noncaregivers, these participants were often characterized as consisting of socially active persons who were recruited from community organizations, senior centers, alumni newsletters, church groups, or other social organizations. "Volunteers" for research projects from such sources can be expected to be relatively healthy and active (Anderson et al., 2014), and findings of biomarker vulnerability in caregivers using this type of research design may simply reflect greater biomarker resilience among the more socially active, healthy volunteer control groups.

When examining our findings alongside the conclusions from the previous narrative reviews of this literature, it is difficult to concur with the more definitive conclusions offered by Lovell and Wetherell (2011) or Fonareva and Oken (2014) that caregiving is consistently associated with biomarker changes of inflammation or dysregulation of the immune system. The more indeterminate "mixed" interpretations offered by Allen and colleagues (2017) or the lack of an association as described by Potier and colleagues (2018) seem to be more in line with the bulk of the research evidence to date. Future research should continue to introduce greater methodological rigor when examining possible biomarker vulnerabilities associated with long-term caregiving. Studies of large and representative, population-based samples with similar recruitment methods for caregivers and noncaregiving controls are needed. Such studies should specify clear inclusion criteria to ensure that the caregivers are actually providing care, and more careful noncaregiving matching criteria to control possible confounding with social activity or other variables. Future studies should also look more carefully at key caregiving subgroups such as those defined by relationship type (e.g., spouse vs. nonspouse caregiving) and the clinical condition of the care recipients (e.g., caring for persons with or without dementia). In certain longitudinal epidemiological investigations, it would also be advantageous to look at changes in biomarkers within individuals who have transitioned from a noncaregiving status into a caregiving role during the course of their participation in those studies. To our knowledge, such intraperson changes on biomarkers in response to the onset of caregiving have never been reported in the research literature.

Limitations to our systematic review and meta-analysis include unknown impacts of some study eligibility decisions. Some otherwise relevant studies were excluded from the meta-analyses because insufficient data were reported in the publication or for other eligibility reasons. For example, two additional population-based studies were identified by our systematic review but not included in the meta-analysis. Dich, Lange, Head, and Rod (2015) collected data on CRP and IL-6 as part of an assessment of allostatic load (AL) but did not report these individual biomarker data. High caregiving burden was found to be associated with higher AL levels, but low caregiving burden was associated with lower AL levels such that the overall caregiving effect appeared to be minimal. Shivpuri, Gallo, Crouse, and Allison (2012) examined CRP as a function of gender and stress associated with a "serious ongoing health problem in someone close to you." This undoubtedly included many caregivers but also included "individuals who are not direct caregivers." They termed this "sympathetic-caregiving stress" and found a very small but statistically significant overall association with CRP that was significantly stronger for women than for men.

Other potential limitations may have been introduced by our decisions to merge effect sizes across multiple different biomarkers into overall, immune, and inflammation outcome categories. Immune and inflammation biomarkers interact, and these dynamic relationships among the biomarkers were not accounted for in our meta-analysis or in most of the studies we reviewed. Although most individual biomarkers were not assessed frequently enough to conduct separate meta-analyses for each measure, we did conduct

separate analyses for IL-6 and CRP and found similar effect sizes as those obtained from more inclusive and heterogenous analyses. Modifying the biomarker categorization decisions or the eligibility criteria for including additional studies would lead to some adjustments in the effect sizes estimated, although we believe such adjustments would be minimal and that the estimated meta-analytic effects would remain near or less than the $d = 0.20$ threshold for a small effect size.

Another limitation of our review and meta-analysis is the preponderance of studies of caregivers of persons with dementia. These studies, therefore, are over-representative of dementia caregivers, who represent only a minority of all caregivers (National Alliance for Caregiving and the AARP, 2015). Because the effect size was slightly larger for dementia caregivers than for all caregivers, the caregiver versus control effects appear to even smaller for the caregivers of persons who are not afflicted with dementia, but additional research is needed for this group to confirm such a trend.

In our view, it is all too common for ongoing research efforts and public health statements on caregiving to perpetuate the narrative that caregiving is an established risk factor for compromised physical health, with clear immune system or proinflammatory pathways often highlighted as possible mechanisms. A recent article in the New York Times (2016), for example, stated that "researchers have found that the human immune system can be weakened by stress and strain for up to three years after caregiving ends. As a result, caregivers can be more prone to having serious illnesses. Yet they rarely complain." Such media reports are often based on statements from researchers that selectively draw on findings from studies reviewed here. Caregiving can be stressful, and caregivers sometimes do need additional supports and services to manage the care of their family members, but caregiving can also lead to personal growth, purpose in life, and health benefits (Roth et al., 2015). Developing a balanced and empirically supported narrative about caregiving that recognizes it as a stressful but also an expected and potentially healthy part of the adult life cycle (Qualls, 2016) is an important challenge for scholars who continue to conduct research on health effects of caregiving.

In summary, there seems to be little replicable research evidence that supports the hypothesis that the stress of family caregiving leads to clinically significant alterations of circulating biomarkers of immunity or inflammation. Overall, average effect sizes are small, and associations reported from multiple convenience samples are often inconsistent. Higher quality studies and population-based studies rarely find statistically significant elevations in circulating inflammatory biomarkers in caregivers compared with appropriately matched noncaregiving controls. Public statements by researchers and health policy experts that continue to perpetuate the physical health risks of caregiving and point to biomarker studies as evidence often pay insufficient attention to the complexities of the studies in this area, the small average effect sizes, the potential for significant selection biases in studies with small convenience samples, and the mixed or inconsistent findings that are usually uncovered in this area of investigation.

Conflict of Interest

None reported.

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