The transition to family caregiving and its effect on biomarkers of inflammation

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Chronic stress has been widely proposed to increase systemic inflammation, a pathway that may link stress with a heightened risk for many diseases. The chronic stress–inflammation relationship has been challenging to study in humans, however, and family caregiving has been identified as one type of stressful situation that might lead to increased inflammation. Previous studies of caregiving and inflammation have generally used small convenience samples, compared caregivers with poorly characterized control participants, and assessed inflammation only after caregivers provided care for extended periods of time. In the current project, changes over a 9-y period were examined on six circulating biomarkers of inflammation for 480 participants from a large population-based study. All participants reported no involvement in caregiving prior to the first biomarker assessment, and 239 participants then took on extensive and prolonged family caregiving responsibilities at some point prior to the second biomarker assessment. Incident caregivers were individually matched on multiple demographic and health history variables with participants who reported no caregiving responsibilities. Of the six biomarkers examined, only tumor necrosis factor alpha receptor 1 showed a significantly greater increase in caregivers compared with controls. This effect was small ($d = 0.14$), and no effects were found for a subset of 45 caregivers who were living with a spouse with dementia. These results are consistent with recent meta-analytic findings and challenge the widespread belief that caregiving is a substantial risk factor for increased inflammation. Future research is warranted on factors that may account for stress resilience in family caregivers.

family caregiving | inflammation | biomarkers | chronic stress

Chronic stress has been widely studied as a possible factor leading to systemic inflammation, compromised immune system functioning, and increased risk for certain diseases (1, 2). Circulating biomarkers of inflammation such as interleukin 6 (IL-6), C-reactive protein (CRP), and tumor necrosis factor alpha receptor 1 (TNFR1) have been linked to loneliness (3), depression (4), and mortality (5, 6) in middle-aged and older adults. Family caregiving has been proposed as a prototypical, naturally occurring chronic stressor that can lead to negative impacts on inflammation, immunity, and illness (7–11), and biomarkers of inflammation provide a promising avenue to further investigate these potential mechanisms (12).

Numerous studies have examined whether caregivers have elevated inflammatory biomarkers compared with noncaregiving controls (13, 14). A recent systematic review and meta-analysis of this literature conducted by our group revealed that 1) most previous studies of caregiving and inflammatory biomarkers used small convenience samples of persons caring for a family member with dementia and compared them with poorly described noncaregiving controls; 2) the overall average effect of caregiving on inflammation markers was statistically significant but of questionable clinical significance; 3) no population-based samples found significant differences between caregivers and controls on biomarkers of systemic inflammation; and 4) meta-analytic effects across the two most frequently assessed biomarkers, IL-6 and CRP, showed no difference between caregivers and controls (15). One important weakness in the existing literature is that biomarker measurements were always done only after caregivers had already been providing care to their family members, usually for several years. We found no previous report in the literature where biomarkers were assessed in a longitudinal fashion, with an initial assessment occurring before individuals took on sustained caregiving responsibilities.

Much of the rationale for studying associations between family caregiving and stress-related biomarkers is based on the premise that caregiving stress is a risk factor for health declines (16) and early mortality (17). Systematic reviews and meta-analyses have generally concluded that caregivers, on average, report more symptoms of depression and other psychological consequences of stress than noncaregiving controls (18–20), but most caregivers also report positive aspects of their caregiving experiences (21). Associations of caregiving with measures of physical health have often been found to be inconsistent and vary on factors such as whether convenience or more representative, population-based samples have been used (19, 22). In addition, several

Significance

Family caregiving has been proposed as a type of chronic stress that may lead to health risks through increased systemic inflammation. However, most previous studies of caregiving and inflammation have used small convenience samples and compared caregivers with poorly characterized noncaregiving controls. In this prospective investigation of 480 participants over a 9-y period, only one of six biomarkers showed a significantly larger increase in persons who became caregivers over that time period compared with noncaregiving controls. The size of this one effect was small, and no biomarker effects were found for a subset of strained spouse caregivers of persons with dementia. The findings are consistent with other population-based studies and suggest minimal systemic inflammation in response to chronic caregiving stress.

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Data deposition: In cooperation with the institutional review board of the University of Alabama at Birmingham, the REGARDS project facilitates data sharing through formal data-use agreements. Investigators who wish to access the data should send their requests to regardsadmin@uab.edu.

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large studies have found that caregivers have significantly lower mortality rates than comparison samples of persons who are not caregivers (21, 23–27), findings that conflict with a widely cited earlier study that reported increased mortality among spouse caregivers who reported some caregiving strain compared with noncaregiving spouses (17).

The present paper reports the results of a prospective, within-person analysis of biomarker changes in individuals who transitioned into a family caregiving role at some point over a 9-y time period while participating in a national longitudinal study. Caregivers were compared with matched noncaregiving controls who were also assessed over this same time period. All participants were free of caregiving activities prior to the first blood sample taken. Those who became caregivers were carefully screened to ensure that they were providing sufficient levels of care (28). We hypothesized that these incident family caregivers would show greater increases over time on biomarkers of systemic inflammation compared with the noncaregiving controls. We also hypothesized that caregiver vs. control differences would be most evident among a subset of caregivers who were coresiding spouses of persons with dementia and who reported at least some caregiving strain.

Methods

Overview of the REGARDS and Caregiving Transitions Study Projects. The Reasons for Geographic and Racial Differences in Stroke (REGARDS) study is a national longitudinal investigation of 30,239 adults of the United States who were 45 or more years of age when enrolled in 2003 to 2007. Exclusion criteria included self-reported race other than African American or white, previous diagnosis of cancer requiring chemotherapy/radiation, or residence in or on a waiting list for a nursing home. African Americans and residents from the southern "stroke belt" region of the United States were oversampled by design. Additional information on the design, sampling, enrollment, and follow-up procedures used in the REGARDS study have been described in detail elsewhere (5, 29).

The Caregiving Transitions Study (CTS) is a nested case–control study within the REGARDS study that enrolled REGARDS participants who transitioned into a family caregiving role at some point between the first and second REGARDS in-home assessments. For each enrolled caregiver, an individually matched REGARDS participant who had never been a caregiver throughout the same time period was enrolled. Among the 597 REGARDS participants who were determined to be eligible for the CTS and invited to participate, 502 (84%) agreed to do so.

Both the REGARDS study and the CTS were reviewed and approved by the institutional review boards of the University of Alabama at Birmingham and each participating institution. Written informed consent was obtained from all participants prior to the first blood sample.

Data Collection Procedures. As part of their participation in the REGARDS project, each participant completed 1) a baseline computer-assisted telephone interview (CATI) that obtained detailed demographic information, stroke risk factor data, health history measures, and original caregiving status; 2) an initial in-home assessment conducted within a few weeks after the baseline CATI that collected biological specimens including blood and urine samples; 3) a second follow-up CATI to get updated risk factor information an average of 9.3 y after the baseline CATI; and 4) a second in-home assessment an average of 9.4 y after the first in-home assessment to collect updated biological specimens. Both in-home assessments were conducted by trained examiners and phlebotomists employed by Examination Management Services, Inc.

Among the queries in the baseline CATI, REGARDS participants were asked "Are you currently providing care on an ongoing basis to a family member with a chronic illness or disability? This includes any kind of help such as watching your family member, dressing or bathing this person, arranging care, or providing transportation?" A total of 26,446 answered "no" and were designated as noncaregivers at the REGARDS baseline. In a REGARDS caregiving screening CATI conducted an average of 11.8 y after the baseline CATI, updated caregiving status information was collected. Specifically, during this screening CATI, REGARDS participants were asked "Are you currently providing care on an ongoing basis to a family member, friend, or neighbor with a chronic illness or a disability? This would include any kind of regular help with basic activities such as dressing, bathing, grooming this person, managing bills, arranging for medical care, watching or supervising this person, or providing transportation." Participants who answered "yes" to this question from the caregiving screening CATI and "no" to the similar question from the REGARDS baseline CATI ∼12 y earlier were further screened for eligibility to be enrolled as incident caregivers in the CTS. Those who answered "no" to the caregiving status questions at both interviews were potentially eligible to serve as matched noncaregiving controls.

Participants who reported transitioning into a caregiving role at the caregiving screening CATI were further asked 1) their relationship to the person they were providing care for; 2) whether they lived with that person; 3) whether that person has "Alzheimer's disease, another form of dementia, or serious memory problems"; 4) how many hours of care they provided per week to that person; 5) how many years they have been providing care because of that person's disability or health problem; and 6) how much of "a mental or emotional strain" it was on them to provide this care (no strain, some strain, a lot of strain). Only persons who provided at least 5 h of care per week and had been providing care long enough to have been caregivers for at least 3 mo prior to the second REGARDS in-home assessment were eligible to be enrolled as incident caregivers. The procedures used to screen, determine eligibility, match, and enroll CTS participants from the parent REGARDS study are described in more detail in a previous paper (28).

Participants. A total of 251 incident caregivers and 251 matched controls were successfully enrolled in the CTS. These caregivers were identified during the caregiving screening CATI (described above) and were later confirmed to be eligible to participate during a subsequent CTS telephone interview. During this CTS interview, each incident caregiver reported the year and month that they started providing assistance to their family member or friend because of a disability or chronic illness. In order to be eligible, this onset of caregiving had to be at least 6 mo after the first REGARDS in-home assessment and at least 3 mo before the second REGARDS in-home assessment. Therefore, all caregivers were free of caregiving activities prior to a first blood sample and were engaged in caregiving activities at the time of the second blood sample. In addition, all enrolled caregivers reported their care recipient received assistance with at least one activity of daily living (ADL) or instrumental activity of daily living (IADL), they were providing at least 5 h of care per week, and they either lived with or within 50 miles of their care recipient. Caregivers were administered the AD8 (30), and all caregivers who reported providing care to a person with dementia or serious memory problems scored above the threshold of 2 or more indicators for dementia on the AD8. Previous analyses have confirmed that the incident caregivers in the CTS reported substantial and sustained exposure to caregiving stress, and that they experienced significant increases in depressive symptoms and perceived stress, on average, after their transitions to the caregiving role (28, 31).

Once an eligible incident caregiver was enrolled in the CTS, a participant from the REGARDS study who matched that caregiver on seven factors (age [±5 y], sex, race, education level, marital status, self-rated health, and self-reported history of serious cardiovascular disease from the REGARDS baseline interview) and who reported no significant family caregiving responsibilities throughout his or her period of participation in the REGARDS study was enrolled as a noncaregiving control participant. In addition, potential noncaregiving controls who would be matched to spouse caregivers had to be married, and potential controls who would be matched to an adult child caregiver had to have at least one living parent. Previous analyses have confirmed the similarity of the enrolled caregivers and controls, including findings that the two groups had similar levels of depressive symptoms and health-related quality of life before the caregivers transitioned into the caregiving role (28).

Biomarker Assay Methods. Fasting morning blood samples were collected by trained phlebotomists from participants at their homes during both of the REGARDS in-home assessments. Samples were centrifuged and shipped overnight on ice to the Laboratory for Clinical Biochemistry Research at the University of Vermont. Samples were then recentrifuged and stored at −80 °C. Additional details on the standardized collection, shipping, and processing of biologic samples in the REGARDS study are available elsewhere (32). The time interval between the first and second REGARDS in-home assessments ranged from 7.6 to 12.4 y and averaged 9.3 y for the participants included in the present analyses.

Six circulating biomarkers of inflammation were assayed for the present analyses. Biomarkers were chosen based on their use in previous studies of caregiving (15) and on whether valid measures could be obtained from frozen blood samples that were several years old. High-sensitivity C-reactive protein was measured using a BNII nephelometer (high-sensitivity CRP; Dade

Behring). The interassay coefficients of variation (CVs) were 3 to 6% with a detection level of 0.16 μg/mL. D dimer was assessed using an immunoturbidimetric assay (Liatest D-DI; Diagnostica Stago; 00515) on a Sta-R analyzer (Diagnostica Stago). The lower limit of detection range of the assay was 0.01 to 20 μg/mL and interassay CVs were 1.48%. Tumor necrosis factor alpha receptor 1 was measured using an R&D Systems enzyme-linked immunosorbent assay (DRT100). The detectable range was 78 to 5,000 pg/mL with an interassay CV of 3.4%. Interleukin 2, IL-10, and IL-6 were measured with a Meso Scale Discovery (MSD) Proinflammatory panel (K15049G). MSD assays were read using a MESO QuickPlex SQ 120. Detectable ranges were as follows: IL-2: 0.07 to 2,860 pg/mL, interassay CV 18.12%; IL-10: 0.02 to 674 pg/mL, interassay CV 10.6%; IL-6: 0.05 to 1,500 pg/mL, interassay CV 5.2%.

The present analyses are based on data from 239 incident caregivers and 241 matched noncaregiving controls for whom at least one of the six biomarker measures was obtained from both of the REGARDS in-home assessments. Among the 502 total participants enrolled in the CTS, usable data from biomarker assays were obtained for between 463 (92%) participants for CRP and 471 (94%) participants for IL-6 and IL-2. For IL-2, 25% of levels from the first assessment and 16% of the levels from the second assessment were below the detectable range, and 0.034 was inserted as the value for these observations, which represents the midpoint between 0 and the lowest detectable score of 0.068.

Statistical Analysis. Frequency distributions were examined at both the first (T_1) and second (T_2) assessments for all six biomarkers and were observed to be highly positively skewed. Consistent with the approach adopted by Jenny and colleagues (33), a log (base 2) transformation was applied to each biomarker at each assessment. In the analytic models, the dependent variable was change over time (Δ) and defined as the difference between T_2 and T_1 on the log (base 2) scores: $\Delta = \text{Log}_2\,(Y_2) - \text{Log}_2\,(Y_1)$, where Y_2 and Y_1 represent the raw values of the specific biomarker of interest at T_2 and T_1, respectively. This is mathematically equivalent to $\Delta = \text{Log}_2\,(Y_2/Y_1)$ and results in a scale of "doubling over time" for the raw biomarker measure (33). That is, when $\Delta = 0$, the biomarker is unchanged over time; when $\Delta = 1$, the level of the biomarker has doubled from T_1 to T_2; and when $\Delta = -1$, the biomarker value at T_2 is 1/2 of its value at T_1.

After the log transformations, each biomarker was further examined for possible outliers using the Tukey (34) interquartile range (IQR) method. Specifically, the IQR, defined as the difference between the 75th (Q3) and 25th (Q1) percentiles, was calculated, and all values that were more than 3*IQR above Q3 were designated as extreme positive outliers [also known as being outside of Tukey's (34) "outer fences"] and recoded as missing. There were no values that were less than 3*IQR below Q1. Using this method, no extreme positive outliers were detected and recoded for CRP, TNFR1, or D dimer. For IL-2, IL-6, and IL-10, values above 0.95, 8.23, and 2.22 pg/mL, respectively, were identified as extreme outliers and recoded as missing. For IL-2 and IL-6, 0.7% of the values (i.e., 7 out of every 1,000) were identified as extreme outliers, and for IL-10, 1.5% of the values were designated as being extreme outliers. Overall, less than 0.5% (<1 out of every 200) values were designated as extreme outliers and recoded as missing.

Analyses of covariance were conducted to examine the predictors of Δ over time. The primary predictor of interest was a dichotomous indicator of caregiver status (incident caregiver vs. control). Covariates in all models were the $\log_2$ score for that biomarker at T_1, and sex, race, and age at T_1. Two sets of analyses were conducted. One set of analyses included all cases (caregivers and controls) who had data available to be analyzed on each biomarker after cases with missing data were excluded, including the recoding of extreme outliers. A second set of analyses was restricted to matched cases with complete data, that is, only dyads in which the caregiver and his or her individually matched control had data to be analyzed on that biomarker. For all models, caregiver vs. control effects were tested for statistical significance ($P < 0.05$), and standardized effect sizes (d) were calculated by dividing the covariate-adjusted differences (caregiver − control) on the Δ change scores by the SD of $\log_2$ of that biomarker observed at T_1. We used Cohen's (35) definitions to interpret effect size, with a $d = 0.20$ considered a "small" effect.

In addition to analyzing all caregivers and controls, an additional set of analyses was conducted for a subset of spouse caregivers of persons with dementia and their individually matched controls. Specifically, we selected 45 dementia caregivers who were all coresiding spouse caregivers, reported either "some" or "a lot" of caregiving strain, and had been providing caregiving assistance for at least 1 full year before the second blood samples were collected. These caregivers were considered to be at particularly high risk for significant caregiving stress and were thought to be more directly comparable to many of the caregivers included in previous studies of caregiving and inflammatory biomarkers (13–15).

Data Availability. In cooperation with the Institutional Review Board of the University of Alabama at Birmingham, the REGARDS project facilitates data sharing through formal data use agreements. Investigators who wish to access the data and code for these analyses should send their requests to regardsadmin@uab.edu.

Results

Descriptive information for the caregiving and control samples is provided in Table 1. As in our previous analyses (28), the retained caregiver and control samples were very comparable in terms of sex, race, age, education, and marital status. Caregivers averaged over 3 y of care provision and over 40 h of caregiving per week. Over 40% reported providing care for an individual with dementia or severe cognitive impairment.

Table 1. Descriptive information for the incident caregivers and matched noncaregiving controls

Variable	Incident caregivers (n = 239)	Noncaregiving controls (n = 241)
Sex, female, *N* (%)	155 (65)	157 (65)
Race, African American, *N* (%)	85 (36)	84 (35)
Education at REGARDS enrollment, *N* (%)		
College graduate	101 (42)	112 (47)
Some college	73 (31)	65 (27)
High school graduate	56 (23)	54 (22)
Less than high school graduate	9 (4)	10 (4)
Marital status at Transitions interview, *N* (%)		
Married/cohabiting	180 (75)	183 (76)
Widowed	18 (8)	22 (9)
Divorced/separated	25 (10)	23 (10)
Single/never married	16 (7)	13 (5)
Age at REGARDS enrollment, y, M (SD)	59.9 (7.7)	59.9 (7.2)
Age at REGARDS second in-home assessment, y, M (SD)	69.1 (7.9)	69.1 (7.4)
Age at Transitions interview, y, M (SD)	71.6 (8.0)	72.2 (7.7)
Duration between REGARDS first and second in-home assessments, y, M (SD)	9.3 (0.9)	9.3 (0.8)
Duration of caregiving before REGARDS second in-home assessment, y, M (SD)	3.4 (2.4)	—
Duration of caregiving before Transitions interview, y, M (SD)	5.8 (2.5)	—
Amount of caregiving time per week at Transitions interview, h, M (SD)	43.2 (29.3)	—
Caregiver's relationship with care recipient, *N* (%)		—
Spouse	120 (50)	
Adult child	60 (25)	
Other	59 (25)	
Care recipient's condition, *N* (%)*		—
Dementia/serious cognitive impairment	111 (46)	
Physical disability/frailty	43 (18)	
Stroke	28 (12)	
Other diseases or disabilities	94 (39)	
Caregiving strain		—
None	36 (15)	
Some	140 (59)	
A lot	63 (26)	

*Percentages exceed 100% because several caregivers reported more than one condition.

Descriptive data for the raw biomarker data (with outliers removed but before log transformation) are provided in Table 2. After log transformation, biomarker levels at T_1 for the participants who later transitioned into caregiving were not significantly different from those levels for controls. All P values for these baseline comparisons exceeded 0.10 with the exception of the comparison for IL-6, where caregivers had elevated levels compared with controls that approached statistical significance ($P = 0.062$). In order to control for this marginal difference and the association between baseline level and change over time, the baseline biomarker level was included as a covariate in the models that tested for differential change in biomarkers over time. Other unadjusted analyses indicated that five of the six biomarkers showed statistically significant increases over time (*SI Appendix*).

The results of the caregiver vs. control comparisons after adjusting for the covariates are summarized in Table 3. The covariate effects indicated that the T_1 value of the biomarker was significantly and negatively related to the $T_2 - T_1$ change score for each biomarker (all $P < 0.0001$ except for TNFR1, where $P = 0.011$). This indicated a typical effect of initial values where positive changes tended to be larger for individuals who had relatively low values at T_1. Participant age was also related to change on four biomarkers (IL-6, TNFR1, D dimer, and IL-2; all P values < 0.005), with older participants showing greater increases on each biomarker after adjusting for the other covariates. In addition, participant race was related to change in D dimer, with blacks showing greater increases over time than whites ($P < 0.0001$).

The standardized caregiving vs. control differences on change as reported in Table 3 were all quite small and none exceeded 0.14 SD units. Thus, all effects were below the prespecified small effect size benchmark. On the 12 caregiving vs. control comparisons conducted, only the matched case analysis for TNFR1 showed a statistically significant effect ($P = 0.033$), with caregivers showing greater covariate-adjusted increases across time than their matched noncaregivers. The analysis of TNFR1 that included all cases, however, only approached conventional levels of statistical significance ($P = 0.095$). In addition, a trend approaching significance was found for caregivers to have smaller increases on IL-2 than controls ($P = 0.072$) but the matched case analysis for that biomarker did not yield a statistically significant difference.

The analyses that were conducted for the subset of 45 coresiding spouse caregivers of persons with dementia who reported strain compared with their 45 individually matched noncaregiving controls revealed no significant differences on any biomarkers (all P values > 0.25). Thus, there was no evidence that this subset of highly stressed caregivers showed significant changes on any of these six biomarkers of inflammation over the 9-y period compared with their matched controls.

Table 3. Effects of caregiver vs. control comparisons on 9-y changes in inflammatory biomarkers

Variable/ comparison	Caregivers N	Caregivers Adj Δ ($T_2 - T_1$)	Controls N	Controls Adj Δ ($T_2 - T_1$)	Diff	*D*	*P*
IL-6							
All cases	228	0.357	237	0.278	0.079	0.099	0.226
Matched cases only	216	0.352	216	0.260	0.093	0.115	0.159
CRP							
All cases	233	−0.040	234	−0.132	0.092	0.058	0.425
Matched cases only	217	−0.050	217	−0.123	0.073	0.046	0.545
TNFR1							
All cases	230	0.271	239	0.235	0.036	0.105	0.095
Matched cases only	220	0.271	220	0.224	0.047	0.137	0.033
D dimer							
All cases	230	0.717	238	0.627	0.090	0.079	0.326
Matched cases only	219	0.697	219	0.621	0.076	0.066	0.427
IL-2							
All cases	229	0.104	236	0.236	−0.102	−0.109	0.072
Matched cases only	218	0.123	218	0.235	−0.112	−0.119	0.141
IL-10							
All cases	224	0.069	229	0.125	−0.056	−0.071	0.347
Matched cases only	206	0.066	206	0.155	−0.089	−0.113	0.167

All analyses conducted after Tukey extreme outliers were recoded as missing and adjusted for the following covariates: sex, race, age at T_1, and $\log_2$ value at T_1. *D*, standardized difference (Diff/SD of $\log_2$ value at T_1); Diff, difference in adjusted Δs (caregivers − controls).

Discussion

The results of these analyses add to the growing literature on the biological and physical health effects of chronic stress associated with family caregiving. The CTS used innovative methods and a population-based sample to examine the impact of caregiving on inflammatory biomarkers prospectively by comparing biomarker results from before and after the transition into the caregiving role. Our findings generally revealed that the transition to family caregiving did not significantly increase inflammatory biomarker levels in comparison with a carefully matched control group of noncaregivers over a similar 9-y period. These results are consistent with previous cross-sectional findings from other population-based studies that have found no associations between family caregiving and inflammatory biomarker levels (36–38).

Table 2. Raw means and SDs on biomarkers of systemic inflammation for incident caregivers and matched noncaregiving controls

Measure	Incident caregivers T_1 M	Incident caregivers T_1 SD	Incident caregivers T_2 M	Incident caregivers T_2 SD	Noncaregiving controls T_1 M	Noncaregiving controls T_1 SD	Noncaregiving controls T_2 M	Noncaregiving controls T_2 SD
IL-6, pg/mL	0.80	0.56	1.04	0.82	0.72	0.42	0.90	0.67
CRP, μg/mL	3.11	3.41	3.57	5.18	3.58	6.41	3.08	4.70
TNFR1, pg/mL	1346.70	338.30	1645.16	524.53	1307.37	309.14	1549.96	428.27
D dimer, μg/mL	0.46	0.45	0.75	0.82	0.46	0.49	0.71	0.96
IL-2, pg/mL	0.12	0.10	0.12	0.08	0.10	0.07	0.13	0.08
IL-10, pg/mL	0.26	0.25	0.26	0.17	0.23	0.13	0.27	0.19

The present results are particularly illuminating in that, unlike previous population-based studies, we were able to assess biomarker levels before the transition into caregiving, to confirm that caregivers were providing care to persons who needed assistance with ADLs or IADLs, and to enroll only caregivers who were providing care for a minimum of 5 h/wk. Results reported elsewhere confirmed that the caregivers in the CTS experienced significant increases in depressive symptoms and perceived stress, on average, and worsening health-related quality of life (31). Standardized effect sizes from those analyses of self-reported distress and quality of life generally exceeded Cohen's (35) benchmark of the medium effect size (0.50 SD units). It is noteworthy, therefore, that this group of caregivers did report typical and substantial elevations in subjective distress and other self-reported sequelae of the caregiving experience but did not show notable increases in systemic inflammation.

The family caregiving population is a diverse group that includes many caregiving relationships (e.g., spouse, adult child, other relative, neighbor, or friend) and provides assistance to care recipients with a wide range of medical conditions and disabilities (e.g., dementia, stroke-related impairments, mobility restrictions, or disabling sensory problems). In the biomarker literature, many studies have been limited to dementia caregivers, and often only to spouses of persons with dementia (15). This group of caregivers is thought to be particularly vulnerable to high levels of stress and high caregiving demands (18, 39). However, even when we restricted our analyses to 45 coresiding, strained, spouse caregivers of persons with dementia compared with their matched controls, we did not detect any significant associations between this type of caregiving and changes in inflammatory biomarkers. Although the sample size of 90 participants for this analysis was substantially reduced, it is still larger than the majority of previous studies of biomarker differences that have been conducted using convenience samples (15).

The one exception to our general lack of statistically significant effects for caregiving was found for TNFR1, where a significantly greater increase was found for caregivers compared with controls in the analysis that was restricted to 220 caregiver and 220 control dyads with complete TNFR1 data extracted from both blood samples. Interestingly, the standardized effect size from this analysis was 0.14 SD units, exactly the same standardized effect size we found across multiple inflammatory biomarkers extracted from 20 different studies in our recent meta-analysis (15). This 0.14 effect size is below Cohen's (35) small effect size of 0.20 and may be of questionable clinical significance (15). It is interesting to note that TNFR1 also showed the strongest longitudinal aging effect (*SI Appendix*), and it has been previously shown to be a relatively strong predictor of mortality (6). Although the TNFR1 effect did not achieve conventional levels of statistical significance when all data were included, this biomarker has not been analyzed as frequently in the caregiving literature as others, such as IL-6 and CRP, and deserves further investigation.

Future research might examine TNFR1 more closely as well as other biomarkers that might be more sensitive to particular causal pathways that potentially link caregiving stress to adverse health outcomes. Our analyses were limited to only six circulating biomarkers of inflammation, selected mostly to facilitate comparisons with previous studies, but there are undoubtedly other biomarkers that might better reflect the chronic stress of caregiving. This includes biomarkers of hormonal activation, such as salivary cortisol (40), and other indicators of both acute and chronic stress responses. It is also important to emphasize that, just because caregivers do not, on average, show elevations of certain biological indicators of physical health vulnerability, there are undoubtedly many individual caregivers who are still facing considerable stress and might benefit from evidence-based, stress-reducing interventions.

The aging of the human population around the world is placing heavy demands on families and communities to provide daily care for the expanding number of older adults with disabilities. In the United States alone, it is estimated that at least 17 million (41) and perhaps as many as 40 million (42) persons serve as informal or family caregivers for older adults. While some of these discrepancies are based, in part, on what constitutes "caregiving," there is no disagreement among the experts that the number of informal caregivers will be increasing dramatically over the next several years. While family caregiving is often characterized as a chronically stressful experience, it is also increasingly appreciated as a positive experience that may provide stress-buffering effects similar to those attributed to volunteerism (21, 43–45). Ongoing research on the overall physical health effects of caregiving should continue to reconcile these two complementary perspectives and advance our understanding of which particular persons might be truly at risk for poorer health outcomes due to the stress of caregiving.

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