Original Contribution

Association Between Informal Caregiving and Cellular Aging in the Survey of the Health of Wisconsin: The Role of Caregiving Characteristics, Stress, and Strain

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The pathophysiological consequences of caregiving have not been fully elucidated. We evaluated how caregiving, stress, and caregiver strain were associated with shorter relative telomere length (RTL), a marker of cellular aging. Caregivers ($n = 240$) and some noncaregivers ($n = 98$) in the 2008–2010 Survey of the Health of Wisconsin, comprising a representative sample of Wisconsin adults aged 21–74 years, reported their sociodemographic, health, and psychological characteristics. RTL was assayed from blood or saliva samples. Median T and S values were used to determine the telomere-to-single copy gene ratio (T/S) for each sample, and log(T/S) was used as the dependent variable in analyses. Multivariable generalized additive models showed that RTL did not differ between caregivers and noncaregivers (difference in log(T/S) = −0.03; $P > 0.05$), but moderate-to-high levels of stress versus low stress were associated with longer RTL (difference = 0.15; $P = 0.04$). Among caregivers, more hours per week of care, caring for a young person, and greater strain were associated with shorter RTL ($P < 0.05$). Caregivers with discordant levels of stress and strain (i.e., low perceived stress/high strain) compared with low stress/low strain had the shortest RTL (difference = −0.24; $P = 0.02$, $P_{\text{interaction}} = 0.13$), corresponding to approximately 10–15 additional years of aging. Caregivers with these characteristics may be at increased risk for accelerated aging. Future work is necessary to better elucidate these relationships and develop interventions to improve the long-term health and well-being of caregivers.

caregivers; caregiver strain; population-based studies; stress, psychological; Survey of the Health of Wisconsin

Abbreviations: SHOW, Survey of the Health of Wisconsin; T/S, telomere-to-single copy gene ratio.

Informal caregiving (i.e., providing unpaid care to a family member or friend with an illness or disability) is critical to the care of the aging and disabled in the United States (1). Such caregivers, however, are themselves at increased risk of poor health outcomes (2–13). As the number of adults and children requiring informal care rises (14), it is increasingly important to understand the health implications for caregivers.

Telomere length, a putative biological marker of cellular aging, may provide valuable information about the pathophysiological consequences of caregiving. Telomeres are DNA-protein complexes that cap the ends of chromosomes, protecting them from degradation during cell division (15). Telomeres generally shorten with age (16–24), and short telomere length has been associated with numerous health

conditions (18, 25–34) and earlier mortality (35–37), although evidence is conflicting (38–41). Short telomere length may be indicative of a poor biological state or higher disease risk (35).

Previous work has provided conflicting evidence for an association between caregiving and shortened telomere length (42, 43). However, perceived stress has consistently been associated with shorter telomeres or reduced telomere maintenance (42, 44–49). Stress theory and recent research suggest that the environment may play a critical role in explaining why some caregivers, but not others, experience elevated stress or adverse health outcomes (50). The details of a caregiver's role and experiences may be important environmental factors that might influence these outcomes and can be

readily monitored in the clinical setting. However, aside from 1 study examining duration of caregiving (42), the associations among caregiving characteristics, caregiver strain, and telomere length have yet to be examined. Elucidating these relationships will improve our understanding of the physiological impact of caregiving and help identify high-risk caregivers and potential points of intervention for improving caregiver outcomes.

In this study, we sought to determine the association between caregiving and telomere length in a population-based sample. Specifically, we aimed to determine whether and to what extent 1) caregivers had shorter telomeres than noncaregivers, 2) global perceived stress in the past year was associated with telomere length, and 3) caregiving characteristics and caregiver strain were associated with telomere length. We further evaluated whether this association differed by level of global stress. Findings from this study should help to clarify the pathophysiological impact of caregiving, improving our ability to identify, monitor, and track high-risk caregivers. Further, the findings will suggest points of intervention to prevent or ameliorate the adverse consequences of caregiving, potentially improving the long-term health of both caregivers and their families.

METHODS

Data source

Data were from the 2008–2010 Survey of the Health of Wisconsin (SHOW). The SHOW is an annual statewide survey of civilian noninstitutionalized adults aged 21–74 years, representative of the state of Wisconsin. A description of SHOW procedures is available elsewhere (51). Briefly, participants were selected from a random sample of Wisconsin households using a 2-stage cluster sampling approach. Participants completed face-to-face interviews, self-administered questionnaires, and a physical examination and provided a blood (venipuncture) or saliva (Oragene; DNA Genotek Inc., Kanata, Ontario, Canada (www.dnagenotek.com)) sample. All informal caregivers who provided samples ($n = 240$) were included in the present study. We randomly selected a subset of noncaregivers with samples ($n = 98$), frequency-matched to the caregivers on age and sex. This study was approved by the Health Sciences Institutional Review Board of the University of Wisconsin-Madison.

Measures

Independent variables. Identification of caregivers. Informal caregivers were identified by the following question: "There are situations in which people provide regular unpaid care or assistance to a family member (including children) or a friend who has a long-term illness or a disability. In the past 12 months, did you provide any such care or assistance to a family member or friend living with you or living elsewhere?" (52).

Global stress. The Global Perceived Stress Scale from the Jackson Heart Study (53) was used to measure global stress over the last 12 months. This scale assesses perceptions of ongoing stressful conditions in 8 domains (i.e., job,

relationships, neighborhood, caring for others, legal problems, medical problems, racism/discrimination, and meeting basic needs). Participants rated each domain on a 4-point Likert scale (ranging from not stressful (0) to very stressful (3)), and scores for the items were summed (possible range, 0–24). Higher scores indicated greater stress.

Caregiving characteristics. Caregivers reported their duration of caregiving (years); number of hours of care provided per week; travel distance from the care recipient (co-resident, ≤20 minutes away, or >20 minutes away); relationship to the care recipient (spouse, adult child (caring for a parent), parent (caring for a child), or other friend/relative); the care recipient's condition (dementia, recovery from surgery, injury, acute illness, or other condition), age, and sex; number of care recipients in the past year; and whether they were currently providing care.

Caregiver strain. A 12-item version of the Caregiver Strain Index (54) was used to evaluate perceived strain among caregivers. This version of the index asked respondents whether 12 statements related to caregiving applied to them (e.g., "It is inconvenient for you"). The number of items endorsed was summed (possible range, 0–12). Higher scores indicated greater strain. Cronbach's α was 0.81.

Dependent variable: telomere length. Telomere length assays were conducted using stored DNA extracted from blood using phenol/chloroform (55) or from saliva ($n = 45$; 32 caregivers (13.3%) and 13 noncaregivers (13.3%)) using the DNA Genotek protocol (www.dnagenotek.com). Relative telomere length was assayed using quantitative real-time polymerase chain reaction (56). This assay uses separate primer pairs to hybridize and amplify 1) telomere hexamer repeats and 2) single-copy gene (β_2-globin) DNA. All polymerase chain reactions were performed on the Applied Biosystems 7900HT Fast Real-Time PCR System (Applied Biosystems, Inc., Foster City, California). The data were then analyzed with Applied Biosystems SDS software (Applied Biosystems, Inc.) to generate the standard curve for each plate. The intraassay coefficients of variation of the threshold cycle values for the telomere and single-gene reactions were 1.27% and 1.41%, respectively. The interplate variations were 4.79% and 4.06%, respectively. All samples were analyzed in triplicate. The median T value and the median S value were used to determine the telomere-to-single copy gene ratio (T/S) for each sample, and the natural logarithm of the ratio, log(T/S), was used in the analyses to account for skewness. A linear transformation of the T/S ratio was used to estimate telomere length in base pairs: base pairs = (T/S) × 1,470.8 + 7,674.5, based on comparisons between telomere restriction fragment lengths, as determined by Southern blot, and T/S ratios among samples previously examined by the laboratory ($n = 16$; $r = 0.57$, $P = 0.02$).

Covariates. Sociodemographic characteristics. Participants reported their age, sex, race/ethnicity (non-Hispanic white vs. other), annual income, educational attainment, employment status (employed in the past week vs. unemployed), type of health insurance (none, public, private, or mixed), marital status (married/partnered, divorced/widowed/separated, or never married), and the number of adults and children in the household. Participants reported their combined annual family income categorically (e.g., $25,000–$29,999).

Table 1. Characteristics of Caregivers and Noncaregivers in the Survey of the Health of Wisconsin, 2008–2010[a]

	Noncaregivers (*n* = 246,927)[b]		Caregivers (*n* = 546,156)[b]	
	Mean (SD)	%	Mean (SD)	%
Sociodemographic Factors				
Age, years	46.7 (13.5)		51.6 (12.7)	
Sex				
Female		55.8		63.6
Male		44.2		36.4
Race/ethnicity				
White (non-Hispanic)		90.5		88.0
Other		9.5		12.0
Annual income (in thousands), dollars	71.8 (37.2)		71.9 (81.8)	
Educational attainment, years	14.6 (2.1)		14.2 (2.5)	
Employment status				
Employed		81.4		69.3
Unemployed		18.6		30.7
Type of health insurance				
None		7.2		5.7
Public		6.0		8.8
Private		77.9		66.1
Mixed		9.0		19.4
Marital status				
Married/partnered		80.6		74.1
Divorced/widowed/separated		7.2		16.8
Never married		12.1		9.1
No. of adults in the household	2.1 (0.6)		2.1 (0.8)	
No. of children in the household	1.0 (1.1)		0.7 (1.1)	
Lifestyle Factors				
Smoking status				
Current smoker		8.7		18.3
Former smoker		30.8		32.9
Never smoker		60.5		48.8
Alcohol consumption status[c]				
Nondrinker		46.6		43.3
Moderate drinker		45.8		41.7
Risky drinker		7.6		15.0
Physical activity, MET-minutes/week	1,761.7 (2,830.5)		2,030.6 (3,011.6)	
Housework, minutes/month	727.5 (1,934.4)		879.4 (1,652.5)	
Fruit/vegetable consumption, servings/day	2.5 (1.6)		2.7 (1.6)	
Percentage of calories derived from fat	34.7 (0.7)		34.9 (0.7)	
Sleep time, hours/night	7.1 (1.2)		6.8 (1.1)	

Table continues

These data were recoded to the midpoint to approximate a continuous measure; the highest category (≥$200,000) was recoded to $392,396 by assuming a Pareto distribution of income (57). Educational attainment was reported as the highest grade or level of schooling completed and was recoded as years of education.

Lifestyle factors. Information on smoking (current, former, or never smoker), alcohol consumption (nondrinker, moderate drinker, or risky drinker), leisure-time and transportation-related physical activity (metabolic equivalent of task (MET)-minutes per week), and diet (fruit/vegetable consumption and percentage of calories derived from fat

Table 1. Continued

	Noncaregivers ($n = 246,927$)[b]		Caregivers ($n = 546,156$)[b]	
	Mean (SD)	%	Mean (SD)	%
Health Factors				
Total no. of health conditions	2.5 (2.0)		2.8 (2.0)	
No. of prescription medications	2.3 (2.7)		2.8 (3.5)	
Global stress[d]	6.2 (3.9)		6.7 (4.3)	
Telomere length (estimated no. of base pairs)	9,121.4 (771.2)		9,015.9 (677.8)	
Caregiving Characteristics				
Duration of caregiving, years			4.8 (6.1)	
Amount of caregiving, hours/week			17.7 (31.1)	
Travel distance from care recipient, minutes				
Co-resident				32.3
≤20				50.6
>20				17.0
Relationship with care recipient				
Spouse				15.9
Adult child (caring for a parent)				44.8
Parent (caring for a child)				10.5
Other friend/relative				28.7
Care recipient's condition				
Dementia				14.9
Recovery from surgery				8.3
Other				76.8
No. of care recipients			1.2 (0.5)	
Caregiver status				
Current caregiver				59.5
Caregiving in the past 12 months				40.5
Caregiver strain[e]			4.8 (3.2)	
Age of care recipient, years			63.8 (25.8)	
Sex of care recipient				
Male				37.4
Female				62.6

Abbreviations: MET, metabolic equivalent of task; SD, standard deviation.

[a] No differences reached statistical significance ($P < 0.05$; χ^2 tests, *t* tests, and Wilcoxon tests were used).

[b] Weighted values. Unweighted totals were 98 for noncaregivers and 240 for caregivers.

[c] Moderate drinking was defined as fewer than 8 drinks per week in the past year for women and fewer than 15 drinks per week in the past year for men. Risky drinking was defined as 8 or more drinks per week in the past year for women and 15 or more drinks per week in the past year for men. Persons who did not report any alcohol consumption in the past year were classified as nondrinkers.

[d] Global stress over the last 12 months was self-reported using the Global Perceived Stress Scale from the Jackson Heart Study (53). Eight items were measured on a 4-point Likert scale (ranging from not stressful (0) to very stressful (3)), and scores were summed (possible range, 0–24); higher scores indicate greater stress.

[e] A 12-item version of the Caregiver Strain Index (54) was used to evaluate perceived strain among caregivers. Respondents were asked whether 12 statements related to caregiving applied to them (e.g., "It is inconvenient for you"). The number of items endorsed was summed (possible range, 0–12); higher scores indicate greater strain.

(58)) was obtained via personal interview. Sleep quality (single-item report on a 5-point Likert scale; dichotomized to excellent/very good/good vs. fair/poor), sleep problems, and nightly sleep duration (hours; continuous nonlinear term) were reported using the self-administered questionnaires.

Health factors. Respondents reported their history of 47 health conditions (see the Web Appendix, available at http:// aje.oxfordjournals.org/), and the number of health conditions was calculated. An inventory of prescription medications taken by the participant was conducted during the home

interview using a standardized protocol (59), and the total number of prescription medications used in the past 30 days was calculated. Height and weight were measured during the examination visit, and body mass index (weight (kg)/height (m)^2) was calculated.

Analytical approach. All analyses were conducted in R 2.15.0 (60). Multiple imputation with predictive mean matching was used to predict the values of missing data (61); 5 imputations were conducted. Nonlinear transformations were allowed when predicting missing values for continuous variables. All analyses were conducted using the imputed data sets. Estimates and standard errors were combined using Rubin's rules (62, 63).

Caregiver and noncaregiver characteristics were compared using cross-tabulations with χ^2 tests, *t* tests, or Wilcoxon tests. All tests of statistical significance were 2-sided. Generalized additive models with thin-plate regression splines were constructed to examine whether 1) caregivers had shorter telomeres than noncaregivers, 2) global stress was associated with shorter telomere length, and 3) caregiving characteristics and caregiver strain were associated with telomere length. Multivariable analyses controlled a priori for caregiver age, sex, race, number of chronic conditions, and prescription medication use. Manual backward selection was used to determine whether additional sociodemographic characteristics were included in the model: All covariates were included simultaneously, and each variable with $P < 0.20$ was removed individually. If removing the variable did not substantially change the β coefficient of the primary independent variable (>10%), it was not included in the final model. The models were also tested while controlling for lifestyle factors that may lie in the pathway between caregiving or stress and telomere length—including diet, exercise, smoking, alcohol consumption, and sleep—and body mass index. Because these factors did not substantively influence the findings, only the results from the parsimonious models are reported. All continuous variables were tested as nonlinear terms in the models; generalized cross-validation (64) was used.

Follow-up analyses were conducted among caregivers in order to determine whether the association of global stress and telomere length differed by the amount of reported caregiver strain. The variables were dichotomized at the median value among caregivers (global stress: 6; strain: 4), and mutually exclusive groups were created. The association between these stress-strain groups and telomere length was evaluated as above.

In order to account for the complex survey design, we then conducted these analyses using sampling weights. Nonlinear terms were included in the models as natural cubic splines, with fixed degrees of freedom estimated from the generalized additive models.

In addition, because mean telomere length differed by tissue source (blood: mean T/S = 0.91; saliva: mean T/S = 1.16 ($P < 0.05$)), we performed a sensitivity analysis dropping the saliva samples.

RESULTS

Table 1 gives the characteristics of caregivers and noncaregivers in this study. Caregivers did not differ significantly from noncaregivers with regard to any of the characteristics.

Unadjusted analyses

In the unadjusted analyses (Table 2), there was no mean difference in telomere length between caregivers and noncaregivers (difference = −0.07; $P = 0.33$). Global stress was nonlinearly associated with telomere length, such that persons reporting moderate global stress (approximately 7–11 points on the global stress scale; data not shown) had longer telomeres. When stress was examined categorically, persons with stress scores of 7–11 had significantly longer telomeres than those with stress scores of 6 or less (difference = 0.14; $P = 0.04$). Among caregivers, providing more hours of care per week and reporting greater strain were associated with shorter telomeres (difference in log(T/S) per doubling of hours = −0.04 ($P = 0.04$); difference in log(T/S) per doubling of strain = −0.06 ($P = 0.05$)).

Adjusted analyses

Caregiver status. In the adjusted analyses, there was no mean difference in telomere length between caregivers and noncaregivers after controlling for covariates (difference = −0.03; $P = 0.64$ (Table 3)). As expected, older age was associated with shorter telomeres ($P = 0.004$; Figure 1).

Global stress. Perceived global stress was significantly nonlinearly associated with telomere length: Persons reporting moderate global stress (about 7–11 points on the Global Perceived Stress Scale) had longer telomeres ($P = 0.01$; Figure 2). When this variable was examined categorically, persons with stress scores of 7–11 had significantly longer telomeres than those with scores of 6 or less (difference = 0.15 (about 184 base pairs); $P = 0.04$ (Table 4)).

Caregiving characteristics. Among caregivers, those who provided more hours of care per week had significantly shorter telomeres (difference in log(T/S) per doubling of hours = −0.04 (about 54 fewer base pairs); $P = 0.004$) (see Table 5, bivariate-adjusted results). In addition, those providing care to persons under the age of 25 years had significantly shorter telomeres than those caring for older persons, equating to as much as a 342-base-pair difference. Finally, greater caregiver strain was associated with shorter telomeres (difference in log(T/S) per doubling of strain = −0.07 (about 99 fewer base pairs); $P = 0.03$). When all of the caregiving characteristics were included in the model simultaneously (see Table 5, multivariate-adjusted results), these findings remained. In addition, persons who did not co-reside with the care recipient had shorter telomeres than those who did. Full regression results are shown in Web Tables 1–7.

In addition, the association between caregiver strain and telomere length differed by the level of stress reported by caregivers. As Figure 3 shows, persons who reported high caregiver strain but low global perceived stress had significantly shorter telomeres than those reporting both low strain and low stress (about 316 fewer base pairs; $P = 0.02$) and borderline significantly shorter telomeres than those with high strain and high stress (about 250 fewer base pairs; $P = 0.08$) or low strain and high stress (about 302 fewer base pairs; $P = 0.05$). The overall interaction did not reach statistical significance (overall $P = 0.13$).

Table 2.   Bivariate Associations Between Caregiving and Stress Factors and Telomere Length (Log(T/S)) in the Survey of the Health of Wisconsin, 2008–2010

	β[a]	95% CI	P Value
Caregiver status			
Caregiver	−0.07	−0.20, 0.07	0.33
Noncaregiver	0	Reference	
Global stress score[b]			
≤6	0	Reference	
7–11	0.14	0.00, 0.28	0.04
≥12	−0.04	−0.21, 0.14	0.67
Duration of caregiving (per doubling), years	−0.02	−0.05, 0.02	0.30
Amount of caregiving (per doubling), hours/week	−0.04	−0.07, 0.00	0.04
Relationship with care recipient			
Spouse	0	Reference	
Adult child (caring for a parent)	0.03	−0.11, 0.18	0.64
Parent (caring for a child)	−0.13	−0.33, 0.07	0.20
Other friend/relative	0.15	−0.05, 0.35	0.13
Travel distance from care recipient, minutes			
Co-resident	0	Reference	
≤20	0.01	−0.15, 0.17	0.92
>20	−0.12	−0.27, 0.03	0.12
Care recipient's condition			
Dementia	0.05	−0.10, 0.20	0.51
Recovering from surgery	−0.08	−0.56, 0.41	0.75
Other	0	Reference	
Care recipient's age, years			
<25	−0.15	−0.37, 0.06	0.16
25–44	−0.02	−0.24, 0.21	0.87
45–64	0.03	−0.19, 0.25	0.80
65–84	−0.03	−0.24, 0.18	0.77
≥85	0	Reference	
Caregiver strain,[c] per doubling	−0.06	−0.12, 0.00	0.05

Abbreviations: CI, confidence interval; T/S, telomere-to-single copy gene ratio.

[a] For continuous covariates, the estimate represents the change in log(T/S) per doubling of the covariate; for categorical covariates, the estimate represents the difference from the reference group.

[b] Global stress over the last 12 months was self-reported using the Global Perceived Stress Scale from the Jackson Heart Study (53). Eight items were measured on a 4-point Likert scale (ranging from not stressful (0) to very stressful (3)), and scores were summed (possible range, 0–24); higher scores indicate greater stress.

[c] A 12-item version of the Caregiver Strain Index (54) was used to evaluate perceived strain among caregivers. Respondents were asked whether 12 statements related to caregiving applied to them (e.g., "It is inconvenient for you"). The number of items endorsed was summed (possible range, 0–12); higher scores indicate greater strain.

When saliva samples were dropped from the analyses, the results were largely unchanged. However, the association

Table 3.   Association Between Caregiver Status and Telomere Length (Log(T/S)) in the Survey of the Health of Wisconsin, 2008–2010[a]

	β[b]	95% CI	P Value
Intercept	−0.21	−0.59, 0.17	
Caregiver status			
Caregiver	−0.03	−0.16, 0.10	0.64
Noncaregiver	0	Reference	
Sex			
Female	0.04	−0.08, 0.16	0.52
Male	0	Reference	
Race/ethnicity			
White (non-Hispanic)	0.05	−0.11, 0.20	0.56
Other	0	Reference	
Employment status			
Employed	−0.14	−0.26, −0.01	0.03
Unemployed	0	Reference	
Educational attainment, years			
<12	0	Reference	
≥12	0.17	0.03, 0.31	0.02
No. of adults in the household	0.07	0.01, 0.13	0.02
No. of health conditions	0.02	−0.01, 0.05	0.21
No. of prescription medications			
0	0	Reference	
≥1	−0.13	−0.28, 0.03	0.11

Abbreviations: CI, confidence interval; T/S, telomere-to-single copy gene ratio.

[a] The model also controlled for age as a nonlinear term (P < 0.01).

[b] For continuous covariates, the estimate represents the change in log(T/S) per unit increase in the covariate; for categorical covariates, the estimate represents the difference from the reference group.

between moderate-to-high stress and telomere length was attenuated slightly (difference = 0.13; P = 0.11 (data not shown)). In addition, the estimate for caring for a person under 25 years of age was attenuated (difference = −0.16; P = 0.11), and the association between strain and telomere length was of borderline significance (difference = −0.09; P = 0.07).

DISCUSSION

To our knowledge, this was the first population-based study to examine the association between caregiving and telomere length. The findings from this study highlight subgroups of caregivers who have shorter telomeres (i.e., those providing more hours of care, caring for a child or young adult, or reporting greater strain) and may therefore be at particularly high risk of poor health outcomes. Further, the findings suggest that stress and caregiver strain have complex, nonlinear associations with cellular aging that are in need of further examination.

Previous studies of the association between caregiving and telomere length have been conducted in small convenience
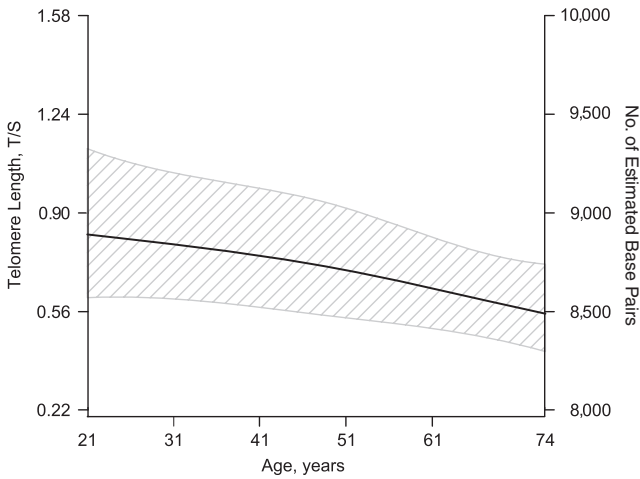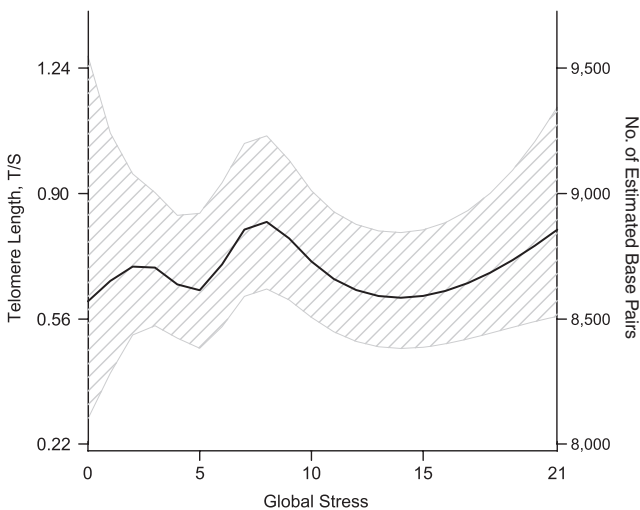
Figure 1. Association between age and telomere length among caregivers and noncaregivers in Wisconsin, Survey of the Health of Wisconsin, 2008–2010. The model controlled for caregiver status, sex, race/ethnicity, employment status, educational attainment, household composition (numbers of adults and children in the household), number of health conditions, and prescription medication use ($P = 0.004$ (generalized additive model)). T/S, telomere-to-single copy gene ratio.

samples, and results have been conflicting (42, 43). The present study provides evidence *against* overall differences in telomere length by caregiver status. This null result may be

Figure 2. Association between global stress and telomere length among caregivers and noncaregivers in Wisconsin, Survey of the Health of Wisconsin, 2008–2010. The model controlled for caregiver status, age, sex, race/ethnicity, employment status, educational attainment, number of adults in the household, number of health conditions, and prescription medication use ($P = 0.01$ (generalized additive model)). Global stress over the last 12 months was self-reported using the Global Perceived Stress Scale from the Jackson Heart Study (53). Eight items were measured on a 4-point Likert scale (ranging from not stressful (0) to very stressful (3)), and scores were summed; higher scores indicate greater stress. T/S, telomere-to-single copy gene ratio.

Table 4. Association Between Global Stress and Telomere Length (Log(T/S)) Among Caregivers and Noncaregivers in the Survey of the Health of Wisconsin, 2008–2010

	β[a]	95% CI	P Value
Intercept	−0.24	−0.64, 0.15	
Global stress score[b]			
≤6	0	Reference	
7–11	0.15	0.01, 0.29	0.04
≥12	−0.08	−0.27, 0.11	0.42
Age, per 10 years	−0.05	−0.10, −0.01	0.03
Sex			
Female	0.04	−0.08, 0.16	0.51
Male	0	Reference	
Race/ethnicity			
White (non-Hispanic)	−0.01	−0.17, 0.14	0.87
Other	0	Reference	
Educational attainment, years			
<12	0	Reference	
≥12	0.19	0.07, 0.32	<0.01
No. of adults in the household	0.08	0.02, 0.15	<0.01
Caregiver status			
Caregiver	−0.04	−0.17, 0.10	0.60
Noncaregiver	0	Reference	
No. of health conditions	0.02	−0.01, 0.05	0.19
No. of prescription medications			
0	0	Reference	
≥1	−0.12	−0.27, 0.04	0.13

Abbreviations: CI, confidence interval; T/S, telomere-to-single copy gene ratio.
[a] For continuous covariates, the estimate represents the change in log(T/S) per unit increase in the covariate; for categorical covariates, the estimate represents the difference in log(T/S) from the reference group.
[b] Global stress over the last 12 months was self-reported using the Global Perceived Stress Scale from the Jackson Heart Study (53). Eight items were measured on a 4-point Likert scale (ranging from not stressful (0) to very stressful (3)), and scores were summed (possible range, 0–24); higher scores indicate greater stress.

attributable to caregiver heterogeneity (7, 65–73). Although subgroup sizes limited our ability to examine this, future work should more closely examine the role of heterogeneity in telomere attrition among caregivers.

While several previous studies have provided evidence that greater psychological stress is associated with shorter telomeres (42, 44–49), we found that participants who reported a moderate-to-high level of global stress in the past year had *longer* telomeres than those with low levels of stress. It is possible that our population-based sample captured a broader swath of the stress distribution than previous convenience-based studies, which may have identified only the associations at the higher end of the stress distribution. In addition, it is possible that psychological stress over short, intermediate, and long terms has differential associations with cellular

Table 5.   Association Between Caregiving Characteristics and Telomere Length (Log(T/S)) Among Caregivers in the Survey of the Health of Wisconsin, 2008–2010

	Bivariate-Adjusted Results (Caregiving Characteristics Modeled Separately)			Multivariate-Adjusted Results[a] (Caregiving Characteristics Modeled Jointly)		
	β[b]	95% CI	P Value	β[b]	95% CI	P Value
Intercept				0.52	−0.05, 1.10	
Caregiving characteristics						
Duration of caregiving (per doubling), years[c]	−0.01	−0.04, 0.01	0.34	−0.02	−0.04, 0.01	0.21
Amount of caregiving (per doubling), hours/week[c]	−0.04	−0.07, −0.01	<0.01	−0.05	−0.08, −0.02	<0.01
Relationship with care recipient[d]						
Spouse	0	Reference		0	Reference	
Adult child (caring for a parent)	0.07	−0.06, 0.19	0.30	0.11	−0.10, 0.33	0.29
Parent (caring for a child)	−0.12	−0.32, 0.08	0.25	0.00	−0.20, 0.20	0.98
Other friend/relative	0.09	−0.11, 0.29	0.37	0.15	−0.07, 0.38	0.18
Travel distance from care recipient, minutes[e]						
Co-resident	0	Reference		0	Reference	
≤20	0.06	−0.07, 0.19	0.39	−0.19	−0.34, −0.04	0.01
>20	−0.02	−0.17, 0.13	0.84	−0.24	−0.45, −0.03	0.02
Care recipient's condition[d]						
Dementia	0.07	−0.11, 0.25	0.45	0.06	−0.09, 0.22	0.43
Recovering from surgery	−0.13	−0.54, 0.28	0.54	−0.20	−0.58, 0.19	0.32
Other	0	Reference		0	Reference	
Care recipient's age, years[f]						
<25	−0.29	−0.44, −0.13	<0.01	−0.26	−0.46, −0.06	<0.01
25–44[g]	−0.12	−0.31, 0.07	0.21	−0.02	−0.25, 0.21	0.88
45–64[g]	−0.08	−0.25, 0.09	0.37	−0.06	−0.29, 0.18	0.64
65–84[g]	−0.08	−0.24, 0.09	0.38	−0.02	−0.16, 0.13	0.84
≥85[g]	0	Reference		0	Reference	
Caregiver strain (per doubling)[h]	−0.07	−0.13, −0.01	0.03	−0.07	−0.13, 0.00	0.05

Abbreviations: CI, confidence interval; T/S, telomere-to-single copy gene ratio.

[a] In the multivariate-adjusted analysis, the model controlled for all variables in the table and all variables listed in footnote c, as well as marital/partner status, employment status, and sex of the care recipient.

[b] For continuous covariates, the estimate represents the change in log(T/S) per doubling of the covariate; for categorical covariates, the estimate represents the difference from the reference group.

[c] In the bivariate-adjusted analysis, the model controlled for age, sex, race/ethnicity, educational attainment ≥12 years, number of adults in the household, number of health conditions, prescription medication use, current caregiving status, and having more than 1 care recipient.

[d] In the bivariate-adjusted analysis, the model controlled for all of the variables listed in footnote c, as well as marital/partner status and number of children in the household.

[e] In the bivariate-adjusted analysis, the model controlled for all of the variables listed in footnote c, as well as employment status, annual income (log-transformed), marital/partner status, and number of children in the household.

[f] In the bivariate-adjusted analysis, the model controlled for all of the variables listed in footnote c, as well as marital/partner status.

[g] Significantly different from <25 years of age (P < 0.05) in both bivariate-adjusted and multivariate-adjusted analyses.

[h] In the bivariate-adjusted analysis, the model controlled for age, sex, race/ethnicity, educational attainment ≥12 years, number of adults in the household, number of health conditions, prescription medication use, and current caregiving status.

aging (21, 74). Interestingly, the "U-shaped" curve observed in this study is reminiscent of the association between stress and other factors, such as resiliency (75) and physiological and mental function (76): While a large amount of stress is deleterious, a small amount may improve fitness. Future work is clearly needed to confirm and further explore this finding.
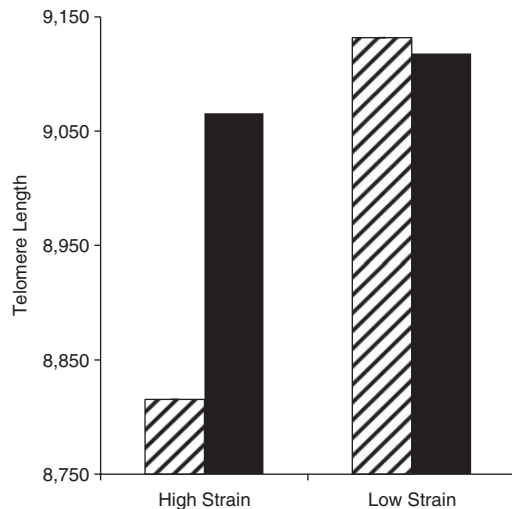
Figure 3. Average telomere length (number of estimated base pairs) according to level of caregiver strain (score of ≤4 vs. >4) and global stress (score of ≤6 vs. >6), Survey of the Health of Wisconsin, 2008–2010. Black bars indicate high stress; striped bars indicate low stress. The model controlled for age, sex, employment status, marital/partner status, race/ethnicity, educational attainment, annual income (log-transformed), household composition (numbers of adults and children in the household), number of health conditions, prescription medication usage, current caregiving status, and having more than 1 care recipient. Average adjusted telomere length in the high-strain/low-stress group was significantly lower than that in the low-strain/low-stress group ($P = 0.02$) and was borderline significantly lower than that in the low-strain/high-stress and high-strain/high-stress groups ($P < 0.10$); the overall P value for the interaction was 0.13 (generalized additive model).

In the only previous study to have examined the association between caregiving characteristics and telomere length, Epel et al. (42) reported that longer duration of care was associated with shorter telomeres. While we found no evidence of this association in our sample, we did find that more hours per week of caregiving, younger age of the care recipient, and greater caregiver strain were associated with shorter telomeres. Psychological aspects, such as feeling more uncertainty or less choice (77, 78) or perceiving a higher level of care recipient disability/need (79), may contribute to poor health outcomes. Interestingly, the association between number of hours per week of providing care and shorter telomere length was not attributable to caregivers' time use (e.g., reduced time spent exercising or sleeping) and was also independent of stress, strain, health factors, and caregivers' health behaviors (data not shown).

Caregivers of persons under the age of 25 years also had significantly shorter telomeres than caregivers of older persons (although this effect was attenuated when saliva samples were dropped). Providing care for a child who is ill or disabled may be considered "off-time" or nonnormative (80) and has been associated with feelings of uncertainty and depression (81, 82), and may therefore be more deleterious to the caregiver. These changes may accumulate over time and may not manifest as health problems until later in life (71), plausibly due to accelerated telomere attrition.

To our knowledge, this is the first study to have found that greater caregiver strain is associated with shorter telomeres. In addition, we found that persons who had high levels of strain but low levels of stress had substantially shorter telomeres than other caregivers, translating to an estimated 7–10 additional years of aging (17, 24, 83). Some caregivers may have underreported their level of perceived global stress (84), potentially because of their engagement in the caregiver role (i.e., being strong for the family), stress habituation, or avoidant coping or denial, which is deleterious over the long term (85–88). Additionally, the associations between global stress and strain with telomere length may differ, as different types of adversity are associated with different biological cascades (89–92). Further, experiencing stress outside of the caregiving realm may indicate greater connection with the community and engagement outside of caregiving, which may be protective (93–98). However, because the overall interaction was not statistically significant, future work with greater statistical power will be necessary to confirm and clarify these findings.

Several potential biological mechanisms also exist that may explain the observed association between greater global stress and longer telomeres and the potential discordance in telomere length by levels of strain and global stress, including telomerase activation, alternative lengthening of telomeres, and changes in the leukocyte subpopulation (15, 99–103). Psychological stress contributes to a biological cascade resulting in increased cellular stressors (e.g., oxidative stress) that may trigger telomerase activation (104) or alternative lengthening mechanisms. Indeed, some studies have found an association between stress or adverse exposures such as caregiving and increased telomerase activation (43, 48, 105–107), which could contribute to telomere lengthening. Finally, telomere length and dynamics differ across different types of white blood cells (103), and observed lengthening of telomeres may be due to changes in the cell mixture (101, 102). Therefore, if caregiving, stress, or strain contributed to different cell-type proportions, this might contribute to observed telomeric differences.

This study has several important implications. The telomere length differences in our study were in line with the magnitudes seen in relation to chronic disease burden (about 132 base pairs) (108) and myocardial infarction (about 300 base pairs) (109), highlighting the potential clinical significance of these findings. Assessing and monitoring hours per week of caregiving, age of the care recipient, and level of caregiver strain may help clinicians identify high-risk caregivers. Second, interventions that reduce psychological distress have been shown to increase telomere length (101, 110), and those that reduce caregiver strain or hours per week of providing care, such as coping-skills training or respite care, should be tested for their impact on cellular aging among caregivers. Self-care behaviors, such as exercise, may also help to prevent telomere attrition and subsequent poor health outcomes. Finally, this study highlights the need for additional research to better understand the role of both caregiving characteristics and stress in telomere dynamics. The potential interaction between caregiver strain and stress in the relationship with telomere length should also be examined further, in order to better understand how these factors may adversely influence caregivers over time.

This study had potential limitations. The use of telomere length as a biomarker of aging, chronic disease, or mortality risk remains controversial. Studies examining the associations between telomere length and mortality have produced mixed results, and telomere length does not meet all of the criteria for a biomarker of aging (41, 111, 112), although recent meta-analyses have provided evidence supporting associations for at least some disease outcomes (112–116). Second, telomere length was assessed at a single time point, and we could not control for innate individual variation in telomere length. Similarly, we could not evaluate the impact of longitudinal changes in stress or strain on telomere length. Third, our sample size did not permit us to examine heterogeneity in the association between caregiving and telomere length. Fourth, telomere length features that may be important, such as the relative sizes of cell subpopulations (101, 103) or the shortest telomeres in the sample (117), were not examined in this study. Differences in cell-type mixtures may be a source of residual confounding. Finally, the biological samples in this study consisted of both blood and saliva samples. When the saliva samples were excluded, some results were attenuated. Our results should be interpreted in light of the sensitivity analysis, and future work will be needed to replicate and confirm our findings.

This study also had several important strengths. The sample was selected from participants in a large population-based study, improving generalizability. We assessed several caregiving factors and both global stress and caregiver strain. Finally, we were able to measure and test numerous covariates in the models, including health behaviors, body mass index, and sociodemographic factors, that may have confounded the associations of interest.

In conclusion, this population-based study provided evidence that caregiving factors, including hours per week of care, caring for a young person, and greater caregiver strain, were associated with shorter telomere length, a marker of accelerated cellular aging. Further, moderate-to-high stress was associated with longer telomeres. The findings suggest that stress and caregiving situations have adverse consequences on a physiological level that may be predictive of future health problems. Future work is necessary to better elucidate these relationships and to develop interventions that will buffer telomere attrition and improve the long-term health and well-being of caregivers and their families.

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